

CLINICAL AND LABORATORY EVALUATION OF 101 PATIENTS WITH INTRAHEPATIC NEONATAL CHOLESTASIS

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ABSTRACT – Background - Intrahepatic neonatal cholestasis can be the initial manifestation of a very heterogeneous group of illnesses of different etiologies. **Aim** - To evaluate and compare clinical and laboratory data among intrahepatic neonatal cholestasis groups of infectious, genetic-endocrine-metabolic and idiopathic etiologies. **Methods** - The study evaluated retrospectively clinical and laboratory data of 101 infants, from March 1982 to December 2005, 84 from the State University of Campinas Teaching Hospital, Campinas, SP, Brazil, and 17 from the Child's Institute of the University of São Paulo, SP, Brazil. The inclusion criteria consisted of: jaundice beginning at up to 3 months of age and hepatic biopsy during the 1st year of life. It had been evaluated: clinical findings (gender, age, birth weight, weight during the first medical visit, stature at birth, jaundice, acholia/hipocholia, choloria, hepatomegaly and splenomegaly) and laboratorial (ALT, AST, FA, GGT, INR). **Results** - According to diagnosis, patients were classified into three groups: group 1 (infectious) n = 24, group 2 (genetic-endocrine-metabolic) n = 21 and group 3 (idiopathic) n = 56. There were no significant differences in relation to the variables: age, gender, stature at birth, jaundice, acholia/hipocholia, choloria, hepatomegaly, splenomegaly, AST, ALT, ALP, GGT, DB and albumin. Significant differences were observed in relation to the following variables: birth weight and weight during the first medical visit. Birth weight of group 1 was lower in relation group 2 and 3. Weight during the first medical visit followed the same pattern. There was a statistically significant difference in relation to the INR, as the patients of the group 2 presented higher values in relation to groups 2 and 3, despite the median was still pointing out normal values. **Conclusions** - There were no significant differences in relation to age, gender, stature at birth, jaundice, acholia/hipocholia, choloria, hepatomegaly, splenomegaly, AST, ALT, ALP, GGT, BD and albumin. Birth weight and the weight during the first medical visit were lower in the group with infectious etiology. In addition, a significant difference in INR reflected impaired coagulation of patients of the group of the genetic-endocrine-metabolic disease.

HEADINGS – Cholestasis, intrahepatic. Jaundice, neonatal.

INTRODUCTION

The frequency of the cholestatic jaundice is difficult to evaluate, varying from 1:2500 to 1:5000 newborns^(3, 6, 9). The initial approach aims to distinguish the diagnosis between intrahepatic causes and extrahepatic, as the latter require precocious surgical intervention⁽¹⁹⁾. In general, intrahepatic neonatal cholestasis (IHNC) represents 2/3 of the cases of neonatal cholestasis^(8, 12, 15, 18, 28). The most common causes of the disease are of infectious origin^(25, 21, 29). In septicemia, signal and symptom manifestations of hepatic origin represent only one component of the involvement of multiple organs, to which the adequate treatment offers the best chance of recovery⁽⁴⁾. Any serious bacterial infection during the neonatal period can result in jaundice⁽²⁶⁾; however, there seems to be a more frequent association with urinary tract infections, especially when the bacterium is *Escherichia coli*⁽¹⁴⁾. In addition to these infections, others have been

observed, such as syphilis, toxoplasmosis, rubella and cytomegalovirus (CMV)^(1, 11, 20, 21, 22, 23).

Despite the many possible etiologies for IHNC⁽⁸⁾, 13%-78% of the cases have been reported to be related to idiopathic etiology^(7, 10, 16, 17, 18, 27). Idiopathic IHNC implies that the liver suffers inflammatory alterations of unknown cause, with no evidence of blockage of the biliary tree, and those infectious agents or metabolic errors for the praised methods have been discarded^(2, 3). Concerning the evolution, there are cases of idiopathic IHNC considered spontaneous, in which there is family recurrence; therefore, sporadic cases could possibly consist in a viral injury or another environmental factor that affected the transitory form of the immature liver of the newborn, however characteristics are similar in both cases^(4, 5).

The objectives of the present study were to evaluate and compare clinical and laboratory data among etiologic groups, searching for clinical and laboratories findings that can help in the diagnostic process.

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METHODS

This study evaluated retrospectively clinical and laboratory data of patients submitted to hepatic biopsy during IHNC investigation, from March 1982 to December 2005. The inclusion criteria consisted of: jaundice beginning at up to 3 months of age and hepatic biopsy during the 1st year of life.

There were evaluated 101 patients (84 from the State University of Campinas Teaching Hospital (UNICAMP), Campinas, SP, and 17 from the Children's Institute of the University of São Paulo (USP). The approach to the diagnosis of NIHC was standardized and a uniform diagnostic approach was taken throughout the observation period.

The information comprised in: neonate's identification, antecedents, clinical findings, physical examination and results of the following laboratorial tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT) international normalized ratio (INR), direct bilirubin (DB) and albumin; carried out in the first medical visit. Hepatic enzymes (AST, ALT, ALP and GGT) are presented in number of times in which the superior limit of normality was reached. Albumin is presented in gram per deciliter (g/dL) and DB in milligram per deciliter (mg/dL).

