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Early Childhood Cholestasis, Causes & Associated Factors in Children

Adnan Y. Mahmood [1], Jalil I. Alezzi [2], Haider Jwad Dawod [3], Mabrook Aidah Bin Mohanna [4]

[1,2] Al Batool Teaching Hospital, Baqubah , Diyala , Iraq
[3] College of Medicine, University of Diyala , Iraq
[4] Sanaa university, College of medicine, Yemen

Correspondence: Adnan Y. Mahmood

Email: ad533hh@gmail.com

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Abstract

Background: Newborn cholestasis is explained as a persisted rise of the serum conjugated bilirubin outside the first two weeks of life. There are many etiologies of newborn cholestasis that must be differentiated since immediate interference may give a better outcome.

Objective: Newborn cholestasis is explained as a persisted rise of the serum conjugated bilirubin outside the first two weeks of life. There are many etiologies of newborn cholestasis that must be differentiated since immediate interference may give a better outcome.

Patients and Methods: A cross-sectional research of forty-eight children consulting the Childhood Wellbeing Teaching Hospital in Baghdad/Medical City from 1st of November 2018 to the 30th of November 2021, complete evaluation by full history, physical checkup and laboratory studies. Cholestasis was demarcated as an extended raise of the levels of conjugated bilirubin outside the 1st 2 weeks of age above 1.0mg/dl(17.1µmol/l) if the whole serum bilirubin(TSB) is <5.0 mg/dL or above 20% of the TSB if the TSB is >5.0 mg/dl.

Results: Out of 48 children involved in the study ,62.5% resided in Baghdad, and the remainder was belonged to other districts. The mean age of children was 11.1 months. The males constituted 58.3% of them. Eleven cases (22.9%) were caused by congenital infection, nine 18.8% had no cause detected, while 16.7% caused by biliary atresia and 16.7% had unidentified etiology, however 10.4% was related to sepsis. Biliary atresia was more frequent in boys in 62.5% compared to 37.5% in females. Family history was positive only in11.1% of idiopathic neonatal hepatitis. It was found that 81% of cholestatic jaundice were caused by congenital infection. In comparison, 62.5% caused by biliary atresia and 60% caused by sepsis appeared on the second week of the child's age, and this difference was significant statistically P-value 0.01.

Conclusion: Innate infections are the most frequent source, where CMV contagion is the most commonly detected. Clinical findings included clay colored stool & elevated alkaline phosphatase concentrations observed primarily on biliary atresia. There are no specific test to identify the etiology of newborn cholestasis.

Keywords: Cholestasis, children, causes, associated factor

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Introduction

Newborn Cholestasis is demarcated as continued raise of the concentrations of conjugated bilirubin outside the initial 2 weeks of life more than 1mg/dl (17.1micromol/l) if the whole serum bilirubin is <5 mg/dL (85.5 µmol/l) or more than 20 % of the total serum bilirubin if the total serum bilirubin is >5 mg/dl (85.5 µmole/L). Neonates with jaundice outside two weeks after birth should be assessed for conjugated hyperbilirubinemia. (1-5). Conjugated hyperbilirubinemia occurs in approximately 1 / 2500 infants and is less common than unconjugated hyperbilirubinemia. (6-9). There are various etiologies of neonatal cholestasis, and essential to be differentiated since immediate interference, the outcomes will be better. Furthermore, other treatable illnesses such as (tyrosinemia, galactosemia, hypothyroidism, and infectious etiologies) initiate early effective therapy. (10-15). If jaundice continues, detection of whole and direct serum bilirubin might be done. (3,16-18). The most frequent etiologies of cholestasis in babies are biliary atresia (BA) (extra & intrahepatic) and neonatal hepatitis (NH), a diagnosis that is imparted to broad-based liver disorders, which occurs secondary to various causes comprising intrauterine infection, endocrine illnesses and inherited error of metabolism (17-23). A hepatic biopsy is the only best absolute analysis in assessing neonatal cholestasis. In numerous center searches, identification of biliary atresia was accurately implied by hepatic biopsy histologic results in 90 to 95 % of circumstances. (24-28). Management is supportive and directed toward promoting development and growth and handling the problems of prolonged cholestasis, such as malabsorption, nutritional deficiencies, pruritis, as well as portal hypertension (29-32). The Kasai portoenterostomy used for biliary atresia at age of 6-8 weeks of age which may be curative (33-38). For children with late hepatic disorder, liver transplant has an accomplishment rate of >85% [6, 20,39-42]. The natural history of cholestatic syndromes in childhood remains unclarified, mainly due to insufficient data in our country. This study aimed to determine the possible causes and some associated factors of neonatal cholestasis in patients consulting the childhood's Wellbeing Teaching Hospital/Baghdad

