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Effect of bilirubin levels in infants on spontaneous activity assessed by the Prechtl method

Wpływ stężenia bilirubiny u noworodków na aktywność spontaniczną ocenianą metodą Prechtla

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Abstract

Introduction: Neonatal jaundice is characterised by a yellow coloration of the skin, mucous membranes, and sclera of the eye resulting from the accumulation of bilirubin in the body. When produced in significant excess, bilirubin can accumulate in the central nervous system causing kernicterus (bilirubin encephalopathy). The diagnosis of jaundice based only on the visual assessment of the degree of yellowing of the skin or sclera and the urine output is not a reliable method. Even the assessment by experienced observers does not correlate with actual measurements of serum bilirubin levels. Therefore, a study was undertaken to determine whether other parameters could clarify the diagnosis of neonatal jaundice during the observation of an infant. **The aim of this study** was to analyse the effect of bilirubin levels on motor activity of the infants studied in terms of the quality of motor patterns assessed using the Prechtl method. **Materials and methods:** The research procedure was multistage and included a retrospective analysis of neonatal medical records, transcutaneous measurement of bilirubin levels, and analysis of neonatal activity performed based on video recordings. A qualitative assessment of neonatal spontaneous activity was performed using the Prechtl GMA method (general movement assessment). The research procedure consisted of two stages. The first stage involved selecting infants who had a good general health status. Based on these criteria, a total of 125 infants were included in the video recording. The second stage of study inclusion took place after video recording. Infants with short periods of wakefulness, prolonged crying, and lying on their side were excluded from further examinations. Ultimately, 52 infants were included in the study. All infants were subjected to the diagnostic method proposed by Prechtl to determine the effect of bilirubin levels on their motor activity. **Conclusion:** Bilirubin levels in the course of physiological jaundice did not affect the quality of motor repertoire in the group of infants studied. Therefore further research is needed.

Keywords: infant, physiological jaundice, motor activity, neurodevelopmental diagnosis of infants

Streszczenie

Wstęp: Żółtaczka noworodków charakteryzuje się żółtym zabarwieniem skóry, błon śluzowych oraz twardówki oka, wynikającym z gromadzenia się bilirubiny w organizmie. Wytwarzana w znacznym nadmiarze bilirubina może się gromadzić w ośrodkowym układzie nerwowym, powodując *kernicterus* (encefalopatię bilirubinową). Rozpoznanie żółtaczki wyłącznie na podstawie wzrokowej oceny stopnia zażółcenia powłok skórnych i twardówki oraz ilości oddawanego moczu nie jest metodą miarodajną. Nawet ocena dokonywana przez doświadczonych obserwatorów nie koreluje z rzeczywistymi pomiarami stężenia bilirubiny w surowicy krwi. Dlatego podjęto badania, aby sprawdzić, czy istnieją inne parametry, które mogą być miarodajne w ocenie żółtaczki noworodków podczas obserwacji dziecka. **Celem badań** była analiza wpływu stężenia bilirubiny na aktywność ruchową badanych noworodków w zakresie jakości wzorców motorycznych ocenianych metodą Prechtla. **Materiał i metody:** Postępowanie badawcze przebiegało wieloetapowo i obejmowało analizę retrospektywną dokumentacji medycznej noworodków, przezskórny pomiar stężenia bilirubiny oraz analizę aktywności noworodków

przeprowadzoną na podstawie nagrań wideo. Jakościowej oceny aktywności spontanicznej noworodka dokonano z wykorzystaniem oceny globalnych wzorców ruchowych metodą Prechtla. Procedura badawcza przebiegała w 2 etapach. Pierwszy etap polegał na kwalifikacji do badań noworodków, które były w dobrym stanie ogólnym. Według tych kryteriów do rejestracji wideo włączono 125 dzieci. Drugi etap kwalifikacji do badań nastąpił po wykonaniu rejestracji wideo. Do dalszych badań nie włączono noworodków z krótkotrwałymi okresami czuwania, wydłużonym okresem płaczu oraz ułożonych na boku. Ostatecznie do badań włączono 52 noworodki. Wszystkie noworodki zostały poddane diagnostyce metodą Prechtla w celu ustalenia wpływu wartości stężenia bilirubiny na ich aktywność ruchową. **Wnioski:** Stężenie bilirubiny w przebiegu żółtaczki fizjologicznej w badanej grupie noworodków nie miało wpływu na jakość repertuaru ruchowego, dlatego należy przeprowadzić dalsze badania w tym zakresie.

