Transient cholestasis in newborn infants with perinatal asphyxia

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In asphyxiated newborn infants, cholestasis often leads to extensive investigations and a cause can rarely be found.

OBJECTIVE: To assess the frequency of transient neonatal cholestasis in an unselected group of asphyxiated newborn infants in a mother-child centre.

METHOD: Charts of 181 asphyxiated newborn infants born with appropriate birth weight for gestational age (AGA) or small weight for gestational age (SGA) at Sainte-Justine Hospital, Montreal, Quebec between 1989 and 1993 were reviewed.

RESULTS: Transient neonatal cholestasis was found in 8.5% of asphyxiated AGA and 33% of SGA newborn infants, compared with 3.94% cholestasis of any etiology in nonasphyxiated SGA infants. Asphyxiated neonates born before the age of 35 weeks had an increased risk for transient neonatal cholestasis (odds ratio 2.84, CI 1.0-8.1).

CONCLUSION: Transient neonatal cholestasis is associated with several contributing factors related to the severity of the neonatal distress. Asphyxia is frequently accompanied by cholestasis in this group of newborns and without symptoms other than uncomplicated cholestasis. Investigations should be focussed on conditions requiring immediate therapy.

Key Words: *Asphyxia; Cholestasis; Newborn*

Pathological neonatal cholestasis is diagnosed as often as one in 500 newborn infants (1). It is a nonspecific feature of a liver disorder that occurs with several congenital diseases such as biliary atresia, α 1-antitrypsin deficiency and other metabolic, endocrine or perinatal infectious maladies. Newborn infants with transient neonatal cholestasis have recently been described, most of whom suffered from asphyxia and/or prematurity (2-4). Though transient, neonatal cholestasis presents in a way that is indistinguishable from that occurring with more severe causes; it is self-limiting and needs neither further investigation nor therapy other than the substitution of lipid-soluble vitamins. Therefore, this condition deserves more precise characterization. Until now, its definition relied exclusively on the serum level of conjugated bilirubin and on the exclusion of the aforementioned diseases. The aim of the present study was to

La cholestase transitoire chez les nouveau-nés présentant une asphyxie périnatale

Chez les nouveau-nés asphyxiés, la cholestase suscite souvent des explorations approfondies, et il est rarement possible d'en trouver la cause.

OBJECTIF : Dans un centre mère-enfant, évaluer la fréquence de la cholestase néonatale transitoire chez un groupe non sélectionné de nouveau-nés asphyxiés.

MÉTHODOLOGIE : À l'Hôpital Sainte-Justine de Montréal, au Québec, entre 1989 et 1993, ont été examinés les dossiers de 181 nouveau-nés asphyxiés au poids de naissance pertinent par rapport à l'âge gestationnel (PAG) ou au poids de naissance insuffisant par rapport à l'âge gestationnel (IAG).

RÉSULTATS : Une cholestase néonatale transitoire a été découverte chez 8,5 % des nouveau-nés PAG et 33 % des nouveau-nés IAG asphyxiés, par rapport à un pourcentage de cholestase de toute étiologie de 3,94 % chez des nouveaux-nés IAG non asphyxiés. Les nouveau-nés asphyxiés nés avant 35 semaines d'âge gestationnel présentent un risque accru de cholestase néonatale transitoire (risque relatif de 2,84, IC 1,0-8,1).

CONCLUSION : La cholestase néonatale transitoire s'associe à plusieurs facteurs contributifs reliés à la gravité de la détresse néonatale. L'asphyxie s'accompagne souvent de cholestase dans ce groupe de nouveau-nés, sans autres symptômes qu'une cholestase sans complication. Les explorations devraient être axées sur les pathologies exigeant un traitement immédiat.

look at the incidence of transient neonatal cholestasis in children with perinatal asphyxia, and to search for associated risk factors.

