Original Article

Knowledge and Practice of Pediatric Providers Regarding Neonatal Cholestasis in the Western Region of Saudi Arabia

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Abstract

Background: Early detection of neonatal cholestasis (NC) is important for better clinical outcomes but can be challenging.

Objective: The objective of this study was to evaluate the knowledge and practice styles of pediatric providers (PPs) regarding NC in the western region of Saudi Arabia.

Methods: This cross-sectional, questionnaire study was conducted between November 2019 and February 2020 in three major cities of the western region of Saudi Arabia (namely, Taif, Makkah and Jeddah). PPs included pediatric residents, pediatric specialists, pediatric consultants and family physicians. The questionnaire included 15 items in five subscales (definition, causes, diagnosis and management of NC and knowledge of guidelines).

Results: A total of 488 participants completed the questionnaire. Only 30.2% were aware of the correct definition of NC ($P < 0.001$). Two-thirds of the respondents did not consider a history of pale stool being important for evaluating NC. The importance of biliary atresia as a serious cause of NC was found to be significantly different between pediatric consultants and other pediatricians ($P < 0.001$). In cases of prolonged NC, 32.4% of the PPs refer to pediatric gastroenterologist. Only 18.9% of the respondents were aware of liver biopsy being the gold standard investigation of NC. The majority of the respondents (41.8%) used ursodeoxycholic acid as a supportive therapy of NC.

Conclusions: This study found a significant deficit in the knowledge and practice styles of PPs in the western region of Saudi Arabia. These findings highlight the need for policymakers to develop educational materials for PPs to increase their knowledge of NC.

Keywords: Biliary atresia, knowledge and practice, neonatal cholestasis, pediatricians, prolonged jaundice, Saudi Arabia

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INTRODUCTION

Neonatal jaundice is common in the first 3 days after birth, but prolonged jaundice, described as a 14-day jaundice, needs diligent evaluation to differentiate between unconjugated hyperbilirubinemia, which is typically mild, and the pathologically related hyperbilirubinemia.[1,2] According to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the

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European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines, cholestasis is defined as reduction in the bile formation or its flow that results in retention of biliary substances within the liver normally excreted into bile and destined for elimination into the intestinal lumen. A diagnosis of cholestasis can be made with serum evaluations, wherein elevation of serum conjugated (or direct) bilirubin and bile acids are clear indications of hepatobiliary dysfunction.[3,4]

Identifying and managing neonatal cholestasis (NC) can be challenging, as the patient may initially appear well and gain weight despite cholestasis.[5] To compound this issue, skill deficits have been noted in pediatric providers' (PPs) diagnosis of cholestasis.[6] However, early detection of NC is important, as it may impact the clinical outcome. According to Benchimol *et al.*,[7] a standardized NC screening could help in the early detection, and thus direct bilirubin rates should be tested in any individual appearing jaundiced and that pediatric hepatologist should automatically be consulted if cholestasis is detected.

Saudi Arabia has a population of about 34 million, of which about 8% are aged 0–4 years,[8] indicating a high birth rate. Therefore, it is important that PPs in Saudi Arabia are familiar with the evaluation of NC for the early diagnosis and timely management. However, no study from Saudi Arabia or the Middle East has assessed the knowledge and practice patterns of PPs toward NC. To fill this gap, this study was conducted with the primary objective of evaluating the knowledge and practice of PPs from Saudi Arabia regarding NC.

METHODS

Study design and participants

This cross-sectional, questionnaire study was conducted between November 2019 and February 2020 in three major cities of the western region of Saudi Arabia (namely, Taif, Makkah and Jeddah) and targeted all PPs registered with Saudi Commission for Health Specialties, Saudi Pediatric Association and the Ministry of Health. The research was approved by the Ethics Committee of King Abdullah International Medical Research Center, Jeddah, Saudi Arabia.

The study defines PPs as physicians or pediatricians involved in teaching pediatric medicine or its research or being involved in their clinical care. PPs includes pediatric interns, pediatric residents, pediatric specialists (registrars), pediatric consultants or family physicians; the current study only considered those involved in neonatal care (i.e., aged <28 days). Based on this, 2478 PPs were found to be eligible. A minimum sample size of 333 was calculated through the Raosoft sample size calculator website. However, to attain a more statistically significant representation of the study population, the author chose a random sample of 650 participants after stratifying for gender and profession.

Data collection tool and procedure

The questionnaire was developed using the cholestatic jaundice guidelines published by ESPGHAN/NASPGHAN and the American Academy of Pediatrics (AAP).[3,4] Its accuracy and functionality were checked by two pediatric gastroenterologists with 5 years of experience, and it was also updated based on the responses of a pilot test conducted on a group of 10 pediatric gastroenterologists (Cronbach's alpha = 0.8). The estimated time for completing the questionnaire was 10 min.

