INTRODUCTION

Neonatal hepatitis is defined clinically as a cholestasis syndrome, with an onset during the first three months of life and natural evolution, subacute or chronic, potentially crrhogenic, biologically through direct hyperbilirubinemia, and histologically by the giantcellular hepatic transformation (multinucleate giant hepatocytes). The etiological factors involved may be multiple, but according to the lesional moment, they may be divided into three large groups. (1):

- Pre-natal aggression- by infectious and/or toxic factors.
- Perinatal aggression- often immunologic factors are involved (mother-fetus incompatibility, transient immune deficiencies, anomalies of cellular immunity, IV administration of fats).
- Post-natal aggressions by excessive strain during severe hemolysis, perinatal hypoxia, modifications of hepatic perfusion determined by the act of birth, difficulties in postnatal hemodynamic adaptation.

Although the presence of one or several etiological factors is often proven, most commonly in these cases we are dealing with patologic pregnancies, pre-maturity or dis-maturity and in a large number of cases the first manifestations are extra-hepatic, only later, after following a complex protocol for the determination of the etiological diagnosis, being able to elucidate the hepatic condition. (2) The high number of cases when the etiology remains unclear must not be neglected, the cases falling under the category of idiopathic neonatal hepatitis. In Romania, much of the neonatal hepatitis in babies remains without a clear etiology due to the lack of possibility to determine a firm diagnosis for metabolic, infectious and/or genetic anomalies (viral serology, enzymatic dosage, screening of neonatal genetic diseases). Therefore we are helpless when confronted to conditions that evolve rapidly in children of very young age, where the evolutive prognosis depends on the earliness of diagnosis.

THE AIM OF THE STUDY

In this respect, the aim of this study is to underline the importance of early diagnosis of cholestasis and to objectify its etiology through a detailed protocol

MATERIAL AND METHOD

The study was both retrospective (January 1st 2005 to November 1st 2006), and prospective (November 1st 2006 to December 31st 2009), when we screened the children admitted to the Second Pediatric Clinic of the Children’s Hospital „Sf.Maria” of Iași for various affections that could generate intra- or extrahepatic cholestasis. Thus we screened a number of 293 children diagnosed with intra- or extrahepatic anomalies that might determine various degrees of cholestasis. For our study we developed a patient chart where we included: personal

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1 Corresponding Author: Paula Popovici, 77, block of flats T9, app.7 Arcu street, Iasi, Romania; e-mail: sacaci_p@yahoo.com; tel +40-0744090216

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CLINICAL ASPECTS

information, clinical and anamnestic data, serology tests performed for the confirmation of diagnosis and for ruling out other etiologies with similar manifestations, using a diagnosis protocol determined previously, imagistic results according to the patology, the final diagnosis. To record the patients we used a computer database that would later allow us to select the children for statistic purposes. The parameters thus obtained were subsequently analysed both individually and comparatively, in an attempt to find correlations between the pathologies diagnosed for these patients and these parameters.

RESULTS

The intra-hepatic pathology was found to occur more often (89.77%) than the extra-hepatic one, and was divided as follows:
- Infectious causes- cytomegalovirus (87 cases), toxoplasma (32 cases), other infectious-toxic causes (8 cases).
- Metabolic causes- cystic fibrosis (46 cases), hypotiroidism (14 cases), Wilson disease (12 cases), glycogenosis type I (3 cases), Gaucher disease (2 cases).
- Idiopathic neonatal hepatitis - 26 cases.
- Anatomic causes- arterio-hepatic dysplasia (Alagille syndrome)- 9 cases, hepatic cyst- 8 cases.

Figure no. 1. Repartition of cases with intrahepatic obstruction

- Infectious
- Metabolic
- Idiopathic
- Anatomic hepatic

- Starting from this incidence, clearly higher in intrahepatic pathology which generates cholestasis, this study means to determine an investigation algorithm that would allow an early therapeutic decision for a baby under suspicion of neonatal hepatitis. To this end, we focused on the lot of children with infectious hepatitis, starting from the five criteria which help determine a diagnosis when faced with a baby with syndromes of cholestasis engendered by intra-hepatic pathology, which are: clinical, biological, radiological, isotopic and morpho-pathologic criteria.

