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Original Article

Analysis of factors affecting the prognosis of neonatal cholestasis

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Abstract: This study aims to analyse the risk factors affecting prognosis of cholestasis in newborns. *A* four-year prospective cohort study was carried out. Neonates with cholestasis were enrolled. The diagnosis of neonatal cholestasis was based on jaundice in the newborn period, direct bilirubin > 2 mg/dl, discoloured stool and elevated liver enzymes. Liver function tests were consecutively monitored weekly during the first month and then monthly until the disease was under control. All cases received oral ursodeoxycholic acid and internal medicine comprehensive treatment. No invalid case was recorded. According to the efficacy of the treatment, all cases were divided into two groups: cure group (group A; n = 69) and improved group (group B; n = 5). The clinical data of the two groups were compared. Selected patient factors were analysed to determine the risk factors affecting the prognosis of cholestasis in newborns. The serum total bilirubin and direct bilirubin levels in group B were significantly higher than those in group A ($P < 0.05$). A strong linear correlation was detected between the level of direct bilirubin (or total bile acid) and the duration of the disease ($r > 0.5$, $P < 0.05$). The curative effects on neonatal cholestasis and bacterial infection, cytomegalovirus (CMV) infection, venous nutrition (> 7 d) and preterm birth were closely related. The above factors were also independent risk factors affecting the prognosis of neonatal cholestasis. The direct bilirubin or total bile acid level was closely related to the duration of neonatal cholestasis. Bacterial infection, CMV infection, venous nutrition (> 7 d) and preterm birth were significant risk factors affecting the prognosis of neonatal cholestasis.

Keywords: Neonate, cholestasis, prognosis, factors

Introduction

Neonatal cholestasis due to abnormal bile acid synthesis in liver cells or dysfunction of bile duct system may lead to excessive serum bile acid and direct bilirubin (D-Bil), jaundice, hepatomegaly, white clay stool and dark urine colour [1, 2]. Neonatal cholestasis is caused by infection, venous nutrition, genetic and metabolic diseases, biliary atresia, haemolytic disease and so on [3-6]. Although neonatal cholestasis is usually reversible after active treatment, it may cause malnutrition, developmental disorders, cirrhosis portal hypertension and end-stage liver disease [7-9]. Liver transplantation is the only means of survival in some serious cases [10, 11]. Improving the prognosis of neonatal cholestasis is currently a hot research topic. Identifying the significant risk factors affecting the prognosis of neonatal cholestasis is necessary to improve the prognosis of neonatal cholestasis and to shorten the course of the disease.

Materials and methods

Subject

Newborn infants with neonatal cholestasis admitted to the neonatal intensive care unit and sick neonatal wards of Zhongshan People's Hospital Affiliated to Sun Yat-Sen University between January 2009 to December 2012 were enrolled in this four-year prospective cohort study. The following information on the neonates with cholestasis was recorded: gestational age, cholestasis symptoms (e.g., jaundice, discoloured stool and dark urine), duration of conjugated hyperbilirubinaemia, therapy [12, 13] (10 mg/kg/d ursodeoxycholic acid and comprehensive medicine treatment), infections, asphyxia, liver function, duration of parenteral nutrition, duration of fasting and mater-

Table 1. The clinical data of the neonates with neonatal cholestasis

	Duration (d)	GA (d)	ALT (U/L)	AST (U/L)	r-GGT (U/L)	T-BIL (μmol/L)	D-BIL (μmol/L)	TBA (μmol/L)
Average	85.95	259.27	87.95	116.39	231.41	139.385	59.24	60.639
Median	62.5	269.5	73.5	90	199.5	111.2	41.65	47.1
Standard error	57.453	27.235	60.02	94.74	157.567	69.4754	47.726	34.0645
25% percentile	42.75	246	62.75	69	120	94.125	28.25	36.675
50% percentile	62.5	269.5	73.5	90	199.5	111.2	41.65	47.1
75% percentile	124	279	88	103	296	157.175	65.52	76.775

Table 2. The comparison of clinical data between A and B group ($\bar{x} \pm s$)

	A group	B group	t	*P* value
Duration (d)	75.93 ± 44.845	224.20 ± 20.693	-7.300	0.000
ALT (U/L)	82.030 ± 49.333	155.000 ± 118.796	-1.493	0.194
AST (U/L)	111.150 ± 93.032	175.830 ± 102.251	-1.621	0.109
r-GGT (U/L)	226.490 ± 155.710	287.170 ± 183.115	-0.903	0.369
T-BIL (μmol/L)	132.978 ± 63.979	212.000 ± 93.464	-2.792	0.007
D-BIL (μmol/L)	50.870 ± 35.317	154.050 ± 69.300	-3.606	0.014
TBA (μmol/L)	59.003 ± 34.670	79.183 ± 19.648	-1.400	0.166

Table 3. The liner regression analysis with factors and duration of disease

	Correlation coefficient (r)	t	*P* value
ALT (U/L)	0.323	2.899	0.003
AST (U/L)	0.231	2.014	0.024
r-GGT (U/L)	0.004	0.034	0.485
T-BIL (μmol/L)	0.379	3.477	0.000
D-BIL (μmol/L)	0.699	11.650	0.000
TBA (μmol/L)	0.549	5.574	0.000

nal history of intrahepatic cholestasis of pregnancy. Liver function tests were consecutively monitored weekly during the first month and then monthly until the disease was under control. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Sun Yat-Sen University. Written informed consent was obtained from all participants.

