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Etiologies and In-Hospital Outcomes of Nonhemolytic Jaundice among Infants at King Abdulaziz University Hospital (KAUH)

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ABSTRACT

Background: most of articles addressed the underlying causes and management of Neonatal Nonhemolytic Jaundice, however only a few have investigated nonhemolytic jaundice among infancy which can turn fatal in severe case, however can be prevented by early diagnosis.

Aim of the Work: was to investigate the most common etiologies of nonhemolytic jaundice among infants presented to at King Abdulaziz University Hospital (KAUH) which may help pediatricians to rearrange their differential diagnosis about nonhemolytic jaundice in infants.

Material and Methods: this is a retrospective observational study of all infants aged between 1-12 months, conducted at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia from January 2016 to November 2017. Data collection was done using Microsoft Excel while data analysis was done using SPSS version 21. Chi -square test was used to test if associations would be appropriate.

Results: out of total 105 patients enrolled in this study, complete data set was available for 88 only patients during 2012. The mean age at presentation in months was 2.73 (± SD 2.21) range from 1 to 12 months. Among the sample, the final outcome was as follows ; 59 (67%) jaundice-free, 14 (15.9%) still diseased and 15 (17%) dead. Sepsis was the most common cause of jaundice with 33 cases (37.5%), followed by biliary atresia 10 cases (11.4%) and congenital hypertrophic pyloric stenosis 7 cases (8%). On the other hand, the least common causes were rare diseases like wolman syndrome, crigler-najjar syndrome and autoimmune hepatitis and each of them represents 1 case. The overall number of deaths in our study was 15 (17%). Seven of them were due to sepsis and 2 were due to biliary atresia.

Conclusion: we hope to help the local physicians in Jeddah to arrange their differential diagnosis of nonhemolytic jaundice among infants and deal with it seriously, due to the high incidence of critical illness and death.

Keywords: Nonhemolytic Jaundice, hyperbilirubinemia, Infant jaundice, KAUH.

INTRODUCTION

Jaundice is defined as a yellowish discoloration of the skin and sclerae that indicates increasing in the bilirubin concentration in the blood due to an abnormality of bilirubin metabolism or excretion. After the neonatal period, the normal serum total bilirubin concentration is below 1 mg/dL [1]. Jaundice usually becomes clinically apparent when the serum bilirubin concentration is more than 2 mg/dL which is double the maximum limit of normal [1]. In our study we will focus on nonhemolytic jaundice in infancy, since there are few studies regarding nonhemolytic jaundice in this age group.There are several etiologies of nonhemolytic jaundice, including breast milk jaundice that present early in the infant lifetime. Also infections may cause jaundice in infants such as urinary tract infection, Cytomegalovirus infection, perinatal congenital infections (TORCH), neonatal hepatitis and sepsis. Additionally, genetic syndromes or diseases associated with jaundice of infant as Crigler-Najjar syndrome, Inborn error of metabolism (galactosemia, tyrosinemia), cystic fibrosis, Biliary atresia, biliary cysts, Alpha1-Antitrypsin deficiency, Neonatal iron storage disease, alagille syndrome and byler disease.Other causes include pyloric stenosis, hypothyroidism, immune thrombocytopenia, hepatic infarction and acute liver failure [2]. According to several studies, the most common causes of nonhemolytic jaundice are Cytomegalovirus infection, sepsis, breast milk jaundice, biliary atresia, neonatal hepatitis and total parenteral nutrition. According to a study conducted in China the main causes of nonhemolytic jaundice in infants is Cytomegalovirus infection, then sepsis and finally breast milk jaundice [3]. Another study found that the incidence of neonatal sepsis ranges from one to five cases per 1000 live births. While, cholestatic jaundice affects approximately 1 in every 2,500 infants [4,5]. It is estimated that approximately 40% of cholestasis in infants is due to neonatal hepatitis [6]. Human cytomegalovirus (CMV) is the commonest etiological agent responsible for causing neonatal hepatitis [7]. Breastfeeding jaundice appears after the first three to five days, peaking within two weeks after birth, and progressively declined to normal levels over 3 to 12 weeks [8]. The incidence is about 1:200 in babies[9] and in rare cases may lead to kernicterus [10]. In April 2017 a study conducted in Korea found that the overall incidence of biliary atresia(BA) was 1.06 cases per 10,000 live births. The incidence of BA was 1.4 times higher in

