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Evaluation of noninvasive methods for diagnosis of cholestasis in infancy

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Abstract

Background

Cholestatic liver disease constitutes a large percentage of chronic liver diseases during infancy. Cholestasis is defined as interference with bile formation or flow owing to pathology anywhere between the hepatocyte and the ampulla of Vater.

Aim

To evaluate the different modalities used for diagnosing cholestasis in infants in Damanhour Medical National Institute (DMNI) to find out the sensitivity and the predictive values of each modality in defining the cause of cholestatic jaundice, whether surgical or medical.

Patients and methods

This study was a retrospective one which included 153 infants who were referred with cholestasis in first year of life to the Pediatric Hepatology Clinic of the Children's Department (DMNI) from June 2013 to December 2018. The medical records of the 153 infants with confirmed cholestasis were reviewed regarding the history and clinical examination, laboratory data, ultrasound, and liver biopsy. The cases were classified into two groups according to the etiology. Group I comprised (Extrahepatic Biliary Atresia) EHBA, and there were 40 patients in this group. Group II comprised non-EHBA (the medical causes of cholestasis), and there were 113 patients in this group.

Results

Nearly half (52%) of the patients were females. There were no significant differences regarding sex between EHAB and non-EHBA patients. An enlarged liver was also a common finding, being present in more than 66% of infants, irrespective of the underlying cause. Splenomegaly was more commonly noted in group II (27.43%) versus group I (12.5%), but the differences were not statistically significant. Persistently day stools were observed by 95% of mothers of babies of group I compared with 15% in group II, with a highly significant statistical difference. No significant differences were found between group I and group II regarding most tests of the biochemical profile, except Gamma-glutamyl transferase (GGT) and alkaline phosphatase (AL Ph), as they were significantly higher in group I compared with group II. However, aspartate transaminase (AST), alanine transaminase (ALT), and partial thromboplastin time were significantly higher in group II compared with group I.

Conclusion and recommendations

It is recommended the use of the developed model, GGT, and AL Ph as first line of investigations, and follow-up for excluding EHBA. Urgent referral of patients to perform a liver biopsy should be done based on the calculated probability of the developed model more than 0.128, GGT more than 500, and Al Ph more than 600. Campaigns to increase awareness among parents and primary care doctors are recommended for early drug and management.

Keywords: Infancy, medical cause of cholestasis, noninvasive methods, surgical

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Introduction

Neonatal cholestasis still represents a significant challenge for primary care clinicians, pediatricians, hepatologists, and pediatric surgeons. The evaluation of cholestasis in infants remains a challenge owing to the diversity of cholestatic syndromes, their obscure pathogenesis, and the nonspecific clinical and pathologic features [1].

Neonatal cholestasis

Primary care clinicians and pediatricians used to physiologic jaundice in newborns and the higher frequency of indirect hyperbilirubinemia, are expected to recognize direct hyperbilirubinemia for the newborn early and to submit him/her urgently to a tertiary hospital.

From here on, the diagnostic challenge is transferred to the hepatologist, who has to consider several causes of intrahepatic and extrahepatic cholestasis.

The surgery for Biliary atresia (BA) should be performed as early as possible [2,3].

It is now recommended that BA should be excluded in all term infants who still have jaundice at 3 weeks of age [4].

No single clinical feature or laboratory parameter has been found to show sufficient sensitivity and specificity to differentiate between BA and other causes of neonatal cholestasis [5,6].

This work aimed to evaluate the different modalities used for diagnosing cholestasis in infants admitted in Damanhour Medical National Institute (DMNI) to find out the sensitivity, specificity, and predictive values of each modality in defining the cause of cholestatic jaundice, whether surgical or medical.

Patients and methods

This study was a retrospective one that includes infants who were referred with cholestasis in first year of life to DMNI Children's Department (from June 2013 to December 2018).

The medical records of the 153 infants with confirmed cholestasis were reviewed for the following data. The ethical committee approval and formal consent was taken.

History and examination

It included age of onset of cholestasis and age of presentation to the pediatric hepatology clinic, as well as symptoms including jaundice, change of color of stools, the color of urine, abdominal distention, vomiting, diarrhea, bleeding, pruritus, fever, and convulsions.

Clinical signs included the presence of jaundice, hepatomegaly, splenomegaly, failure to thrive, scratch marks, cardiac murmurs, lower limb edema, ascites, and dysmorphic features.

Laboratory data

Liver enzymes (including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, Gamma-glutamyl transferase (GGT)), serum bilirubin (both direct and indirect), serum albumin, and total proteins; prothrombin time and partial thromboplastin time (PT and PTT); hepatitis markers (HBs Ag, HCV antibody, Cytomegalovirus (CMV) IgM, and EBV IgM); and urine analysis and culture were done.

Metabolic screen

It included nonglucose-reducing substances in the urine, blood glucose level, serum alpha 1-antitrypsin level, and others, according to the case.