Patients and Methods

A cross-sectional study of forty-eight babies consulting the Childhood Wellbeing Teaching Hospital in Baghdad/Medical City from 1st of November 2018 to the 30th of November2021. The patients were assessed by full history, exam and laboratory tests. Cholestasis was demarcated as an extended raise of the levels of conjugated bilirubin outside the 1st 2 weeks of age above 1.0mg/dl(17.1µmol/l) if the whole serum bilirubin(TSB) is <5.0 mg/dL (85.5 µmole/l) or above 20 per cent of the TSB if the TSB is >5.0 mg/dl (85.5 µmole/L). (5,9). The evaluation included a history that includes [maturity, gender, weight at birth, blood group and mother and baby, age, onset of jaundice, the color of feces, household similar history or any hepatic or long-lasting illness, history of miscarriage or baby death. Full physical examination, and any significant systemic signs or findings were taken into consideration. Laboratory tests which included liver enzymes (alanine transferase, aspartate transferase, alkaline phosphate) conjugated and unconjugated bilirubin level, prothrombin time (PT), partial thromboplastin time(PPT), kidney function tests. Full blood count and blood picture, CRP, blood culture, general urine examination, urine culture, abdominal ultrasound, and specific tests were done for most of the children as needed, which included TORCH screen, thyroid gland tests (T3, T4, TSH), metabolic screen we depended on (MS/MS) and liver biopsy for selected patients. The scientific council of the Arab Board of

ORIGINAL RESEARCH
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Pediatrics approved the study protocol. approval of the hospital director was taken, as well as verbal permission from patients families (parents or other relatives). Patients' information was remained confidential (electronic) and not revealed to non-legal individuals. Statistical analysis: SPSS version 21 was applied for information entrance and scrutiny, results were displayed as count and percent, mean and standard deviancy were used, and appropriate statistical tests were used for data analysis.

Results

The mean age of children was 11.1 months±12.4 SD, and girls were 20(41.7%), and boys were 28 (58.3%), (30) 62.5% came from the capitol, and the others were from other districts of the report group. The results showed that 11(22.9%) were caused by inborn infection (Cytomegalovirus infection 10 cases (91%) was the most typical cause of intrauterine infections and 9 (18.8%) of conditions were no etiology found, 8(16.7%) instigated by biliary atresia, 8(16.7%) of unidentified source, as seen in table.1

Table 1. Etiology of cholestasis in patients group

The Etiology	Frequency	Per cent
Congenital infections	11	22.9
INH	9	18.8
Biliary atresia	8	16.7
Sepsis	5	10.4
Progressive familial intrahepatic cholestasis	2	4.2
Alagille syndrome	1	2.1
Choledochal Cyst	1	2.1
Galactosaemia	1	2.1
Hypothyroidism	1	2.1
Tyrosinemia	1	2.1
Unspecified	8	16.7
Total	48	100.0

There was considerable correlation between the etiologic cause and timing of beginning of jaundice, where 81% of cholestatic jaundice were caused by congenital infection. In comparison, 62.5% caused by biliary atresia and 60% caused by sepsis appeared on the second week of the child's age, and this difference was significant statistically (P-value 0.01), as seen in the table.2

Diyala Journal of Medicine

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Table 2. Relationship between etiology of the disease and time of appearance of jaundice after birth.

Diagnoses		Time of onset of jaundice				
		<1 week		≥1 week		
	Total No.	No.	%	No.	%	P-value
Congenital infection	11	9	81.8%	2	18.2%	0.01
Idiopathic neonatal hepatitis	9	7	77.8%	2	22.2%	
Biliary atresia	8	3	37.5%	5	62.5%	
Sepsis	5	2	40.0%	3	60.0%	

The highest percentage of jaundice triggered by inborn infection and idiopathic neonatal hepatitis (63.6%, and 55.6%, respectively) were presented with intermittent clay color feces. In contrast, all that was triggered by biliary atresia manifested with continuing clay-colored feces and altogether that were produced by septicemia were presented with standard colored feces, with a difference statistically significant as seen in table.3.

