Evaluation of Infants with Neonatal Cholestasis: Experience of a Tertiary Referral Center in Turkey

Neonatal Kolestazlı İnfantların Değerlendirilmesi: Türkiye'den Bir Üçüncü Basamak Referans Merkezinin Deneyimi

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ABSTRACT Objective: Neonatal cholestasis can be the initial evidence of a heterogeneous group of diseases of different etiologies. The aim of the study is to evaluate the patients with neonatal cholestasis and analyse the etiologic factors, diagnostic tools and outcome. **Material and Methods:** Seventy-five patients (65% males, 45% females) between 0-6 months of age with neonatal cholestasis were retrospectively evaluated; analysed for the clinical, laboratory, radiological, scintigraphic data and histopathological findings from liver biopsies. **Results:** Eighty per cent of the infants' admitted to our hospital because of prolonged jaundice. The onset of the jaundice was in the first week of life in 64% of the cases, but admission time of the referral center was median two months. Biliary atresia (BA) was determined in 21 (28%), neonatal hepatitis (NH) in 54 (72%) of the patients. Biliary atresia group had significantly more frequent acholic stool, relatively lower aspartate aminotransferase, but higher gamma-glutamyl transpeptidase, and serum protein levels. Liver biopsy and hepatobiliary scintigraphy were the most sensitive methods for differentiation BA from NH ($p<0.05$). During the follow-up period, 13 of the patients (18%) died, whereas cholestasis improved in 14 of the patients with NH (27%) within median 6 months. Survival rate at one year was 45.5% for the patients with BA, and 87% for the patients with NH. So patients with NH had better prognosis ($p<0.05$). **Conclusion:** It has been evident that early diagnosis and intervention of treatable causes of neonatal cholestasis have a vital importance.

Key Words: Jaundice, neonatal; cholestasis; biliary atresia

ÖZET Amaç: Neonatal kolestaz farklı nedenlerle oluşan heterojen bir grup hastalığın ilk bulgusu olabilir. Bu çalışmanın amacı neonatal kolestazlı hastaların değerlendirilmesi ve etyolojik faktörler, tanı yöntemleri ve sonuçlarının incelenmesidir. **Gereç ve Yöntemler:** Neonatal kolestazı olan, yaşları 0-6 ay arasında değişen 75 hasta (%65'i erkek, %45'i kız) geriye dönük olarak değerlendirildi; klinik, laboratuvar, radyolojik, sintigrafik verileri ve karaciğer biyopsilerindeki histopatolojik bulguları incelendi. **Bulgular:** Bebeklerin %80'i uzamış sarılık nedeniyle hastanemize başvurmuştu. Olguların %64'ünde sarılık yaşamın ilk haftasında başlamasına rağmen ortanca başvuru zamanı iki aydı. Hastaların 21'inde (%28) bilier atrezi (BA), 54'ünde (%72) neonatal hepatit (NH) saptandı. Bilier atrezi grubunda akolik dışkı daha sık, aspartat aminotransferaz görece düşük, ancak gama-glutamil transpeptidaz ve serum protein düzeyleri yüksek saptandı. Karaciğer biyopsisi ve hepatobilier sintigrafi BA'nın NH'den ayrımında en duyarlı yöntemlerdi ($p<0,05$). İzlem sırasında 13 hasta (%18) kaybedildi, ancak NH'li 14 hastada (%27) kolestaz ortanca 6 ay içinde düzeldi. Bilier atrezili hastaların bir yıllık yaşam oranı %45,5 iken, NH tanılı hastaların %87 idi. Neonatal hepatitli hastaların prognozları daha iyiydi ($p<0,05$). **Sonuç:** Erken tanı ile neonatal kolestazın tedavi edilebilir nedenlerine müdahale edilmesinin yaşamsal önemi olduğu açıktır.