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female patients. Additionally, significant seasonal variation was observed; in particular, the incidence of BA was 2 times higher from June through August than from December through February. There is significant gender-associated differences and seasonal variation with respect to the incidence of BA[11]. In an Iranian study in 2015 there were 76 infant patients with clinical finding of jaundice. The onset of jaundice was from first day to the fifty two days of life. In this study, the most common causes of cholestatic jaundice were biliary atresia (24.6%), idiopathic neonatal hepatitis (24.6%) and bile ducts paucity (intrahepatic atresia) (10.3%) [12]. Jaundice is seen in 40 to 60 percent of children who receive long-term PN [13]. The appearance and severity of the jaundice depend on the duration of total parenteral nutrition [14]. On the other hand, other studies mentioned the least common causes of nonhemolytic jaundice such as biliary cysts, idiopathic hypertrophic pyloric stenosis and Alpha-1-antitrypsin deficiency. The incidence of biliary cysts in Western populations has been estimated to be 1:100,000 to 1:150,000 [15]. The incidence is higher in some Asian countries (up to 1:1000) [16]. The majority of patients with biliary cysts were presented before the age of 10 years [17]. A total of 2534 infants were diagnosed with idiopathic hypertrophic pyloric stenosis (IHPS) during the study period, giving an overall incidence of IHPS of 2.0 per 1000 live births (LB) in seven well-defined European regions [18]. Hyperbilirubinemia in IHPS occurring in 14 percent of cases [19]. Alpha-1-antitrypsin deficiency (AATD) prevalence in Western Europe and in the USA is estimated at approximately 1 in 2,500 and 1: 5,000 newborns [20]. Wolman syndrome is a rare autosomal recessive disease, infantile-onset form of lysosomal acid lipase (LAL) deficiency and one of its clinical presentations is jaundice [21]. The exact prevalence of Wolman disease is not known at this time to the rarity but it was estimated in German cohort study as 1:350,000[22]. Another study suggested the prevalence as high as 1:4200 in the Iranian-Jewish people of the Los Angeles [23]. An Egyptian study published in 2015 showed that jaundice represented 4.93% of clinical signs diagnoses among neonates with suspected sepsis, also in another study, jaundice considered as one of the signs which caused by sepsis, but actually no study in infants was done [24]. Since there are deficient information regarding nonhemolytic jaundice in infant age grop. Hence, we focused on nonhemolytic jaundice in infancy. Moreover, we aimed to compare our findings to other researches in order to find the most common etiologies and outcomes. By doing so, we may help pediatricians to rearrange their differential diagnosis of nonhemolytic jaundice in infants. Comparing the outcomes of these causes in our setting with others' should provide prespective on the quality of health services. In this study we aim to investigate the etiologies and outcomes of nonhemolytic jaundice among infants at King Abdulaziz University Hospital (KAUH)

PATIENTS AND METHODS

This is a retrospective observational study that was conducted at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia from January 2016 to November 2017. KAUH is one of the biggest tertiary referral and teaching centers in the western region of Saudi Arabia with a capacity of 800 beds. Approval of the Institutional Review Board (IRB) of King Abdulaziz University Hospital has been taken. **Selection of participants:** The hospital electronic records of KAUH were used for data collection. ***Exclusion criteria:*** Infants aged either below 1 month or above 12 months, preterm infants, patients with hemolytic cause and incomplete data. Out of total 105 patients enrolled in this study, 17 patients were excluded due to missing data. Hence, complete data set was available for only 88 patients. **Measurement:** We formulated a data sheet based on previous studies in the literature. Variables were obtained from the hospital electronic records. The variables of the data collection sheet are demographic data such as age, gender nationality and duration of the admission, admission diagnosis hospital duration. Also, the laboratory investigations which included complete blood count (CBC), total and direct bilirubin, liver function tests and final diagnosis. ***Statistical analysis:*** The data was finally constructed in an excel sheet (Microsoft Excel 2014) then was transformed to SPSS (version 21) for analysis. Categorical variables including primary variables were described using a frequency table while continuous variables for normal distribution were described using mean, standard deviation, and range. The data, later on, was processed to find the statistical significance. For all statistical tests, p values smaller than 0.05 were considered significant.