Data of imaging studies

Abdominal ultrasound was done, stressing on the hepatic parenchyma, echogenicity, liver enlargement, spleen enlargement, visualization of the gall bladder, the presence of dilated intrahepatic bile ducts, or common bile duct (as regards patency, dilatation, or cystic changes).

Liver biopsy

If done, we commented on the architecture, presence of bile duct proliferation, portal fibrosis, portal inflammatory cells, giant cells, and lobular inflammation.

Results

This study was conducted on 153 infants who were referred with cholestasis in first year of life to the Pediatric Hepatology Clinic of the Children's Department (DMNI). There were 74 (48.4%) males and 79 (51.6%) females. Their age ranged from 7 to 330 days (Table 1).

Other causes of cholestasis in infancy (non-EHBA) included idiopathic hepatitis, which was diagnosed in 24%, CMV hepatitis (10%), the paucity of intrahepatic bile duct 'syndromic (Alagille syndrome) and nonsyndromic' (19%), and metabolic causes (21%).

Table 2 shows that lipid storage disease was the most common metabolic disorder in the studied infants, followed by α1-antitrypsin.

Table 3 show laboratory markers in all studied infants.

ALT level was higher in the metabolic group and the least in Extrahepatic Biliary Atresia (EHBA), but with no significant difference. AST level was significantly higher in the metabolic group than in EHBA. GGT and AL Ph were significantly higher in EHBA than other groups; GGT was the least in the metabolic group, whereas alkaline phosphatase (AL Ph) was the least in the

Table 1 Distribution of all studied infants according to the etiology of cholestasis

Etiology of cholestasis	*n* (%)
EHBA	40 (26.1)
Idiopathic hepatitis	37 (24.2)
CMV hepatitis	15 (9.8)
Paucity of OHBD	29 (19.0)
Metabolic group	32 (20.9)
Total	153 (100.0)

Table 2 Distribution of metabolic causes of cholestasis among all studied infants

Metabolic causes of cholestasis	*n* (%)
α1-antitrypsin	7 (21.9)
Lipid storage disease	15 (46.9)
GSD	3 (9.4)
Galactosemia	6 (18.8)
Fructose intolerance	1 (3.1)
Total	32 (100.0)

idiopathic hepatitis group. Total serum bilirubin and direct serum bilirubin were significantly less in the metabolic group than in other groups; total serum bilirubin was highest in the paucity of OHBD, whereas direct serum bilirubin was the highest in EHBA. Total proteins were higher in the paucity of intrahepatic bile ducts (IHBD) and least in CMV hepatitis but with no significant difference. Serum albumin was higher in CMV hepatitis and the least in EHBA but with no significant difference. PT level was higher in CMV hepatitis and the least in the paucity of OHBD but with no significant difference. PTT level was significantly higher in CMV hepatitis and the least in EHBA.

Discussion

A variety of disorders can present with cholestasis during the neonatal period, with biliary atresia as the most frequent cause and idiopathic cases as the second collective entity. A previous study reported that 35% of infants with neonatal cholestasis had biliary atresia, and 30% were considered as idiopathic cases having neonatal hepatitis [5]. Other causes included α1AT deficiency (17%), congenital viral infections (9%), Alagille syndrome (6%), and choledochal cysts (3%). Almost 25 years later, this retrospective study confirms these data in part as biliary atresia accounted for ~41% of all infants with neonatal cholestasis who were referred to our hospital.

Neonatal cholestasis is a severe disorder in early childhood, with pretransplant mortality that is not negligible, as especially for children with biliary atresia, it was ~12%. Biliary atresia was the most frequent disorder in our and previously reported cohorts [6], leading to liver transplantation. Although only infants with biliary atresia died after transplantation in our cohort, the intraoperative complications could have also affected infants with other causes of neonatal cholestasis. The majority of those infants who died before liver transplantation had disorders with an unfavorable prognosis (three with syndromic variants of biliary atresia, one with complex malformation syndrome, and one with Zellweger's syndrome), and only one child had nonsyndromic biliary atresia. However, the fact that syndromic variants seem to carry a higher complication rate may depend on the small series, as previous multicenter studies did not find a difference between syndromic and nonsyndromic variants of biliary atresia [7,8].

It is the late referral of children with biliary atresia that is widely suggested to be accountable for increased mortality [8,9], as the success rate of the Kasai procedure is closely associated with the age at the time of surgery [9,10].

