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PREVALENCE AND CLINICAL CORRELATES OF PROLONGED NEONATAL JAUNDICE AMONG NEONATES WITH JAUNDICE AT KENYATTA NATIONAL HOSPITAL, NAIROBI
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PREVALENCE AND CLINICAL CORRELATES OF PROLONGED NEONATAL JAUNDICE AMONG NEONATES WITH JAUNDICE AT KENYATTA NATIONAL HOSPITAL, NAIROBI

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ABSTRACT

Background: **Prolonged neonatal jaundice is jaundice beyond fourteen days in term and twenty-one days in pre-term babies. The common causes are biliary atresia, metabolic conditions and infections. Work up for neonates with jaundice as per international guidelines is extensive and may not be available in developing countries. In Kenya, the prevalence and aetiology of prolonged jaundice has not been published.**

Objectives: **Primary: To determine the prevalence of prolonged neonatal jaundice among neonates admitted with jaundice.**

Secondary: To describe laboratory and radiological investigations, aetiology and short-term outcomes for babies admitted with prolonged neonatal jaundice.

Design: **A retrospective, cross-sectional study**

Setting: **Children's wards and newborn unit, Kenyatta National Hospital.**

Subjects: **A total of 360 files of neonates with jaundice were analyzed manually using a data collection tool.**

Results: **Of 360 eligible neonates, fifty-six (16%) neonates had prolonged jaundice. There were sixty-seven preterm and 293 term babies and 91% had conjugated hyperbilirubinemia. Fifty-two (93%) had full blood count done and the remaining first tier tests were done in less than 50% of patients. The most common causes were viral hepatitis (25%), bacterial sepsis (23%), biliary atresia (4%) and cholecystitis. One out of 8 pre-terms and 4 out of 48 term neonates died during the first admission.**

Conclusion: **The prevalence of prolonged neonatal jaundice amongst infants admitted with jaundice was 16%. Patients with prolonged neonatal jaundice were not fully evaluated even for first tier as per international guidelines, but infections were the most common cause. The short-term mortality of prolonged neonatal jaundice was 10%.**

INTRODUCTION

Jaundice is the yellow discoloration of sclera, mucous membranes, skin and bodily fluids, due to accumulation of bilirubin in the circulation and tissues(1). Prolonged neonatal jaundice (pNNJ) occurs beyond 14 days of life in term babies and 21 days in preterm babies(2)(3). Up to 15% of all new-borns have prolonged jaundice(4), and up to 40% of these have benign unconjugated hyperbilirubinemia(5). The remaining have conjugated hyperbilirubinemia and liver disease, of which, the most commonly identifiable cause in the American population include: biliary atresia (25%–35%), genetic disorders at 25%, metabolic diseases at 20%, and α1-antitrypsin deficiency (10%). In developing countries, urinary tract infections (UTI) also reported to be a significant cause(6).

The clinical presentation of pNNJ is varied with signs and symptoms dependent on the underlying cause and features of hepatic failure, if present(7). Clinically, patients with cholestatic liver disease have dark urine and pale stools, in addition to jaundice, but otherwise look well. Fever, non-specific symptoms like lethargy, sleep disorders, feeding difficulties may be present as part of sepsis presentation. Features of liver failure including easy bruising, itchiness, skin rash, hepatosplenomegaly, bleeding tendencies may also be present(8).

All neonates who present with jaundice beyond 2 weeks of age need to be evaluated. First, to differentiate neonatal cholestasis from unconjugated hyperbilirubinemia, and, if cholestasis is present, to rapidly identify those causes that are amenable to medical or surgical treatment(9).

The European and North American paediatric gastroenterology, hepatology and nutrition societies (ESPGHAN, NASPGHAN) recommend a targeted approach to investigate patients with prolonged NNJ according to the common causes in developed countries (10). The following table includes the tests to be done as first line (tier 1) and second line (tier 2).

