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Original Article

Why Infants with Some Inherited Metabolic Diseases do not Develop Neonatal Indirect Hyperbilirubinemia ? An Overlooked Detail

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ABSTRACT

Aim: Although indirect hyperbilirubinemia is the most common neonatal problem in term newborns, it is rarely observed in newborns with some inherited metabolic diseases. Therefore, we aimed to compare the frequency of indirect hyperbilirubinemia in newborns with these diagnoses and compare them with healthy newborns.

Materials and Methods: In the study group, term newborns with inherited metabolic diseases characterized by metabolic acidosis and/or hyperammonemia were included retrospectively and prospectively between January 1st, 2001, and December 31st, 2014. Healthy-term newborn infants were prospectively included in the control group.

Results: In the study group (n=106), 63.2% of the patients had organic acidemia, 20.8% urea cycle disorders, 4.7% mitochondrial diseases, 5.7% fatty acid oxidation disorders, and 5.7% other diseases, while the control group included 126 healthy term newborns. Mean serum indirect bilirubin levels were significantly lower in the study group compared to the control group (5.8±5.4 mg/dL vs 13.9±4.1 mg/dL, p<0.00, respectively). The frequency of phototherapy was 11.3% in the study group and 23.8% in the control group (p<0.05). While the incidence of jaundice was significantly lower in organic acidemia, urea cycle disorder, and fatty acid oxidation disorders (p<0.05), there was no difference in mitochondrial disease compared to the control group (p>0.05).

Conclusion: This was the first epidemiological study aiming to determine a very low incidence of neonatal jaundice in newborns with inherited metabolic diseases characterized by metabolic acidosis and/or hyperammonemia. The exact pathophysiological mechanism of this strikingly low incidence of indirect hyperbilirubinaemia in these newborns should be investigated with prospective biochemical, enzymatic, molecular, and genetic studies.

Keywords: Indirect hyperbilirubinemia, inherited metabolic diseases, metabolic acidosis, hyperammonemia, organic acidemia

Introduction

Physiologic jaundice is defined as indirect hyperbilirubinemia. It occurs due to neonatal bilirubin metabolism in term infants, appearing after 24 hours of age and it resolves by approximately 2 to 3 weeks of age. Neonatal indirect hyperbilirubinemia is the most common neonatal problem and it is observed in nearly 20-50% of term newborns in the first weeks of life (1,2). In Turkey,

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the frequency of jaundice requiring phototherapy in term newborn infants has been reported to range between 10-50% depending on the source (3-6).

Inherited metabolic diseases are a group of diseases which occur as a result of a deficiency of an enzyme or carrier protein in the synthesis or degradation pathways of protein, carbohydrate, and fat. Although their frequencies increase in certain racial and ethnic groups, especially in societies where consanguineous marriages are common, their general prevalence is 1:4,000-1:5,000 (7-9). Our unit is a reference center for pediatric inherited metabolic diseases in Turkey. For many years, we have noticed that indirect hyperbilirubinemia was very rare among newborns who had severe metabolic acidosis and/or hyperammonemia.

We thought that determining the accuracy of this very interesting observation could provide a different perspective on bilirubin metabolism and metabolic diseases. Therefore, we aimed to define the frequency of physiologic jaundice in newborns who had inherited metabolic diseases characterized by metabolic acidosis and/or hyperammonemia and compare this with the frequency of physiologic jaundice in healthy newborns.

Materials and Methods

This study was conducted in the divisions of Neonatology and Pediatric Metabolic Diseases and Nutrition covering the period between January 1st, 2001, and December 31st, 2014. The Hacettepe University Non-invasive Clinical Research Ethics Committee approved this study (approval no.: GO-14/410, date: 23.07.2014) and informed consent forms were obtained from the parents of each patient.

Study Group

The study group comprised term newborn infants who were hospitalized in the neonatal intensive care unit with a diagnosis of inherited metabolic disease which was characterized by metabolic acidosis and/or hyperammonemia within the first 28 days of life. Preterm infants and infants with congenital anomalies or chromosomal abnormalities were excluded.

In our unit, the diagnosis of metabolic disease is made by biochemical, metabolic, and molecular tests such as blood and urine amino acid levels, plasma lactic acid, and pyruvic acid levels, urine organic acid profile, plasma ammonium levels, carnitine profile and amino acid analysis, and genetic tests. The diagnosis of hyperammonemia was defined as a plasma ammonia level >100 µmol/L (10). The type of acid-base imbalance was determined according to the acid-base nomogram (11).