Słowa kluczowe: noworodek, żółtaczka fizjologiczna, aktywność ruchowa, diagnostyka neurorozwojowa niemowląt

INTRODUCTION

Neonatal jaundice is characterised by a yellow coloration of the skin, mucous membranes, and sclera of the eye resulting from the accumulation of bilirubin in the body. A healthy infant produces approximately 6–10 mg bilirubin/kg BW/day. Produced in significant excess, bilirubin causes critical values to be reached, resulting in its accumulation in the central nervous system and causing kernicterus, which is a serious clinical condition leading to neurological problems. It is known that neonatal jaundice progresses in the cephalocaudal direction, that is, first we observe yellowing of the skin on the baby's face and neck, then chest, umbilical region, lower abdomen, and limbs. If the distal parts of the infant's body are yellowed, it is reasonable to assume that bilirubin levels are elevated[1]. The visual assessment of neonatal jaundice is aided by the Kramer scheme, used since the 1970s, which was developed from studies of populations of healthy children and is correlated with the approximate serum bilirubin levels depending on the area of skin yellowing in the infant[2,3]. Early clinical signs of hyperbilirubinaemia include reluctance to suckle, apathy, hypotonia, and impaired reflexes, all of which resolve with prompt initiation of treatment. The diagnosis of jaundice based only on visual assessment of the degree of yellowing of the skin or sclera and the urine output is not a reliable method. Even the assessment of experienced investigators does not correlate with actual measurements of serum bilirubin levels[4]. Therefore, in infants with markedly yellow skin, transcutaneous bilirubin (TcB) measurement is performed, which significantly limits the frequency of blood sampling necessary to control the bilirubin level[5]. Jaundice is observed in 60–70% of full-term and 80% of preterm infants. The occurrence of jaundice in infants without abnormalities diagnosed in laboratory examinations and in good clinical condition is a physiological phenomenon. Physiological jaundice does not require any treatment[6].

The study was undertaken to find out whether other parameters could further improve the diagnosis of neonatal jaundice during the observation of an infant. Therefore, the spontaneous activity of infants was analysed.

AIM OF THE STUDY

The aim of this study was to analyse the effect of transcutaneously measured bilirubin levels on motor activity of the infants studied in terms of the quality of motor patterns assessed using the Prechtl method.

MATERIALS AND METHODS

The research procedure was multistage and included a retrospective analysis of neonatal medical records, transcutaneous measurement of bilirubin levels, and analysis of neonatal activity performed based on video recordings.

A retrospective analysis of medical records was performed among infants hospitalised in the neonatal ward of the Piekary Medical Centre (Piekarskie Centrum Medyczne Sp. z o.o.) at St. Luke Municipal Hospital in Piekary Śląskie. Data were collected from the medical records of infants born during the examination conducted in 2019 and 2020. The study was approved by the University's Bioethics Committee for Scientific Research at the Academy of Physical Education in Katowice (Decision No. 5/2018 of 19 April 2018). The study included infants who were in good general condition, without perinatal complications, on the second or third days of life, born between 37 and 42 weeks of gestation, scored at least 8 on the Apgar scale, and whose parents gave written consent.

Bilirubin levels were evaluated based on transcutaneous bilirubin (TcB) measurements performed with a Minolta JM-103 jaundice meter according to Kramer's method consisting of bilirubin measurements in different parts of the body. In the examinations according to the Kramer protocol, the following ranges of bilirubin were adopted as normal: 4–8 mg/dL on the head, 5–12 mg/dL on the chest, 8–16 mg/dL on the abdomen, 11–18 mg/dL on the limbs, and more than 18 mg/dL on the hands and feet[3]. The head measurement was considered crucial for the classification of infants into the jaundice group. The procedure was justified by the fact that the infants were examined on the 2nd or 3rd day of life, and jaundice appeared first on the head and then on the chest, abdomen, and hands and feet[7].