Anahtar Kelimeler: Sarılık,yenidoğan; kolestaz; biliyer atrezi

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Cholestasis is a term described for conditions associated with retention of substances normally excreted in bile; characterized by acholic stool, dark urine and direct hyperbilirubinemia.[1-3] Neonatal cholestasis has been reported to occur 1 in 2500-5000 infants, in consequence of obstruction of the bile flow through the intrahepatic or extrahepatic biliary tract or impaired bile formation by the hepatocyte (e.g. infectious, toxic, genetic or metabolic diseases).[1,4] The two most common causes are extrahepatic biliary atresia (BA) and neonatal hepatitis (NH), accounting for 50% to 70% of cases.[5,6] Early diagnosis is necessary for medical treatment of metabolic and infectious liver diseases and surgical management of BA.[1] In this study, we aimed to analyse the clinical, laboratory data, imaging methods and outcome of the patients with neonatal cholestasis.

MATERIAL AND METHODS

PATIENTS AND CLINICAL DATA

Seventy-five subjects with neonatal cholestasis who admitted to our Pediatric Gastroenterology department in two years period were retrospectively evaluated for the clinical, laboratory, radiological, scintigraphic, histopathological data, follow-up course and outcome. The study was approved by the local ethics committee.

All infants were younger than 6 months of age and had direct bilirubin exceeding 2 mg/dL or 20% of the total bilirubin. The patients' birth weight, gestational history, intrapartum events, postnatal course, beginning time of the jaundice, nutrition and infection status, urine and stool features were recorded. After obtaining detailed history physical examination was done. Eyes were examined by an ophthalmologist. The laboratory studies such as urine analyses, liver and thyroid function tests were evaluated. Results of the metabolic screening, serologies of toxoplasmosis, rubella, cytomegalovirus (CMV), herpes virus, syphilis, serum alpha 1-antitrypsin levels, sweat chloride test, radiological studies (ultrasonography, hepatobiliary scintigraphy, echocardiography), and liver biopsies were also evaluated.

Hepatobiliary scintigraphy was performed in 59 of the subjects (79%) using technetium-labeled iminodiacetic acid analogues, after receiving phenobarbital at a dose of 5 mg/kg/day, two divided doses, orally for five days. During scintigraphy, when radioactive tracer passed through the small bowel within 24 hours, BA was ruled out. Percutaneous liver biopsy was performed to 39 (52%) of the subjects using the Menghini technique. Biliary atresia was suggested when biopsy showed bile ductular proliferation, portal tract fibrosis and bile plugs on portal triads. Bile duct paucity is defined histologically in a full-term or older infant as a ratio of bile duct to portal tract that is less than 0.5 in a minimum of ten portal tracts. Hepatocellular and canalicular cholestasis with variable degrees of giant cell transformation are suggestive for progressive familial intrahepatic cholestasis (PFIC). Parenteral nutrition-associated cholestasis is a clinical diagnosis based on the use of total parenteral nutrition (TPN) for two weeks or longer before onset of cholestasis in the absence of any other identifiable cause, and gradually improvement after discontinuation of TPN.[1] The diagnosis of NH including intrauterine infection, genetic syndromes, endocrine disorders and inborn errors of metabolism was based on clinical and laboratory data and nonspecific hepatic inflammation on liver biopsy. Idiopathic neonatal cholestasis was described when cholestasis occurred in the first three months of life, and no identifiable causes could be determined.

STATISTICAL ANALYSIS

The numeric data were expressed as mean (SD) or median (min-max) in respect to the variables which were normally distributed or not. Student's *t-test* and x^2 test were used for the comparison of descriptive measures and categorical variables. Survival rates were calculated using the Kaplan-Meier method. Analyses were performed using the SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL). When p value was ≤ 0.05 considered statistically significant.

RESULTS

Forty-nine (65%) of the subjects were male, 26 (35%) were female, and median age at the time of initial referral was 2 months (range, 0-6 months). Referral complaints were jaundice in 47 (63%), jaundice and pale stool in 9 (12%), jaundice and abdominal distension in 4 (5%), bleeding in 2 (3%) of the patients. Eleven of the patients (15%) admitted to the hospital for other complaints, so cholestasis was detected incidentally. The onset of jaundice was within the first week of life in 37 of the infants (49%). However 4 infants with BA (19%), and 3 with NH (6%) had no jaundice until two months of age. There was no significant difference between patients with NH or BA for gender, age, beginning time of the jaundice, referral time and complaint.