In the study group, demographic and clinical data [gender, gestational age, birth weight, intrauterine growth status (12)], delivery type, Apgar score at the 5th minute, the need for resuscitation at birth, the presence of perinatal hypoxia (13), clinical symptoms and signs, nutritional status (type of enteral feedings such as breast milk or formula), the development of indirect hyperbilirubinemia and the need for phototherapy or exchange transfusion, and laboratory data [complete blood count and peripheral blood smear, infant and maternal blood groups, serum total/direct and indirect bilirubin levels, glucose-6-P-dehydrogenase (G6PD) enzyme activity, serum thyroid-stimulating hormone (TSH) level, hepatic and renal function tests, blood gas analysis, plasma lactic acid, pyruvic acid, ammonia levels, urine and blood amino acids, tandem mass spectrometry and special metabolic examination results] were obtained from the medical records. The need for phototherapy or exchange transfusion for indirect hyperbilirubinemia and the prognosis (survival/mortality) of the patients were noted retrospectively (14).

Control Group

As the control group, healthy-term newborn infants who were born at the department of obstetrics on single days of the month between September 1st and December 31st 2014 were prospectively included. Newborns diagnosed with any diseases during the study period were excluded.

These newborn infants were followed for at least 2 days at the hospital. After discharge, they were followed by physical examination or by telephone call once every week in order to monitor for the development of neonatal hyperbilirubinemia until the end of the 28th day of life. Demographic data and nutritional characteristics (breast milk, breast milk + formula, or formula feeding) were noted. Laboratory examinations for hyperbilirubineamia were performed in cases with suspected physiologic jaundice during their follow-up.

In our unit, for those newborn infants with physiologic jaundice, complete blood count and peripheral blood smear, serum total bilirubin, direct bilirubin, and indirect bilirubin levels, infant and maternal blood groups, and direct Coombs test are routinely performed. In newborns requiring phototherapy, G6PD enzyme activity, serum TSH, and urine and blood amino acids are examined. The need for phototherapy or exchange transfusion is determined

according to the nomogram of the American Academy of Pediatrics, Clinical Practice Guideline, Subcommittee on Hyperbilirubinemia (14).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows 15.0, Chicago, USA) program. The Kolmogorov-Smirnov test was used to test the normality of the data distribution. Continuous parameters are presented as mean ± SD and median (25^{th} and 75^{th} percentile). Categorical parameters are presented as percentages. The Mann-Whitney U test was used to compare the two groups. The relationship between categorical variables was analyzed using X^2 test (Pearson chi-square, Fisher's exact chi-square). Statistical significance was accepted as $p<0.05$.

Results

The study group comprised 106 newborns with inherited metabolic diseases characterized by metabolic acidosis and/or hyperammonemia. A total of 156 babies were born during the study period. However, 30 babies with various diseases (congenital heart disease, genetic disease, etc.) were excluded from this study. The control group comprised 126 healthy-term newborns.

The demographic and clinical characteristics of the study and control groups are shown in Table I. Although the mean gestational ages of the two groups were similar, the mean birth weight in the study group was significantly lower than the control group as the frequency of small for gestational age infants was higher in the study group ($p<0.01$). The rate of cesarean delivery in the control group was higher ($p<0.05$).

The inherited metabolic diseases of the study group are given in Table II. The most frequent inherited metabolic disease group was organic acidemias and amino acid disorders (n=67, 63.2%). In the study group, 20 (18.9%) cases just had metabolic acidosis, 24 (22.6%) cases just had hyperammonemia and 30 (28.3%) cases had a combination of both metabolic acidosis and hyperammonemia.

