Etiological factors of cholestasis in infancy and early childhood in Children Welfare Teaching Hospital

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Abstract:

Background: Neonatal cholestasis is defined as prolonged elevation of the serum level of conjugated bilirubin beyond the first 14 days of life. There are many causes of neonatal cholestasis which must be identified because early intervention may result in a better outcome, such as surgical intervention in biliary atresia within two months from birth, or effective dietary management in metabolic disorders like galactosemia.

Objective: To determine the causes of early childhood cholestasis in children attending the Children Welfare Teaching Hospital in Baghdad and to study some of associated factors in infancy and early childhood cholestasis.

Patients and method: This is a cross sectional descriptive study conducted on 48 patients attending the Children Welfare Teaching Hospital in Baghdad for the period of 1 November 2015 to 15 January 2016. These cases were evaluated by thorough history, examination and investigations.

Results: Of the 48 patients enrolled in this study, 30 (62.5%) lived in Baghdad, and the remaining 37.5% were referred from other governorates. The mean age of the patients was 11.1 ± 12.4 months, with 20 females (41.7%) and 28 males (58.3%). The results revealed that 11 (22.9%) were the result of congenital infections, 9 (18.8%) were idiopathic in origin, 8 (16.7%) were caused by biliary atresia, 8 (16.7%) of unknown origin, 5 (10.4%) were caused by sepsis (mainly *staphylococcus*, *streptococcus species*, *E.coli*, *staphylococcus aureus)*, 2 (4.2%) were caused by progressive familial intrahepatic cholestasis and 1 (2.1%) case was caused by each of the following causes: Alagille syndrome, Choledochal cyst, Galactosemia, hypothyroidism and Tyrosinemia**.**

Conclusion: Congenital infections were the most common cause in this study, of which the most common is cytomegalovirus (CMV). Clay color stool and high alkaline phosphatase levels were found mostly in biliary atresia. No method by itself is sufficient to diagnose the cause of neonatal cholestasis. Diagnosis can only be established using all available methods.

Keywords: Cholestasis, children, etiology.

Introduction:

Neonatal cholestasis is defined as prolonged elevation of the serum levels of conjugated bilirubin beyond the first 14 days of life. Early intervention results in a better outcome such as surgical intervention in biliary atresia before two months and the effective management of disorders like (Tyrosinemia, galactosemia, hypothyroidism, and infectious causes) (1, 2). Cholestasis in the neonate may be the initial manifestation of numerous and potentially serious disorders, the clinical manifestations are usually similar and provide very few clues regarding the etiology (3, 4, 5).

The most common causes of Cholestasis in infancy are biliary atresia (BA) and Neonatal Hepatitis Syndrome (NHS), a term which is given now to nonspecific hepatic inflammation, which develops secondary to many different etiologies including intrauterine infections, endocrine disorders and inborn errors of metabolism (3,6,7). Cholestasis in a newborn can be caused by infectious, genetic, metabolic, or undefined abnormalities giving rise to mechanical obstruction of bile flow or to functional impairment of hepatic excretory function and bile secretion (2, 6-8). Investigations needed to reach the diagnosis can be classified into three main categories (6, 7, 10, and 11): Laboratory studies, imaging studies and percutaneous liver biopsy which is the single most definitive investigation in the evaluation of neonatal cholestasis. Several studies in different centers indicated that a diagnosis of biliary atresia was correctly reached by liver biopsy histological findings in 90 - 95 % of cases (12, 13).

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Patients &Method:

This is across sectional descriptive study conducted on 48 patients attending the Children Welfare Teaching Hospital in Baghdad for the period of 1 November 2015 to 15 January 2016. The cases were evaluated by thorough history, examination and investigations. Cholestasis was defined as the prolonged elevation of the serum levels of conjugated bilirubin beyond the 1st 14 days of life greater than 1.0 mg/dl (17.1 micromol/l) if the total serum bilirubin is < 5.0 mg/dl (85.5 micromole/l) or greater than 20% of the total serum bilirubin if the total serum bilirubin is > 5.0 mg/dl (85.5 micromole/l). (1, 2)

Inclusion criteria: All infants with cholestasis persisting beyond two weeks in the neonatal period or cholestasis lasting for four weeks or more in older infants (2). Thorough history was taken including: Gestational age, gender, birth weight, blood group of the mother and the child, age at time of appearance of jaundice, stool color, family history of the same condition or any liver or chronic disease, mother's history of previous abortion or infant death].

