

PAUCITY OF INTRAHEPATIC BILE DUCTS IN INFANCY - experience of a tertiary center

Adriana Maria Alves De TOMMASO, Agnes Sumi KAWASAKI and Gabriel HESSEL

ABSTRACT – *Background* - Intrahepatic cholestasis secondary to paucity of bile duct is an alteration of the anatomic integrity of the biliary tract. Can be defined only histologically and, clinically, two categories are recognized: syndromic and non-syndromic, where the prognosis is generally more severe. *Aim* - To evaluate the history, clinical and biochemical characteristics, etiology and improvement of children who have paucity of intrahepatic bile duct followed at tertiary center. *Patients and Methods* - Eleven children with paucity of intrahepatic bile duct, followed at the Pediatric Hepatology Service of the University Hospital, Campinas, SP, Brazil, were evaluated in the period from 1986 to 2001. *Results* - Among the patients, three presented the syndromic and eight the non-syndromic form (two with α -1-antitrypsin deficiency, one with lues, one secondary to sepsis, three with probable etiology by cytomegalovirus and one without a definite etiology). Referral ranged from 31 to 1185 days. Birth weights ranged from 1920 g to 3590 g. Most of the patients presented pale stools. The median bile duct/portal tract ratio was 0.14. The majority of the children presented a favorable follow-up, regardless of the form of presentation. *Conclusion* - Paucity of intrahepatic bile ducts should be considered in children with cholestasis and its differentiation from extrahepatic causes of neonatal cholestasis is important in order to avoid surgery. Diagnosis of non-syndromic form should not be regarded as unfavorable prognosis, as the evolution is probably related to the etiology in this form of presentation.

HEADINGS – Cholestasis, intrahepatic. Bile ducts, intrahepatic.

INTRODUCTION

Cholestasis is the reduction or the interruption of the bile flow to the duodenum. It is classified in causes intrahepatic and extrahepatic⁽¹⁰⁾.

Intrahepatic cholestasis may have a viral, metabolic, or toxic origin. It also can be secondary to abnormality of biliary secretion as a result of hepatocyte dysfunction or abnormal excretion, derived from alteration of anatomic integrity of the biliary tract⁽³⁾. The latter is denominated paucity of the intrahepatic bile ducts and comprises about 6.7% of the causes of intrahepatic cholestasis⁽¹⁰⁾. It is defined only histopathologically and requires a sufficiently large liver that contains at least five portal tracts⁽²⁾. The ratio of bile duct to the number of portal tracts (BD:PT) lies between 0.9 to 1.8 in term children and a ratio ≤ 0.5 is considered hypoplasia or paucity of the intrahepatic bile ducts⁽⁶⁾.

Two categories of paucity of intrahepatic bile duct are recognized: syndromic and non-syndromic. The syndromic form is also termed Alagille syndrome or arteriohepatic dysplasia. It is a multisystem autosomal dominant disorder with a prevalence of 1:100,000 live births⁽⁷⁾. The gene involved is JAG 1, located in the short arm of chromosome 20⁽⁸⁾. At least three of five major features are necessary for the diagnosis: characteristic facies, chronic cholestasis, cardiovascular abnormalities, vertebral arch defects and presence of posterior embryotoxon⁽⁷⁾. The

prognosis varies according to the severity of hepatic or cardiac affection⁽⁷⁾.

The non-syndromic form has been described in association with various abnormalities: metabolic or viral diseases (cytomegalovirus (CMV), rubella), chromosomal disorders (trisomy 18 and 21), altered bile acid metabolism and cystic fibrosis. Most cases are classified as primary or idiopathic⁽⁶⁾. In such cases the prognosis is, in general, more severe. About half of the patients develop liver failure and die in infancy, making liver transplantation the only valid therapeutic solution⁽¹⁾. However, complete clinical and histopathological resolution of non-syndromic form has been described⁽²⁾.

The objective of this study was to evaluate the history, clinical and biochemical characteristics, etiology and follow-up of children with paucity of the intrahepatic bile ducts, followed at a tertiary center.

PATIENTS AND METHODS

Patients

Eleven children with paucity of intrahepatic bile duct, followed at the Pediatric Hepatology Service of the University Hospital, Medical Sciences Faculty, State University of Campinas, Campinas, SP, Brazil, were evaluated in the period from 1986 to 2001.

