Original Research

THE CHARACTERISTICS OF PROLONGED NEONATAL JAUNDICE INVESTIGATED AT PRIMARY HEALTH CLINICS IN KOTA BHARU, KELANTAN

Hazlienor Mohd Hatta, Mohd Ikhwan Azmi, Nik Aida Nik Adib, Najihah Mahfuzah Zakria, Latifah Dahalan

Kota Bharu District Health Office, Kelantan, Malaysia Ministry of Health

**Corresponding author:* drhazlienor@hotmail.com

ABSTRACT

Introduction: Prolonged neonatal jaundice is affecting 15-40% of breastfed new-borns. Although breastmilk jaundice is the common aetiology, undetected pathological causes could lead to unfavourable sequelae. This study described the characteristics, aetiology and burden of prolonged neonatal jaundice investigated at the primary care level in Kota Bharu district. **Methods:** This cross-sectional study was done from July till December 2019, involving 14 health clinics in Kota Bharu. Selection criteria involved term new-borns at day 14 of life or preterm at day 21 of life that had visible jaundice or serum bilirubin >85µmol/l. Clinical details, investigations, and management were carried out based on normal practice at the clinics. A registry was established to capture the burden. **Results:** Prolonged jaundice were detected among 22.5% [95% CI 21.5, 23.6] of new-borns attending primary health clinics in Kota Bharu. A total of 291 cases were further analysed; 275 (94.5%) were term new-borns and 243 (83.5%) were breastfed. Affected new-borns underwent blood and urine sampling with multiple follow-ups. On average, jaundice subsided within 12 days [SD=5.5, 95% CI:11.7, 13.1] after detection of this condition. Majority had prolonged unconjugated hyperbilirubinemia (98.6%) and main aetiology was breastmilk jaundice (84.5%). Minority had hypothyroidism (3.4%) and conjugated hyperbilirubinemia (1.7%). Out of 129 cases sent for urine culture, 12 (9.3%) had significant growth, mostly *E.coli*. **Conclusion:** The majority of neonates with prolonged jaundice were term and breastfed. While the main aetiology was breastmilk jaundice, other underlying pathologies were also identified. As the burden of this condition is high, multistage investigation is strongly recommended. Urinary tract infections screening should be routinely considered.

Keywords: hyperbilirubinemia, neonatal jaundice, prolonged jaundice

Introduction

Prolonged neonatal jaundice is a common condition affecting 15-40% of all new-borns (Gilmour, 2004). It is defined as neonatal jaundice persisting beyond 14 days of life in a full-term infant or 21 days in a preterm baby (Malaysia Ministry of Health, 2017). The vast majority of new-borns with prolonged jaundice has unconjugated hyperbilirubinemia, where breastmilk jaundice is identified as the major cause (Agrawal et al., 2017). Although breast milk jaundice is benign, easily manageable and subsided spontaneously requiring no intervention, it is a diagnosis of exclusion as prolonged neonatal jaundice may also be a manifestation of more serious diseases (Preer & Philipp, 2011).

Prolonged conjugated hyperbilirubinemia is often pathological; affecting 1/2500 live birth whereas the incidence of biliary atresia is 1:18000 in the general population (Hodgson et al., 2018). It may present with dark coloured urine and pale stool but normal history and physical examination in the early stage of diseases are usual (Hodgson et al., 2018). As such, late presentation and referral to tertiary centre are common resulting in delayed intervention and poor prognosis. Congenital hypothyroidism, haemolytic diseases, urinary tract infections (UTIs), other infectious and genetic disorders are among the causes of prolonged neonatal jaundice that require prompt detection and early treatments to avoid unfavourable sequelae (Agrawal et al., 2017). Other aetiology of prolonged neonatal jaundice includes the inborn error of metabolism, intestinal obstruction, pyloric stenosis, glucuronyl transferase enzyme deficiency or rare conditions such as Criggler-Najjar or Gilbert syndrome (Andre & Day, 2016).

