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Evaluating the Frequency of Etiological Causes of Unconjugated Hyperbilirubinemia in Term Neonates Hospitalized in the Pediatric Unit of Shahid Motahari Hospital in Urmia

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Abstract

Introduction: Icterus or jaundice is one of the most common problems in the neonatal period. Non- diagnosis of its pathological type increases the probability icterus, associated with significant morbidity. This research was conducted to evaluate the causes of indirect hyperbilirubinemia in neonates, admitted to Shahid Motahari Pediatric Hospital in Urmia. Methodology: This descriptive cross-sectional research was carried out on neonates admitted to Shahid Motahari Pediatric Hospital in Urmia and all term neonates hospitalized with unconjugated hyperbilirubinemia were included into study using simple census sampling method. Information on the age of the neonates, the gender of neonates, the gestational age, the type of neonate nutrition, the birth weight, and the hospitalization, neonates tests including complete blood count (CBC) and total bilirubinemia, unconjugated bilirubinemia and conjugated bilirubinemia during hospitalization and discharge, G6PD (6 phosphate dehydrogenase enzyme glucose), direct coombs test, neonatal and maternal blood group, RH), and tests for hydration including serum sodium, BUN and creatinine were collected. Data were analyzed using SPSS version 21 and presented in the Mean ± SD form. Results: In this research, 486 patients were evaluated in general. The most common causes of icterus included exacerbated physiological icterus (78.5%) dehydration-induced icterus (10%) and ABO incompatibility (7%) with G6PD enzyme deficiency (2.5%) and RH incompatibility (0.6%) and positive coombs icterus (0.4%). In addition, 274 patients were male (56%) and 212 patients were female (43%). Moreover, 88% of neonates, hospitalized due to unconjugated hyperbilirubinemia, were breastfed. Conclusion: This research revealed that the most common cause of severe icterus in this area was unknown. ABO incompatibility and glucose 6 phosphate enzyme deficiency were other common causes of severe icterus.

Keywords: Neonatal Hyperbilirubinemia, Causes of Icterus, Neonatal Icterus

Introduction

Neonatal jaundice or icterus affects one neonate out of two neonates around the world. Jaundice is the result of accumulation of bilirubin in the blood, since embryo hemoglobin is metabolized by the immature liver (Brits et al., 2018; Riordan & Gazzin, 2018). High serum levels of bilirubin can cause irritation, poor nutrition and dizziness in neonates (Chee et al., 2018). As a destruction of worn-out red blood cells during enzymatic reactions, unconjugated bilirubin is resulted. If the unconjugated bilirubin level reaches more than 5 mg / dl, hyperbilirubinemia occurs in neonates (Muchowski, 2014). Increased production of bilirubin due to the destruction of embryo red blood cells and the transient restriction in bilirubin conjugation by immature liver leads to icterus (Zahedpasha et al., 2014). As unconjugated bilirubin is due to neurotoxic potential solubility in fat, the neonate with severe unconjugated hyperbilirubinemia is exposed to increased risk of icterus. Kernicterus is a complication, which can lead to permanent mental and physical disabilities in neonates (Dennery et al., 2001; Bhutani et al., 1999). Abnormal and pathologic increase in unconjugated bilirubin with the risk of passing through blood-brain barrier leads to encephalopathy and kernicterus. Symptoms such as non-breastfeeding, reduced reflexes, opisthotonos, body spasm and seizures, and initial signs of kernicterus are neonatal icterus cases (Behraman et al., 2000). Kernicterus or encephalopathy caused by hyperbilirubinemia leads to problems in the central nervous system of neonates. Depending on involvement site of disease, it leads to symptoms in patients (Dennery et al., 2001). An encephalopathy is associated first with severe jaundice, numbness, hypotonia, and poor feeding. Then, it can be associated with moderate stupor, hypotonia, and excessive crying. The acute developed stage of bilirubin encephalopathy is probably irreversible and might be associated with lack of feeding, apnea, seizure and even death (Jajosky & Jajosky, 2017). Acute bilirubin encephalopathy is an important factor in the rate of death among children, especially in African countries, and it leads to death of thousands of children annually (Diala et al., 2018).