Twenty-six of the 32 patients (81%) with familial consanguinity had NH, and 6 (19%) had BA. Neonatal hepatitis was determined in 15 (83%) of the 18 infants with low birth weight. Twelve of the 13 premature infants (92%) had NH. There was no significant difference found between two groups for consanguineous marriage, low birth weight, prematurity or family history of cholestatic disease.

On physical examination; hepatomegaly was detected in 60 (80%), hepatosplenomegaly in 30 (40%), congenital heart disease in 10 (13%) (ventricular septal defect in 3, patent foramen ovale in 3 and patent ductus arteriosus in 4), skeletal abnormalities in 3 (4%) of the 75 infants. One subject had cataract (with galactosemia), one had coloboma (with tyrosinemia), and one had microphtalmia (with BA) on ophthalmologic examination. In patients with NH, 35% of the patients weight, and 25% of the patients height were below 3rd percentile. In patients with BA, 33% of the patients weight, and 14% of the patients height were below 3rd percentile. There was no significant difference between patients with NH or BA for weight or height percentiles. Seven of the 21 infants (33%) with acholic stool had NH. Otherwise, 7 of the subjects (33%) who had intermittent coloured stool diagnosed as BA according to hepatobiliary scintigraphy or liver biopsy. There was a statistically significant difference of acholic stool for distinction BA from NH with 62% sensitivity and 85% specificity ($p<0.05$).

All of the patients had increased liver function tests on laboratory evaluation. BA group had significantly lower aspartate aminotransferase (AST), but higher gamma-glutamyl transpeptidase (GGT), serum protein levels ($p<0.05$). Elevated GGT levels were determined in 19 of the subjects with NH (36%) and 18 with BA (82%). The sensitivity and specificity of the serum GGT level for distinction BA from NH were 76% for the cut-off level of 336 U/L. Clinical characteristics and laboratory data of the patients with neonatal cholestasis are presented in Table 1.

On abdominal ultrasonography, 3 of the 5 patients (60%) whose gallbladder could not be visualized had BA. Doppler ultrasonography revealed that one subject had portal vein thrombosis and he was treated with low molecular weight heparin. Seven of the 31 patients (23%) with normal ultrasonographic findings were diagnosed as BA. There was no significant difference between the two groups for abdominal ultrasonography.

Hepatobiliary scintigraphy failed to show biliary excretion into the gastrointestinal tract in 21 infants, and 18 (86%) of them were diagnosed as BA. In other three patients who showed no biliary excretion, two of them had ductal paucity, and one had neonatal hemochromatosis. There was a statistically significant difference of scintigraphy for dis-

TABLE 1: Clinical characteristics and laboratory data of the patients with neonatal cholestasis.

	NH (n=54)	BA (n=21)	p
Hepatomegaly (n [%])	41 (76)	19 (90)	>0.05
Splenomegaly (n [%])	21 (39)	7 (33)	>0.05
Acholic stool (n [%])	7 (13)	14 (66)	<0.05
AST (U/L)*	284±35	194±23	<0.05
ALT (U/L)*	172±26	116±17	>0.05
GGT (U/L)*	273±47	829±140	<0.05
Conjugated bilirubin (mg/dL)*	4.7±0.4	5.8±0.4	>0.05
Serum protein (mg/dL)*	5.05±0.1	5.5±0.1	<0.05

*Values as mean±SD.

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BA: Biliary atresia; GGT: Gamma-glutamyl transpeptidase; NH: Neonatal hepatitis.

tinction BA from NH with 100% sensitivity and 63% specificity ($p<0.05$).

Percutaneous liver biopsy revealed BA in 14 infants, NH in 13, cirrhosis in 4, PFIC in 5, bile duct paucity in one, hemochromatosis in one, tyrosinemia in one. There was a significant difference in liver biopsy for distinction BA from NH ($p<0.05$).