Table I. Demographic and clinical characteristics of study and control groups

	Study group (n=106)	**Control group (n=126)**	**p value**
Gender (M/F), n (%)	60/46 (56.6/43.4)	69/57 (54.8/45.2)	0.779
Gestational age (weeks)*	38.6±1.2 (37.0-42.0)	38.5±0.9 (37.0-41.1)	0.242
Birth weight (grams)*	3.138±488 (2.015-4.230)	3.307±417 (2.450-4.630)	**0.005**
Small for gestational age, n (%)	12 (11.3)	2 (1.6)	**0.002**
Parental consanguinity, n (%)	68 (64.2)	16 (12.7)	**0.002**
Type of delivery (V/CS), n (%)	53/53 (50.0/50.0)	42/84 (33.3/66.7)	**0.010**
Apgar score (5^{th} min)*	9.8±0.7 (6-10)	9.8±0.6 (7-10)	0.459
Resuscitation at birth, n (%)	10 (9.4)	12 (9.5)	0.981
Perinatal hypoxia n (%)	1 (0.9)	-	0.457
Age at hospitalization (days)*	9.2±7.2 (0-28)	-	-
Hospitalization duration (days)*	13.5±9.8 (1-50)	2.2±1.1 (1-5)	-
Accompanying disorders, n (%) Blood culture (+) sepsis DIC Multiple organ failure	 28 (26.4) 32 (30.2) 17 (16.0)	 - - -	-
Blood pH*	7.29±0.16 (6.87-7.58)	-	-
Plasma HCO_3 level (mmol/L)*	17.8±7.6 (3.7-40.9)	-	-
Metabolic acidosis n (%)**	50 (47.2)	-	-
Plasma ammonia level (µg/dL)*	271 (34-2.554)	-	-
Hyperammonemia (>100 µmol/L), n (%)**	54 (50.9)	-	-
Mortality, n (%)	14 (13.2)	-	-

*Mean ± standard deviation,
**More than one laboratory abnormality can be found in each patient
V: Vaginal birth, CS: Caesarean section, DIC: Disseminated intravascular coagulation

Table II. Inherited metabolic diseases in the study group (n=106)	
Inherited metabolic diseases	**n (%)**
Organic acidemia and amino acid disorders Maple syrup urine disease (MSUD) Methylmalonic acidemia Propionic acidemia Isovaleric acidemia	67 (63.2) 29 (27.4) 18 (17.0) 14 (13.2) 6 (5.7)
Urea cycle disorders Carbamoyl phosphate synthetase deficiency (CPS 1) Ornithine transcarbamylase deficiency (OTC) Argininosuccinate synthase deficiency (ASS) Argininosuccinate lyase deficiency (ASL) Others	22 (20.8) 2 (1.9) 1 (0.9) 12 (11.3) 4 (3.8) 3 (2.8)
Fatty acid oxidation disorders	6 (5.7)
Mitochondrial disease	5 (4.7)
Others Congenital lactic acidosis Inherited disorders of gluconeogenesis Pyruvate carboxylase deficiency Glutathione synthetase deficiency	6 (5.7) 2 (1.9) 1 (0.9) 1 (0.9) 2 (1.9)

The comparison of the clinical and laboratory findings of the study and control groups in terms of neonatal hyperbilirubinemia is given in Table III. Laboratory examination was performed with the suspicion of physiologic jaundice in 78 of the term healthy newborns. The mean hemoglobin level was significantly lower and the frequency of hemolytic findings on peripheral blood smear was higher in the study group when compared to the control group (13.8±2.7 gr/dL vs 16.8±2.6 gr/dL, p<0.001, and 17.9% vs 3.2% p<0.01, respectively). However, serum mean total and indirect bilirubin levels and the frequency of phototherapy were found to be significantly lower in the study group (6.6±5.6 mg/dL vs 14.6±4.2 mg/dL, and 5.8±5.4 mg/dL vs 13.9±4.1 mg/dL, and 11.5% vs 23.8%, p<0.05, respectively).

The comparison of each inherited metabolic disease group in the study group and the control group in terms of neonatal hyperbilirubinaemia is shown in Table IV.

Table III. Clinical and laboratory findings of the study and control groups in terms of neonatal hyperbilirubinemia			
Clinical and laboratory findings	**Study group (n=106)**	**Control group (n=126)**	**p value**
Color of the skin, n (%) Normal (pink) Light (pale) Icteric (yellow)	 39 (36.8) 35 (33.0) 32 (30.2)	 42 (33.3) 9 (7.1) 75 (59.5)	 0.582 **0.000** **0.000**
Nutritional status Breast milk Breast milk + Formula Formula	 76 (71.7) 18 (16.9) 12 (11.4)	 69 (54.8) 37 (29.4) 20 (15.8)	 0.089 0.068 0.432
Onset (diagnosis) of jaundice (day)*	2.9±0.9 (2-5)	2.8±0.9 (1-5)	0.431
	n=106	**n=78**	
Hematocrit (%)*	40.5±7.9 (23.2-65.4)	50.3±8.0 (33.8-66.4)	**0.000**
Hemolytic findings on peripheral blood smear, n (%)	19 (17.9)	4 (3.2)	**0.001**
Maternal-fetal blood group incompatibility, n (%) Rh ABO Rh+ABO	10 (9.4) 3 (2.8) 6 (5.7) 1 (0.9)	31 (24.6) 13 (10.3) 15 (11.9) 3 (2.4)	0.696
Positive direct Coombs test, n (%)	1 (0.9)	4 (3.2)	0.068
G6PD deficiency, n (%)	-	1 (0.8)	1.000
High serum TSH, n (%)	3 (2.8)	3 (2.4)	0.082
Time of bilirubin measurement (day)	9.9±6.5 (1-28)	9.5±3.8 (1-28)	0.516
Total bilirubin (mg/dL)*	6.6±5.6 (0.2-22.0)	14.6±4.2 (7.1-27.6)	**0.000**
Direct bilirubin (mg/dL)**	0.6 (0.01-4.90)	0.6 (0.3-2.7)	0.541
Indirect bilirubin (mg/dL)*	5.8±5.4 (0.1-20.6)	13.9±4.1 (6.5-26.3)	**0.000**
Phototherapy, n (%)	12 (11.3)	30 (28.3)	**0.014**
Duration of phototherapy (hours)	32.0±11.8 (24-48)	34±16.9 (24-96)	0.712
Exchange transfusion, n (%)	-	-	-