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The causes of non-hemolytic unconjugated hyperbilirubinemia are icterus caused by maternal milk, Crigler–Najjar syndrome, congenital infections (TORCH) and acquired infections, occult bleeding polycythemia, skin bruises, gastrointestinal obstruction such as pyloric stenosis and hypothyroidism. No specific reason can be attributed for many cases of jaundice in neonates, and exacerbated or non-specific physiologic icterus is reported in this regard. However, it has been reported in recent years that issues such as jaundice caused by breast milk and dehydration are involved in this regard (Behraman et al., 2000). In a research conducted by Lavagno et al., neonatal hypernatremia along with breastfeeding was identified in neonates aged over 21 years and had birth less than 10%. Cesarean delivery, preterm delivery, breast abnormalities, or breast feeding problems, maternal overweight, lack of breastfeeding experience, and low education level of mother showed significant relationship with hypernatremia (Lavagno et al., 2016). This research was conducted given the prevalence of dehydration caused by breast-feeding and owing to various causes of unconjugated jaundice and its prevalence, and high rate of neonatal hospitalization due to jaundice, and lack of a new study on the most common causes of jaundice. After identifying the most important and common causes of neonatal jaundice and predisposing factors, we hope to take measures such as adequate training for mothers and families in order to prevent and timely treatment in order to prevent complications and reduce the days of hospitalization due to jaundice.

Methodology

This descriptive and cross-sectional research was carried out on neonates hospitalized in Motahari Hospital in Urmia and all term neonates who were diagnosed with unconjugated hyperbilirubinemia were included in the study using simple census sampling method. A researcher-developed checklist was used to collect the data. The first section of the checklist related to recording the demographic information such as age during hospitalization, gestational age, and weight during hospitalization, birth weight, gender, delivery method. Other information included the type of neonate feeding (breast milk, breast milk and formula, breast milk and water and sugar, or exclusively baby formula). In this research, a weight loss of more than 7% was considered as a significant dehydration. The descriptive statistics of data were analyzed using SPSS software version 21.

Results

In this descriptive and cross-sectional research, medical records of hospitalized infants with diagnosis of unconjugated hyperbilirubinemia in Motahari Hospital of Urmia from 2016.9.23 to 2017.9.23 were examined. In this research, the etiologic causes of unconjugated hyperbilirubinemia and the causes of unconjugated hyperbilirubinemia in terms of age, gender and type of feeding, and the rate of birth weight loss compared to the first day and the frequency of severe hyperbilirubinemia (Bilirubin> 25) and its causes and frequency of blood transfusion in neonates with unconjugated hyperbilirubinemia were examined. The majority of hospitalized neonates (86%) were hospitalized in the first week and the mean age was 5.14 days with a standard deviation of 0.38. In addition, 53 (11%) neonates were hospitalized in the second week of life and 14 cases (3%) had age over 14 days. The oldest neonate was 29 days of old and the youngest one was one day old. Among infants hospitalized due to unconjugated hyperbilirubinemia, 274 neonates (56%) were male and 212 neonates were female (43%). The mean weight of neonates at hospitalization time was 3045.10 g with a standard deviation of 62.17 and the mean birth weight of neonates was 3089 g with a standard deviation of 58.28. The minimum weight of hospitalization was 1500 g and the maximum hospitalization weight was 4500 grams. In neonates hospitalized due to icterus, the mean and standard deviation of serum bilirubin level was 4.8 and 18.56 mg, respectively. The mean and standard deviation of serum bilirubin level at discharge time was 1.23 and 8.03 mg, respectively. The most common causes of hospitalization due to icterus among the neonates were exacerbated physiologic icterus (80%). Other causes were dehydration-induced icterus (45 cases, 9.25%) and ABO incompatibility (35 cases, 7%) and G6PD enzyme deficiency (12cases, 12.5%), and RH incompatibility (3 cases, 0.6%), and icterus caused infants by other blood subgroups (2 cases, 0.4%). Among neonates hospitalized due to unconjugated hyperbilirubinemia, 274 neonates were male (56%) and 212 were female (43%). In the conducted research, 427 hospitalized neonates (88%) with unconjugated hyperbilirubinemia fed breast milk, 15 neonates (3%) used baby formula, and 25 neonates used baby formula and breast milk simultaneously, and 19 neonates (4%) used breast milk and water and sugar for feeding. Neonates with physiological weight loss (7-10%) were also examined in this research and 114 hospitalized neonates (23%) had a weight loss of more than 7%, which based on the cause of unconjugated hyperbilirubinemia, they are presented in Table 1. In our research, 56 of neonates had weight loss over 10%, which are presented separately in Table 2 based on the icterus etiology.