The infectious cause for NH was identified in 5 of the 75 infants, 4 of them had CMV infection and one had septicemia, died in despite of appropriate antibiotherapy. Two infants with CMV infection were treated with gancyclovir, then direct bilirubin and liver enzymes returned to normal levels. Metabolic or genetic causes were identified in 8 of the 75 infants, 2 of them with galactosemia had favourable outcome with lactose free diet. One of the patients with neonatal hemochromatosis and one with tyrosinemia who died from hepatic failure. One patient with Pompe disease, one with neonatal hemochromatosis and one with hemophagocytic lymphohistiocytosis left follow-up. Cholestasis was resolved by hormone replacement in one infant with hypothyroidism. Sweat chloride test and serum alpha-1 antitrypsin levels were normal in all detected infants. Parenteral nutrition-associated cholestasis was defined in two preterm infants and it resolved after termination of TPN. Eight patients with PFIC had chronic unremitting conjugated hyperbilirubinemia and recurrent acholic stool. After other metabolic and anatomic causes were excluded, liver biopsy showed hepatocellular and canalicular cholestasis. One patient with Jeune Syndrome (asphyxiating thoracic dystrophy) had typical radiographic findings including a bell-shaped thorax with short, horizontally oriented ribs, irregular costochondral junctions, and polydactyly. The etiology of the cholestasis could not be determined in 29 of the infants (Table 2).

TABLE 2: Etiology of the neonatal cholestasis.

Diagnosis Risk Factors	Frequency (n)	(%)
Biliary atresia	21	28
Neonatal hepatitis	54	72
Progressive familial intrahepatic cholestasis	8	10
Cytomegalovirus infection	4	5
Parenteral nutrition related cholestasis	2	2.7
Galactosemia	2	2.7
Neonatal hemochromatosis	2	2.7
Familial hemophagocytic lymphohistiocytosis	1	1.4
Congenital hypothyroidism	1	1.4
Jeune syndrome	1	1.4
Septicemia	1	1.4
Portal vein thrombosis	1	1.4
Tyrosinemia	1	1.4
Pompe disease	1	1.4
Idiopatic	29	39
Total	75	100

As a result, 21 (28%) of the patients were diagnosed as BA, 54 (72%) were diagnosed as NH. All infants with chronic cholestasis received ursodeoxycholic acid (15-20 mg/kg/d divided into three doses orally) and supportive nutritional management including fat-soluble vitamins, and a diet that is rich of medium chain fatty acids until resolution of cholestasis. Median follow-up time was 4 months (range, 1-40). Hepatoportoenterostomy was performed to 12 (57%) of the patients with BA, whereas 2 of the patients' parents refused surgery. Overall three patients (one of them after Kasai portoenterostomy, and two with cirrhosis and end-stage liver disease) underwent liver transplantation. During follow-up period 46 of the patients (64%) survived, whereas cholestasis improved within median 6 months (range, 2-17) in 14 patients with NH (27%). Four of them after hepatoportoenterostomy, in total 7 of the patients with BA died. Two of the patients with PFIC, one with tyrosinemia, one with neonatal hemochromatosis, and other two with idiopathic NH died from sepsis and end stage liver failure. Patients outcome in NH group were significantly better from BA group ($p<0.05$). Survival rate at one year was 45.5% for the patients with BA, and 87% for the patients with NH. There was a significant difference in survival between two groups which are shown on Figure 1 ($p<0.05$).

DISCUSSION

Defining the cause of the neonatal cholestasis is difficult, because of the several possible diagnoses with similar clinical presentations or laboratory tests. Early intervention with surgical management

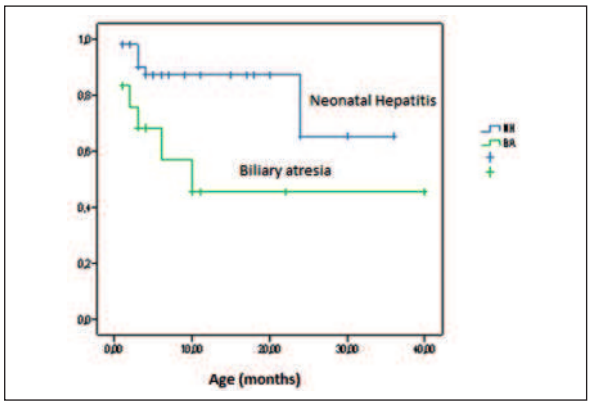

FIGURE 1: Survival of the patients with neonatal hepatitis and biliary atresia.