*Mean ± standard deviation, **Median
G6PD: Glucose-6-P-dehydrogenase

Table IV. Comparison of specific inherited metabolic disease groups of the study group and control group in terms of neonatal hyperbilirubinemia

	Organic acidemia and MSUD[a] (n=67)	**Urea cycle disorders[b] (n=22)**	**Mitochondrial disease[c] (n=5)**	**Fatty acid oxidation disorders[d] (n=6)**	**Control group[e] (n=126)**	**p value**
Hemoglobin (gr/dL)*	13.4±2.4 (9.1-20.3)	15.4±3.2 (8.1-22.1)	12.4±2.4 (9.8-15.7)	12.7±1.9 (10.0-15.3)	16.8±2.6 (11.6-22.5)	**0.000**[a-e] 0.050[b-e] **0.001**[c-e] **0.000**[d-e]
Hematocrit (%)*	39.5±7.1 (27.9-60.4)	45.0±9.6 (23.2-65.4)	36.1±6.4 (28.1-44.0)	38.3±5.8 (30.0-46.4)	50.3±8.0 (33.8-66.4)	**0.000**[a-e] **0.017**[b-e] **0.000**[c-e] **0.001**[d-e]
Total bilirubin (mg/dL)*	6.3±6.0 (0.2-22.0)	6.7±4.9 (0.4-19.6)	6.9±5.9 (0.35-13.7)	5.9±2.6 (0.9-7.6)	14.6±4.2 (7.1-27.6)	**0.000**[a-e] **0.000**[b-e] **0.000**[c-e] **0.000**[d-e]
Direct bilirubin (mg/dL)**	0.4 (0.0-4.7)	0.8 (0.0-4.9)	0.8 (0.1-2.9)	0.8 (0.3-1.0)	0.6 (0.3-2.7)	0.052[a-e] **0.000**[b-e] **0.019**[c-e] 0.688[d-e]
Indirect bilirubin (mg/dL)**	4.1 (0.1-20.6)	4.3 (0.3-18.1)	6.9 (0.2-10.8)	6.1 (0.7-7.3)	13.8 (6.5-26.3)	**0.000**[a-e] **0.000**[b-e] **0.000**[c-e] **0.000**[d-e]
Clinical jaundice, n (%)	25 (37.3)	4 (18.2)	2 (40.0)	1 (16.7)	75 (59.5)	0.154[a-b] 0.795[a-c] 0.381[a-d] **0.001**[a-e] 0.299[b-c] 0.933[b-d] **0.000**[b-e] 0.409[c-d] 0.386[c-e] **0.039**[d-e]
Phototherapy, n (%)	10 (14.9)	2 (9.1)	-	-	30 (23.8)	0.571[a-b] 0.378[a-c] 0.335[a-d] 0.087[a-e] 0.492[b-c] 0.452[b-d] 0.123[b-e] 1.000[c-d] 0.216[c-e] 0.176[d-e]

*Mean ± standard deviation, **Median
[a]: Organic acidemia and MSUD, [b]: Urea cycle disorders, [c]: Mitochondrial disease, [d]: Fatty acid oxidation disorders, [e]: Control group
MSUD: Maple syrup urine disease

In the study group, the mean hemoglobin and hematocrit levels were significantly lower in all disease groups except for urea cycle disorders ($p<0.001$). The mean total and median indirect bilirubin levels were found to be significantly lower in all disease groups than in the control group ($p<0.001$). While the frequency of jaundice was significantly lower in the organic acidemia, urea cycle disorder, and fatty acid oxidation disorder groups when compared to the control group ($p<0.05$), there was no difference for mitochondrial disease ($p>0.05$). The frequency of phototherapy was lower in the inherited metabolic disease groups compared to the control group, but no statistically significant difference was found ($p>0.05$).