Table 1: The cause of unconjugated hyperbilirubinemia based on a weight loss of over than 7%

Cause	f	Percentage
Physiologic icterus	65	57
Dehydration-induced icterus	31	28
ABO incompatibility	9	8
G6PD Enzyme deficiency	7	5
RH incompatibility	2	2

Table 2: The cause of unconjugated hyperbilirubinemia based on weight loss more than 10%

Cause	f	%
Physiologic icterus	32	57
Dehydration-induced icterus	14	25
ABO incompatibility	5	9
G6PD Enzyme deficiency	3	5
RH incompatibility	2	4

In this study conducted on patients hospitalized with icterus, 15 patients had hyperbilirubinemia (Bilirubin> 25), which was the most common icterus etiology in these patients was unknown (74%), followed by ABO incompatibility (14%) and G6PD enzyme deficiency (8.5 Percentage) and RH incompatibility (3%), respectively. Among the patients hospitalized due to icterus, 26 cases (5.3%) had blood transfusion and the mean bilirubin was 28.45 ± 35. The most common known cause of blood transfusion was ABO incompatibility (19%). Other causes were G6PD enzyme deficiency (11%), RH incompatibility (4%), and other incompatibility causes of the blood subgroups (8%), respectively, and in 65% of cases, no specific cause was found for icterus.

Discussion

Neonatal jaundice is considered as one of the most common diseases in the first week of life in neonates with preterm labor and premature neonates. It is the most common cause of re-hospitalization after discharge of mothers (Behrman et al., 2005; Ogunfowora et al., 2006). Non-focused hyperbilirubinemia in most of neonates is a natural transition phenomenon and it is result of several physiological processes (Melton & Akinbi, 1999). In some neonates, bilirubin level might increase too much and cause acute and chronic bilirubin encephalopathy, leading to damage to brain (Bindu et al., 2017; Bin-Nun et al., 2018). Parents' inadequate thinking about jaundice in neonates might delay their referring to physician and exacerbate the neonatal jaundice (Onyearugha et al., 2010). Therefore, the primary care provider (mother) should diagnose the jaundice and take the neonate for physician for quick care and management (Braveman et al., 1995). The current cross sectional and descriptive study was conducted to evaluate the frequency of etiologic causes of unconjugated hyperbilirubinemia in term neonates. In our research, the most common causes of hospitalization due to icterus among the neonates was exacerbated physiologic icterus (81%), followed by dehydration-induced icterus with 45 cases (9.25%) and ABO incompatibility with 35 cases (7%) and G6PD enzyme deficiency with 12 cases (2.5%), RH incompatibility with 3 cases (0.6%) and icteric caused by other blood subgroups (0.4%), respectively. In a research conducted by Rennie et al., out of 16 hospitalized, 6 neonates had G6PD enzyme deficiency (37.5%), 5 neonates were recognized with ABO incompatibility (31.25%), and three neonates were recognized with RH incompatibility (18.75%) (Rennie et al., 2017). In a research conducted by Behjati et al on 346 neonates, ABO incompatibility was the most common cause of hyperbilirubinemia. The incidence of apnea was 12%, with no direct death caused by it was found (Behjati et al., 2009). Among neonates hospitalized due to unconjugated hyperbilirubinemia, 274 neonates were male (56%) and 212 were female (43%). In this research, the majority of hospitalized neonates (86%) were hospitalized in the first week of life with a mean age of 5.14 days with standard deviation of 0.38, and 53 neonates (11%) were hospitalized in second week of life, and 14 cases (3%) had age over 14 days. In a research conducted by Fok et al., the male gender and the age under one week are considered as icterus factors, confirming our findings (Fok et al., 1986) .