RESULTS

A total 105 patients were enrolled in this study, 17 of which were excluded due to missing data. Thus, complete data set was available for only 88 patients during 2012. Most of the patients were males (54 versus 34 females with a ration of 61.4% and 38.6% respectively. The mean age at presentation in month was 2.73 (± SD 2.21) ranging from 1 to 12 months. Among the sample, the final outcome was as follows: 59 participants (67%) were jaundice-free, 14 infants (15.9%) were diseased, 15 (17%) dead. The baseline demographic characteristics of the study group are presented in **Table 1**. The cause of hyperbilirbubinemia was identified in 75 cases (85.2%) while 13 cases (14.8%) were unidentified as shown in **Table 2**. The results analysis revealed that sepsis (33 infants= 37.5%) was the most common cause, followed by biliary atresia (10 infants= 11.4%) and congenital hypertrophic pyloric stenosis (7 infants= 8%). On the other hand, the least common causes were rare diseases like wolman syndrome, Crigler-najjar syndrome and autoimmune hepatitis and each of them represented only 1 case. The mean length of hospital stay of each diagnosis is shown in fig. 1, according to this figure, autoimmune hepatitis and biliary atresia represented higher mean length of hospital stay. The overall number of deaths in our study was 15 (17%). Seven of them were due to sepsis and 2 of them were due to biliary atresia as shown in **Table 3** which represents the outcome of the three most common etiologies of nonhemolytic jaundice in our study.

Table 1: Baseline demographic characteristics of the study group

Variable	No. (%) of infants n = 88
Gender, male	54 (61.4%)
Age at onset, month, mean±SD	2.73 (± SD 2.21) (1-12)
Length of hospital stay: -7 days and less -8 days to 30 days - More than 30 days	 37 (42%) 42 (47.7%) 9 (10.2%)
Final outcome: -Jaundice free -Still diseased -Dead	 59 (67%) 14 (15.9%) 15 (17%)
Total bilirubin level, mean ± SD	135.2 ± 111.01

Table 2: Etiologies of nonhemolytic jaundice among infants

Cause	No. of infants (%) n = 88
Sepsis	33 (37.5)
Biliary atresia	10 (11.4)
Congenital hypertrophic pyloric stenosis	7 (8)
Hypothyroidism	5 (5.7)
Progressive familial intrahepatic cholestasis (PFIC)	4 (4.5)
Neonatal hepatitis	4 (4.5)
Metabolic liver disease	3 (3.4)
Urinary tract infection (UTI)	3 (3.4)
Allagile syndrome	2 (2.3)
Autoimmune hepatisis	1 (1.1)
Crigler-najjar syndrome	1 (1.1)
Toxic liver disease with cholestasis	1 (1.1)
Wolman syndrome	1 (1.1)
Unidentified	13 (14.8)

Table 3: Outcome of the three most common etiologies of nonhemolytic jaundice

	Sepsis (N=33)	Biliary atresia (N=10)	Congenital hypertrophic pyloric stenosis (N=7)	P value
Number of deaths (%)	7(21.2)	2(20)	0(0)	0.41
Mean length of hospital stay	15.4	18.9	8.4	0.39
Mean total bilirubin level	77.7	131.3	111.7	0.02