Discussion

This is the first epidemiological study in the literature which has demonstrated that the incidences of neonatal jaundice and the need for phototherapy are very low in newborns

with certain inherited metabolic diseases characterized by metabolic acidosis and/or hyperammonemia. In most of these infants, serum indirect bilirubin levels were found to be even lower than the physiological levels. In our unit, the incidence of neonatal hyperbilirubinemia requiring phototherapy or exchange transfusion has been reported to be nearly 25% (15). However, our observation about the low incidence of neonatal hyperbilirubinemia in newborn infants with some inherited metabolic diseases has been an overlooked detail for many years.

In the literature, we could not find any research investigating the incidence of neonatal jaundice in cases of inherited metabolic diseases. We find it interesting that this topic had not attracted the attention of researchers until this time. Essentially, our research was mainly an epidemiological study, and therefore our discussion about the possible mechanisms of 'low indirect bilirubin levels in newborn infants with some inherited metabolic diseases' would be theoretical and speculative, depending on the existing literature.

This situation might be explained by the following possible enzymatic and genetic changes in heme metabolism; 1) HO enzyme inhibition, 2) Biliverdin reductase inhibition, 3) UDP-glucuronyltransferase (UDPGT) activation, 4) Beta-glucuronidase inhibition and reduction of enterohepatic circulation, and 5) Genetic polymorphisms or mutations which lead to metabolic changes.

Bilirubin production begins with the conversion of the heme ring into biliverdin by the microsomal rate-limiting HO enzyme (16,17). It has been accepted that HO-1, one of the three isoforms of the enzyme, and its enzymatic products; biliverdin and carbon monoxide, have important biological roles in the interaction between cells during vascular endothelial structuring. HO-1 is present in all tissues and vascular smooth muscle cells and it is regulated by hypoxia, inflammation, oxidant mediators, nitric oxide, and hemodynamic forces. It has been shown that extracellular acidosis and hypoxia induce HO-1 expression (18-22). In one study, the half-life of HO-1 mRNA increased from 3.5 hours to 6.5 hours by lowering the extracellular pH from 7.4 to 6.8 (23). Based on studies like this, it can be thought that extracellular acidosis may cause an increase in bilirubin production. However, this finding is not compatible with our pathophysiological hypothesis (inhibition of HO) or the results of our study. The effects of metabolic acidosis on HO-1 enzyme activity in other cells are not known.

Another step in bilirubin production is the reduction of biliverdin to bilirubin by the cytosolic biliverdin reductase enzyme. In human biliverdin reductase studies, with the use of urea as a denaturing agent, the enzyme activity increases up to 3.5 M urea concentration and decreases enzyme activity at higher concentrations (24). This finding is also against our pathophysiological hypothesis. In this case, in urea cycle disorders characterized by low serum urea levels, an increase in serum bilirubin level should have been observed due to the increase in biliverdin reductase enzyme activity. However, in our study, the mean serum indirect bilirubin level in cases with urea cycle disorder was found to be quite low compared to the control group.

The function of UDPGT, an enzyme responsible for the conversion of indirect to direct bilirubin, drug metabolism, and detoxification in the liver, is genetically determined by single gene polymorphisms and these lead to functionally altered protein or expression levels (25). In rat astrocyte cell culture, with an increase in the synthesis of proinflammatory cytokines and free oxygen radicals in the inflammation induced by lipopolysaccharide, glucuronidation activity also increased. It has been determined that this occurs with an increase of the mRNA of the UGT1A6 isoform (26). In addition, UGT1A1 activity was increased in diabetic and fasting rats in animal studies (27). In our study, it can be thought that metabolic acidosis, hyperammonemia, and accompanying infections induced UGT1A1 activity in the liver by increasing the inflammatory response and this contributed to the decrease in the indirect bilirubin level. However, this pathophysiological mechanism cannot be considered to be responsible for the entire clinical status. Furthermore, this mechanism does not explain the increased incidence of indirect hyperbilirubinemia in otherwise healthy newborns with neonatal sepsis or urinary tract infections.