To date, various guidelines are implemented in different parts of the world in regards to the management of prolonged jaundice. It often includes risk assessment or red flags, a thorough history and physical examination as well as a set of laboratory investigations (Rennie et al., 2010). Feeding history, stool and urine colour as well as a complete physical examination are also necessary to identify the cause of prolonged neonatal jaundice (Fawaz et al., 2017). The routine screening varies from as minimal as serum bilirubin with differential count to extensive combinations of multiple blood and urine investigations. This condition is often investigated by paediatricians in tertiary hospitals but in Kota Bharu, it is being done at primary health clinics since the introduction of the Integrated Plan for Detection and Management of Neonatal Jaundice in the year 2017. As a large number of new-borns are affected by this condition, the workload in managing prolonged neonatal jaundice is undeniably enormous, but to date, there is no registry available at the state or local level that can capture the reality of it. With this background in mind, this study intended to shed some knowledge on the characteristics and aetiology of prolonged neonatal jaundice, the extent of investigation required as well the current burden in managing this condition at the primary care level in the Kota Bharu district.

Methods

This cross-sectional study was carried out at 14 government health clinics located in the Kota Bharu district. These clinics were the primary care clinics that could carry out investigations required for the management of prolonged neonatal jaundice and received referrals for the said condition from all other clinics located in the district. All term new-borns attending these clinics between July to December 2019

screened for prolonged neonatal jaundice were recorded in a registry established at each clinic. Cases were selected for this study from the registry using systematic random sampling in which sample size and sampling interval were predetermined for each clinic based on the population size while the first case was chosen by rolling a dice. Premature babies of <35 weeks or birth weight <2000g are more prone for elevated serum bilirubin and more severe sequelae at a lower level of hyperbilirubinemia (Maisels et al., 2012), hence were excluded from this study. The sample size was calculated with a 5% absolute precision and 95% confidence level based on the estimated incidence of prolonged neonatal jaundice at 20%.

Detailed information about the neonates, physical examinations, the results of investigations done and further management were carried out based on normal practice at the clinics. The number of visits and purpose of each follow up were also recorded. Obtained materials were translated into data collection forms by trained medical officers. Cases enrolled in this study were followed up until jaundice resolved or until 8 weeks of life, whichever earlier.

Prolonged neonatal jaundice was defined as visible jaundice or total serum bilirubin (TSB) of >85 μmol/L or 5 mg/dL that persists beyond 14 days of life in a term baby or 21 days in a preterm baby (Malaysia Ministry of Health, 2017). Risk stratifications were based on the Integrated Plan for Detection & Management of Neonatal Jaundice (Malaysia Ministry of Health, 2017); high risk–ill/septic looking, respiratory distress, poor feeding, lethargy, poor perfusion; moderate risk–conjugated hyperbilirubinemia, severe jaundice (TSB >300 μmol/l), new onset of jaundice after day seven of life, pale stool, dark yellow urine, poor weight gain, hepatosplenomegaly, predominant bottle-fed >50%, jaundice over one month not investigated before, other suspected medical condition, significant family history; low risk–well babies with good weight gain, exclusively breastfed or >50% breastfed, bright yellow stool, normal clinical examination. The diagnosis was determined by the attending medical officers or physicians based on the guideline.

Demographic, clinical characteristics and laboratory investigations were summarized and tabulated. Descriptive data were expressed as mean and standard deviation for normally distributed data while categorical data were presented as frequency and percentage. The comparison of means was carried out using Student's *t*-test. A value of p <0.05 is considered statistically significant. The data was analysed using SPSSv25.

The study was registered under the National Medical Research Register (NMRR-19-1481-49038) and approved by the National Medical Research and Ethics Committee and was conducted as part of the routine management for the said condition with written consent taken from the guardian.