Department of Pediatrics of the Medical Sciences School, State University of Campinas – FCM/UNICAMP, Campinas, SP, Brazil.

Address for correspondence: Dr. Adriana Maria Alves De Tommaso - Rua Luso Ventura, 42 - Jardim Santa Genebra - 13080-570 – Campinas, SP, Brasil. E-mail: amdettommaso@mpcnet.com.br

Methods

Study protocol – A protocol was prepared to collect the following data: identification, gestational/neonatal antecedents, presenting signs and symptoms, clinical findings at the first admission, laboratory data (serum levels of bilirubin, aminotransferases, alkaline phosphatase, gammaglutamyl transferase and serologies), as well as etiologic investigation and clinical/biochemical follow-up.

Liver biopsy – A percutaneous liver biopsy, performed at ages of 37 to 1265 days (median 69 days), were obtained by Menghini technique using sedation with midazolam and/or meperidine, fixed in 10% formaline and visualized by optical microscopy. Three patients were also submitted to surgical biopsy to obtain a larger fragment.

RESULTS

Eleven patients (6 girls and 5 boys), aged between 31 and 1185 days (median 68 days) were evaluated. All the patients except one presented more than five portal tracts at histology and the median of the BD:PS ratio was 0.14. Only one patient presented three portal tracts and no bile duct could be visualized, although he had all the Alagille syndrome characteristics (typical facies, butterfly vertebrae, cardiac abnormality and presence of posterior embryotoxon).

Except for one of the mothers, all had attended the prenatal clinic and three of those presented infection during gestation (lues, infection of urinary tract and papillomatosis). All but two were termed babies. Birth weights ranged from 1920 g and 3590 g (median 2695 g). Regarding the presenting signs and symptoms, all presented jaundice, seven presented choloria (median at the beginning = 25 days) and eight presented alterations in stool coloration (six acholia and two fecal hypocholia, median at the beginning = 35 days).

At the first admission the median weight was 3745 g and six patients had hepatomegaly (liver edge palpable more than 3 cm below the costal margin⁽¹²⁾, associated with splenomegaly in four). The laboratorial data is presented on Table 1.

TABLE 1 - Median and serum value limits for bilirubin and hepatic enzymes in patients with paucity of intrahepatic bile ducts
Hepatic enzyme are divided by upper reference value

	Value variation	Median
Direct bilirubin (DB)	0.9-15.5 mg/dL	7.8 mg/dL
Total bilirubin	4.0-74.2 mg/dL	18.6 mg/dL
Aspartate aminotransferase (AST)	0.5-16.0	4.5
Alanine aminotransferase (ALT)	0.6-13.4	3.6
Alkaline phosphatase (ALP)	0.7-6.9	1.9
Gammaglutamyl transferase (GGT)	1.2-35.9	3.3

The diagnosis was syndromic form in three patients and non-syndromic form in eight patients (two with α -1-antitrypsin deficiency, one with lues, one secondary to sepsis, three with probable CMV etiology and one without a defined etiology).

In the follow-up, all of the patients with the syndromic form presented clinical and laboratorial improvement. Of the children with the non-syndromic form, only one (probable etiology by the CMV) presented a poor evolution, with development of cirrhosis and indication of liver transplant (Table 2).

TABLE 2 - Evolution of patients with paucity of intrahepatic bile ducts

Diagnosis	Evolution
Syndromic form (3)	Clinical and laboratorial improvement
α -1-Intitrypsin deficiency (2)	Clinical and laboratorial improvement (1) Death secondary varicella (1)
Lues (1)	Clinical and laboratorial improvement
Sepsis (1)	Clinical and laboratorial improvement
Probable cytomegalovirus etiology (3)	Clinical and laboratorial improvement (1) Cirrhosis and indication of liver transplant (1) Death secondary acute respiratory failure (1)
Undefined etiology	Clinical and laboratorial improvement

DISCUSSION

The present study draws attention to the late referral of most patients to the service, given the importance of excluding extrahepatic causes of neonatal cholestasis. In this regard, it should be emphasized that most of them were term babies, with appropriate birth weights, and eight infants presented early abnormal stools, a suggestive sign of extrahepatic cholestasis⁽¹⁾. A male preponderance was not observed in those cases, as found by others^(6, 13).