In order to establish the IHNC etiology, the following examinations were reviewed: liver biopsy, alpha-1-antitrypsin serum, sweat sodium and chloride, innate metabolism errors in urine, polimerase chain reaction (PCR) and CMV antigenemia, serology of: CMV, HIV, EBV, rubella, toxoplasmosis and syphilis.

Ethical aspects

The present research study was approved by the Medical Research Ethics Committees of both institutions.

Statistical analysis

In order to verify if there was association with the categorical variable, the Qui-square test was used. When the expected values were under 5, the Fisher's exact test was used⁽²⁴⁾.

For comparing the continuous variable among the groups, the analysis of variance (ANOVA) and Tukey's tests was performed to identify the differences⁽¹³⁾. Significance was established as $P < 0.05$ in all tests.

RESULTS

According to diagnosis, patients were classified into three groups: group 1 (infectious) $n = 24$, group 2 (genetic-endocrine-metabolic) $n = 21$ and group 3 (idiopathic) $n = 56$. The diagnosis of NIHC is presented in Table 1.

The median age of patients at initial presentation was 2 months and 7 days. There was no statistical difference among the groups ($P = 0.595$). Patients were predominating boys in all groups ($P = 0.770$).

Table 2 shows clinical characteristics during the first medical visit (age, gender, birth weight, weight during the first medical visit, stature at birth, jaundice, acholia/hypocholia, choluria,

hepatomegaly and splenomegaly) of the groups. There were no significant differences among the groups according the variables: age, gender, jaundice, acholia, choluria, hepatomegaly and splenomegaly. However, a significant difference was observed according the variables: birth weight and weight during the first medical visit. Birth weight of group 1 was lower in relation to groups 2 and 3 ($P = 0.002$). The weight during the first medical visit followed the same pattern ($P = 0.047$).

TABLE 1. Etiology of intrahepatic neonatal cholestasis (NIHC)

Groups	Etiology	n
1	Neonatal sepsis	9
	Cytomegalovirus	7
	Urinary infection tract	4
	Syphilis	2
	Toxoplasmosis	2
2	Alfa1-antitripsyn deficiency	5
	Other metabolic diseases	5
	Galactosemia	4
	Allagile's syndrome	2
	Byler's disease	1
	Cystic fibrosis	1
	Secondary to use of parenteral nutrition	1
3	Down's syndrome	1
	Panhypopituitarism	1
	Idiopathic	56
Total		101

TABLE 2. Clinical characteristics of the patients during the first evaluation, in accordance with the groups. Numbers in parentheses correspond to the numbers of patients evaluated in the different groups. n = total number of patients, M = male, F = female. Median values: Age (months), Weight expressed in grams (g) and stature in centimeters (cm). SD = Standard deviations

	n	Infectious NIHC (24)	Genetic-endocrine- metabolic NIHC (21)	Idiopathic NIHC (56)	P
Age (months)	101	2.40 (SD = 1.15)	2.04 (SD = 1.24)	2.43 (SD = 1.68)	0.595
Gender M/F	101	17/7	13/8	39/17	0.770
Birth weight (g)	96	(21) 2160g (SD = 843)	(20) 2820g (SD = 612)	(55) 2750g (SD = 763)	0.021 *
Weight during the first medical visit (g)	81	(20) 3105g (SD = 931)	(18) 3725g (SD = 1122)	(43) 3970g (SD = 1074)	0.047 **
Stature at birth (cm)	69	(13) 44,5 (SD = 4.69)	(12) 47 (SD = 4.22)	(44) 48 (SD = 5,22)	0.683
Jaundice	98	(23) 21	(21) 19	(54) 51	0.657
Acholia/ hiphocolia	94	(20) 12	(19) 10	(55) 38	0.403
Choluria	80	(19) 10	(17) 8	(44) 30	0.241
Hepatomegaly	94	(22) 20	(20) 15	(52) 44	0.439
Splenomegaly	93	(22) 11	(19) 5	(52) 19	0.287

*ANOVA - P-value = 0.021

**ANOVA - P-value = 0.047

Tukey's test: (1 ≠ 2; 1 ≠ 3; 2 = 3)

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Table 3 shows the laboratorial tests carried out in the beginning of the inquiry (ALT, AST, ALP, GGT, BD, albumin and INR), using comparison between groups. There was significant difference in relation to the INR ($P = 0.033$). The group 2 presented a higher value in relation to group 1 and 3; however, the median one still was pointing out normality values. Four patients evolved to death: three of the group 2 (two with metabolic disease and one with Allagile's syndrome) and one patient of the group 3 (idiopathic). The autopsy of this last patient showed intense hepatocellular necrosis, positive serology for the virus of the

TABLE 3. Median of results of the laboratory tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gama glutamyltransferase (GGT), albumin, international normalized ratio (INR) and direct bilirubin (BD) carried out in the first medical visit. Hepatic enzymes (AST, ALT, ALP and GGT) are presented in number of times in which the superior limit of normality was reached. Albumin is presented in gram per deciliter (g/dL) and DB in milligram per deciliter (mg/dL). The numbers in parentheses represent the number of patients whose data were obtained from each group