Physical examination included: General examination, abdominal examination for organomegaly, ascites, any features of congenital anomalies, and any significant systemic signs or findings. Investigations were done in a stepwise approach. All the patients were sent for general investigations (liver functions: Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, direct and indirect bilirubin level, prothrombin time, and partial thromboplastin time: renal functions: Blood urea and serum creatinine), complete blood picture and blood film, C- reactive protein, blood culture, general urine examination and urine culture, and abdominal ultrasound. Specific investigations as needed include: TORCH screening (IgM and IgG for CMV, Herpes, Rubella, and Toxoplasmosis) conducted in the Central Public Health Laboratory, thyroid function test (T3, T4, and TSH), screening for inborn errors of metabolism which were conducted in Lebanon and ultrasound guided percutaneous liver biopsy for 13 patients when the initial investigations failed to reach the diagnosis and no contraindications were identified to perform the procedure. The study protocol was approved by the Scientific Council of the Arab Board of Pediatrics. Agreement of the hospital administration office was obtained with verbal consent from patients relatives (parents or care-takers). Data of patients was kept in a secured computerized database and was not disclosed to non-authorized persons. SPSS version 20 software was used for data entry and analysis, Standard Chi-square test was used to determine the associations between two categorical variables. Yates correction formula and fishers exact test were applied for chi-square test whenever it was needed, *P* value of less than 0.05 was considered as statistically significant.

Results:

A total of 48 patients were enrolled in this study, with an age range of 4 weeks to 13 months, and a mean age of 11.1 months ± 12.4. There were 20 females (41.7%) and 28 males (58.3%).

Table (1) shows that 11 (22.9%) of the cases were caused by congenital infections, mainly CMV (10 cases - 91%) and Toxoplasmosis (one case - 9%). Idiopathic neonatal hepatitis was found in 9 cases (18.8%), biliary atresia in 8 (16.7%), unknown causes in 8 (16.7%), sepsis in 5 (10.4%) (*staphylococcus aureus*, *streptococcus species*, *E-coli*,), PFIC in 2 (4.2%) and 1 (2.1%) case was caused by each of the following causes: Alagille syndrome, Choledochal cyst, Galactosemia, hypothyroidism and Tyrosinemia.

Table 1:- Distribution of the causes of jaundice in the study group

Causes		Number	%
Infections	Congenital	11	22.9
	Sepsis	5	10.4
Idiopathic Neonatal hepatitis (INH)		9	18.7
Biliary Atresia		8	16.6
Progressive familial intrahepatic cholestasis		2	4.2
Choledochal Cyst		1	2.1
Genetic and Inborn Errors	Alagille syndrome	1	2.1
	Galactosemia	1	2.1
	Hypothyroidism	1	2.1
	Tyrosinemia	1	2.1
Unknown		8	16.7
Total		48	100

A significant association was found between the etiological factors and time of appearance of jaundice, where 81% of the cases caused by congenital infection and 77.8% of the Idiopathic neonatal hepatitis (INH) cases presented within the first week of life while 62.5% of the biliary atresia cases and 60% of the sepsis cases presented on the second week of life, (P-value 0.01), table 2.

Table 2: Distribution of the study group by the cause and age at onset of jaundice

Diagnoses	Total	Age at onset of jaundice				
		<1 week		≥1 week		
		No.	%	No.	%	P-value
Congenital infections	11	9	81.8	2	18.2	0.01
INH	9	7	77.8	2	22.2	
BA	8	3	37.5	5	62.5	
Sepsis	5	2	40.0	3	60.0	

Table 3 shows that the highest most of the cases of jaundice caused by congenital infections or idiopathic neonatal hepatitis presented with intermittent clay colored stool (63.6%, 55.6% respectively), while all cases caused by biliary atresia presented with persistent clay colored stool and all cases caused by sepsis presented with normal colored stool.

Table 3: Distribution of the study group by the cause of Jaundice and stool color

Diagnoses	Total	Stool Color						p-value
		Clay stool		Intermittent clay		Normal		
		No.	%	No.	%	No.	%	
Congenital infections	11	0	0	7	63.6	4	36.4	0.01
INH	9	2	22.2	5	55.6	2	22.2	
BA	8	8	100.0	0	0	0	0	
Sepsis	5	0	0	0	0	5	100.0	

No significant differences were found (P- value ≥ 0.05 for all) with regards to levels of ALT, AST, TSB and direct bilirubin among patients according to different causes of jaundice. The only significant difference was found with Alkaline phosphatase level (p=0.01), table 4.