Furthermore, the analysis of neonatal activity was based on video recordings with a Sony HDR-AS200V camera with

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Full HD 1080p resolution (1,920 × 1,080, 60 fps). The measuring station for recording the infant consisted of a tabletop measuring 1 × 1 m and a rack with a mounted camera mounting system, placed at a height of 1 m above the tabletop surface. At the time of recording, the infant was placed in the supine position in a hospital crib on the measuring station. The station was set up in a designated area in the neonatal ward throughout the study period. During the examination, the infant had only a disposable diaper on and was lying on a blanket, the corners of which were wrapped under the mattress of the hospital bed so that nothing restricted his or her movements. The infant was examined upon awakening and after feeding. The environmental conditions during the examination, i.e. temperature, lighting, and noise level, were in accordance with the regulations of the neonatal ward to ensure physical and psychological comfort to the infants. The examination was performed with respect for the dignity and intimacy of the infant being examined. During the recording, the infant was under the supervision of the investigator, who ensured that the infant was not crying or sucking on a pacifier or being touched by the researcher, parent/legal guardian or other people. The examination was non-invasive and carried no risks identified to date. Since meeting the above conditions was difficult due to the age of the subjects, it was decided that the recording would last about 10 minutes, from which three-minute sections of the study were selected. The recording time needed for the analysis according to the Prechtl general movement assessment (GMA) method was set at 3 minutes of undisturbed observation of the infant in the state of active wakefulness (eyes open, no crying – levels 3 and 4 according to the Prechtl classification of infant behaviour)[8,9]. A qualitative assessment of neonatal spontaneous activity was performed using the Prechtl GMA method. The method involves assessing the integrity of the infant's nervous system by evaluating global movements (GMs) from pre-recorded videos. GMA is a recognised tool used in early infant diagnosis[8]. GMs are a component of a child's spontaneous activity as early as at 9–12 weeks' postmenstrual age. They are characterised by a variety of movements of the upper and lower limbs, and body trunk. Their intensity, strength, and speed increase and decrease, and they have a gradual beginning and end. These are mostly complex sequences of limb extension and flexion movements with rotations. These components make movement smooth, and give the impression of complexity and variability[8,9]. From the day of birth until 6–9 weeks of age (post-term age), general movements (GMs) are termed writhing movements (WMs). WMs are characteristic of normal development and are referred to as normal general movements (N). They are characterised by small to moderate movement amplitude, and slow to moderate speed. Rapid and large limb extension movements can be occasionally observed. Writhing movements are in the form of an ellipse, which creates an impression of the writhing quality of movement[9,10].

Abnormal global movements observed in the above age group included poor repertoire (poor repertoire, PR), chaotic movements (chaotic, Ch), and synchronised contraction (cramped-synchronised, CS). Poor repertoire is characterised by motion sequences in which the movements of the individual parts of the body are not sufficiently complex, while the variation of speed and amplitude is reduced. Chaotic movements refer to movements of all limbs with great amplitude, uncoordinated and sudden. Synchronised contraction is a term describing torn and fluid motions. They are characterised by the simultaneous contraction and relaxation of all muscles of the limbs and trunk[9,10].

Fifty-two recordings, with three-minute segments of undisturbed spontaneous neonatal activity were included in the analysis. The research team consisted of five physiotherapists experienced in using the above-mentioned method. Three-minute sections of the recordings were independently assessed by three of five physiotherapists who independently analysed every recording and assessed the infant's spontaneous movements for the presence of writhing or poor repertoire movements. No chaotic or cramped-synchronised movements were observed in any of the recordings. In the case of disagreements in the assessment of the video, the disputed video was analysed again and evaluated jointly by the same three experts. Finally, the infants were divided into two groups: the PR group, where poor repertoire was found, and the N group, where writhing movements were observed.