The questionnaire included 15 items in five subscales: Practice and demographics characteristics (four items); causes and definition of cholestasis (five items); cholestasis diagnosis and management (four items); knowledge level regarding the recently published guideline on cholestatic jaundice by ESPGHAN/NASPGHAN (one item); and source of cholestasis-related information (one item). All items were multiple-choice questions, including some using a Likert-like scale (sometimes, most of the time, all of the time, seldom and never).

The data were collected through face-to-face interviews in the majority of cases, with most being conducted at the institutions of the PPs. These were carried out by medical interns who had volunteered for this study and undergone a briefing for the same. In case of unavailability, participants were contacted with the questionnaire through E-mail. The PPs were from Jeddah (two university hospitals, two privates hospitals and five governmental hospitals), Makkah (two private hospitals and three governmental hospitals) and Taif (one governmental hospital and one private hospital). A cover letter was attached with the questionnaire providing a short description of the study and stating that all data obtained would be strictly confidential, anonymity would be maintained, no identifying details would be collected or recorded, and that participation was voluntary. No monetary or nonmonetary benefits were provided to the respondents. Response to the survey was considered as consent for participation, and the same was stated at the end of the questionnaire.

Statistical methods

Data were manually entered in Microsoft Excel and all entries were later cross verified. Data were analyzed using the SPSS software for Windows (version 20.0; IBM

Corp., Armonk, NY, USA). The results are presented as percentages, and Person's Chi-square test was used to determine and compare the categorical variables between the groups. $P < 0.05$ was considered significant.

RESULTS

Demographics

Of the 650 PPs approached for participation in this study, 526 were for face-to-face interviews and 124 received the questionnaire through e-mail. A total of 522 responses were received, but 18 were excluded due to incomplete or missing data, and another 16 were excluded because they were pediatric gastroenterologists, and their inclusion would likely positively skew the data. Therefore, responses from 488 participants (75% response rate) are considered for all further evaluations.

The majority of the respondents were male ($n = 268$; 55%) and aged 31–40 years (49%). In terms of profession, 46% were pediatric residents, 16% were pediatric consultants and 14% were family physicians [Table 1].

Definition, causes, diagnosis and management of neonatal cholestasis

Significantly few respondents were aware of the correct definition of NC ($n = 138$, 28%; $P < 0.001$). Of these, 53%, 18% and 16% were pediatric residents, consultants and specialists, respectively; 69% were from government hospitals and 27% were from private hospitals. Similarly, significantly few participants were aware of cholestasis workup for jaundice of >2 weeks (25.4%) and a history of pale stool (28.1%) [Table 2].

In terms of diagnosis, only 18.9% reported that biliary atresia should be first ruled out, with significant differences between pediatric consultants and other PPs ($P < 0.001$). Further, only 92 respondents (18.9%) were aware of liver biopsy being the gold standard investigation for NC. In cases of prolonged cholestasis, 28.3% referred the cases to pediatric gastroenterologists, with most referrals by pediatric consultants and fewest by interns ($P < 0.001$). Pediatric consultants and pediatric residents preferred ursodeoxycholic acid as the supportive therapy more often than other PPs, but the difference was not statically significant ($P = 0.06$) [Table 3]. The second most used/preferred supportive therapy after ursodeoxycholic acid was fat-soluble vitamins.

In terms of management of prolonged NC, 32.4% of PPs evaluate the patient at a clinic every 2 months, 28.3% refer to pediatric gastroenterologist, 24.2% refer to pediatric surgeons and 15% seek hereditary cholestasis testing [Figure 1]. Regarding the guidelines' awareness and knowledge, 37% had very limited and 11% had no awareness of the NASPGHAN/ESPGHAN guidelines for the evaluation of NC [Table 4]. In terms of source of information, 51.2% of the respondents obtained information from medical journals, 37.9% from conferences, 3.6% from newsletters, 4.5% from the Internet and 2.8% from pharmaceutical company–sponsored symposia.

Table 1: Demographic characteristics of the respondents

Demographic parameter	Proportion of respondents, %
Designation (*n*)	
Pediatric intern (47)	9.6
Pediatric resident (226)	46.3
Pediatric specialist (Registrar) (69)	14.1
Pediatric consultant (76)	15.6
Family physician (70)	14.3
Age (*n*=488)	
≤30 (104)	21.3
31-40 (241)	49.4
41-50 (63)	12.9
≥50 (80)	16.4
Gender (*n*=488)	
Male (268)	54.9
Female (220)	45.1
Type of institution (*n*=486)	
University hospital (44)	9.1
Governmental hospital (285)	58.6
Private hospital (157)	32.2

DISCUSSION

According to the NASPGHAN/ESPGHAN guidelines, elevated direct/conjugated bilirubin levels >1.0 mg/dL (17 mmol/L), irrespective of the total bilirubin, warrant the evaluation for NC.[4] According to AAP, direct bilirubin >20% of total bilirubin (>5 mg/dL) is defined as conjugated hyperbilirubinemia, and this a biomarker of NC.[3] The latter reference range was used in our study and only 28.3% of PPs were found to be aware of the same. Similarly, Christakis *et al.*[9] found the AAP's clinical practice guideline was not considered very helpful by most pediatricians and practitioners, which appears to be the case in this study as well.