Table 4: Mean values of liver function indicators according to cause of Jaundice

Liver Function Test	Cause of Jaundice	No.	Mean	SD	p-value
Alanine Amino-transferase (U/L)	Congenital infections	11	144.1	70.7	0.5
	INH	9	56.7	34.9	
	B.A	8	139.0	258.3	
	PFIC	2	78.5	14.8	
Aspartate Amino-transferase (U/L)	Congenital infections	11	201.2	117.2	0.8
	INH	9	130.6	145.2	
	B.A	8	200.1	186.8	
	PFIC	2	102.0	19.7	
Alkaline Phosphatase (U/L)	Congenital infections	11	277.5	203.4	0.01
	INH	9	151.7	140.9	
	B.A	8	692.5	312.1	
	PFIC	2	1183.5	426.1	
Total Serum Bilirubin (mg/dl)	Congenital infections	11	8.1	203.4	0.08
	INH	11	7.6	3.1	
	B.A	9	12.6	3.4	
	PFIC	2	13.5	5.0	
Direct Serum Bilirubin (mg/dl)	Congenital infections	11	6.5	3.2	0.3
	INH	9	6.2	3.2	
	B.A	8	8.6	2.9	
	PFIC	2	10.9	12.7	

Discussion:

In the current study the most common cause of jaundice was congenital infections, followed by Idiopathic Neonatal Hepatitis, biliary atresia, sepsis, and to a lesser extent by genetic causes and inborn errors of metabolism. Eight cases were considered of unknown origin even after thorough investigations. This is in agreement with a study conducted in India by Matthai et al (14), in which six out of 14 cases with neonatal hepatitis were due to CMV and two were positive for Herpes, both of which are congenital infections. BA was diagnosed in 7 (18.9%), NH in 6 (16.2%), and metabolic causes in 5 cases metabolic causes, and one case due to hypothyroidism. Our results disagree with those of Al-Azzawi et al (15) in Iraq, which shows that BA was the most common cause of cholestatic jaundice diagnosed in 22 cases (44%), followed by Neonatal hepatitis syndrome 17 cases (34%). Our results also disagree with those of Dehghani et al (16) in Iran where BA and INH were diagnosed in 30 cases each (24.6%), followed by paucity of intrahepatic bile ducts in 16 cases (13.1%) as the most common causes of cholestasis, while genetic and metabolic disorders were seen in 8.2%, and progressive familial intrahepatic cholestasis in 4.1% of cases. This disagreement may be due to decline of the standards of antenatal care during the past few years in Iraq as well as the small number of patients who underwent liver biopsy. Eight cases remained as unknown etiology, which may contribute to the lower percentages of both BA and INH. In the current study, CMV infection was found to be the most common cause of intrauterine infections 10 cases (91%), while there was only one case of Toxoplasmosis (9%), in agreement with the findings of Deghady et al (17) in Alexandria who found CMV in 41.4% of their cases, HSV in 10.3%, CMV + HSV in 20.9%, and Toxoplasmosis in 6.9%. And also, this study agrees with Matthai J et al, study(14) ,in India in which Among 8(21.6%) with congenital infections 6(16.2%) were due to cytomegalovirus and 2(5.4%) were positive for Herpes. The center where the study was conducted lacks facilities for advanced metabolic and genetic testing. Many cases did not undergo liver biopsy due to delays in case referral, uncorrectable PT and PTT, and family refusal. As a result, eight cases (16.7%) were considered as unknown cause. The study conducted by Dehghani et al (16) in Iran had 28 cases (22.9%) in which the causes of cholestasis were labeled as "unknown" and the study of Al-Azzawi et al (15) in Baghdad had 9 cases (18%) where no definite cause could be found. In the current study INH was more common in males 7 cases (77.8%) than females 2 cases (22.2%), which agrees with the findings of Wongsawasdi et al (18) in Chiang Mai University, with 13 males and 10 females. We found BA to be also more common in males (5 cases - 62.5%) than females (3 cases - 37.5%) contrasting Wondsawadi where there was 14 males and 17 females with BA. In total, there was a male predominance in our series (28 - 58.3%) compared to 20 females (41.7%). Dehghani et al (16) series had 20 males with INH and only 10 females, while there were 13 males with BA and 17 females. Their series included 122 cases, compared to our smaller 48 cases. The preference of males in our community may have contributed to this finding. In the current study, persistent clay-color stool was seen in all patients with BA, while INH cases had more intermittent clay stool. Dehghani et al (16) had the same finding, with 54 of all cholestasis cases (44.3%) had clay-color stool, 20 out of 30 infants with BA (66.7%) and 12 out of 30 with INH (23.7%) had clay-color stool. Wongsawasdi et al (18) found that acholic and pale yellow stools were significant in BA cases compared to those in NH. Ağın et al (19) in Turkey found that acholic stools were observed in all patients in the BA group but only in 10 cases (37%) in the non-BA group. Sinha et al. (20) found that all patients with BA

presented with varying degrees of conjugated jaundice and pale non-pigmented stools. The onset of jaundice in the current study was more frequent during the first week of life in INH cases while in BA cases it happened mainly after the first week of life. This was helpful in identifying the causes of the disease. Dehghani et al (16) found no significant correlation between the age of jaundice onset and the cause of cholestasis. In the current study the S-ALP mean level showed a significant difference mainly between the BA and INH, with the higher level being in favor of BA rather than INH. Total and direct serum bilirubin levels and both S-ALT, S-AST were not significantly different, in agreement with Al-Azzawi et al (15). Deghady et al (17) found that transaminases were specific in differentiating BA from NH or other causes of cholestasis but did not address the differences in S-ALP level. Dehghani et al (16) found no differences in S-ALP level between different types of cholestasis.