METHODS

To select charts for review, a database was used that registered each patient admitted to the neonatology department between 1989 and 1993 as well as definitive diagnoses and complications. Asphyxia was defined by the presence of postanoxic encephalopathy defined by an abnormal Apgar score (a one-minute Apgar score of less than four, a five-minute Apgar score of less than seven, and/or the need for immediate resuscitation or intubation); clinical signs of encephalopathy; and its confirmation by appropriate examinations such as electroencephalogram and brain imaging

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TABLE 1
Characteristics of asphyxiated appropriate birth weight (14) and growth retarded (6) newborns with cholestasis

Sex	Bilirubin ($\mu\text{mol/L}$)		Age (day)	TPN (days)	GA (weeks)	BW (grams)	Apgar*	pH†	Ventilation (days)	Glucose (mmol/L)	Comorbidity
m	39	156	day 2	none	36	2900	3 2 5	6.9	3	1.1	Myeloproliferative syndrome
m	52	114	day 4	4-15	41	3410	1 3 4	6.9	10	12.7	Meconium aspiration
m	88	322	day 4	5-12	34	2100	2 6 8	7.0	5	2.3	Muscular VSD, HMD
m	109	250	day 5	none	38	3340	1 3 5	6.8	6	0.2	
m	40	246	day 3	5-17	28	1200	4 4 4	7.2	13	3.1	IVH grade 4
m	41	204	day 4	none	28	1250	0 2 7	7.0	5	2.3	
m	55	189	day 4	10-29	29	1449	1 1 2	6.7	13	6.7	
m	21	81	day 4	7-22	35	1930	1 1 1	7.2	20	1.3	
m	26	140	day 3	3-8	24	875	1 4 4	7.2	104	1.9	HMD
m	30	190	day 4	4-41	27	1230	0 4 6	7.2	19	nd	
f	27	61	day 2	4-18	41	4135	1 3 3	6.9	21	3.6	Meconium aspiration
f	36	206	day 6	7-87	30	1380	2 4 4	7.2	6	4.0	NEC, IVH grade 3
f	50	233	day 6	5-16	33	1905	1 3 3	nd	2	3.3	Myotonic dystrophy of Steinert
f	30	184	day 5	4-39	25	980	2 3 6	7.2	35	3.2	IVH grade 4
m	28	122	day 3	4-10	36	1920	1 4 5	nd	10	1.7	IVH grade 4
m	48	231	day 6	4-21	37	1365	2 2 4	nd	67	2.5	Pierre Robin syndrome
m	117	269	day 5	8-23	38	1940	1 5 7	7.2	15	2.5	RTN, ASD, BPD
f	35	120	day 4	4-24	29	720	3 6 7	7.0	9	1.8	
f	53	165	day 5	3-98	33	1720	1 1 1	7.2	100	1.4	Myotonic dystrophy of Steinert
f	33	185	day 3	5-19	33	1300	0 6 7	7.1	33	3.1	Meconium aspiration

*Apgar 1, 5, and 10 minute value; †First pH measured, umbilical or capillary blood from the neonate. ASD/VSD Atrial or ventricular septum defect; BPD Bronchopulmonary dysplasia; BW Birth weight; f Female; GA Gestational age; HMD Hyaline membrane disease; IVH Intraventricular hemorrhage; m Male; nd No data; NEC Necrotizing enterocolitis; RTN Renal tubular necrosis; TPN Total parenteral nutrition

techniques (echography, computed tomography). Cholestasis was defined as conjugated bilirubin of more than $18 \mu\text{mol/L}$ and/or greater than 20% of the total bilirubin concentration (1,5,6). Bilirubin was measured in the clinical biochemistry laboratory at Sainte-Justine Hospital, Montreal, Quebec by automated colorimetric methods (Beckman Synchron CX-5, Beckman Coulter Canada Limited, Mississauga, Ontario). Cholestatic newborns with proven inborn errors of metabolism, infections, malformations and hypothyroidism were excluded from the study.

The results were statistically evaluated by the Mann-Whitney U test for comparison of groups with different sizes and without normal distribution, by the χ^2 test for comparison of group sizes and by logistic regression for multivariate analysis.

