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Original article

Idiopathic neonatal hepatitis: a long term follow-up study

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SUMMARY

Background: **Idiopathic neonatal hepatitis (INH) is the term given to any hepatitis that occurs from birth up to the 4th month of life and remains etiologically unclassified after clinical and laboratory evaluation. Our purpose was to find symptoms, natural history or factors associated with hepatobiliary disease in infancy and long term prognosis of non-familial type of INH.** ***Methods:*** **We followed up 33 cases of INH over a period of 12 years. Features of INH included: a) presence of conjugated hyperbilirubinaemia ≥3mg% lasting for more than 2 weeks during the first 4 months of life, b) biochemical and histological features of hepatocellular damage and c) exclusion of all other causes of conjugated hyperbilirubinaemia.** ***Results:*** **Jaundice was developed in all but one child. The liver was palpable in all patients and spleen was present in nineteen patients. Twelve patients with severe anemia (Hb<6gr%) required a blood transfusion. Associated features were history of prematurity (14), perinatal asphyxia (7), septicemia (9), respiratory distress syndrome (4), and hypoglycemia (5). All patients had abnormal liver function tests indicative of cholestasis while percutaneous liver biopsy revealed histological changes of neonatal hepatitis in all patients with changes of giant cell hepatitis in 9 neonates and non-specific changes (extramedullary haemopoiesis) in 4 neonates. According to the outcome, 10 patients had a moderate to severe outcome regarding liver disease. Two of them died, one from septicemia and the other from fulminant hepatic failure at the age of 6 and 9 weeks respectively. The remaining 8 patients are still being followed up because they developed features of possible chronic liver disease. A second liver biopsy in these children revealed mild fibrosis in three and findings of non-specific "hepatitis" in five. Twenty-three infants made a regular recovery from liver disease.** ***Conclusion:*** **We consider that the outcome of INH is good despite the serious problems that may present early in the course of the disease and the overall mortality seems to be low. Associated problems such as developmental delay should be recognized and addressed promptly.**

Key words: Cholestasis, jaundice neonatal hepatitis, idiopathic neonatal hepatitis.

Abbreviations: INH Idiopathic Neonatal Hepatitis
EHBA Extra Hepatic Biliary Atresia
NH Neonatal Hepatitis
LFT Liver Function Test

INTRODUCTION

Cholestasis in early infancy represents a diagnostic dilemma. The majority of these infants suffer either from extrahepatic biliary atresia (EHBA) or neonatal hepatitis (NH).[1,2] In about 25% to 50% of infants presenting with conjugated hyperbilirubinaemia within the first three months of life, no cause is found. These infants are considered to have idiopathic neonatal hepatitis (INH).[3-6] INH is considered to be a distinct entity with characteristic clinical, biochemical and histological features.[3,7-9] Some authors believe it represents a form of neonatal hepatitis[6,10] associated with an underlying disease (e.g. infection, inborn error of metabolism, etc.) which, despite not being obvious at the onset, becomes apparent later[3,8,10,11] after extensive evaluation.[3,12] Based on epidemiological data, two categories of idiopathic neonatal hepatitis have been identified, the familial and the non-familial or sporadic type.[1,13]

Our purpose was to focus on symptoms, natural his-

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tory and factors associated with hepatobiliary disease in infancy and the long-term prognosis of the non-familial type of INH.

PATIENTS AND METHODS

One hundred thirty-nine children with moderate to severe neonatal hepatitis were admitted to the 1st and 3rd Department of Pediatrics at Hippokration University Hospital of Thessaloniki, from February 1984 to June 1997. An extensive clinical and laboratory evaluation was performed (Table 1) to exclude all possible causes of neonatal hepatitis. More especially, the LFT tests included total bilirubin, serum aminotransferases, serum albumins, alkaline phosphatase and serum gamma-glutamyl transpeptidase estimated by routine methods (Department of Biochemistry, Hippokration Hospital, Thessaloniki, Greece). The normal values of LFT tests were as follow: total bilirubin 0.1-1.1 mg/dl, alanine aminotransferase 7-33 iu/L, aspartate aminotransferase 10-34 iu/L, serum gamma-glutamyl transpeptidase 10-49 iu/L, alkaline phosphatase 40-600 iu/L and total serum albumins 6.0-8.7 g/dl.

We found forty-one infants with features of idiopathic neonatal hepatitis (INH). The features for the diagnosis of INH included: a) the presence of conjugated hyperlibirubinaemia ≥ 3mg% lasting for more than 2 weeks in the first 4 months of life, b) biochemical and/or histological features of hepatocellular damage and c) exclusion of all other causes of conjugated hyperbilirubinaemia. During the study eight patients dropped out die to no compliance. Regular follow-up was finally achieved for 33 infants (twenty-three boys and 10 girls).