- Clinical criteria- the presence of ore or more of the following:
  → cholestatic jaundice of variable intensity, acholic feces, hyperchromic urine
  → hepatosplenomegaly (constant), splenomegaly
  → slow evolution and often favourable response to corticotherapy
  → the presence of generic manifestations- alteration of general status, fever, no gain weight

In the lot of children infected with cytomegalovirus, the clinical signs of cholestasis were met in 36.78% of the cases. The main clinical signs in this lot were the sclerotegumentary jaundice and the hepatomegaly. Other associated clinical signs were: tegumentary pallor biologically confirmed as light-to-moderate anemia (36.78%), chorioretinitis (25%), microcephaly (19%), cutaneous hemangioma (13.7%).

Another category that was screened was that of the children infected with toxoplasma, in which sclerotegumentary jaundice was present at birth in 50% of the cases, without modifications in the aspect of the feces or of the urine. Other associated clinical signs were: tegumentary pallor (68.75%), ocular impairment (37.5%), ponderal hypotrophy (37.5%), delay in psycho-motor development (25%), hydrocephalus (10%).

- Biological criteria- such as:
  B Cholestasis syndrome (total and direct bilirubin is increased, as are 3GT, alkaline phosphatase, lacticdehydrogenase, cholesterol, total fats, biliary pigments are present in feces and urine)
  B Moderate cytolysis syndrome
  B Non-specific inflammatory syndrome
  B Hepatocellular insufficiency syndrome
  B Moderate hemolitic anemia with negative Coombs test

The syndrome of cholestasis and a moderate cytolysis were met in all the cases, the presence of cholestasis being the main criterion of inclusion in this study. The syndrome of hepatocellular insufficiency was met less often (2% of the cases), it being present in the cases where the evolution was unfavourable despite the correct treatment. A light asymptomatic thrombocytopenia was met in most cases of hepatitis induced by the cytomegalic virus (83%).

- The Radiologic criteria (positive cholangiography) as well as the isotopic ones (hepabiliary scintigraphy with visualisation of the trace in the intestinal tract were only used when there was a suspicion of malformative causes.

- Morphological criteria: hepatocytary necrosis (usually focal), hepatocytary unrest, giant cell transformation, hepatocytary and canaliculous cholestasis, centers of extramedular eritropoesis, moderate portal and lobular inflammation. The ductular and ductal cholestasis, as well as the proliferative structures of these structures are absent or minimal. Lobular or portal fibrosis are minimal or absent at first, but appear during the evolution, and are in general a factor of negative prognosis.(3)

Figure no. 2. Multinucleate hepatocytes with bile HEx200 - collection Dr. D. Mihaila - Children’s Hospital « Sf Maria » Iași

The histopathologic modifications in the cytomegalovirus infection were characteristic, of the type: lymphocytary inflammatory infiltrate with nests of atypical lymphoid elements, macro- or microvesicular steatosis, by lesions to the biliary epithelium we get ductopenia with the transformation of hepatocytes into giant multinucleate cells, large amphiphile, intranuclear viral inclusions, with clear space around, ‘owl’s eye’, these inclusions are surrounded by an
inflammatory reaction.

Figure no. 3. Hepatitis with CMV “owl’s eye” in the biliary epithelium—colection Dr. D. Mihaila—Hospital of Children «Sf Maria» Iaşi

DISCUSSIONS

The evolutive prognosis of neonatal hepatitis depends on the etiological agent. In the cases of random neonatal hepatitis full recovery occurs in approximately half the cases, persistent inflammation occurs in 10%, cyrrhosis in 2% and death in 30% of the cases recorded. Family cases have higher death rates (60%), full recovery in 30% of the cases and the development of chronic hepatitis in 10%.(1,4)

Using the above-mentioned criteria it is very important to find the children with neonatal hepatitis, by identifying those children with cholestasis, or persistent jaundice, to give a correct diagnosis as early as possible, using non-invasive methods, to differentiate between the atresia of the biliary ducts and the neonatal hepatitis, the former being solved by early surgery (Kassai intervention), and the prognosis influenced by the time of surgery (optimal in the first 6 to 8 weeks of life).

CONCLUSIONS

Cholestasis represents an important cause of morbidity and mortality whose etiology must be determined as early as possible, as the choice of the best treatment is often connected to the moment of diagnosis as well as to the therapeutic possibilities. Within the larger group of cholestatic affections in children, neonatal hepatitis occurs frequently and diagnosing it requires an accurate clinical examination correlated to a detailed protocol that must be acquired by all the physicians involved in the care of this category of patients.

BIBLIOGRAPHY