Variables	n	Infectious NIHC (24)	Genetic-endocrine- metabolic NIHC (21)	Idiopathic NIHC (56)	P
ALT	92	(20) 3.62	(21) 3.80	(51) 3.48	0.397
AST	96	(20) 5.28	(21) 6.69	(55) 5.4	0.462
AlkPhos	80	(18) 1.67	(18) 1.39	(44) 1.50	0.893
GGT	76	(17) 3.91	(18) 5.57	(41) 4.31	0.676
Albumin (g/dL)	62	(17) 3.70	(12) 3.27	(33) 3.91	0.074
INR	70	(15) 1.04	(15) 1.24	(40) 1.10	0.033*
DB (mg/dL)	78	(22) 5.73	(20) 6.55	(56) 6.91	0.683

* ANOVA - Pvalue = 0.033

Tukey's test (1 ≠ 2; 1 = 3; 2 ≠ 3)

acquired immunodeficiency (HIV-AIDS) and negativity for HIV in the liver biopsy using PCR.

DISCUSSION

There was accordance with the literature concerning the clinical findings, in which jaundice was the main manifestation, followed by acholia and choluria⁽²¹⁾. Birth weight values and the weight during the first medical visit were lower in the group with infectious etiology, possibly reflecting the impaired growth expected in cases of neonatal diseases and congenital infections. Differences of clinical presentation were not observed either among other clinical findings (gender, age, stature at birth, jaundice, acholia/hypochole, choluria, hepatomegaly, splenomegaly) or among the following laboratory tests: aminotransferases, AlkPhos, DB and GGT. This last test was evaluated by WANG et al.⁽²⁷⁾, who concluded that normal or low levels of GGT could indicate greater severity of idiopathic IHNC, although reversible. INR statistical significant difference reflected impaired coagulation of patients of the group of the genetic-endocrine-metabolic disease. This data may reflect severity of these cases, since three of the four deaths occurred in the group of the genetic-endocrine-metabolic disease.

CONCLUSION

There were no differences between the groups of infectious, genetic-endocrine-metabolic and idiopathic etiologies regarding to: age, gender, stature at birth, jaundice, acholia/hypochole, choluria, hepatomegaly, splenomegaly, ALT, AST, AlkPhos, GGT and DB.

Birth weight and the weight during the first medical visit were lower in the group with infectious etiology. In addition, a significant difference in INR reflected impaired coagulation of patients of the group of the genetic-endocrine-metabolic disease.

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RESUMO – Racional - A colestase neonatal intra-hepática pode ser a manifestação inicial de um grupo muito heterogêneo de doenças de diferentes causas.

Objetivos - Avaliar e comparar características clínicas e laboratoriais entre os grupos de colestase neonatal intra-hepática de causa infecciosa, genético-endócrino-metabólica e idiopática. **Métodos** - Foram revistos os prontuários de 101 pacientes com diagnóstico de colestase neonatal intra-hepática no período de março de 1982 a dezembro de 2005, 84 avaliados no Hospital das Clínicas da Universidade Estadual de Campinas, SP, e 17 no Instituto da Criança da Universidade de São Paulo. Os critérios de inclusão foram: história de surgimento de icterícia até 3 meses de idade e realização da biópsia hepática durante o primeiro ano de vida. Foram avaliados: quadro clínico (gênero, idade, peso ao nascimento, peso à primeira consulta, estatura ao nascimento, icterícia, acolia ou hipocolia, colúria, hepatomegalia e esplenomegalia) e laboratorial (ALT, AST, FA, GGT, INR, BD). **Resultados** - Os pacientes foram divididos em grupos, de acordo com o diagnóstico etiológico: grupo 1 (infeccioso) n = 24; grupo 2 (genético-endócrino-metabólico) n = 21 e grupo 3 (idiopático) n = 56. Não houve diferença estatisticamente significativa em relação às variáveis: gênero, idade, estatura ao nascimento, icterícia, acolia/hipocolia, colúria, hepatomegalia, esplenomegalia, AST, ALT, FA, GGT, BD e albumina. O peso ao nascimento e o peso na primeira consulta dos pacientes com colestase neonatal intra-hepática de etiologia infecciosa foi menor. Houve diferença estatisticamente significativa em relação ao INR: os pacientes com causas genético-endócrino-metabólicas apresentaram valor mais prolongado, porém com a mediana se situando dentro dos valores de normalidade. **Conclusão** - Não houve diferença estatisticamente significativa entre os grupos em relação às variáveis: gênero, idade, estatura ao nascimento, icterícia, acolia/hipocolia, colúria, hepatomegalia, esplenomegalia, AST, ALT, FA, GGT, BD e albumina. Os pacientes com colestase neonatal intra-hepática de causa infecciosa apresentaram menores valores de peso em relação às demais causas e o INR foi mais prolongado nos pacientes com causas genético-endócrino-metabólicas, demonstrando alterações na função de coagulação.

DESCRIPTORES – Colestase intra-hepática. Icterícia neonatal.

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