Surprisingly, about two-thirds of the respondents of this study were unaware of pale stool color being an important history screening for evaluating NC. Menz *et al.*[6] concluded that 28.5% of PPs were uncomfortable in determining if the stool was pale, thereby highlighting the importance of increasing awareness regarding the use of guidelines. They also demonstrated that there was a gap in knowledge regarding biliary atresia and one-third of PPs in that study were not aware at what point biliary atresia was detected. In our study, 18.9% of PPs reported that biliary atresia should

Table 2: Correlation between responders' status and definition of cholestasis

Demographic variable	Definition of NC is direct bilirubin >20% total bilirubin, *n* (%)	Work up for cholestasis is mandatory if jaundice >2 weeks, *n* (%)	Stool color (pale stool) is important history for evaluating NC, *n* (%)
Title			
Pediatric intern	7 (5.1.)	20 (16.1)	5 (3.6)
Pediatric resident	73 (52.9)	64 (51.6)	72 (52.6)
Pediatric specialist	22 (15.9)	20 (16.1)	32 (23.4)
Pediatric consultant	25 (18.1)	10 (8.1)	19 (13.9)
Family physicians	11 (8.0)	10 (8.1)	9 (6.6)
Total	138 (28.3)	124 (25.4)	137 (28.1)
P	<0.001	<0.001	<0.001
Institution type			
University hospital	5 (3.7)	20 (16.1)	3 (2.2)
Government hospital	94 (69.1)	49 (39.5)	66 (48.9)
Private hospital	37 (27.2)	55 (44.4)	66 (48.9)
P	<0.001	<0.001	<0.001

NC – Neonatal cholestasis

Table 3: Correct responses regarding selected aspects of the diagnosis and management of neonatal cholestasis

Title of pediatric providers'	Biliary atresia should be ruled out first in NC, *n* (%)	Liver biopsy is most definitive investigation of NC, *n* (%)	Ursodeoxycholic acid is a supportive therapy of cholestasis, *n* (%)	Refer to pediatric gastroenterologist if the child has prolonged cholestasis, *n* (%)
Pediatric intern	3 (3.3)	5 (5.4)	11 (5.4)	15 (10.9)
Pediatric resident	19 (20.7)	24 (26.1)	67 (32.8)	38 (27.5)
Pediatric specialist	11 (12.0)	16 (17.4)	30 (14.7)	18 (13.0)
Pediatric consultant	50 (54.3)	28 (30.4)	51 (25.0)	47 (34.1)
Family physicians	9 (9.8)	19 (20.7)	45 (22.1)	20 (14.5)
Total	92 (18.9)	92 (18.9)	204 (41.8)	138 (28.3)
P	<0.001	<0.001	0.061	<0.001

NC – Neonatal cholestasis

Table 4: Awareness of cholestatic guidelines

Parameter	All of the time (100%), *n* (%)	Most times (51%-99%), *n* (%)	Sometimes (50%), *n* (%)	Seldom/rare (1%-49%), *n* (%)	Never (0%), *n* (%)
Awareness of NASPGHAN and ESPGHAN guidelines	59 (12.2)	52 (10.7)	137 (28.3)	181 (37.4)	55 (11.4)

NASPGHAN – North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; ESPGHAN – European Society for Pediatric Gastroenterology, Hepatology and Nutrition

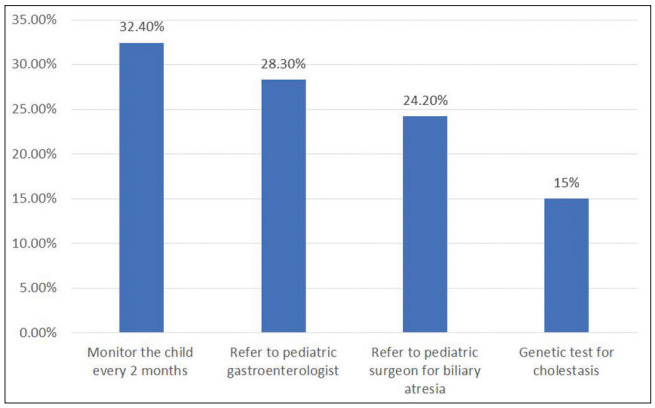

Figure 1: Responders' status and strategies for the management of prolonged neonatal cholestasis

first be ruled out in NC. Lack of awareness is problematic, as it minimizes the sense of urgency, and thus may contribute to complications in the treatment of biliary atresia. Therefore, there is a need to raise awareness regarding screening for NC in Saudi Arabia for earlier diagnosis.