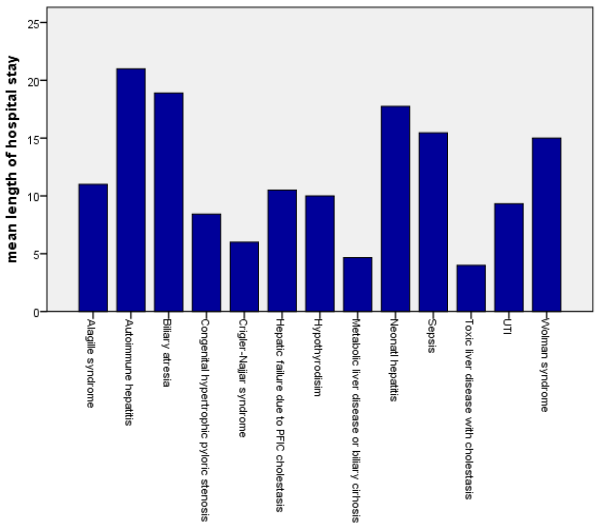

Fig. 1: Mean length of hospital stay of each diagnosis

DISCUSSION

Our study assessed the etiologies and outcomes of nonhemolytic jaundice among infants.We found that the most common etiologies were sepsis, Idiopathic, biliary atresia and congenital hypertrophic pyloric stenosis, respectively. In a study conducted in china showed the main causes of nonhemolytic jaundice among infants were Cytomegalovirus infection, then sepsis and finally breast milk jaundice [3].Other study in Iran showed that the most common causes of cholestatic jaundice were biliary atresia, Idiopathic neonatal hepatitis and intra-hepatic atresia[12].These studies' findings relatively support our results regarding the most common causes of nonhemolytic jaundice among infants. We suggest about the differences in the ordinal causes are due to geographical variations, familial aggregation and possibly regarding dietary basis.In our study, sepsis was the most common etiology and we found that the mean length of stay was15.4 days with case fatality rate 21.2%. In comparison to other study conducted in the United states which had mean length of stay 31 days with case fatality rate 10.6%. We suppose that length of stay in hospital is shorter in our setting and that may be due to the higher case fatality rate in our setting in comparison to this study[25]. In infantile hypertrophic pyloric stenosis, case fatality rate in our setting was 0% in comparison to other study conducted in Cameroon[26] which had a case fatality rate of 9.5%, we suppose that this difference is due to higher health quality service provided in our setting and may be due to their higher number of cases included in their study. According to our result mean length of stay for infantile hypertrophic pyloric stenosis was 8.4 days in comparison to the previous study mentioned above which had median hospital stay of 4.7 ± 1.1 days. We think that the period of hospital stay in our study is longer in comparison to the setting of the other study, and that could be due to different hospital protocols and guidelines, in addition to the quality of health service provided [26]. In Biliary Atresia, in our study the mean total length of hospital stay was 18.9 days, in comparison to other study conducted in U.S. which has mean total length of stay 14.5- 19.7 days, we suppose that the difference is due to multi-factors related to the availability of surgeries related to the disease, success rates, and the availability of liver transplantation [27].

CONCLUSION

In the present study, we found that the most common cause was as follows ; sepsis, then biliary atresia, followed by congenital hypertrophic pyloric stenosis. The fatality case rate was high for sepsis and biliary atresia respectively in comparison to the other causes of nonhemolytic jaundice among infants. According to our results, we hope to help the local physicians in Jeddah to arrange their differential diagnosis and deal with it seriously, due to the high incidence of critical illness and death.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. **Oranit Shaked and Barbara M Peña (2017):** Evaluation of jaundice caused by hyperbilirubinemia in children, can be retrived from: https://www.uptodate.com/contents/evaluation-of-jaundice-caused-by-unconjugated-hyperbilirubinemia-in-children
2. **Zhonghua G, Zang B, Za Z (2015):** Etiologies of nonhemolytic jaundice in infants: a retrospective analysis of 3113 cases, 23(6):454.
3. **Phares CR, Lynfield R, Farley MM *et al.* (2008):** Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA., 299(17):2056-65.
4. **Dick MC, Mowat AP(1985**): Hepatitis syndrome in infancy--an epidemiological survey with 10 year follows up. Archives of disease in childhood, 60(6): 512-516.
5. **Balistreri WF (1985**): Neonatal cholestasis. J Pediatr., 106: 171-184.
6. **Ozkan TB, Mistik R, Dikici B, Nazlioglu HO(2007**): Antiviral therapy in neonatal cholestatic cytomegalovirus hepatitis. BMC Gastroenterol., 7: 9.
7. **Fischler B, Casswall TH, Malmborg P, Nemeth A(2002**): Ganciclovir treatment in infants with cytomegalovirus infection and cholestasis. J Pediatr Gastroenterol Nutr., 34: 154-157.
8. **Maisels MJ, Clune S, Coleman K *et al.* (2014**): The natural history of jaundice in predominantly breastfed infants. Pediatrics, 134:e340.