Criteria of diagnosis

Criteria for diagnosis of neonatal cholestasis included the following [14, 15]: jaundice in the newborn period, total bilirubin > 5 mg/dl, D-Bil and total bilirubin ratio > 20%, discoloured stool and elevated liver enzymes. Other causes of neonatal cholestasis, such as biliary atresia, choledochal cyst, bile duct dilatation, bump oppressive and aneurysm surgery disease and metabolic diseases, were excluded using abdominal ultrasound, magnetic resonance cholangiopancreatography and metabolic screening.

Criteria of curative effect

The curative effect of neonatal cholestasis was evaluated using the following criteria [16]: improvement of the clinical signs (such as jaundice, discoloured stool and dark urine) and excessive serum alanine transaminase (ALT), bilirubin, bile acid and D-Bil.

Groups

All cases received oral ursodeoxycholic acid and internal medicine comprehensive treatment. According to the efficacy of the treatment, the cases were divided into three groups [16]: cured, improved and invalid. The cured group was characterised by absence of clinical signs (such as jaundice, discoloured stool and dark urine) and normal levels of excessive serum ALT, bilirubin, bile acid and D-Bil. The improved group was characterised by better clinical signs and declined excessive serum ALT, bilirubin, total bile acid (TBA) and D-Bil by more than half. The invalid group was characterised by unimproved clinical signs and excessive serum ALT, bilirubin, and bile acid, as well as a decline or elevation in D-Bil by less than half. No invalid case in all participants was recorded. Therefore, all cases were divided into two groups: cured group (group A; n = 69) and improved group (group B; n = 5).

Statistical analysis

All data were assessed by SPSS 17.0 program. Linear correlation between the factors and the course was analysed with t test. Cross tabulations were analysed using chi-square and Mann

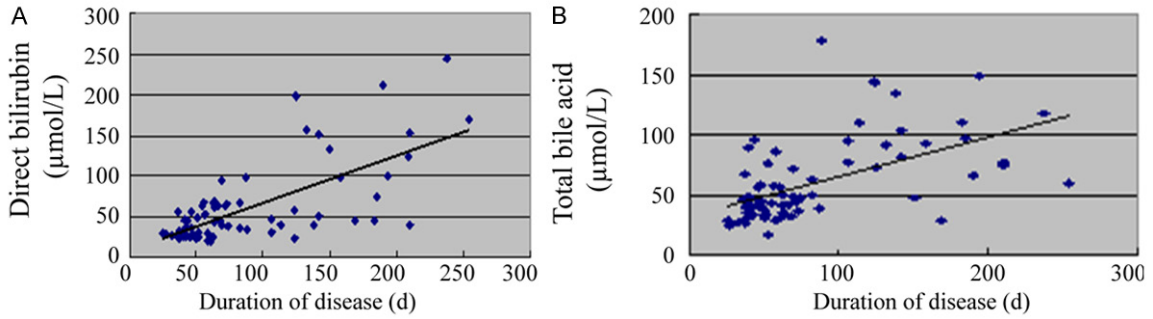

Figure 1. Correlation analysis. A: Between serum direct bilirubin and duration of disease. B: Between serum total bile acid and duration of disease.

Table 4. The comparison of the proportion of factors between A and B group [number(%)]

	Number	Bacterial infection	CMV infection	Male	Parenteral nutrition (≥ 7 d)	Hypoxia	Preterm birth	Mother with ICP
A group	69	24 (34.8)	11 (15.9)	37 (53.6)	18 (26.1)	19 (27.5)	18 (26.1)	8 (11.6)
B group	5	4 (80)	3 (60)	2 (40)	4 (80)	1 (20)	4 (80)	1 (20)
X^2		5.487	5.900	0.347	6.487	0.134	6.487	0.308
P value		0.019 (< 0.05)	0.015 (< 0.05)	0.556 (> 0.05)	0.011 (< 0.05)	0.714 (> 0.05)	0.011 (< 0.05)	0.579 (> 0.05)

Table 5. Logistic regression analysis

	Partial regression coefficient (B)	Standard error (SE)	*p* value	Risk of odds ratio (OR)	95% CI for OR
Bacterial infection	-75.176	1.238E4	0.047	9.375	1.035-84.902
CMV infection	-1.543	2.356E4	0.033	7.909	1.181-52.972
Gender	72.491	1.248E4	0.560	0.577	0.091-3.669
Parenteral nutrition	-71.861	2.830E4	0.035	11.333	1.187-108.199
Hypoxia	38.956	1.828E4	0.716	0.658	0.069-6.267
Preterm birth	-71.861	2.830E4	0.035	11.333	1.187-108.199
Mother with ICP	-0.940	1.455E4	0.584	1.906	0.189-19.241

Whitney U tests. Correlation between multiple factors and prognosis of neonatal cholestasis was analysed using multivariate LOGLSTIC regression analysis, in which $P < 0.05$ was considered statistically significant.