Liver biopsy was performed percutaneously by single use Mengini needle (Hepafix 1,2 B Braun Melsungen AG) on all patients and considered successful only when at least 5 portal spaces were included in the tissue obtained. All biopsies were done in the surgical department with the patient fully anesthetized by a skilled anesthetist. The obtained tissue was placed in a 10% formol solution and sent to the pathology laboratory. Eight patients had a second liver biopsy due to the persistence of clinical and laboratory findings (persistence of jaundice, hepatomegaly and transaminasaemia). All these children are still being followed up.

The observation period for every child ranged from 9 months to 12 years with 3-6 month follow-ups for clinical and laboratory evaluation. The patients were discharged from the study after being on clinical remission with a normal biochemical profile for at least 6 months.

RESULTS

Mode of presentation: Jaundice developed during the first two weeks of life in twenty and up to the 3rd month of life in twelve patients. In all cases total bilirubin was elevated over 12mg% (mean±SD, 13.35±2.45). One patient was not clinically jaundiced. Associated features were history of prematurity, perinatal asphyxia, septicemia, respiratory distress syndrome, and hypoglycemia (Table 2). The liver was palpable in all patients at least

Table 1. Protocol for the study of Idiopathic Neonatal Hepatitis in early infancy

1. Detailed history
2. Physical examination
3. Daily stool color obsevation
4. **Urine tests:** Routine
   Bacterial culture
   CMV culture
5. Blood tests for the following:

   Liver function tests: alanine and aspartate aminotransferase, alkaline phosphate, γ-glutamyl-transpeptidase, and serumproteins

   Clotting studies: prothrombin and partial thromboplastine time

   Viral studies: heaptitis B, Rubella, toxoplasma, cytomegalovirus and Ebstein Barr viruses

   Metabolic screen: plasma and urine aminoacids, urine reducing substances, serum a1-antithrypsin levels

   a1-antithrypsin phenotype estimation
6. **Imaging studies**: abdominal ultrasound scan, scintigraphy scan
7. **Liver biopsy**: percutaneous liver biopsy
8. **Maternal antiodies** for CMV, toxoplasma, rubella, herpes simplex

Table 2. Clinical features of Idiopathic Neonatal Hepatitis

	No of patients
Jaundice	32
Hepatomegaly	33
Splenomegaly	19
Prematurity	14
Septicaemia	9
Respiratory Distress Syndrome	4
Asphyxia	7
Anemia	12
Hypoglycemia	5
Pale stools	33

3-4 cm below costal margin with splenomegaly (about 1-2 cm below costal margin) found in nineteen patients. Twelve patients had severe anemia (Hb<6 gr%) requiring a blood transfusion. Two infants who died from sepsis or fulminant hepatic failure had signs of severe liver disease at the time of death (jaundice, acholic stools and hepatomegaly combined with splenomegaly, gastrointestinal bleeding, laboratory and histologic signs of neonatal hepatitis).

Laboratory evaluation: All patients had abnormal liver function tests indicative of cholestasis. More especially, serum aminotransferases were elevated to at least 2-3 times normal (mean±SD, 185±52), serum alkaline phosphatase was mildly elevated and usually no more than two times (mean±SD, 575±145), serum gamma-glutamyl transpeptidase was usually elevated to about 3 to 5 times normal (mean±SD, 175±45) and serum albumins were normal.

Liver biopsy: Percutaneous liver biopsy revealed histological changes of neonatal hepatitis in all patients with changes of giant cell hepatitis in 9 neonates and non-specific changes (extramedullary haemopoiesis) in 4 neonates. Severe periportal fibrosis, portal inflammation and diffuse giant cell transformation was detected in two infants at autopsy (Fig. 1). Furthermore, two children had severe inflammation and small bile duct paucity.

Clinical outcome (Fig. 2): According to the outcome, the patients were classified in two groups: **Group one (10 patients):** the patients of this group had a moderate to severe outcome regarding liver disease. Two of them died, one from septicemia and the other from fulminant hepatic failure at the age of 6 and 9 weeks respectively (subgroup 1). The rest of the patients in this group are still being followed up because they developed features