Table 1

Targeted investigations of the persistently jaundiced infants reproduced from ESPGHAN and NASPGHAN guidelines 2017

TIER 1	TIER 2
Complete blood count + differential	Metabolic etiology
International normalized ratio (INR)	Ammonia, lactate, cholesterol
Liver function test + albumin levels	RBC galactose-1-phophate and uridyltransferase
Blood glucose	Urine succinyllacetone and Organic acids
α -1- antitrypsin phenotype	Urine bile salt species
Thyroid function tests	DNA-PCR for CMV, HSV
Urine analysis	Sweat chloride tests
Urine culture	Genetic sequencing
Urine reducing substances	CXR
Cultures of blood and other fluids	SPINE XRAY
Fasting ultrasound	ECHO
	Cholangiogram
	Liver biopsy

Early diagnosis and timely referral for management are key to better prognosis in the neonate(11). The first aim, in the management of infants with pNNJ, is to

recognize diseases responding to specific medical therapy i.e. congenital CMV infection, urinary tract infection, hypothyroidism, etc, and to early surgical intervention (biliary atresia, choledochal cyst)(12).

The outcomes of prolonged neonatal jaundice are good, with up to 90% survival, in patients with timely evaluation and management of underlying cause(13). For prolonged unconjugated jaundice, almost all patients recover by 8 weeks of age with no complications(14). The general outcome in conjugated hyperbilirubinaemia depends on specific identified aetiology of prolonged jaundice.

The differential diagnosis is broad and therefore investigations need to be tailored to the common causes of pNNJ in Kenya. In order to know how to evaluate patients, we need to know what is more common in our setting and thus to come up with our own evaluation and management guidelines.

This study aims to get the burden of the condition and thus serve as a starting point towards evaluating the disease in Kenya's main referral centre, Kenyatta National Hospital (KNH). It also aims to evaluate the short-term outcomes and mortality associated with prolonged neonatal jaundice in KNH.

METHODOLOGY

This was a retrospective, cross-sectional study, carried out in the pediatric wards and new-born unit of Kenyatta National Hospital (KNH) in Nairobi, Kenya, which is a tertiary level, national referral hospital.

Data was collected covering a 3-year period (January 2016 – December 2018), using a structured, paper-based data abstraction tool. The 368 files were collected from medical records, starting from the most recent admissions going backwards, selected randomly. The variables of interest included, neonate biodata, age at presentation, investigations done, length of stay and survival.

From the completed paper-based tools, data was entered into a password controlled Epinfo database by trained research assistant and exported to Stata version 15.1(Stata corp, college station, TX, USA) statistical software for statistical analysis.

Ethical considerations: Ethical approval was sought from the Kenyatta National Hospital Ethics Research Committee.

Study limitations: The study relied on manually written medical records, so loss of information was noted, which was countered by non-response factor. Since the study was carried out in a national referral hospital, its finding may not be generalizable to other hospitals (lower level hospitals).

Being a study at a resource limited centre, not all investigations were done for every patient as recommended by international guidelines and this would hinder the results on aetiology.

RESULTS

A total of 377 patient files numbers were selected for file retrieval. Nine files were missing and from the 368 files available, 8 were excluded due to record of patients receiving total parenteral nutrition (TPN). From those, 56 patients were noted to have prolonged jaundice.

The period prevalence was 16% (56/368, 95% CI 12 to 20%). The key subgroups of patients with prolonged neonatal jaundice were according to gestation. Among the 67 neonates born preterm, 8 had prolonged jaundice: a prevalence of 12% (95% CI 5.2% to 22%). While from the 293 neonates born term, 48 had prolonged jaundice: a prevalence of 16% (95% CI 12 to 21%). Males and females had similar prevalence of 51% and 49% respectively. Table 2 below shows a summarized description of participants included.

Table 2
Descriptive characteristics of study participants

Characteristics	All neonates (N=360)	Type of Jaundice		
		Prolonged jaundice (N=56)	Non-prolonged jaundice (N=304)	P-value
Age at presentation in days#	3 (2-6)	7 (2-18.5)	3 (2-5)	<0.001
Gender-Female	166 (46)	27 (49)	139 (46)	0.66
Male	192 (54)	28 (51)	164 (54)	
Gestation in weeks#	38 (37-38)	38 (37-38)	38 (37-38)	0.59
Born preterm	67 (19)	8 (14)	59 (19)	0.37
Born term	293 (81)	48 (86)	245 (81)	
Age in days of Jaundice onset#	3 (2-4)	3 (2-6)	3 (2-4)	0.58
Age in days of Jaundice subsided#	10 (7-13)	49 (30-120)	8.5 (6-11)	<0.001
Time with jaundice in days#	6 (4-9)	42 (25-89)	5 (3-7)	<0.001