The Italian Guidelines for NC Management recommends the use of biochemical tests for investigating all cases of NC.[10] However, despite advances in lesser invasive diagnostic tools, liver biopsies remain the gold standard.[11] Surprisingly, in our study, only about 19% of the respondents were aware of liver biopsy being the most definitive investigation of NC, highlighting the insufficiency in the PPs of the study. The role of liver biopsy in the diagnosis of biliary atresia and some metabolic liver diseases is critical in the assessment of NC. However, liver biopsy has complications such as abdominal pain, perforation of gall bladder, bile peritonitis, hemobilia and hemothorax.[10]

In a study from the United States, Petrova *et al.*[12] found that pediatricians initiated the phototherapy treatment at serum bilirubin levels lower that that recommended by AAP. These and our study findings highlight the general lack of understanding of NC among pediatricians. Ursodeoxycholic acid is an epimer of chenodeoxycholic acid that is used as a choleretic and it changes the

composition of bile. The mechanism of its action includes the protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion and protection of hepatocytes against bile acid-induced apoptosis.[10] In our study, only about 42% of the respondents used ursodeoxycholic acid as a supportive treatment of cholestasis, highlighting the need for educating PPs regarding the preferred supportive treatment.

The management strategy of prolonged NC varied, with the majority (32.4%) of the participants reported evaluating the patients every 2 months, followed by about 28% referring such cases to pediatric gastroenterologists. Similarly, Palermo *et al.*[13] had also found variance in the management of prolonged NC. There is a need for standardization regarding management owing to its criticality, as it could inadvertently result in delays in the diagnosis of treatable diseases such as hypothyroidism, tyrosinemia and biliary atresia. In the future, large-scale prospective studies should also assess the role of follow-up of NC in pediatric clinical practice.

Surprisingly, about 24% of the participants in the current study reported referring cases of prolonged NC to pediatric surgeons. The author believes that such patients should mainly be referred to pediatric gastroenterologists/hepatologists rather than to pediatric surgeons. Much of the management can be provided through a co-care model between the pediatricians and the pediatric gastroenterologist. Pediatric surgeons will have a very low threshold for surgical intervention, and this may not always be the right strategy. Recent procedures continue to minimize the resources for early detection and diversion without the overhaul of the treatment programs.[10]

In a study by Gartner *et al.*,[14] where 443 pediatricians and 444 neonatologists were surveyed to determine their practice patterns in neonatal hyperbilirubinemia, the opinion regarding the AAP guideline to treat neonatal jaundice widely varied. The role for genetic tests is becoming increasingly affordable and relevant in the diagnosis of genetic disorders such as progressive familial intrahepatic cholestasis, galactosemia and inborn errors of bile acid metabolism. Whole-exome sequencing or whole-genome sequencing is an effective and noninvasive diagnostic tool for NC.[15]

This study found that respondents in the studied region of Saudi Arabia have poor adherence to guidelines such as NASPGHAN and ESPGHAN guidelines, which may also be expected given that these guidelines provide recommendations to highly specialized pediatric gastroenterologists. The results of previous studies[6,9] and our study collectively show the broad differences in diagnostic and knowledge and therapeutic techniques regarding NC among PPs, indicating the need for greater education to promote evidence-based practice through curriculum modifications, improving the standards of continuing medical education programs, facilitating resources, etc., to overcome such challenges.

A key strength of this study is the large sample size and its representativeness of the studied region. However, further research is required from other regions of Saudi Arabia to provide a national representation of this topic. A limitation of this study is that there is likeliness of response bias – only PPs with interest in NC may have been more likely to have responded, and thus is it possible that knowledge of NC may be even lower than that being reported in this study. Another limitation is that the years of experience and academic credentials (such as fellowships, additional certifications, etc.,) were not collected, which may have been confounding factors in the percentage of correct responses.

CONCLUSIONS

This study found significant differences between PPs in terms of practice and knowledge regarding the definition, diagnosis and management of NC. The identification of these gaps may be helpful for policy-makers to produce targeted instructional resources on NC for PPs.

Ethical considerations

The Ethics Committee of King Abdullah International Medical Research Center, Jeddah, Saudi Arabia, provided approval for this study (Reference No. RJ20/029/J; Date: March 12, 2020). The study was conducted in line with the guidelines of the Declaration of Helsinki, 2013. Agreeing or responding to the survey was considered as consent for participation.

Peer review

This article was peer-reviewed by four independent and anonymous reviewers.

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Conflicts of interest
There are no conflicts of interest.

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