RESULTS

Of a total of 6737 patients admitted to the neonatology department of Sainte-Justine Hospital between 1989 and 1993, and registered in a neonatology database, 256 (3.8%) were classified as asphyxiated, 659 (9.78%) as small neonates for their gestational age (SGA), and 24 (0.36%) as a combination of both. Of all those registered cases, 212 charts of asphyxiated neonates with appropriate weight for their gestational age (AGA) (90 females), and 22 (12 female) charts of SGA neonates were available for study (after exclusion of one with polycystic kidney disease, one with generalized cytomegalovirus infection, and one with urea cycle disease). Of the AGA and SGA cases, 49 (20 female) and four (two female), respectively, died within the first 48 h of life. Thus, data were analyzed from a total of 181 (163 AGA and 18 SGA) asphyxiated

infants surviving the first 48 h of their life.

A total of 14 (8.5%, four term and 10 preterm infants) asphyxiated AGA infants and six (33%, one term, five preterm) SGA infants had cholestasis. In both groups, cholestasis developed more frequently in premature newborns. The characteristics of infants with cholestasis are given in more detail in Table 1.

Further characteristics

Alanine aminotransferase and aspartate aminotransferase were measured in eight of 20 cholestatic infants and normalized in all after the end of total parenteral nutrition (TPN) (Table 1). Bilirubin values were controlled in 13 of 20 cholestatic patients until normalization occurred.

Emergency cesarean section was performed in 55.2% of pregnancies with asphyxiated neonates (82 in AGA and 18 in SGA), and in 12 of 20 (60%) children with additional transient neonatal cholestasis.

AGA children were born prematurely in 50.9% (83 of 163) versus 86% (12 of 14) of AGA asphyxiated children with transient neonatal cholestasis. SGA children were born prematurely in 77.3% (17 of 22) versus 83% (five of six) of cases of cholestasis (Table 2).

Intubation and ventilation were necessary in 113 of 163 (69.0%) of the asphyxiated AGA infants and in 16 of 18 (89%) of the asphyxiated SGA neonates. The average duration of ventilation in AGA children without cholestasis was 5.4 days (median one day, range zero to 91 days) versus 20.5 days (median 13 days, range five to 114 days) in those with

TABLE 2

Comparison of clinical characteristics of neonates with appropriate birth weight for gestational age (AGA), and small birth weight for gestational age (SGA) with asphyxia, with and without cholestasis (CS), with regard to sex, gestational age in weeks and birth weight (grams)

Neonates	Asphyxia and AGA without CS n=148	Asphyxia and AGA with CS n=14	P*	Asphyxia and SGA without CS n=12	Asphyxia and SGA with CS n=6	P*
Sex	66f/83m	4f/10m		7f/5m	3f/3m	
Gestational age mean (SD)	36 (5)	32 (5)	0.005	34 (3)	34 (4)	0.8
Birthweight mean (SD)	2,705 (982)	1,973 (973)	0.01	1,529 (695)	1,637 (604)	0.9

*Mann-Whitney U test. f Female; m Male

cholestasis ($P < 0.0001$). In SGA infants without cholestasis, the average duration of ventilation was 13.3 days (median 3.5 days, range zero to 84 days), and for those with cholestasis it was 43 days (median 22.5 days, range five to 116 days) ($P = 0.04$, Mann-Whitney U test). Multivariate analysis of sex, apgar scores, gestational age and duration of ventilation showed an increased risk of developing cholestasis for children of any weight born before the age of 35 weeks (2.84, CI 1.0-8.1).

Antibiotic therapy was initiated in 124 of 163 AGA infants (75.6%), in 100% of SGA asphyxiated neonates, and in 100% of infants with cholestasis. Antiepileptics were used in an equal proportion of asphyxiated newborns of each group (six of 18 (33%) SGA, 48 of 163 (29%) AGA and in five of 20 (25%) infants with cholestasis).

All infants required nasogastric tube feeding for enteral nutrition with Similac (Abbot Laboratories, St Laurent, Quebec) or mother's milk. If oral feeding was not tolerated by day 4, TPN was initiated. TPN was started in 44% (41 of 93) of premature asphyxiated AGA infants, in 8% (seven of 90) of term asphyxiated AGA neonates, and in 14 of 18 (78%) SGA infants, compared with 18 of 20 (90%) infants with cholestasis at diverse moments after birth.