Table 3 Distribution of all studied infants according to the final diagnosis and laboratory markers

Major groups	Mean±SD	*P*
ALT		
EHBA	166.53±93.47	0.228
Idiopathic hepatitis	194.70±97.53	
CMV hepatitis	188.33±76.06	
Paucity of IHBD	216.38±154.64	
Metabolic group	249.75±157.51	
AST		
EHBA(a)	176.13±99.45	0.005
Idiopathic hepatitis	240.38±130.96	
CMV hepatitis	249.00±162.42	
Paucity of IHBD	302.76±204.61	
Metabolic group	342.19±252.90	
GGT		
EHBA	850.08±369.8	0.001
Idiopathic hepatitis	166.46±172.15	
CMV hepatitis	185.13±194.50	
Paucity of IHBD	229.28±180.12	
Metabolic group	133.38±97.51	
AL Ph		
EHBA(a)	950.15±220.68	0.001
Idiopathic hepatitis	282.24±122.73	
CMV hepatitis	334.67±156.23	
Paucity of IHBD	432.69±204.59	
Metabolic group	331.06±126.94	
Major groups		
Total bilirubin		
EHBA	9.70±2.70	0.001
Idiopathic hepatitis	9.19±5.45	
CMV hepatitis	8.73±4.51	
Paucity of IHBD	10.62±5.35	
Metabolic group	6.30±4.85	
TP		
EHBA(a)	6.54±57	0.147
Idiopathic hepatitis	6.40.±1.16	
CMV hepatitis	6.20±0.91	
Paucity of IHBD	6.77±0.67	
Metabolic group	6.22±1.19	
ALB		
EHBA	3.23±0.31	0.743
Idiopathic hepatitis	3.28±0.53	
CMV hepatitis	3.39±0.44	
Paucity of IHBD	3.32±0.52	
Metabolic group	3.35±0.55	
PTT		
EHBA(a)	35.55±6.97	0.039
Idiopathic hepatitis	38.96±9.28	
CMV hepatitis	43.19±10.35	
Paucity of IHBD	38.82±10.50	
Metabolic group	40.84±12.11	

IHBD, intrahepatic bile duct; PTT, partial thromboplastin time; TP, total protein.

Besides age at hepatoportoenterostomy, several other risk factors for failure of Kasai surgery have been described and include histologic features (small or absent bile ducts at the portal plate) and recurrent episodes of cholangitis. It is reported that children with biliary atresia referred for surgery before 60 days of age do markedly better with the reestablishment of bile flow in more than 80% than those older than 90 days at the time of operation [10–12]. This had been shown both in the short-term and in the long-term course [13,14]. The earlier the surgery was performed, the later the liver transplantation was usually needed. In the short term, infants who earlier received a Kasai procedure less frequently developed intrapulmonary vascular dilatations, a condition preceding the development of an hepatopulmonary syndrome (HPS) [14]. In the long term, every second infant with biliary atresia who underwent surgery less than 30 days of age was still living with his/her own liver ten years later compared with 15% of those treated after 90 days of age [13]. In our cohort, infants with biliary atresia were initially presented to a secondary health care provider with a mean age of 37 days; the mean age at diagnosis was 62 days. This is in line with the average age at diagnosis of biliary atresia, for example, in the USA [15] and Germany[16] (~60 days). The Kasai procedure was performed soon after diagnosis at a mean age of 66 days, demonstrating that the late diagnosis of biliary atresia caused the delay in appropriate treatment. The majority of the children in this cohort (~70%) underwent surgery before 10 weeks of age, and only 27% before 60 days. Hence, corrective surgery within the first 2 months of age is still by far not the routine although substantial efforts have been undertaken to overcome this problem [15,16].

Conclusions and recommendations

Conclusions

From the results of the present study, we can conclude the following:

(1) The developed model is considered 'excellent' in excluding EHBA in infants with cholestasis (area under the curve = 0.997).
(2) The use of a combination of ultrasonography and biochemical markers in the suggested model can predict EHBA by 87% and exclude EHBA by 100% (negative predictive value 100%) using the cut-off value of the developed model.
(3) The patient whose calculated probability is less than 0.128 is predicted to be non-EHBA at 100% precision (can exclude EHBA by 100%).
(4) GGT, Al Ph levels, and clay-colored stool are considered 'excellent' in excluding EHBA in infants with cholestasis.
(5) GGT level less than 500 can exclude EHBA by 100%, whereas level more than 500 can predict EHBA by 85.1%.
(6) Al Ph level less than 600 can exclude EHBA by 100%, whereas level more than 600 can predict EHBA by 78.4% only.
(7) Visualization of GB by ultrasound is considered 'good' in excluding EHBA in infants with cholestasis.
(8) AST, ALT, and PTT levels; hepatomegaly (s&s); and increased liver size by ultrasound have the least diagnosis performance in our study in differentiating EHBA from non-EHBA.

Recommendations

(1) Use of the developed model in clinical practice for early detection of EHBA and proper diagnosis and management should be done.
(2) Use of GGT and AL Ph as first line of investigations and in follow-up is required for excluding EHBA.
(3) Urgent referral of patients to undergo a liver biopsy if calculated probability of the developed model is more than 0.128, GGT level is more than 500, or Al Ph level is more than 600 before irreversible changes occur.
(4) A good filling system is required for the improvement of data in DMNI for future researches.
(5) Validation of the developed model in the future, and more extensive studies are required.
(6) Campaigns to increase awareness among parents and primary care physicians should be initiated.

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Conflicts of interest

There are no conflicts of interest.

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