Results

Demographic & Clinical Characteristic

Prolonged neonatal jaundice was detected among 1,407 (22.5%) out of 6,242 new-borns that attended the 14 major government health clinics in the Kota Bharu district. A total of 291 cases were included in this study and further analysed. The characteristics of these babies are summarized in Table 1. Antenatally, 106 (36.4%) of the mothers were diabetic while 5 (1.7%) had thyroid disorders. None of the cases had any family history of liver or kidney disease. All cases were screened for Glucose-6-phosphate dehydrogenase (G6PD) deficiency and congenital hypothyroidism at birth with one case had abnormal cord Thyroid Stimulating Hormone (TSH) level. About 197 (67.7%) cases relied on parental reporting in regards to stool colour while 79 (27.1%) cases had history supplemented with stool chart and 15 cases (5.2%) had their stool inspected. Only 3 (1.0%) cases had reported dark-coloured urine, while 2 (0.6%) other cases had pale stool, and one (0.3%) case had poor feeding, the rest of the cases had no other associated symptoms with normal physical assessments besides prolonged jaundice. Upon assessment, nine (3.1%) of the cases had new-onset jaundice after day seven of life while 282 (96.9%) already had jaundice since the early neonatal period. The majority (96.2%) of neonates were assessed within the recommended time frame (at day 14 or 21 of life).

Table 1: The characteristic of neonates investigated for prolonged jaundice at primary health clinics in Kota Bharu district (n=291).

Characteristic	**n (%)**
Age at diagnosis (days of life)	16.4 (2.5)*
Preterm	22.5 (3.1)*
Term	16.2 (1.9)*
Gender	
Female	146 (50.1)
Male	145 (49.9)
Race	
Malay	283 (97.3)
Chinese	4 (1.4)
Siamese	4 (1.4)
Gestation	
Term (<37 weeks)	275 (94.5)
Preterm (≥37 weeks)	16 (5.5)
Birth weight (kg)	2.91 (0.65)*
<2.50	45 (14.6)
2.50-3.99	244 (83.8)
≥4.00	2 (0.6)
Mode of delivery	
Spontaneous Vaginal	230 (79.0)
Instrumental	11 (3.8)
Caesarean	50 (17.2)
New-onset jaundice	
Yes	9 (3.1)
No	282 (96.9)
Feeding status	
Exclusive breastfeeding	243 (83.5)
Predominant breastfeeding	31 (10.7)
Predominant bottle-feeding	10 (3.4)

Blood group 'O' mother	
Yes	106 (36.4)
No	185 (63.6)
Rhesus negative mother	
Yes	2 (0.6)
No	289 (99.4)
G6PD deficiency	
Yes	4 (1.4)
No	287 (98.6)
History of phototherapy for jaundice	
Yes	85 (29.2)
No	206 (70.8)
History of siblings with prolonged jaundice	
Yes	36 (12.4)
No	255 (87.6)
Family history of blood disorder	
Yes	8 (2.7)
No	283 (97.3)
Parental consanguinity	
Yes	3 (1.0)
No	288 (99.0)

* Mean (SD)

Blood Investigation

Prolonged neonatal jaundice was detected via capillaries TSB screening for 284 (97.6%) cases, while the remaining seven (2.4%) had it identified visually. As depicted in Table 2, the mean capillaries TSB measured at diagnosis in preterm babies was significantly higher than in term babies. The venous TSB at detection of prolonged jaundice was less than 200μmol/l for 221 (75.9%) cases while 63 (21.6%) had TSB >200μmol/l. No severe hyperbilirubinemia exceeding 300μmol/l was observed in this study. The extent and yield of other investigations were summarized in Table 3**.** Isolated elevated Alkaline phosphatase (ALP) was seen in 17 (5.8%) new-borns; two were premature infants and 15 were term babies; five (1.7%) of them had an increasing trend of ALP upon repeated sampling while the rest were self-limiting. A total of 397 tubes of blood samples were obtained throughout investigations; rejected samples among these were low at 7.8% mainly due to insufficient samples (4.8%) and clotted specimen (1.3%) which required resampling.

Table 2: Comparison of serum bilirubin of term and preterm new-borns investigated for prolonged jaundice at primary health clinics in Kota Bharu districts (n=291).

Characteristic	mean±SD [95% CI][#]	*p* value[$]
Mean capillaries TSB at diagnosis (µmol/l)	162.8±44.0 [157.6, 168.0]	
Preterm	189.3±30.5 [172.4, 206.2]	0.004
Term	161.3±44.9 [155.9, 166.7]	
Mean venous TSB at diagnosis (µmol/l)	142.1±60.9 [1351, 149.1]	
Preterm	141.9±60.2 [134.8, 149.0]	0.825
Term	145..4±75.0 [105.4, 185.4]	

[#]Values in parentheses are 95% confidence interval (CI) for means
[$]Analysis by Student's *t*-test

Table 3: The investigations carried out for prolonged neonatal jaundice at primary health clinics in Kota Bharu other than TSB and differential count (n=291).