Table 3. Relationship between etiology of the disease and stool color of patients with jaundice

Diagnoses	Feces color									p-value
	Clay stool			intermittent clay			Normal			
	Count	Row N %	Column N %	Count	Row N %	Column N %	Count	Row N %	Column N %	
Congenital infection	0	0.0	0.0	7	63.6%	58.3%	4	36.4%	36.4%	0.01
Idiopathic neonatal hepatitis	2	22.2%	20.0%	5	55.6%	41.7%	2	22.2%	18.2%	
Biliary atresia	8	100.0%	80.0%	0	0.0	0.0	0	0.0	0.0	
Sepsis	0	0.0	0.0	0	0.0	0.0	5	100.0%	45.5%	

No significant difference was detected (Pvalue≥0.05 for altogether) with respects to the level of liver enzymes, TSB and direct bilirubin amongst babies owing to diverse etiologies, and only substantial variance was seen with Alkaline phosphatase concentration (p=0.01) as shown in the table.4

ORIGINAL RESEARCH
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Table 4. The different Lab. tests matching with etiological factors.

Lab Tests	Etiology	N	Mean	Std. Deviation	p-value
ALT(U/L)	Congenital infection	11	144.1	70.7	0.5
	INH	9	56.7	34.9	
	Biliary atresia	8	139.0	258.3	
	PFIC	2	78.5	14.8	
AST(U/L)	Congenital infection	11	201.2	117.2	0.8
	INH	9	130.6	145.2	
	Biliary atresia	8	200.1	186.8	
	PFIC	2	102.0	19.7	
Alkaline Phosphatase (U/L)	Congenital infection	11	277.5	203.4	0.01
	INH	9	151.7	140.9	
	BA	8	692.5	312.1	
	PFIC	2	1183.5	426.1	
TSB(mg/dl)	Congenital infection	11	8.1	203.4	0.08
	INH	11	7.6	3.1	
	Biliary atresia	9	12.6	3.4	
	PFIC	2	13.5	5.0	
Direct(mg/dl)	Congenital infection	11	6.5	3.2	0.3
	INH	9	6.2	3.2	
	Biliary atresia	8	8.6	2.9	
	PFIC	2	10.9	12.7	

Ultrasound scanning of the abdomen found that 19(39%) of patients showed enlarged liver, 29.1% was normal, 7(14.6%) enlarged liver with signs of biliary atresia, 7(14.6%) enlarged liver and spleen and just one choledochal cyst as shown in the table.5

Table.5. Abdominal ultrasound findings for the studied 48 patients.

Ultrasound findings	Frequency	Per cent
Enlarged liver	19	39.6
Enlarged liver with signs of Biliary atresia	7	14.6
Enlarged liver and spleen	7	14.6
Choledochal Cyst	1	2.1
Normal	14	29.1
Total	48	100.0

The enlarged liver was more evident in patients with BA, INH, and congenital infections, 87.5% of biliary atresia cases had characteristics signs by ultrasound test, which is a significant finding P value 0.001. The typical ultrasound finding was found in all cases of sepsis, as seen in the table.6

ORIGINAL RESEARCH
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Table 6. Relationship of ultrasound finding and etiological factors.

Etiology		Abdominal US				p-value
		enlarged liver with signs of Biliary atresia	enlarged liver	enlarged liver &spleen	Normal	
Congenital infection	No.	0	6	2	3	0.001
	% within etiology	0.0	54.5%	18.2%	27.3%	
Idiopathic neonatal hepatitis (INH)	No.	0	5	2	2	
	% within etiology	0.0	55.6%	22.2%	22.2%	
Biliary atresia(BA)	No.	7	0	1	0	
	% within etiology	87.5%	0.0%	12.5%	0.0	
progressive familial intrahepatic cholestasis(PFIC)	No.	0	1	1	0	
	% within etiology	0.0	50.0%	50.0%	0.0	
Sepsis	No.	0	0	0	5	
	% within etiology	0.0	0.0	0.0	100.0%	

Of 13 patients with liver biopsy, it was found that 9(18.8%) of them showed idiopathic neonatal hepatitis characteristics,4.2% showed PFIC characteristics,2% biliary atresia characteristics and 2% of nonspecific findings, as seen in the table.7.