of BA or medical treatment of other metabolic or infectious diseases is essential for long term survival.[1] In developing countries, delay in presentation and diagnosis are the most important factors that result in poor prognosis in infants with cholestasis.[6] This study was conducted in a tertiary pediatric referral center in Turkey; we assessed onset of jaundice in the first week of life in the majority of cases (64%), but admission to a referral center at median two months like the previous studies have been reported.[6,7] Delayed presentation is likely to be associated with increasing hepatocellular damage and greater difficulty in differentiating BA from NH.[8] It was reported that onset of jaundice before two weeks of life refers to BA with 92% sensitivity, and 37% specificity.[9]

Previous reports showed that infants with NH were frequently male, low birth weighted, or premature, but they were not statistically significant in this study.[10] Although considerable proportion of the cases' parents had consanguineous marriage, the rate of diagnosis of inborn errors of metabolism was only 10%. This may be explained by the high rate of diagnosis of idiopathic NH (39%), and current causes of cholestasis could not have been identified.

Persistent acholic stool is an important feature of BA. In this study, 67% of the infants with BA, and 13% with NH had acholic stool. We found a significant difference of acholic stool for distinction between BA and NH with 62% sensitivity, and 85% specificity. Çayır et al. also reported that acholic stool had 67% sensitivity, and 71% specificity for distinction between BA and NH.[9] During the initial phase of BA stool may contain some bile pigment but in severe cholestasis, by virtue of defective bile acid excretion from hepatocytes, acholic stool may occur in infants with NH. Persistent coloured stool rules out BA, but intermittently acholic stool can be seen in both conditions.[1,11] In Taiwan, a universal screening system using an infant stool colour card was established to promote the early diagnosis for BA, and this enhanced early referral, timely performance of Kasai operation and better outcome.[12]

The initial assessment should confirm rapidly that cholestasis is present, provide a baseline assessment of severity of liver dysfunction, and exclude potentially treatable infectious and metabolic disorders. Because the lack of specific clinical features and overlap of many diagnostic studies, most cholestatic infants require a stepwise, comprehensive evaluation.[1] Liver biochemical tests show nonspecific and variable elevation in neonatal cholestasis; but both our study, and studies reported by Mieli-Vergani et al, and Dehghani et al. revealed that relatively lower AST and higher GGT levels were seen in infants with BA.[8,13] We also detected in infants with BA, serum protein levels were high from infants with NH, which might be explained by infants with NH had more metabolic or infectious diseases that caused malnutrition. In patients with NH, 35% of the patients weight, and 25% of the patients height were below 3rd percentile. In patients with BA, 33% of the patients weight, and 14% of the patients height were below 3rd percentile. But we did not find any significant difference between the two groups for weight or height percentiles.

Abdominal ultrasonography can demonstrate cystic or obstructive dilatation of the biliary tree in neonatal cholestasis. Sensitivity of small or absent gallbladder varies from 73% to 100% for distinction between BA and NH in several studies.[1] However in our study 23% of the patients with normal ultrasonographic findings were diagnosed as BA. This study and Doğancı et al. showed no statistically significant difference of ultrasonography for distinction BA from NH.[14]

Hepatobiliary scintigraphy also makes a remarkable contribution to differential diagnosis especially in differing abnormal excretion and liver uptake patterns. Phenobarbital is used for five days before scintigraphy to enhance excretion of the tracer which is a potent inducer of hepatic enzymes and increases bilirubin conjugation.[15] Infants with NH, who have long term cholestasis, uptake of the tracer to the liver can decrease, even 25% of the cases show no biliary excretion.[16] In our study, 5 of the 54 patients with NH, hepatobiliary scintigraphy failed to show biliary excretion into the gastrointestinal tract. Eventually this study and previous studies showed that scintigraphy is sensitive for detecting BA but not so specific in distinction from NH.[9,10,15,17]