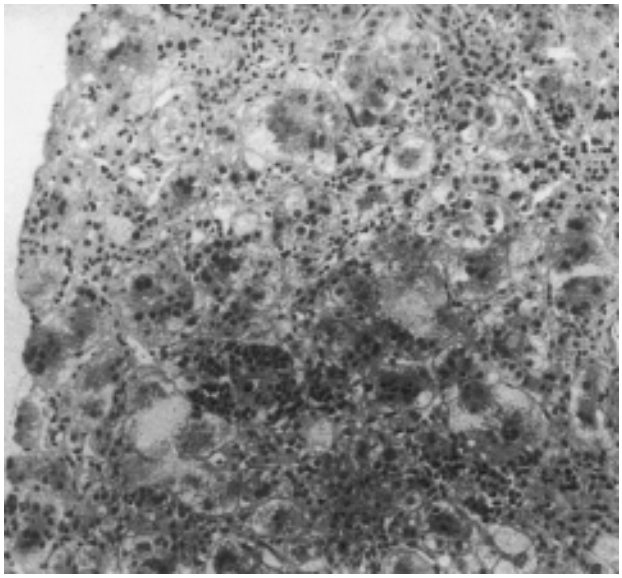

Figure 1. Liver biopsy: Disruption of normal liver architecture, presence of extramedullary haemopoiesis and widespread transformation of the hepatic cells to giant cells AEX200.

of possible chronic liver disease (jaundice for more than six months, slightly palpable liver and mild transaminasaemia). A second liver biopsy was performed revealing mild fibrosis and inflammatory cell infiltrate in the portal tract and hepatic parenchyma in three and findings of non-specific "hepatitis" in five children. Two out of eight infants (one male and one female) had prematurity and developmental delay (Denver Screening Test) (subgroup 2). **Group two (23 patients):** Twenty-three infants were included in this group (16 males and 7 females). These patients made a regular recovery from liver disease. The follow up period ranged from 1 to 9 years (mean of 4.2 years). Jaundice subsided progressively within a period ranging from 3 to 11 months after the initial evaluation (mean±SD, 4.5±1.9 months). One premature baby had moderate developmental delay with spastic diplegia. Two other premature infants and one small for dates, were found to have mild to moderate speech and motor delay at the age of 3, 4 and 5 years respectively. Seven children (5 premature and 2 fullterm infants) had neonatal asphyxia in combination with cholestasis.

Patients at risk of developmental delay (premature, small for dates, asphyxied infants, etc.) were also followed up at the developmental clinic and periodically assessed with the Denver's Test.

At the end of the follow up period, most children of this group were free of symptoms of liver disease. LFT's were normal with the exception of two patients who had