Table.7. Finding of liver biopsy of 13 studied patients

	Frequency	Per cent
Idiopathic neonatal hepatitis	9	69.21
PFIC	2	15.38
Biliary atresia	1	7.69
Nonspecific findings	1	7.69
Total	13	100.0

The study revealed a significant association (P value 0.02) between etiological factors and the family history of patients, which should withdraw the attention toward the etiology of cholestasis, as seen in the table.8.

ORIGINAL RESEARCH
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Table 8. Relationship between the most common causes of cholestasis & family history of cholestasis

			Family history		p-value
			N-ve	P+ve	
Etiology	Congenital infection	Count	10	1	0.02
		% within etiology	90.9%	9.1%	
	Idiopathic neonatal hepatitis	Count	8	1	
		% within etiology	88.9%	11.1%	
	Biliary atresia	Count	8	0	
		% within etiology	100.0%	0.0%	
	Sepsis	Count	5	0	
		% within etiology	100.0%	0.0%	

There was no significant relationship between gender of the children and the etiological factors P value0.7 , as seen in table 9.

Table 9. Relationship of etiological factors and gender of 48 patients.

Diagnoses		Gender		
		Male	female	*P value*
Congenital infection	Count =11	6	5	0.7
	% within Diagnoses	54.5%	45.5%	
Idiopathic neonatal hepatitis	Count =9	7	2	
	% within Diagnoses	77.8%	22.2%	
Biliary atresia	Count =8	5	3	
	% within Diagnoses	62.5%	37.5%	
Sepsis	Count =5	3	2	
	% within Diagnoses	60.0%	40.0%	

ORIGINAL RESEARCH
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Discussion

Hyperbilirubinemia is a usual symptom in the first 14 days of life, which can be physiological or due to breast milk. Nonetheless, if it continues for over 14 days, it implies a crucial reserve (28-30). The cholestasis analysis has been a big task for pediatricians, and the prompt verdict is critical since the efficacy of therapy is more in early identification. For instance, various studies revealed that detecting biliary atresia in the first two months of life is much better for the efficiency of operation than in three months (31-33). Even if an exact therapy is unavailable, an early opinion can lead to quickly reassuring therapy to decrease the problems of cholestasis, like hemorrhage caused by vitamin K defect. (28,42,43) . We found that, the most common cause was a congenital infection, 22.9%, followed by idiopathic neonatal hepatitis, 18.8%., while one patient 2.1% was related to each of the following etiologies: Alagille syndrome, choledochal cyst, galactosemia, hypothyroidism plus tyrosinemia ,however 16.7%) were of unknown origin, this is in agreement with Matthai J, et al. and other studies (25,34), and from 14(38.8%) with neonatal hepatitis, 16.2% were related to CMV, and 5.4%) were positive for herpes virus which suggests that 21.6% due to congenital infections as the most common cause. BA was seen in 7(18.9%), NH in six cases 16.2%), five patients had metabolic etiologies, one with hypothyroidism, these findings disagrees with previous studies (35,44-48), which revealed that BA was the commonest etiology of cholestatic jaundice. Moreover this study disagrees with most recent studies (36,49-51). This disagreement may be due to declines in antenatal care and maternal health in the last years in our country as well as clinical awareness about the etiology of the problem. Also, a small number of patients underwent liver biopsies, where 8 cases (16.7%) of unknown etiology, and this decreased the percentage of both BA and INH. We found CMV infection in ten cases 91% which is the most frequent agent of intrauterine infections, followed by toxoplasmosis infection and this is in agreement with other studies (35,42,43,50). Moreover, our finding agrees with Matthai J, Paul S. et al. (32). Genetic and metabolic diseases were detected in 8.2%, progressive familial intrahepatic cholestasis in 4.1% of patients. These findings are like Dehghani SM et al. study (36). Due to the lack of facilities for metabolic and genetic testing in our center as well as many patients did not have a liver biopsy; which may be due to postponements in cases referral, abnormal PT, PTT, family rejection and the fact that absence of liver transplant center, eight patients (16.7%) considered as having unknown cause, as in Dehghani SM et al. study (36). Moreover, in Al-azzawi study (35), in Baghdad 9 patients (18%), had no obvious etiology to be uncovered. The current study showed that INH was more frequent in 7 boys (77.8%) than in two females (22.2%), which agree with. WongsawasdiL et al. study (37), in Chiang Mai University, in which the male was 13 cases and female was 10 cases, also B. A was more frequent in males, with 5 (62.5%) as compared with 3 (37.5%) in females, which disagree with that study, which show 14 cases and 17 cases, and this is due to that in our studied patients, males constitute 28(58.3%) which were higher as compared with females 20 (41.7%).also, this study matches with Dehghani SM et al. study (36) , in which INH was detected in 20 males, and 10 cases were females, while BA had 13 cases were male, and 17 cases were female, which disagrees with our study; this is because the study took a large sample(122 cases), while our sample was only 48 cases; moreover our community paid more attention to males than females. In this study, the persistent clay-color stool was more frequent in all patients with BA, while in Wongsawasdi study INH, had more intermittent clay feces, and this agrees with Dehghani SM et al. study (36) and similar to Wongsawasdi L et al. study (37) in