#-results presented as median (IQR), P-values of variables with median are from Wilcoxon ranksum test, the rest are from chi-square test

Among the 56 neonates with prolonged jaundice, evaluation of neonatal sepsis was as follows: 52(93%) had total blood count done. From those, 7(14%) had low WBC count, 11(21%) had leucocytosis and the remaining 34(65%) had normal WBC count. Haemoglobin levels were normal in 50% of patients enrolled. Of the remaining, 24(46%) had moderate anaemia and 3.9% had severe anaemia at presentation. Urinalysis and urine culture were done for 17 (30%) and 14 (25%) respectively. There were six bacterial isolates from the urine culture: two E. coli, two Klebsiella pneumonia and two Enterococcus. Blood culture were done for 19 (34%) neonates and four staphylococcal species were isolated. These included staphylococcus epidermidis, staphylococcus haemolyticus, staphylococcus lantus, coagulase negative staphylococci.

Liver function tests were done for 53 (95%) neonates. All the participants had hyperbilirubinemia of which 91% had cholestatic jaundice and remaining 9.4% had indirect/mixed hyperbilirubinemia. There were 27 (48%) INR test done of which 17 (63%) were normal and 10 (37%) were abnormal. Albumin levels test were done for 48 (86%), of which 26 (54%) were normal and 22 (46%) were abnormal.

For associated endocrine/metabolic disorders, the following evaluation was noted to have been done: Blood glucose was done for 17 (30%) neonates, and no abnormality was noted. Thyroid function test was done for 28 (50%) neonates. There were no cases of hypothyroidism reported and only 1(2%) case of hyperthyroidism. Urine reducing sugars were done for 9 (16%) neonates, of which 7 (78%) were normal and 2 (22%) were abnormal.

Aetiology was determined by the diagnosis given according to the doctors' notes in collaboration with the results of the investigations recorded above. Most common diagnosis assigned included: viral hepatitis (25%), bacterial sepsis (23%), cholecystitis (5%) and breastfeeding jaundice (7%). Biliary atresia was reported in 7(13%) of patients who had either diagnosis from abdominal ultrasound or liver biopsy. Twelve (21%) of patients had no known diagnosis.

Alagille syndrome, Downs syndrome and breastfeeding jaundice were among the diagnoses recorded as per expert consultants' opinion. No specific tests were recorded to prove these diagnoses.

Of the 360 neonates enrolled to the study, 328 (91%) were discharged home while 32

(8.9%) neonates died. A detailed summary of the patient characteristics as per the short-term outcomes has been outlined in table 3 below.

Table3

Characteristics of patients with prolonged neonatal jaundice

	Discharged home (N=51)	**Died (N=5)**	**P-value**
Age when jaundice noted in days#	7 (2-6)	1 (1-6)	0.27
Gender-Female	23 (85)	4 (15)	0.16
Male	27 (96)	1 (3.6)	
Gestation in weeks#	38 (37-38)	38 (38-38)	0.88
Born preterm	7 (88)	1 (12)	0.55
Born term	44 (92)	4 (8)	
Time with jaundice in days#	43 (25-99)	32 (30-34)	0.58

#-results presented as median (IQR), P-values of variables with median are from Wilcoxon ranksum test, the rest are from Fisher's exact test.

DISCUSSION

The prevalence of prolonged neonatal jaundice at 16% (95% CI 12 to 20%) of all patients admitted with neonatal jaundice at Kenyatta National Hospital, was comparable to previous studies. A North American study found prevalence of 21% (5), whereas Chaudhary et al (2006) in Eastern Nepal documented prevalence to be 9.2%(6). There was no difference in male: female ratio in the neonates admitted with prolonged neonatal jaundice. This was also comparable to studies done in Iran(15) by Sana Ullah et al, where no difference in gender was reported.