Investigation	n (%)	Contributory samples[a], n (%)[b]
Haemoglobin	140 (48.1)	27 (19.3)
Full Blood Picture	1 (0.3)	0 (0.0)
Direct Coombs Test	1 (0.3)	0 (0.0)
Reticulocyte count	1 (0.3)	0 (0.0)
Alkaline phosphatase (ALP)	284 (97.6)	17 (5.9)
Aspartate Transaminases (AST)	284 (97.6)	8 (2.7)
Alanine Transferase (ALT)	284 (97.6)	19 (6.5)
Thyroid Stimulating Hormone (TSH)[c]	245 (84.2)	31 (12.7)
Free T4 (fT4)[d]	33 (11.3)	10 (30.3)
Renal profile	6 (2.1)	0 (0.0)
Urinalysis	225 (77.3)	29 (12.9)
Urine culture	129 (44.3)	12 (9.3)

[a] Reference values were based on age group available in Nelson Textbook of Pediatrics, 21st Edition Edition (Kliegman et al., 2019)
[b] The percentage of contributory abnormal sample was compared to the number of each particular test
[c] TSH values of >6 µmol/l are determined as abnormal by local laboratory
[d] only four cases had persistent low fT4 on repeated sampling

Urine Investigation

The majority of new-borns were screened for UTIs (Table 3) in which urine samples were obtained by either urine bag or clean catch method. A total of 129 (44.3%) cases had urine samples sent for urine culture in which 27 (20.9%) cases were screened due to poor weight gain, predominant bottle-feeding or conjugated hyperbilirubinemia. Twelve (4.1%) cases had positive urine culture with significant growth (7 *E.coli*, 3 *Enterobacter sp*, 2 *K.pneumonia*) that make out the rate of 9.3%. However, we only included the number of cases tested for bacteriuria as the denominator when assessing the rate (n=129). Only one of the cases diagnosed with UTIs had poor weight gain, while the rest of the cases had no symptoms other than jaundice. A total of 93 (72.1%) urine specimens sent for urine culture yielded mixed or insignificant growth. Out of 12 cases whose urine culture had significant growth, only five of them had abnormal urinalysis (leucocyte detected in the urine of four cases while one case had traces of leucocyte and blood). Two cases that had positive urine nitrite had insignificant growth. A total of 386

containers of urine samples were obtained throughout investigations; rejected samples among these were 4.4% mainly due to empty containers submitted by parents (2.8%) and leaked containers (0.8%) which required resampling.

Management and follow-ups

The cases were stratified into different risk groups of which only one (0.3%) case was high risk, 46 (15.8%) cases had moderate risk, 189 (64.9%) cases had low risk, while 55 (18.9%) cases had inadequate information to be stratified into risk categories (Table 4). Parental issues were observed among 22 (7.6%) cases; mainly defaulters (10), refusals for multiple blood takings (8), and difficulty in obtaining urine samples (6). On average, a new-born required three follow-up visits after the detection of prolonged neonatal jaundice. Jaundice subsided within 12 days [SD=5.5, 95% CI: 11.7, 13.1] with 85 (29.2%) cases were discharged at 1-week follow-ups after being screened for the condition. Jaundice subsided by the fourth week of life for 150 (51.6%) cases while 134 (46.0%) cases by the sixth week of life. Only one high-risk case, five cases with persistently elevated ALP and four cases with persistent hypothyroidism were referred to the tertiary centre for further investigation and management.

Table 4: Risk stratification based on underlying risks of neonates investigated for prolonged jaundice at primary health clinics in Kota Bharu districts (n = 291).