ORIGINAL RESEARCH
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Turkey, alcoholic stool was observed in all patients in the BA group but only in 10 cases (37%) in the non-B.A group [38]. Our finding also agrees with the Sinha CK et al. study and others (39,42,43), in which all patients with BA present with changing levels of obstructive jaundice and light non-pigmented feces. In this study, the onset of jaundice in INH is more in the initial seven days of life, while in BA, mainly after the initial 7 days of life, and this helped identify the etiology of the disease, Which disagrees with the Dehghani SM et al. study (36), in which there was no substantial relationship between the age of jaundice commencement and the etiology of Cholestasis. This study revealed that B. A cases did not correlate with family history, and 11.1% of INH cases had a household record of a alike disorder, as in Ağın M et al. study (38), in Turkey in which none of the BA cases had a family history of a similar disease. In this research, the alkaline phosphatase concentration shows a significant alteration, largely between the BA and INH had high S.ALP levels in preference of BA. In contrast, the total and direct serum bilirubin levels and both S.ALT S.AST show no significant difference, and this agrees with Al-azzawi S et al. study (35), in Baghdad in which the biochemical profile showed that S.ALP level was increased in BA patients rather than in NH and total serum bilirubin transaminases levels have no influence on the differential diagnosis, since both of them may similar enzymes changes. In the Dehghani SM et al. study (36), the parallel of liver function tests in various etiologies of cholestasis does not help determine the causes of cholestasis, and this agrees with our study. In contrast, the ALP in our study was significant finding, which is different from that study. Furthermore, this study disagrees with other studies (39,40,41) in which transaminases were definite in discriminating biliary atresia from neonatal hepatitis or other etiologies of cholestasis. This study revealed that 39.6% of cases had hepatomegaly, and 14.6% had hepatomegaly with the signs of BA and 14.6%had hepatosplenomegaly, which means collectively that 66.8% of cases had hepatomegaly and 14.6% had splenomegaly which is in agreement with Dehghani SM et al. study [36]. In this study, all the cases of B. A had hepatomegaly, and 12.5% had splenomegaly. In comparison, in INH, 77.8% had hepatomegaly, and 22.2 % had splenomegaly, which agrees with the Dehghani SM et al. study (36), in which there was no relationship between the etiologies of cholestasis and the presence of hepatomegaly and splenomegaly, and in comparison, with Deghady AM et al. study (40), in Alexandria, in which 94.2% of BA cases had hepatomegaly is slightly lower than our study, and 96.6% of INH cases had hepatomegaly, which is higher than our study; splenomegaly was found in 29.4% of BA cases and in 69% of INH cases in that study, which is higher than our study. Moreover our findings are similar to Al-azzawi S et al. report (35) in Baghdad in which enlarged liver was also discovered in all patients with BA. The limitations of this study are lack of family compliance and delayed cases referral, and the necessity for teaching of practitioners and pediatricians about the etiologies of cholestasis and its identification, and the lack of electron microscopy and immunohistochemical study by liver biopsy, the need for further investigations like hepatobiliary scintigraphy, and the limitation of facilities that needed for the diagnosis of genetic and metabolic disorders.

Conclusion

inborn infections are the most frequent etiology in this study, in which CMV infection was the utmost frequent etiology of intrauterine infections. Constant mud color feces, high alkaline phosphatase concentration mainly observed in BA. There was no specific procedure to identify the etiology of newborn with cholestasis. Certainly, the identification may only be proved utilizing all existing procedures.