Results

General information

During the study period, 81 neonates with neonatal cholestasis were admitted to our neonatal department. We excluded seven neonates because of biliary atresia, choledochal cyst and metabolic diseases. A total of 74 patients were included in this study. No cirrhosis, liver failure, death and other adverse reactions were observed. The average duration of jaundice was approximately 86 d, which was similar to a domestic research [17]. The average serum ALT and r-GGT were approximately 87.95 and 116.39 U/L, respectively. The average serum D-Bil and TBA were approximately 59.24 and 60.639 μmol/L, respectively. The clinical data of the patients are summarised in **Table 1**.

Clinical characteristics

The serum total bilirubin and D-Bil levels in group B were significantly higher than those in group A ($P < 0.05$). The duration in group B was significantly longer than that in group A ($P < 0.05$). No significant differences in serum ALT, AST, r-GGT and bile acid levels were found between the two groups ($P > 0.05$). The data of the two groups are summarised in **Table 2**.

Correlation analysis

A positive linear correlation was detected between the levels of serum total bilirubin,

D-Bil, TBA, ALT and AST and the duration of the disease ($P < 0.05$). A strong linear correlation was found between the level of D-Bil (or TBA) and the duration of the disease ($r > 0.5$, $P < 0.05$). However, no linear relationship was found between the level of serum r-GGT and the duration of the disease ($P > 0.05$, T. (**Table 3**; **Figure 1**).

Neonatal cholestasis

The proportion of patients combined with bacterial infection, cytomegalovirus (CMV) infection, parenteral nutrition (≥ 7 d) and premature birth in group B were significantly higher than those in group B ($P < 0.05$). No significant differences in gender, hypoxia and maternal history of intrahepatic cholestasis of pregnancy were found between the two groups. The variables in the logistic regression model were further analysed. The curative effects on neonatal cholestasis and bacterial infection, CMV infection, venous nutrition (> 7 d) and preterm birth were closely related. The above factors were also independent risk factors affecting the prognosis of neonatal cholestasis (**Tables 4** and **5**).

Discussion

Neonatal cholestasis refers to dysfunction of liver cells and (or) capillary bile secretion in newborns, resulting in impaired bile flow and accumulation of fatty acid, bilirubin and other substances in the liver and blood [18]. According to the different positions, cholestasis was divided into the following: 1) hepatocellular cholestasis; 2) biliary cholestasis, which was divided into intrahepatic cholestasis and extrahepatic biliary cholestasis; and 3) mixed cholestasis. In this study, patients with biliary atresia, choledochal cyst, bile duct dilatation, bump oppressive and aneurysm surgery disease and metabolic diseases were excluded.

A linear positive correlation was detected between the levels of serum total bilirubin, D-Bil, TBA, ALT and AST and the duration of cholestasis. A strong linear correlation was noted between the duration of cholestasis and the levels of D-Bil and TBA. The higher the levels of serum D-Bil and bile acid, the longer the duration of cholestasis. Thus, the duration of neonatal cholestasis can be shortened by reducing the levels of serum total bilirubin, D-Bil, bile acid, ALT and AST.

The pathogenesis of neonatal cholestasis is complex. A foreign study found that the incidence of neonatal cholestasis is closely related to genetic family history and maternal infection [7]. Preterm infants and low-birth weight infants were the neonates at high risk of intrahepatic cholestasis. This high risk may be associated with growth retardation, intravenous nutrition, complication, genetic diseases and congenital infection [19-21]. CMV infection has two forms of transmission: maternal and horizontal. The prognosis of CMV infection in infants is commonly reversible, but a few can occur with severe hepatitis and hepatic function failure. Bacterial infection is also an important factor that causes infantile cholestasis, such as septicaemia and urinary tract infection. The newborn bile excretion system development is not perfect, so resistance to toxin and bacterial clearance ability are not strong. Intrahepatic cholestasis is associated with Gram-negative bacterial infections [22]. The present study showed that bacterial infection, CMV infection, venous nutrition (> 7 d) and preterm birth are independent risk factors affecting the prognosis of neonatal cholestasis. Some domestic and foreign reports support this conclusion [23, 24].

In conclusion, bacterial infection, CMV infection, venous nutrition (> 7 d) and preterm birth are significant risk factors affecting the prognosis of neonatal cholestasis. Therefore, good perinatal maternal health, prevention of neonatal infection, avoidance of premature delivery, and shortening the duration of intravenous nutrition should be emphasised to improve the prognosis of neonatal cholestasis, shorten the duration of neonatal cholestasis, reduce the suffering of patients and save on medical expenses.

Disclosure of conflict of interest

None.

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