Conclusion:

Congenital infections are the most common cause of cholestasis.

CMV infection is the most common cause of intrauterine infections.

Persistent clay color stool and high alkaline phosphatase levels are found mostly in Biliary Atresia.

No method by itself is sufficient to diagnose the cause of neonatal cholestasis. Indeed, diagnosis can only be established using all available methods.

Authors' Contributions:

Dr.Mohammad Fadhil Ibraheem: Conceived and designed the analysis, perform the analysis, and wrote the paper.

Dr. Adnan Yahya Mahmood: collect the data, perform the analysis, and wrote the paper.

Dr. Jasim Mohamed Salih: collect the data, perform the analysis, and contribute data and analysis tool.

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العوامل المسببة لحدوث الركود الصفراوي في الطفولة المبكرة في مستشفى حماية الأطفال التعليمي

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الخلاصة:
الخلفية: يتم تعريف الركود الصفراوي لحديثي الولادة على أنه ارتفاع مستمر في مستوى المصل من البيليروبين المترافق بعد الأيام الـ14 الأولى من الحياة. هناك العديد من الأسباب لحدوث الركود الصفراوي لحديثي الولادة ويجب تفريقها عن بعض لأن التدخل المبكر قد يؤدي إلى نتيجة أفضل مثل التدخل الجراحي في رتق القناة الصفراوية في غضون شهرين من الولادة والتدبير الفعال للاضطرابات الأخرى القابلة للعلاج مثل أرتفاع الجالاكتوز في الدم وبدء العلاج في وقت مبكر.
الهدف: تحديد أسباب الركود الصفراوي في مرحلة الطفولة المبكرة في الأطفال الذين راجعوا مستشفى حماية الأطفال التعليمي في بغداد ودراسة بعض العوامل المصاحبة للركود الصفراوي في مرحلة الطفولة المبكرة.
المرضى والمنهجية: دراسة وصفية مقطعية لـ 48 مريض راجعوا مستشفى حماية الأطفال التعليمي في بغداد للفترة من الأول من نوفمبر 2015 إلى الخامس عشر من يناير 2016. وقد تم تقييمهم من خلال التاريخ المرضي والفحوصات السريرية والمختبرية.
النتائج: تم تسجيل مجموعة من 48 مريضا في هذه الدراسة، وظهر أن 30 مريضا (62.5٪) كانوا يعيشون في بغداد أما الباقين فكانوا من محافظات أخرى، وكان متوسط عمر المرضى 11.1 ± 12.4 شهراً. وكان عدد الإناث 20 (41.7٪) والذكور 28 (58.3٪) من مجموعة الدراسة. أظهرت النتائج أن 11 حالة (22.9٪) سببها عدوى خلقيّة، 9 (18.8٪) من الحالات كانت مجهولة السبب، 8 (16.7٪) سببها رتق القناة الصفراوية، 8 (16.7٪) من أصل غير معروف، 5 (10.4٪) بسبب الخمج (المكورات العنقودية بشكل رئيسي، الأنواع العقدية، بكتريا القولون)، 2 (4.2٪) الناجمة عن ركود صفراوي داخل الكبد التدريجي و 1 (2.1 ٪) كان السبب كل من الحالات التالية: متلازمة الاجايل، تكيس الصفراء، أرتفاع الجالاكتوز في الدم، قصور الغدة الدرقية وزيادة التايروسين في الدم.
الاستنتاج: كانت العدوى الخلقية هي السبب الأكثر شيوعًا في هذه الدراسة، وعدوى الفيروس العملاق هي السبب الأكثر شيوعًا للإصابة بالتهابات داخل الرحم, لون الغائط الطيني، ومستويات فوسفاتاز القلوية العالية تكون موجودة غالباً في الرتق الصفراوي. لا تكفي أي طريقة بحد ذاتها لتشخيص سبب الركود الصفراوي عند حديثي الولادة. في الواقع، لا يمكن تحديد التشخيص إلا باستخدام جميع الطرق المتاحة.
الكلمات المفتاحية: ركود صفراوي، الأطفال، المسببات.