The laboratory investigations done in the study group was varied, with almost all neonates having full blood count and liver function tests done. The remaining tests were done in less than 50% of patients with prolonged neonatal jaundice. Lack of local guidelines to assist in evaluating these patients and also lack of resources to perform certain tests like TORCHES screen in full, urine reducing sugars which were supposed to be sent to outside laboratories and financial implications on the patients' guardians, were all attributed to hinder full evaluation.The insufficient evaluation may have an implication on accuracy of the results on possible aetiology reported in this study.

In developed countries, biliary atresia is reported to be most common cause of prolonged jaundice, followed by genetic and metabolic conditions (1). Viral infections were not that common (18), whereas in some developing countries like Nepal reported that cultural practices may contribute to prolonged jaundice (6). Bacterial infections, especially urinary tract infections with E. Coli were the main cause of prolonged neonatal jaundice in Nigeria and Iran (19)(20). In Egypt, a study done at a university hospital revealed CMV and Reovirus being attributed to cholestatic jaundice in neonates (21).

In this study, the cause of prolonged neonatal jaundice was majorly attributed to viral hepatitis. This was based on positive IgG or IgM titers on the TORCHES screen done, in absence of any other possible cause from other tests done. The main viruses reported positive were CMV in 12 (44%) and rubella in 8(30%). This was followed by

bacterial sepsis (23%) from either neonatal sepsis or underlying UTI. Full description of bacteria isolated was not possible but from the patients who had cultures done, the main isolates included staphylococcal species, E. coli, Klebsiella Pneumonia and Enterococcus.

From the study group, 21% had no known cause. Lack of full evaluation could be an attributing factor, in addition to idiopathic neonatal jaundice. Biliary atresia, breastfeeding jaundice, cholecystitis, G6PD deficiency on the other hand only accounted for 5%, 7%, 5% and 2% respectively.

From urine cultures, the main isolates were E. coli, Klebsiella and Enterococcus at roughly similar percentages of 15%, 14% and 14% respectively. This result could vary if 100% of patients had urine cultures done, instead of the reported only 25% of study participants having the test done. Blood cultures were done on 34% of patients and main causative organism reported to be Staphylococcal spp. The bacterial isolates noted were comparable to studies done in other developing countries like Nepal, New Zealand and Iran (20)(22)(17)

In this study, 91% of neonates were discharged home for follow up and 8.9% died at first admission. This may not be accurately comparable to other studies since all other studies reviewed long term outcomes for 2-15 years of age. This study was looking at short-term outcome, at first admission. We were not able to review any study done on short-term outcomes from the database searched.

The total number of patients with prolonged jaundice who died was 5 (8.9%). There was a similar finding noted in patients with non-prolonged jaundice, in whom 27(8.9%) died. Among patients with prolonged jaundice, there was no difference between those discharge home and those who died with regards to their gender (P=0.16) or gestation age in weeks (P=0.88).

However, neonates in whom jaundice was noted at a very young age were more likely to die compared to those who started developing jaundice at later age in days; median (IQR) of 1 (1 – 6) Vs. 7 (2 – 6) respectively, P=0.007. This was attributed to worse clinical condition or co-morbidities of patients presenting early in the course of disease compared to those presenting at a later age in days.

CONCLUSION

The prevalence of prolonged neonatal jaundice amongst infants admitted with jaundice at KNH was 16%. There was no male or female predilection. A majority of the patients did not have the full evaluation done as per tier 1 recommendations, with only 3.5% of patients noted to have full work up with results.

Missing data on results of investigations also contributed to this finding, but the most common cause was noted to be viral hepatitis especially CMV and rubella, followed by bacterial sepsis.

A high mortality of 8.9% of neonates with prolonged jaundice was noted. The patients with early onset had a higher chance of dying than those who had a later onset of jaundice in days. A systemic approach to evaluating neonates with prolonged jaundice is recommended.

REFERENCES:

1. Feldman AG, Sokol RJ. Neonatal Cholestasis. Neoreviews. 2013 Feb;14(2).

2. Balistreri WF. Neonatal cholestasis. J Pediatr. 1985 Feb;106(2):171–84.

3. Najati N, Gharebaghi MM, Mortazavi F. Underlying etiologies of prolonged icterus in neonates. Pakistan J Biol Sci PJBS. 2010 Jul;13(14):711–4.