Liver biopsy remains the gold standard for differentiating causes of neonatal cholestasis with high sensitivity and specificity.[9,14,18] In the present study, concordant with the literature, 21 (28%) of the 75 patients had BA, 54 (72%) had NH with 29 (39%) of them were idiopathic. Previous studies showed that infants with NH had variable prognosis, but in 60% to 70% of cases liver functions might return to normal ranges with optimal nutritional support.[19] In the presence of cholestasis, caloric intake should be approximately 125% of the recommended dietary allowance based on ideal body weight, and fat soluble vitamin supplementation should be initiated. Infant formulas containing medium chain triglycerides will provide better energy balance, because they are relatively water-soluble, and can be directly absorbed in the portal circulation.[20] Ursodeoxycholic acid is a choleretic, nontoxic bile acid, which has been used for cholestatic liver disease in children safely. The various mechanisms of action of this bile acid include direct cytoprotection and immunomodulation.[15] In this study, liver function tests of one fourth of the infants with NH who were treated medically, improved within median 6 months.

Bile flow of infants with BA who undergoes Kasai portoenterostomy within the first 2 months improves in 70% to 80% of cases, otherwise when it is performed after 3 months bile flow improves one fourth of the cases. Admission time is the key to success in Kasai operation.[21] In this study Kasai operation was performed to 12 of the patients with BA but four of them died. Postoperative clearance of jaundice is a strong indicator for the success of the Kasai operation thus the need for liver transplantation. BA is the leading cause of end-stage liver disease and the most common indication of liver transplantation in the childhood.[11,22,23] In a study from Turkey which evaluated 27 patients with BA, delay of the diagnosis resulted in death about half of the cases in the postoperative period, and 30% of the cases underwent liver transplantation.[24] However the Netherlands Study Group on Biliary Atresia reported performance of surgery before two months of age and clearance of jaundice associated independently with 4 year transplant-free survival.[25] In developed countries short term clearance of jaundice can be achieved with Kasai portoenterostomy in approximately 50% to 60% of the children, and one third of the patients can survive with native liver up to the age of 10 years.[26] This result should draw the attention of health care providers to the need for urgent evaluation of infants with prolonged jaundice in our country.

In conclusion, infants jaundiced at 2-4 weeks of age should be evaluated promptly with clinical, laboratory and imaging techniques. It has been evident that early diagnosis and intervention of treatable causes of neonatal cholestasis have a vital importance.