ORIGINAL RESEARCH
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Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023AHI808).

Conflict of interest

The author acknowledges no conflict of interest in this study

Recommendations

Good maternal and antenatal care to control and reduce the risk of congenital infections. A significant number of cholestasis in this study has unknown etiology, so we recommend to establish center or units in children hospitals for metabolic diseases screening.

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ORIGINAL RESEARCH
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اسباب الركود الصفراوي لحديثي الولادة في مستشفى حماية الاطفال التعليمي

عدنان يحي محمود[١], جليل إبراهيم العزي[٢], حيدر جواد داود[٣], مبروك عيظه بن مهنا[٤]

الملخص

الخلفية الدراسية: يعرف الركود الصفراوي عند الأطفال حديثي الولادة على أنه ارتفاع مستمر في البيليروبين المترافق في الدم بعد الأسبوعين الأولين من الحياة. هناك العديد من مسببات الركود الصفراوي عند الأطفال حديثي الولادة والتي يجب التمييز بينها لأن التداخل الفوري قد يعطي نتيجة أفضل.

الهدف من الدراسة: الكشف عن أسباب الركود الصفراوي في مرحلة الطفولة المبكرة ودراسة بعض العوامل المرتبطة به.

طرق العمل: بحث مقطعي لثمانية وأربعين طفلاً يراجعون مستشفى صحة الطفولة التعليمي في بغداد / المدينة الطبية في الفترة من ١ نوفمبر ٢٠١٨ إلى ٣٠ نوفمبر ٢٠٢١، التقييم الكامل عن طريق التاريخ الكامل والفحص البدني والدراسات المخبرية. تم تحديد الركود الصفراوي على أنه زيادة ممتدة في مستويات البيليروبين المترافق بعد الأسبوعين الأولين من العمر فوق ١ ملجم / ديسيلتر) إذا كان البيليروبين في المصل بأكمله (TSB) أقل من ٥ ملجم / ديسيلتر أو أعلى من ٢٠٪ من TSB إذا كان TSB أكبر من ٥ ملجم/ديسيلتر.

النتائج: من بين ٤٨ طفلاً مشاركاً في الدراسة، كان ٦٢,٥٪ يقيمون في بغداد، والباقي ينتمي إلى مناطق أخرى. وكان متوسط عمر الأطفال ١١,١ شهرا. وشكل الذكور ٥٨,٣٪ منهم. إحدى عشرة حالة (٢٢,٩٪) كانت ناجمة عن عدوى خلقية، وتسع حالات (١٨,٨٪) لم يتم اكتشاف سبب لها، في حين أن ١٦,٧٪ كانت ناجمة عن رتق القناة الصفراوية و١٦,٧٪ كانت مسبباتها غير محددة، ولكن ١٠,٤٪ كانت مرتبطة بالإنتان. وكان رتق القناة الصفراوية أكثر شيوعاً عند الأولاد بنسبة ٦٢,٥٪ مقارنة بـ ٣٧,٥٪ عند الإناث. كان تاريخ العائلة إيجابيًا فقط في ١١,١٪ من حالات التهاب الكبد الوليدي مجهول السبب. وقد وجد أن ٨١٪ من حالات اليرقان الركودي كانت بسبب عدوى خلقية. بالمقارنة، ٦٢,٥٪ ناجمة عن رتق القناة الصفراوية و٦٠٪ ناجمة عن الإنتان ظهرت في الأسبوع الثاني من عمر الطفل، وكان هذا الفرق ذو دلالة إحصائية بقيمة P-0.01.

الاستنتاجات: تعد العدوى الفطرية المصدر الأكثر شيوعًا، حيث تكون عدوى الفيروس المضخم للخلايا (CMV) هي الأكثر شيوعًا. وشملت النتائج السريرية البراز ذو اللون الطيني وارتفاع تراكيز الفوسفاتيز القلوية التي لوحظت في المقام الأول على رتق القناة الصفراوية. لا يوجد اختبار محدد لتحديد مسببات الركود الصفراوي عند الأطفال حديثي الولادة.

الكلمات المفتاحية: الركود الصفراوي، الأطفال، الأسباب، العوامل المرتبطة به .

البريد الالكتروني : ad533hh@gmail.com

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[٢,١] مستشفى البتول التعليمي
[٣] كلية الطب جامعة ديالى
[٤] كلية الطب جامعة صنعاء