Risk Categories[e]	**n (%)**
High risk	
Poor feeding	1 (0.3)
Moderate risk	
Poor weight gain	22 (7.6)
New-onset jaundice	8 (2.8)
Predominant bottle-feeding	8 (2.8)
Conjugated hyperbilirubinemia	4 (1.4)
Dark urine	3 (1.0)
Pale stool	1 (0.3)
Low risk	189 (64.9)
Unknown risk	55 (18.9)

[e]Neonates may have multiple underlying risks

Aetiology of prolonged neonatal jaundice

The majority of the neonates had prolonged unconjugated hyperbilirubinemia (98.6%) in which the main aetiology was breastmilk jaundice while 26 (8.9%) cases had underlying pathologies (Table 5). Four (1.4%) cases had conjugated hyperbilirubinemia but no case of biliary atresia was reported in this study. A total of 19 (6.5%) cases with moderate risk had undergone inadequate investigations to identify the causes. Out of 63 cases that had TSB > 200 µmol/L, only six cases (9.5%) had underlying pathologies. Out of 10 (3.4%) cases that had hypothyroidism, six cases were transient.

Table 5: The aetiology for prolonged jaundice among neonates investigated at primary health clinics in Kota Bharu district, (n = 291).

Aetiology	n (%)
Prolonged unconjugated hyperbilirubinemia	287 (98.6)
Breast milk jaundice	246 (84.5)
Hypothyroidism	10 (3.5)
Urinary tract infection	11 (3.8)
Sepsis	1 (0.3)
Unknown	19 (6.5)
Prolonged conjugated hyperbilirubinemia	4 (1.4)
Urinary tract infections	1 (0.3)
Transient cholestasis	3 (1.1)

Discussion

Almost one-fourth of new-borns were affected by prolonged jaundice in Kota Bharu. This rate is higher than a study done in Perak at 15.8%(Tan et al., 2019) while the prevalence is reported to be around 15-40% worldwide (Laving et al., 2019). The vast majority of prolonged jaundice cases in the Kota Bharu district were term, breastfed and healthy new-borns, while the main aetiology was breastmilk jaundice, in keeping with other studies (Agrawal et al., 2017). The rate of conjugated hyperbilirubinemia among neonates in this study was low. Only a small portion of cases in this study had hypothyroidism; this could be explained by the effectiveness of the national screening program for congenital hypothyroidism done in this country allowing this pathology to be detected earlier (Wong et al., 2015). Primary congenital hypothyroidism occurs in approximately one in every 4000 new-borns but the incidence is much higher in Malaysia that is 1 in 1170 live birth and is one of the common causes of prolonged neonatal jaundice (Wong et al., 2015). In regions where new-borns screening program for congenital hypothyroidism is not done, thyroid function tests are widely recommended to be included as a routine investigation for new-borns with prolonged jaundice (Honarpisheh, 2002). Less than 6% of new-borns in this study had isolated elevated ALP. A study conducted in Scotland revealed 13.3% of infants referred for prolonged jaundice had isolated elevated alkaline phosphatase lever that required no intervention as they were self-limiting (McEleavey et al., 2007).

Some suggested that in the presence of normal conjugated bilirubin, the cause for prolonged jaundice in neonates with TSB <200μmol/l is mostly benign (Preer & Philipp, 2011). However, the majority of cases that had underlying pathology in this study had TSB <200μmol/l at the time of diagnosis. This finding is also observed by other researchers (Andre & Day, 2016), suggesting that TSB value should not be the only indicator for further evaluation. The current guideline recommends assessment and relevant investigation for prolonged neonatal jaundice to be conducted at 14 and 21 days for the term and preterm babies respectively (Malaysia Ministry of Health, 2017). Most neonates in this study were assessed and investigated within the recommended timeframe and earlier, compared to babies that were referred to the tertiary centre without prior investigation according to a study in Perak that documented the mean age seen at hospital at 20.9 days (Tan et al., 2019). The medical practitioners in this study relied on parents in regards to stool colour in most of the cases. Objective assessment of

infant's stool colour by either direct inspection and stool chart need to be emphasized to identify conditions associated with biliary obstruction, particularly biliary atresia (S. P. Paul & Kirkham, 2016).