In this research, 427 neonates hospitalized (88%) due to unconjugated hyperbilirubinemia and breastfed and 15 neonates (3%) used baby formula and 25 neonates used baby formula and breast milk simultaneously. In addition, 19 neonates (4%) used breast milk and sugar and water for feeding. In a study conducted by Pound et al., most of neonates who had high bilirubin fed breast milk (Pound et al., 2015). In a research conducted by Fok et al., breastfeeding was one of the risk factors for severe icterus, which it is not possible to judge on this issue in this study (Fok et al., 1986). In our research, 54 hospitalized neonates (11%) had weight loss more than 10%, which physiologic icterus (57%) and dehydration-induced icterus (25%), ABO incompatibility (9%), and G6PD enzyme deficiency (5%), and RH incompatibility (4%) were respectively were the main cause of unconjugated hyperbilirubinemia in patients. In the study conducted by (Salas et al., 2009), 60% of neonates admitted due to lack of breast-feeding had a weight loss of more than 10% and there was a direct correlation between the increase in bilirubin level and the severity of weight loss, and 24.2% of the neonates had evidence for the benefit of dehydration and 26.8% of them had nutritional problems .Premature jaundice caused by breast milk occurs in the first week of life, which some researchers call it physiologic jaundice or jaundice caused by lack of breastfeeding. Although all breastfeeding neonates with significant weight loss has no Jaundice in the first week, jaundice is associated with weight loss and it does not seem that weight loss to be cause of jaundice, but it is more possible that weight loss to exacerbate the jaundice (Boskabadi et al., 2011). Thus, it is recommended that mothers have frequent breastfeeding in the first days of delivery in order to reduce weight loss of neonates and its complications including jaundice and hypernatremia.

In our research, out of 35 patients hospitalized due to icterus, 35 patients (12%) had severe hyperbilirubinemia (Bilirubin> 25), while in the study conducted by (Fok et al., 1986) to evaluate the causes of severe icterus among neonates, the incidence of severe icterus among total icterus was reported to be 23.9%, which the cause of it might be due to the difference in the definition of severe icterus in the two

studies, since icterus above 25 was considered as base of severe icterus, while in the study conducted by FOK et al, icterus above 12 was the base of severe icterus. In a study conducted by Najib et al., severe icterus in neonates with icterus was reported between 12 and 15, which is similar to information obtained in this study (Najib et al., 2013). In our research, the most common cause of severe icterus was unknown, which the most icterus etiology in these patients was unknown (74%) and no known cause was found for it. It was followed by ABO incompatibility (14%) and the G6PD enzyme deficiency (8.5%), and RH incompatibility (3%), respectively. In a research conducted by Najib et al., unknown causes of icterus accounted for 56.6% of causes of icterus, ABO and RH incompatibility accounted for 5.9% of causes of icterus, G6PD enzyme deficiency accounted for 25.5% of causes of icterus and sepsis accounted for 12% causes of icterus. In a study conducted by (Sgro et al., 2006), 258 neonates with severe hyperbilirubinemia were investigated. In this research, 93 (36%) neonates were diagnosed with underlying cause of icterus, which ABO incompatibility in 48 cases (18%) and G6PD deficiency in 20 cases (7%) and other blood incompatibilities in 12 cases (6.4%) were the most commonly reported as known causes of icterus. This result is in line with that of present study.

Conclusion

The research results revealed that the most common cause of severe icterus is unknown in this area. However, ABO incompatibility, glucose 6-phosphate dehydrogenase deficiency, and RH incompatibility and positive coombs icterus were recognized as the causes exaggerating the icterus.

Recommendations

Given the importance and complications of severe icterus and its high prevalence in this area, and as many studies have not been conducted so far, it is recommended that further studies to be carried out on its causes, especially on other causes of it such as drugs used by mother during delivery so that their impact on the incidence of icterus to be examined.

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