REFERENCES

1. Suchy FJ. Approach to the infant with cholestasis. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. Liver Disease in Children. 3rded. New York: Cambridge University Press; 2007. p179-89.
2. Dinler G, Koçak N, Yüce A, Gürakan F, Ozen H. Ursodeoxycholic acid therapy in children with cholestatic liver disease. Turk J Pediatr 1999;41(1):91-8.
3. Götze T, Blessing H, Grillhösl C, Gerner P, Hoerning A. Neonatal cholestasis-differential diagnoses, current diagnostic procedures, and treatment. Front Pediatr 2015;3:43.
4. Ukarapol N, Wongsawasdi L, Ong-Chai S, Riddhiputra P, Kongtawelert P. Hyaluronic acid: additional biochemical marker in the diagnosis of biliary atresia. Pediatr Int 2007; 49(5):608-11.
5. Sokol RJ, Mack C, Narkewicz MR, Karrer FM. Pathogenesis and outcome of biliary atresia: current concepts. J Pediatr Gastroenterol Nutr 2003;37(1):4-21.
6. Lee WS. Pre-admission consultation and late referral in infants with neonatal cholestasis. J Pediatr Child Health 2008;44(1-2):57-61.
7. Öztürk Y, Çabuk N, Büyükgebiz B. [Approach to neonatal cholestasis]. Turkiye Klinikleri J Med Sci 2000;20(3):178-86.
8. Mieli-Vergani G, Howard ER, Portman B, Mowat AP. Late referral for biliary atresia-missed opportunities for effective surgery. Lancet 1989;1(8635):421-3.
9. Çayır H, Altuntaş B, Ertan Ü. [Differential diagnosis of extrahepatic biliary disease from hepatocellular disease in neonatal cholestasis; prospective analysis of 37 patients]. Turkiye Klinikleri J Pediatr 1998;7(4):175-81.
10. Kuloğlu Z, Ödek Ç, Kırsaçlıoğlu CT, Kansu A, Erden E, Girgin N. [Analysis of 50 patients with neonatal cholestasis]. Çocuk Sağlığı ve Hastalıkları Dergisi 2008;51:140-6.
11. Talachian E, Bidari A, Mehrazma M, Nickkhah N. Biopsy-driven diagnosis in infants with cholestatic jaundice in Iran. World J Gastroenterol 2014;20(4):1048-53.
12. Hsiao CH, Chang MH, Chen HL, Lee HC, Wu TC, Lin CC, et al. Universal screening for biliary atresia using an infant stool color card in Taiwan. Hepatology 2008;47(4):1233-40.
13. Dehghani SM, Haghighat M, Imanieh MH, Geramizadeh B. Comparison of different diagnostic methods in infants with cholestasis. World J Gastroenterol 2006;12(36): 5893-6.
14. Boskovic A, Kitic I, Prokic D, Stankovic I, Grujic B. Predictive value of hepatic ultrasound, liver biopsy, and duodenal tube test in the diagnosis of extrahepatic biliary atresia in Serbian infants. Turk J Gastroenterol 2014;25(2): 170-4.
15. Poddar U, Bhattacharya A, Thapa BR, Mittal BR, Singh K. Ursodeoxycholic acid-augmented hepatobiliary scintigrapy in the evaluation of neonatal jaundice. J Nucl Med 2004;45(9):1488-92.
16. Gilmour SM, Hershkop M, Reifen R, Gilday D, Roberts EA. Outcome of hepatobiliary scanning in neonatal hepatitis syndrome. J Nucl Med 1997;38(8):1279-82.
17. Kwatra N, Shalaby-Rana E, Narayanan S, Mohan P, Ghelani S, Majd M. Phenobarbital-enhanced hepatobiliary scintigraphy in the diagnosis of biliary atresia: two decades of experience at a tertiary center. Pediatr Radiol 2013;43(10):1365-75.
18. Dehghani SM, Efazati N, Shahramian I, Haghighat M, Imanieh MH. Evaluation of cholestasis in Iranian infants less than three months of age. Gastroenterol Hepatol Bed Bench 2015;8(1):42-8.
19. A-Kader HH, Balistreri WF. Cholestasis. In: Behrman RE, Kliegman RM, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. 18thed. Philadelphia: Saunders; 2007. p.1668-75.
20. De Bruyne R, Van Biervliet S, Vande Velde S, Van Winckel M. Clinical practice: neonatal cholestasis. Eur J Pediatr 2011;170(3) 279-84.
21. Davenport M, Caponcelli E, Livesey E, Hadzic N, Howard E. Surgical outcome in biliary atresia: etiology affects the influence of age at surgery. Ann Surg 2008;247(4):694-8.
22. de Carvalho E, Ivantes CA, Bezerra JA. Extrahepatic biliary atresia: current concepts and future directions. J Pediatr (Rio J) 2007;83(2): 105-20.
23. Kelly DA, Davenport M. Current management of biliary atresia. Arch Dis Child 2007;92(12): 1132-5.
24. Aydoğdu S, Özgenç F, Atik T, Unal F, Tokat Y, Yagci RV. Biliary atresia in Turkish children. Pediatr Int 2004;46(2):158-61.
25. de Vries W, de Langen ZJ, Groen H, Scheenstra R, Peeters PM, Hulscher JB, et al; Netherlands Study Group of Biliary Atresia and Registry (NeSBAR). Biliary atresia in the Netherlands: outcome of patients diagnosed between 1987 and 2008. J Pediatr 2012; 160(4):638-44.e2.
26. Howard ER, Davenport M. The treatment of biliary atresia in Europe 1969-1995. Tohoku J Exp Med 1997;181(1):75-83.