A bilirubin comparison between the PR and N groups was performed. The data obtained was entered into Microsoft Excel tables and analysed with R in the RStudio environment. Statistical analysis was performed using Student's *t*-test and Mann–Whitney *U* test to compare the quantitative variables in two groups – the Mann–Whitney *U* test was computed in cases where one of the following assumptions was not fulfilled: distribution normality (Shapiro–Wilk test), variance homogeneity (*F* test) or group number equality (chi-squared test). The independence of two nominal variables was assessed using Fisher's exact test. The relationship between the quantitative variable and the nominal dichotomous variable was verified on the basis of the point-biserial correlation coefficient. The significance level was set to alpha = 0.05. In case of statistical significance of a test, the effect size was evaluated and only effects larger than or equal to moderate were reported.

The research procedure consisted of two stages. The first stage was to select infants who had a good general health status, without perinatal complications, on the 2nd or 3rd days of life, born between 37 and 42 weeks of gestation, and scored at least 8 on the Apgar scale. Based on these criteria, a total of 125 infants were included in the study for video recording at this stage. Among the eligible infants, there were 52% (n = 65) females and 48% (n = 60) males. In this group of infants, the mean birth weight was 3,401.6 g and body length was 55.46 cm (Tab. 1).

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Parameter	*M*	*SD*	Min	Max	Q25	*Me*	Q75
Body mass [g]	3,401.60	463.62	2,160.00	4,380.00	3,150.00	3,360.00	3,740.00
Body length [cm]	55.46	2.70	46.00	62.00	54.00	56.00	57.00
Head circumference [cm]	33.61	3.35	0.00	37.00	33.00	34.00	35.00
Chest circumference [cm]	33.80	1.78	27.00	37.00	33.00	34.00	35.00
Apgar score [points]	9.96	0.23	8.00	10.00	10.00	10.00	10.00
M – mean; ***SD*** – standard deviation; **Min** – minimum; **Max** – maximum; **Q25** – first quartile; ***Me*** – median; **Q75** – third quartile.							

*Tab. 1. Characteristics of infants included in the first stage of the study (*n *= 125)*

Infants (*n* = 52)	*M*	*SD*	Min	Max	Q25	*Me*	Q75
Body mass [g]	**3,392.31**	**465.53**	**2,300**	**4,380**	**3,087.5**	**3,300**	**3,757.5**
Body weight of infants with normal bilirubin [g]	3,497.5	405.37	2,780	4,200	3,125	3,630	3,750
Body weight of infants with above-normal bilirubin [g]	3,345.56	487.91	2,300	4,380	3,087.5	3,200	3,757.5
Body length [cm]	**54.69**	**7.38**	**5**	**60**	**54**	**56**	**57**
Body length of infants with normal bilirubin [cm]	54.08	8.72	54.08	59	54	56	57
Body length of infants with above-normal bilirubin [cm]	56.06	2.17	52	60	54.75	56	57.25
Head circumference [cm]	**33.76**	**1.34**	**31**	**37**	**33**	**34**	**34.25**
Head circumference of infants with normal bilirubin [cm]	33.71	1.39	31	37	33	34	34
Head circumference of infants with above-normal bilirubin [cm]	33.88	1.26	31	36	33	34	35
Chest circumference [cm]	**33.87**	**1.61**	**31**	**37**	**33**	**34**	**35**
Chest circumference of infants with normal bilirubin [cm]	33.67	1.79	31	37	33.67	1.79	31
Chest circumference of infants with above-normal bilirubin [cm]	34.31	1.01	33	37	34	34	35
Apgar score [points]	**9.94**	**0.31**	**8**	**10**	**10**	**10**	**10**
Apgar score of infants with normal bilirubin	10	0	10	10	0	10	10
Apgar score of infants with above-normal bilirubin	9.81	0.54	8	10	10	10	10
M – mean; ***SD*** – standard deviation; **Min** – minimum; **Max** – maximum; **Q25** – first quartile; ***Me*** – median; **Q75** – third quartile.							

*Tab. 2. Characteristics of infants included in the second stage of the study (*n *= 52) according to body mass, body length, head and chest circumference, and Apgar score*

The second stage of the research procedure took place after video recording. Based on the analysis of the research material, infants with short periods of wakefulness, prolonged crying, and lying on their side were excluded from further examinations. Ultimately, a total of 52 infants were included in the study (24 females and 28 males). The mean birth weight in this group was 3,392.31 g, body length was 54.69 cm, head circumference was 33.76 cm, and chest circumference was 33.87 cm (Tab. 2).