Analyzing the etiologies of the non-syndromic form it can be observed that over half of these were secondary to infectious causes. We are found only one reference in the literature of paucity of intrahepatic bile ducts secondary to congenital lues⁽¹¹⁾, probably because these infants are not referred to tertiary centers, being satisfactory outcome.

CMV infection has been associated with a number of liver lesions. Three of our patients presented positive serologie (IgG / IgM) and in one of them we search CMV in the liver tissue by polymerase chain reaction (PCR). It should not be affirmed that CMV is, certainly, the causative agent of hypoplasia, as the same has not been studied in the liver tissue by PCR in all of them; nevertheless, the patients did not present other possible etiologies and, with one exception, showed good improvement. CMV has been observed as the cause for hypoplasia by others^(4,5), through serological tests and the presence of cytomegalic inclusion cells in the tissue. We do not found the CMV inclusions in the patients of this study, although the diagnosis should not be ruled out by their absence⁽⁹⁾.

Despite of the small number of patients in both groups (syndromic and non-syndromic), a worse outcome for patients with the non-syndromic form was not observed. WITZLEBEN⁽¹⁴⁾ refer that the paucity of intrahepatic bile ducts may be only one aspect or manifestation of a disease primarily characterized by other features, or it may be the principal cause of distress and a major feature in defining a disorder. Because of the wide range of circumstances in which paucity occurs, the prognosis is highly variable and depends on the underlying condition. So he separated the patients with the non-syndromic form into two groups: those with progressive and those with a benign form of the illness.

We considered necessary to classify the non-syndromic form into two groups: 1) patients with a definite etiology, which could be defined as secondary non-syndromic hypoplasia, and 2) patients without a definite etiology, which could be defined as primary non-syndromic hypoplasia.

Paucity of intrahepatic bile ducts should be considered in children with cholestasis. Differentiation from extrahepatic neonatal cholestasis

is important to avoid the need for surgery. The non-syndromic form of biliary hypoplasia should not be considered, at first, as a poor prognosis, since recuperation is probably associated with the etiology of this disease form, reserving a worse prognosis for the primary or idiopathic cases.

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RESUMO – Racional - A hipoplasia das vias biliares intra-hepáticas é causa de colestase secundária a uma alteração na integridade anatômica do trato biliar. A definição é dada pelo exame histopatológico e, do ponto de vista clínico, pode ser classificada em síndrômica e não-síndrômica onde o prognóstico é, geralmente, mais grave. **Objetivo** - Avaliar a história, características clínicas e bioquímicas, etiologia e evolução de crianças com hipoplasia das vias biliares intra-hepáticas acompanhadas em serviço terciário. **Casística e Métodos** - Foram avaliadas 11 crianças com hipoplasia das vias biliares intra-hepáticas acompanhadas no ambulatório de Hepatologia Pediátrica do Hospital de Clínicas da Faculdade de Ciências Médicas da Universidade Estadual de Campinas, SP, no período de 1986 a 2001. **Resultados** - Dos pacientes avaliados, três apresentavam a forma síndrômica e oito a forma não-síndrômica (dois com deficiência de α -1-antitripsina, um com lues, um como secundário a sepse, três com provável etiologia pelo citomegalovírus e um sem etiologia definida). A idade à época da primeira consulta variou de 31 a 1185 dias. O peso de nascimento variou de 1920 g a 3590 g. A maior parte dos pacientes apresentava alteração na coloração das fezes como apresentação inicial do quadro clínico. A mediana da relação ducto/espaco porta foi de 0,14. Com relação à evolução, a maioria das crianças apresentou evolução favorável, independente da forma de apresentação. **Conclusão** - A hipoplasia das vias biliares deve ser considerada em crianças com colestase e sua diferenciação com as causas extra-hepáticas de colestase neonatal é importante para se evitar cirurgia. O diagnóstico da forma não-síndrômica não deve ser considerado como de mau prognóstico, pois provavelmente, a evolução deve estar relacionada com a etiologia dessa forma de apresentação.

DESCRITORES - Colestasia intra-hepática. Vias biliares intra-hepáticas.

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