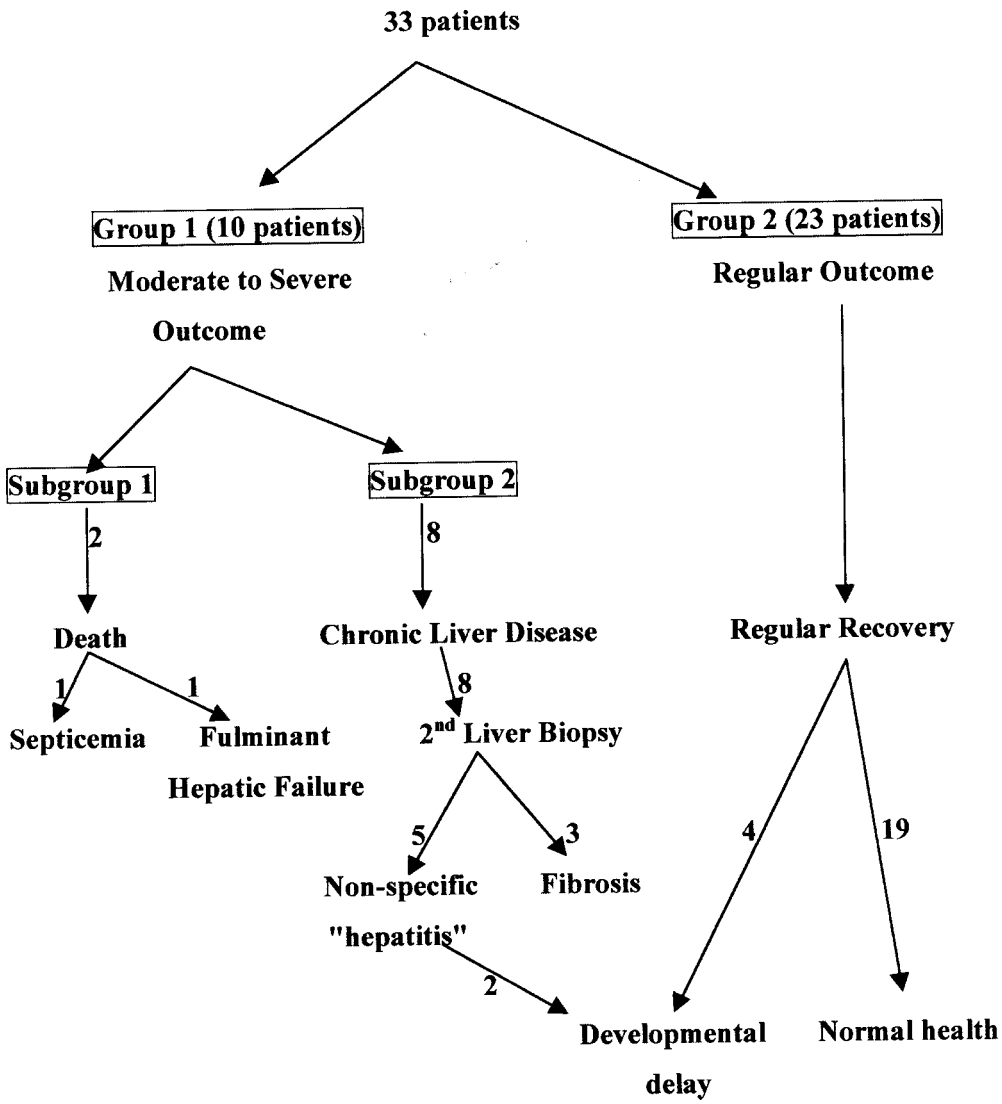

Figure 2. Clinical outcome of 33 patients with Idiopathic Neonatal Hepatitis

slight elevation of aminotransferases (AST 40-60 iu/ml).

DISCUSSION

Neonatal hepatitis syndrome is a term given to a non-specific hepatic inflammation, which develops secondary to many different etiologies.[8] INH, also known as giant cell hepatitis and cryptogenic hepatitis, is responsible for 50-70% of the NH cases.[3] By definition, no causative agent can be found in a baby with INH.[1,4] It is now considered a dinstict clinical entity with biochemical and histological features[3,8] of cholestasis.

INH is more common in males, small for dates and premature neonates.[1,8] In half of the cases it presents with jaundice in the first 2 weeks of life with the other half becoming apparent up to the 4th month of life.[8] In our study, there was a significant predominence of males, (male to female ratio 2.3:1) and 60% of our patients developed jaundice during the first 2 weeks after birth. A history of prematurity was also present in 14 infants. These data are in accordance with the international literature.[3,8]

The overall prognosis in INH is difficult to estimate, because of the variability of the clinical course and the unclear pathogenesis.[14,15] Nevertheless the prognosis is generally good, although different studies have shown different mortality rates. Danks et al mentioned a 30% overall mortality in the 1st year of life[10] comparer to 55%

mortality described by Henriksen et al in 1981.[4] Other studies showed a better outcome with a significantly lower mortality rate ranging from 6.5%[6] to 12.9%.[11] A positive family history is associated with an underlying bile acid metabolism disorder and carries a bad prognosis.[16] Other predictors of poor prognosis include prolonged severe jaundice (beyond six months of age), acholic stools, persistent hepatomegaly and severe inflammation on biopsy.[1] Biochemical parameters, such as bilirubin and transaminases and growth patterns have shown little importance as predictive markers.[16] Maggiore et al[17] found that persistently normal serum gGT levels might be considered as a sign of poor prognosis. In our study the mortality rate was low. Only two patients died, one from septicemia and the other from hepatic failure at the ages of 6 and 9 weeks respectively. Eight of our patients continue to have clinical and laboratory evidence of possible progressive hepatic disease with the liver biopsy showing periportal fibrosis in three of them. The patients who died had a higher bilirubin level, probably because of the coexistent sepsis and hepatic failure. No difference was found regarding the γGT level in our patients.

It is worth mentioning that 13 patients developed severe anemia of unknown origin. They needed blood transfusion and had an excellent outcome. All these were either preterm or fullterm infants with or without a history of septicemia in the neonatal period. Our search in the national literature failed to reveal a similar case and we attributed the anemia to the prematurity and septicemia. Furthermore, septicemia may be present in the perinatal history of infants with INH. It is well known that acute neonatal hepatitis may present as "septicemia" with mild jaundice in the neonatal period.[15,18]

Ten of our patients suffered from isolated perinatal asphyxia with subsequent development of neonatal hepatitis. We included these infants in INH group. New data coming forward[19,20] suggest that isolated perinatal asphyxia must be taken into account as a precursor of early neonatal cholestasis in both preterm and in-term newborns, in the absence of other predisposing insults to the liver.[21] Vajro et al[22] suggest that after promt exclusion of other forms of progressive neonatal cholestatic disease, recognition of isolated perinatal asphyxia per se as a likely causal factor may allow the clinician to observe a reasonable period of waiting and avoid time-consuming or invasive investigation. This is an interesting opinion but needs more confirmatory studies.

In conclusion, our study showed that the outcome of INH is good despite the problems encountered in the perinatal period. Though the clinical presentation is usually quite severe with acholic stools, hepatosplenomegaly amanifestations (e.g. hypoglacaemia, prematurity etc) the overall mortality seems to be low apart from the familial cases. Associated problems such as developmental delay should be recognized and addressed promptly.

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