9. **Centers for disease control and prevention (2014):** Jaundice, available at: https://www. cdc.gov/breastfeeding/disease/jaundice.htm
10. **American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004):** Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics, 114(1):297.
11. **Lee KJ, Kim JW, Moon JS, Ko JS (2017):** Epidemiology of Biliary Atresia in Korea. J Korean Med Sci., 32(4):656-660.
12. **Dehghani SM *et al.*(2015):** Evaluation of cholestasis in Iranian infants less than three months of age. Shahid Beheshti University of Medical Sciences, 8(1):42-48.
13. **Kelly DA (1998):** Liver complications of pediatric parenteral nutrition--epidemiology. Nutrition, 14(1):153-7
14. **Christensen RD, Henry E, Wiedmeier SE *et al.* (2007):** Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. J Perinatol., 27(5):284.
15. **Lipsett PA, Pitt HA, Colombani PM *et al.* (1994):** Choledochal cyst disease. A changing pattern of presentation. Ann Surg., 220(5):644.
16. **O'Neill JA (1992):**Choledochal cyst. Curr Probl Surg. , 29:361.
17. **Singham J, Yoshida EM, Scudamore CH(2009):** Choledochal cysts: part 2 of 3: Diagnosis. Can J Surg., 52:506.
18. **Pedersen RN, Garne E, Loane M, Korsholm L, Husby S, a EUROCAT Working Group, Pedersen RN, Garne E, Loane M, Korsholm L, Husby S(2008):** Infantile hypertrophic pyloric stenosis: a comparative study of incidence and other epidemiological characteristics in seven European regions. The Journal of Maternal-Fetal & Neonatal Medicine, 21(9):599-604.
19. **Hua L, Shi D, Bishop PR *et al.* (2005):** The role of UGT1A1*28 mutation in jaundiced infants with hypertrophic pyloric stenosis. Pediatr Res., 58(5):881.
20. **Laura Fregonese and Jan Stolk (2008):** Hereditary alpha-1-antitrypsin deficiency and its clinical consequences, Orphanet Journal of Rare Diseases, 3(1):16.
21. **Al Essa M, Nounou R, Sakati N *et al.* (1998):** Wolman disease: The King Faisal specialist hospital and research centre experience. Ann Saudi Med., 18:120–4.
22. **Muntoni S, Wiebusch H, Jansen-Rust M, Rust S, Seedorf U, Schulte H, Berger K, Funke H, Assmann G(2007):** Prevalence of cholesteryl ester storage disease. Arterioscler Thromb Vasc Biol., 27:1866–8.
23. **Valles-Ayoub Y, Esfandiarifard S, No D, Sinai P, Khokher Z, Kohan M, Kahen T, Darvish D(2011):** Wolman disease (LIPA p.G87V) genotype frequency in people of Iranian-Jewish ancestry. Genet Test Mol Biomarkers, 15:395–8.
24. **Camacho-Gonzalez A, Spearman PW, Stoll BJ(2013):** Neonatal Infectious Diseases: Evaluation of Neonatal Sepsis. Pediatric clinics of North America, 60(2):367-389.
25. **Watson R, Carcillo J, Linde-Zwirble W, Clermont G, Lidicker J and Angus D (2003):** The Epidemiology of Severe Sepsis in Children in the United States. American Journal of Respiratory and Critical Care Medicine, 167(5):695-701
26. **Ndongo R, Tolefac P, Tambo F, Abanda M, Ngowe, M, Fola O, Dzekem B, Weledji P, Sosso M and Minkande J (2018):** Infantile hypertrophic pyloric stenosis: a 4-year experience from two tertiary care centres in Cameroon. BMC Research Notes, 11(1).
27. **Lao O, Larison C, Garrison M, Healey P and Goldin A (2010):** Steroid use after the Kasai procedure for biliary atresia. The American Journal of Surgery, 199(5):680-684.