Phenobarbital is one of the most important anticonvulsant drugs used in newborn infants. In addition, it induces the activity of the UGT1A1 enzyme and is therefore an important drug in newborns with prolonged indirect hyperbilirubinemia of unknown cause (28). In our study, phenobarbital was given as an anticonvulsant drug in 24.5% of the newborns with inherited metabolic diseases. It is suspected that phenobarbital could be one of the factors contributing to the low levels of indirect bilirubin levels in the study group.

Studies have shown that hyperammonemia causes disturbances in bilirubin metabolism in hepatocytes, but its pathophysiological mechanism is not known exactly (29). It is thought that the increase in ammonia affects the expression of enzymes in bilirubin metabolism by reducing energy synthesis. In another study, hyperammonemia was found to inhibit cell growth, induce

apoptosis, damage the mitochondria, and lead to a reduction in energy synthesis, eventually affecting the expression of enzymes related to bilirubin metabolism (30). "Multidrug resistance protein 2 (MRP2)" is an adenosine triphosphate dependent pump which enables the excretion of bilirubin glucuronides from hepatocytes to the bile ducts. Ammonia affects MRP2 expression by decreasing energy synthesis and it causes an increase in conjugated bilirubin in the serum by decreasing bilirubin excretion (31-33). Consistent with this information, the mean conjugated bilirubin level in urea cycle disorders was significantly higher than the control group, but the mean indirect bilirubin level was significantly lower than the control group.

The β-glucuronidase enzyme, which is present in high levels in the small intestine in newborns, converts conjugated bilirubin in its mono- or diglucuronide form back into unconjugated bilirubin, allowing it to enter enterohepatic circulation. This physiological event contributes to the development of physiological neonatal jaundice by increasing the indirect bilirubin load in the plasma and must be conjugated in the liver (34). There is no research in the literature on the activity of the β-glucuronidase enzyme or its genetic polymorphisms which alter activity in newborns with inherited metabolic disease. Theoretically, in the study group, it was expected that there was insufficient enteral nutrition due to feeding difficulties and vomiting which started in the first days of life. This leads to an increase in enterohepatic circulation and leads to a tendency to indirect hyperbilirubinemia. However, in the vast majority of these newborns, the indirect bilirubin level remained well below the physiological levels. Consequently, the hypothesis of β-glucuronidase inhibition is unlikely to be valid in the pathophysiological process.

In our study, the frequency of phototherapy was found to be similar in those cases with metabolic acidosis or hyperammonemia and those without. This finding suggests that the lower frequencies of physiologic jaundice and phototherapy in newborns with inherited metabolic diseases could be due to the primary metabolic disease rather than metabolic acidosis or hyperammonemia. There is no study on genetic polymorphisms or mutations related to both metabolisms in these infants. Therefore, it is difficult to comment on this issue.

Study Limitations

The most important limiting aspect of our study was its retrospective evaluation of a part of the study group. It is recommended to investigate the alteration of heme metabolism with prospective biochemical and molecular studies in large case series.

Conclusion

Many studies have shown that many enzymes involved in heme metabolism and indirect bilirubin have antioxidant and anti-inflammatory effects (35-38). However, the neurotoxic effect of high indirect bilirubin levels in newborns is also well known. The levels of indirect bilirubin which are beneficial as an antioxidant and those which are harmful as a neurotoxic molecule for the newborn are unknown. We wonder if the low indirect bilirubin levels we have determined in those newborns with inherited metabolic diseases characterized by metabolic acidosis and/or hyperammonemia are beneficial or detrimental to these newborns. The answers to these questions should be investigated with prospective biochemical, enzymatic, molecular, or genetic studies in light of the findings of our study.

Key message: Although it is the most frequent neonatal disorder, the frequency of neonatal jaundice has been observed to be lower in newborns with inherited metabolic diseases characterized mainly by metabolic acidosis and/or hyperammonemia.

Ethics

Ethics Committee Approval: EThe Hacettepe University Non-invasive Clinical Research Ethics Committee approved this study (approval no.: GO-14/410, date: 23.07.2014).

Informed Consent: Informed consent forms were obtained from the parents of each patient.

Authorship Contributions

Concept: G.K.Ö., A.K., Design: G.K.Ö., A.K., Data Collection and/or Processing: G.K.Ö., A.K., Analysis and/or Interpretation: G.K.Ö., A.K., H.T.Ç., Ş.Y., M.Y., T.C., Literature Search: G.K.Ö., A.K., Writing: G.K.Ö., A.K.

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