In the group of infants included in the second phase of the study (n = 52), the mean bilirubin level measured transcutaneously on the head in the frontal region was 6.6 mg/dL. However, in the group of infants with above normal bilirubin levels (n = 16), the mean value was 9.51 mg/dL (with the normal range up to 8 mg/dL) (Tab. 3, 4). The transcutaneous bilirubin measurements were conducted between 25 and 72 hours of infants' life.

RESULTS

We analysed the effect of bilirubin levels on neonatal spontaneous activity in terms of speed, acceleration, motor indices, and motor pattern quality. The transcutaneous screening protocol involved the measurement of TcB, excluding the areas of skin with nevi, bruising, or any other abnormality present, as recommended by the device manufacturer. In the study group of infants, bilirubin levels were measured transcutaneously on the head in the frontal region, and data were obtained on the mean bilirubin level, which was 6.6 mg/dL (6.21 mg/dL in female infants and 6.93 mg/dL in male infants).

The effect of the child's classification in the normative range of bilirubin on motor activity was investigated using video recordings based on the Prechtl method (Tab. 5).

Inclusion in a normative group with respect to bilirubin levels in the head does not affect motor activity, understood as classification in the group with normal or low movement repertoire. In addition, a low point-two-series correlation coefficient in combination with a p-value at the significance limit indicates that there is no correlation between the variables (Tab. 6).

DISCUSSION

Infants are at high risk for significant hyperbilirubinemia Therefore, the evaluation of bilirubin levels in infants is important, as they change during the subsequent days of life and may not reach their maximum until the day of discharge from the hospital. Consequently, it is essential to perform appropriate clinical assessment of the child's

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Bilirubin level [mg/dL]	*M*	*SD*	Min	Max	Q25	*Me*	Q75
Bilirubin, transcutaneous evaluation at the head ($n = 52$)	6.60	2.68	0	11.40	5.40	6.70	8.40
Above-normal bilirubin, transcutaneous evaluation at the head ($n = 16$)	9.51	1.04	8.1	11.40	8.85	9.35	9.95
Normal bilirubin, transcutaneous evaluation at the head ($n = 36$)	5.31	2.10	0	8	3.80	6.15	6.73
M – mean; ***SD*** – standard deviation; **Min** – minimum; **Max** – maximum; **Q25** – first quartile; ***Me*** – median; **Q75** – third quartile.							

Tab. 3. Characteristics of infants included in the study according to the normal transcutaneous bilirubin level assessed on the head in the frontal region

Transcutaneous evaluation of bilirubin level on the head [mg/dL]	*M*	*SD*	Min	Max	Q25	*Me*	Q75
Infants ($n = 52$)	6.60	2.68	0	11.40	5.40	6.70	8.40
Female infants ($n = 24$)	6.21	2.54	0	10.80	5.33	6.50	7.52
Male infants ($n = 28$)	6.93	2.79	0	11.40	5.40	6.85	9.07
M – mean; ***SD*** – standard deviation; **Min** – minimum; **Max** – maximum; **Q25** – first quartile; ***Me*** – median; **Q75** – third quartile.							

Tab. 4. Bilirubin levels measured by transcutaneous method on the head in the frontal region of infants by sex

Prechtl assessment	Transcutaneous evaluation of bilirubin level on the head [mg/dL]						
	M	*SD*	Min	Max	Q25	*Me*	Q75
N ($n = 23$)	5.78	2.77	0.0	10.8	3.8	6.5	7.1
PR ($n = 29$)	7.25	2.45	1.4	11.4	6.1	7.2	9.0
N – normal, **PR** – poor repertoire; ***M*** – mean; ***SD*** – standard deviation; **Min** – minimum; **Max** – maximum; **Q25** – first quartile; ***Me*** – median; **Q75** – third quartile.							

Tab. 5. Bilirubin levels measured by transcutaneous method on the head in the frontal area of infants, depending on the Prechtl assessment

Classification in the normative range of bilirubin	Assessment according to Prechtl			
	N (*n*)	PR (*n*)	N (%)	PR (%)
Normal bilirubin by transcutaneous head assessment	17	19	33	37
Above normal bilirubin in the transcutaneous assessment on the head	12	4	23	8
Level of statistical significance	Fisher's exact test, p-value = 0.077		Chi-square test of independence, p-value = 0.119	
N – normal; **PR** – poor repertoire.				