Breast milk jaundice is benign, easily manageable and subsided spontaneously requiring no intervention but it is a diagnosis of exclusion, hence, combinations of blood and urine investigations are necessary to identify other pathologies (Preer & Philipp, 2011). As this study demonstrated that jaundice may have subsided early and extensive investigations revealed low yield, we supported the national recommendation of multistage approach - to obtained serum total and direct bilirubin at two weeks of life in low-risk babies, and if still jaundiced at three weeks, to consider serum bilirubin with differential count, urine microscopy, fT4 and TSH, and FBC with reticulocyte count (Malaysia Ministry of Health, 2017). Similarly, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends total serum and conjugated bilirubin for 2-week-old jaundiced infants that can be delayed another week for breast-fed infants with a normal physical assessment and no history of dark-coloured urine or acholic stool (Fawaz et al., 2017). Meanwhile, the National Institute for Health & Care Excellence (NICE) recommended that if still jaundice at three weeks, a formal investigation for prolonged neonatal jaundice should include conjugated bilirubin, full blood count (FBC), mother and baby's blood group including direct antigen test (Coombs' test), urine culture and routine metabolic screening including for congenital hypothyroidism (Rennie et al., 2010).

The rate of UTIs in this study is 9.3% in which urine culture was not considered as a routine investigation for prolonged jaundice in the Kota Bharu district. The overall global prevalence of UTIs among new-borns with prolonged jaundice is around 11% but it greatly varies worldwide; ranging from 0.2% in the United Kingdom (Steadman et al., 2016) to as high as 53.9 % in Iran (Tola et al., 2018). The debates among researchers are ongoing in regards to UTIs screening methods among new-borns with prolonged jaundice. Although UTIs may present with low-grade fever, poor feeding, grunting, lethargy, diarrhoea and vomiting; it was diagnosed among 7.5% of afebrile, asymptomatic, jaundiced new-borns (S. Paul, 2012). This study along with other researchers supports the recommendation by NICE to include urine culture in routine screening for prolonged neonatal jaundice (Chen et al., 2011; S. P. Paul & Kirkham, 2016; Rennie et al., 2010) while some others recommended otherwise (Chowdhury et al., 2015; Steadman et al., 2016). In the current study, over half of the urine samples that yielded significant growth had normal urinalysis; in concordance with other studies (Chen et al., 2011; S. P. Paul & Kirkham, 2016). Urine bag is convenient to collect urine in the primary health clinic setting and the clean-catch method is recommended by NICE (Rennie et al., 2010) but the majority of samples taken by these methods in this study yielded insignificant or mixed growth. Further training and improvisations of these methods need to be done to minimize the risk of contamination as although urine catheterization had better yield, it is more invasive, costly and not applicable in a busy clinic setting.

These infants will need further investigations and extra follow-ups compared to non-jaundiced infants with the possibility of multiple sampling due to difficulty in obtaining samples; highlighting the need to enhance resources at primary health clinics to cater for this common condition. As extensive

investigations are costly with low yield, as well as the workforce implication on the primary care facilities, they should not be done routinely for all jaundiced new-borns. More health personnel should be skilled to obtain clinical specimens to reduce the need for resampling. Regular training by laboratory technicians regarding the needs and importance of fulfilling sample's criteria, proper specimen's handling and transportation are important to minimize the rejection of samples.

The limitation of this study was that we weren't able to report the true incidence of prolonged neonatal jaundice as some new-borns may be investigated directly at the tertiary centre, at private facilities or other districts. However, to our knowledge, this is the first study that describes the characteristic of prolonged neonatal jaundice and captures its burden in the district for a better understanding and management of the said condition.

Conclusion

The vast majority of prolonged neonatal jaundice cases in Kota Bharu district were term, breastfed and healthy new-borns, while the main aetiology was breastmilk jaundice. Although this condition is a common occurrence while the major cause is benign, the evaluation for other underlying pathology is of importance. Early recognition and intervention may prevent unfavourable sequelae in neonates with underlying pathology. Further studies need to be done to assess the magnitude of UTIs among infants with prolonged jaundice and the need to screen for it as part of routine investigation of this condition. The cost-effectiveness, workforce implication and difficulty of obtaining samples in infants need to be considered while investigating this condition, hence, multistage approaches are recommended. As the burden of prolonged neonatal jaundice is high, appropriate allocations of resources are necessary.

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Conflicts of Interest

The author declares no conflicts of interest.

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