Follow-up

Seven of 18 cholestatic children had only one measurement of direct bilirubin before starting TPN; there was no further increase in six of 18 infants, whereas in five of 18 infants direct bilirubin was elevated after starting TPN. The latter group had controls until normalization after the end of TPN. Three children died during the first year of life, and follow-up time of the remaining children was between one and 12 years. Follow-up was necessary for neurological, behavioural, visual, auditive and infectious problems, requiring liver function tests in three patients (one growth failure, two antiepileptic treatments), which were normal. No overt chronic liver disease developed.

The control group consisted of SGA neonates without asphyxia ($n = 635$). Cholestasis was found in 25 (3.94%) children. It was associated in one case with Nieman-Pick disease and in another with biliary atresia, in seven with intestinal diseases needing surgical intervention, in four with complex cardiopathies, in nine with infections, in all infants with TPN and in three patients without TPN, but with ventilation and antibiotic therapy. Five patients died of suspected infection, and three were autopsied. These revealed cirrhosis in the

patient with biliary atresia and giant cell hepatitis in another with congenital infection. Follow-up disclosed chronic hepatitis B in one patient.

DISCUSSION

Neonatal cholestasis is a condition that demands extensive work-up to exclude inborn errors of metabolism, intrauterine infections, endocrine dysfunction or malformation. Frequently, these investigations do not yield positive findings, and if the cholestasis resolves spontaneously, the condition is called transient neonatal cholestasis. Asphyxiated infants seem to be at risk for this type of transient cholestasis (7). The present study defines the incidence of transient neonatal cholestasis in asphyxiated infants.

Transient neonatal cholestasis was found in 8.5% of AGA and in 33% of SGA asphyxiated neonates. Cholestatic neonates of both groups were severely affected, as shown by longer periods of mechanical ventilation and a larger number of patients requiring antibiotic therapy and TPN, when compared with asphyxiated newborns without cholestasis. It therefore seems that severe illness is an additional risk factor for the development of cholestasis in asphyxiated neonates. Other factors, such as family or pregnancy history, could not explain the severe perinatal illness or the occurrence of cholestasis in these neonates. Prematurely-born infants were more frequently cholestatic than children born at term, but the difference by univariate analysis was significant only in AGA infants. Multivariate analysis showed an increased risk for all infants born before the age of 35 weeks. Using data from the same registry, we found that elevated direct bilirubin, including all etiologies, occurred in 3.9% of nonasphyxiated SGA neonates, and transient neonatal cholestasis in three (4%). The mechanism leading to cholestasis in asphyxia is not well understood. It is thought to be of multifactorial origin. Inefficient enterohepatic circulation, immaturity of bile secretion (8) and lack of enteral nutrition (7) may combine with fetal distress and reduced splanchnic blood flow, inducing poor oxygenation of the liver and bowel. The subsequent decreased expression of bile acid transport proteins of basolateral and apical hepatocyte membranes may further impair the immature secretion of bile acids (9-11) and enhance physiological cholestasis in the neonate.

Most of the infants (13 of 20) qualifying for the diagnosis of transient neonatal cholestasis had levels of conjugated bilirubin that slightly exceeded the upper normal limit. None of them had acholic stools, and liver function tests

were not done routinely. However, none of the results obtained called for further investigations. None of these children had liver biopsy, and none of them developed liver disease. Thus, the population analyzed in the present study may differ not only in the severity of cholestasis from that described by Jacquemin et al (2), but also in its duration, in the degree of neonatal distress and in comorbidity; we can assume that patients seen at Bicêtre (Paris, France) (2) represent those referred with more severe neonatal cholestasis whereas the patients described in the present study represent the patient population of a mother-child centre. In spite of advances in the molecular mechanisms of cholestasis, the exact etiology of asphyxia and, therefore, of transient neonatal cholestasis in asphyxiated neonates remains unknown, and the reason for cholestasis may not be the same in the patients from Bicêtre and in our population.

CONCLUSIONS

We found that asphyxia, duration of ventilatory support, gestational age of less than 35 weeks and male sex are risk factors for transient neonatal cholestasis. This, in conjunction with intrauterine growth retardation, increases the risk for newborn infants to develop transient neonatal cholestasis by 33%. Transient neonatal cholestasis is thus by far the most frequent etiology of cholestasis in asphyxiated SGA newborn children.

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