Tab. 6. Classification in the N or PR group according to the Prechtl assessment with reference to classification in the normative range of bilirubin measured on the head in the frontal area

well-being and behaviour to look for features indicative of jaundice. The management includes a visual assessment of yellowing of the skin and sclera, apathy, reluctance to suck, and reduced urine output. Clinical examination of the infant for jaundice should be done, if possible, in bright, natural light, especially in babies with darker skin tones[11].

This raises the question of whether an experienced investigator is able to assess the level of neonatal jaundice based solely on a visual assessment of the degree of yellowing of the skin. In order to make the observation of the infant more accurate, our study attempted to analyse the spontaneous activity of the infant using the Prechtl assessment method.

In the study, the highest bilirubin level measured on the head in the frontal region was 11.4 mg/dL (normal range: 4–8 mg/dL). It may be conjectured that slightly elevated bilirubin levels do not differentiate infants in terms of global movements. In the available literature, there are no reports of motor disorders in infants with slightly elevated bilirubin levels. There are described syndromes of bilirubin-induced neurologic dysfunction (BIND) in infants with moderate hyperbilirubinemia who presented impaired sucking reflex, numbness, sleeplessness, and hypotonia[12–14], and acute bilirubin encephalopathy (ABE) in infants with severe hyperbilirubinaemia, whose symptoms are similar to BIND during the first days, later progressing to coma, high-pitched crying, and hypertonia[15]. Both qualitative analysis of motor patterns (writhing movements) and quantitative analysis (evaluation of kinematic parameters) showed no statistically significant differences between infants with normal and elevated bilirubin levels.

The experts selected infants with normal (N) movements and poor repertoire (PR). However, different motor levels did not show any associations with bilirubin levels. The proposed methodology for the evaluation of kinematic parameters of limb movements allowed for the analysis of differences in velocity and acceleration between the group of infants with elevated and normal bilirubin levels. The analysis revealed no significant differences between these parameters. Slightly exceeded bilirubin levels do not significantly affect the kinematic parameters of the infants' spontaneous motor activity. However, the accuracy of the measurement method used in our study, as well as the impact of the activity conditions limit the opportunities for observing possible small changes in velocity in cases of neonatal physiological jaundice.

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Therefore, transcutaneous bilirubin measurements have been conducted for many years as a screening test for neonatal physiological jaundice, reducing the need for invasive blood sampling for testing[16,17]. Most researchers note that TcB is the best way to avoid unnecessary blood sampling, thus reducing stress for infants and their caregivers alike. This management also reduces the cost of medical care and, most importantly, is performed without risk to the health and life of the infant[18–20]. Furthermore, as the early discharge of infants from the hospital is a common practice, transcutaneous bilirubinometry becomes a screening test that can be performed during home visits. Maisels et al. took a similar position and recommended TcB measurements as a first-line screening tool to determine whether TSB should be measured[20]. Furthermore, Romagnoli et al. reported that the highest sensitivity of TcB measurements was achieved after 60 hours of infant life[21]. In our study, transcutaneous bilirubin measurement of infants was conducted between 25 and 72 hours of their life. Afanetti et al. demonstrated that transcutaneous bilirubinometry was a safe and cost-effective screening method for severe hyperbilirubinemia in preterm and full-term infants of diverse ethnicity[22]. Also Cat et al., based on a study on 105 infants, found that TcB measurement was a reliable parameter for the evaluation of jaundice[23].

CONCLUSIONS

1. Bilirubin levels in physiological jaundice did not affect the quality of motor repertoire in the group of infants studied.
2. No correlation was found between the neonates classified in the normative group of head bilirubin levels and their motor activity as measured by the Prechtl method, as the group is small and the quality of the movement repertoire is difficult to assess, i.e. brief waking phases, prolonged screaming, and the lateral position of the newborns examined.

Conflict of interest

The authors report no financial or personal relationships with other persons or organisations that could negatively influence the content of the publication and claim rights to this publication.

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