4. Logan S, Stanton A. Screening for biliary atresia. Lancet (London, England). 1993 Jul;342(8866):256.

5. Maisels MJ, Clune S, Coleman K, Gendelman B, Kendall A, McManus S, et al. The natural

history of jaundice in predominantly breastfed infants. Pediatrics. 2014 Aug;134(2):e340-5.
6. Scrafford CG, Mullany LC, Katz J, Khatry SK, LeClerq SC, Darmstadt GL, et al. Incidence of and risk factors for neonatal jaundice among newborns in southern Nepal. Trop Med Int Health. 2013 Nov;18(11):1317–28.
7. Gilmour SM. Prolonged neonatal jaundice: When to worry and what to do. Paediatr Child Health. 2004 Dec;9(10):700–4.
8. Group young infants clinical signs study. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet (London, England). 2008 Jan;371(9607):135–42.
9. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants. J Pediatr Gastroenterol Nutr [Internet]. 2017;64(1):154–68. Available from: http://insights.ovid.com/crossref?an=00005176-201701000-00023
10. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutriti. J Pediatr Gastroenterol Nutr. 2017 Jan;64(1):154–68.
11. Lane E, Murray KF. Neonatal Cholestasis. Vol. 64, Pediatric Clinics of North America. 2017. p. 621–39.
12. Pierro A, Koletzko B, Carnielli V, Superina RA, Roberts EA, Filler RM, et al. Resting energy expenditure is increased in infants and children with extrahepatic biliary atresia. J Pediatr Surg. 1989 Jun;24(6):534–8.
13. McKiernan PJ. The infant with prolonged jaundice: investigation and management. Curr Paediatr [Internet]. 2018 Apr 6;11(2):83–9. Available from: http://dx.doi.org/10.1054/cupe.2000.0160
14. Fischler B, Lamireau T. Cholestasis in the newborn and infant. Clin Res Hepatol Gastroenterol [Internet]. 2014;38(3):263–7. Available from: http://www.sciencedirect.com/science/article/pii/S2210740114000655
15. Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in Neonates: Types, Causes, Clinical Examinations, Preventive Measures and Treatments: A Narrative Review Article. Vol. 45, Iranian Journal of Public Health. 2016. p. 558–68.
16. Kaini NR, Chaudhary D, Adhikary V, Bhattacharya S, Lamsal M. Overview of cases and prevalence of jaundice in neonatal intensive care unit. Nepal Med Coll J. 2006 Jun;8(2):133–5.
17. Tola HH, Ranjbaran M, Omani-Samani R, Sadeghi M. Prevalence of UTI among Iranian infants with prolonged jaundice, and its main causes: A systematic review and meta-analysis study. J Pediatr Urol. 2018 Feb;
18. Mowat AP, Psacharopoulos HT, Williams R. Extrahepatic biliary atresia versus neonatal hepatitis. Review of 137 prospectively investigated infants. Arch Dis Child. 1976 Oct;51(10):763–70.
19. Olusanya BO, Osibanjo FB, Mabogunje CA, Slusher TM, Olowe SA. The burden and management of neonatal jaundice in Nigeria: A scoping review of the literature. Vol. 19, Nigerian Journal of Clinical Practice. 2016.
20. Malla T, Sathian B, Karmacharya Malla K, Adhikari S. Urinary Tract Infection in Asymptomatic Newborns with Prolonged Unconjugated Hyperbilirubunemia: A Hospital based Observational study from Western Region of Nepal. Kathmandu Univ Med J (KUMJ). 2016;14(53):41–6.
21. Amer OT, Abd El-Rahma HA, Sherief LM, Hussein HF, Zeid AF, Abd El-Aziz AM. Role of some viral infections in neonatal cholestasis. Egypt J Immunol. 2004;11(2):149–55.
22. Andre M, Day AS. Causes of prolonged jaundice in infancy: 3-year experience in a tertiary paediatric centre. N Z Med J. 2016;129(1429).
23. Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. Ital J Pediatr. 2015 Oct;41:69