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Original Articles

# FOLLOW-UP OF NEUROPSYCHOLOGICAL DEVELOPMENT DURING THE FIRST POSTNATAL YEAR IN INFANTS WITH NEONATAL JAUNDICE

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## Summary

It is believed that 98% of newborns have elevated serum bilirubin levels, but only about 60% have clinic of jaundice. Severe late neurological effects should not be observed if the serum bilirubin levels are well controlled. To follow-up the motor and mental development during the first year of life in infants suffered from neonatal jaundice. The study includes 92 term babies, divided in four groups: A – without jaundice, B – with jaundice treated by phototherapy in the 1st week , C – intensive jaundice during the first 14 postnatal days , D – intensive prolonged jaundice . Studied indicators: birth weight , gestational age, sex, delivery mode, Apgar score, maternal age and education, domicile, bilirubin serum levels during hospital stay, transcutaneous bilirubin levels ambulatory. Neuro-psychological development was assessed monthly until the 1-year-age.We found that groups were comparable across the all indicators except for residence, with significant difference for groups B and D. There was a statistically significant development delay in the Group D compared to the other three groups in the all studied age periods. All the cases of prolonged jaundice were resolved until the age of 3rd month. According to our data, prolonged jaundice compromises the first-year-psychomotor-development of the infants.

**Key words:**jaudice, infant, follow-up

## Introduction

Neonatal jaundice is clinically presented by a yellowish discoloration of the skin, mucous, and sclera in newborns, which is caused by high serum bilirubin levels.

Icterus can be observed in newborns when the total bilirubin level is 5.0-6.0 mg/dL (86-102 μmol/L) and more [1, 2]. Clinically manifested neonatal jaundice is present in approximately 60% of term newborns and 80% of premature newborns [2]. Neonatal jaundice is one of the main reasons for unscheduled doctor visits during the first month of life [3].

Physiological neonatal jaundice occurs after the 24th hour of birth. The peak is between the 3rd and the 6th day, and jaundice resolves around the 14th day. Icterus prolongs if the serum levels of total bilirubin stay above 171 μmol/L after the 14th day in term

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newborns or the 21st day in premature babies. The frequency of prolonged icterus ranges from 2 to 15% [4].

Follow-up aims to strictly observe the neuro-psychological development of children aged 0 to three years. The motor, sensory, emotional-social and speech development are evaluated dynamically [5, 6]. Neonatal jaundice is an important clinical problem, and the question arises whether clinically manifested neonatal jaundice may compromise developmental outcomes.

The aim of that study was to follow-up the neuropsychological development during the first year of life in infants who had neonatal jaundice.

## Material and Methods

This prospective 1-year study included patients treated in Medica University Hospital, Rousse.

Inclusion criteria were:

Gestational age (GA)≥37 gestational weeks (GWs);

Follow up to the age of 1 year.

Exclusion criteria included:

Lost to follow-up or dead.

Exchange transfusion.

Grouping of the patients

Group A – without jaundice;

Group B – with jaundice treated by phototherapy only in the 1st week of life and resolved to the 14th postnatal day;

Group C – intensive jaundice requiring a complex treatment (phototherapy in the neonatal unit and ursodeoxycholic acid administered on an out-patient basis) and resolved by the 14th day;

Group D – prolonged jaundice (lasting more than 14 days), requiring complex treatment.

### *Studied Indicators*

The studied indicators were as follows: birth weight (BW), gestational age (GA), sex, delivery mode – partus normalis (PN) or Cesarean section (CS), Apgar score at 1st and 5th minute, mother's age, education, and domicile.

The levels of total and direct bilirubin were assessed during the hospital stay and, if needed (levels above 171 μmol/L), at the end of 2nd week) until they became normal.

If the mother was Rhesus negative, umbilical cord blood bilirubin was examined by the protocol.

Transcutaneous bilirubin measurement was performed at the 20th postnatal hour in all the newborns. Then it was measured daily until discharge from the neonatal unit. If the transcutaneous level was abnormal, serum levels of total and direct bilirubin were examined. If elevated values were confirmed, treatment with phototherapy was initiated. Transcutaneous bilirubin measurements at 12th-14th and 28th-30th days were performed on an outpatient basis. Ursodeoxycholic acid 10 mg/kg/24 hours was prescribed to children with intensive jaundice and treated with prolonged intensive phototherapy. In the cases of prolonged icterus, transcutaneous bilirubin levels were monitored weekly until normal values were reached (maximum until the end of the third month). There were no deviations in the liver function test of all newborns tested.

The neuropsychological development of the children was assessed during the first 12 months of life. Four indicators were monitored: motor activity, sensory activity, emotional-social development, and speech development. We referred to standards set in "Methods of assessing the intellectual development from birth to the age of 3 years" of Manova-Tomova [6]. We calculated the developmental coefficient (CoD) according to the following formula: CoD=MAx100/CA, where MA is mental age and CA is chronological age. The interpretation of the CoD-score is shown in Table 1.

**Table 1.** Interpretation of the CoD-score

| **Assessment of neuro-psychological development** | Very high | High | Normal | Low |
|---|---|---|---|---|
| **CoD-score** | >120 | 111-120 | 86-110 | <85 |

## Results

Ninety-two (92) newborns, treated in Medica University Hospital, Rousse, Bulgaria, were evaluated from 01.01.2017 until 31.12.2017. The demographic data of the groups are shown in Table 2.

We found that the groups are comparable in all indicators except for domicile, and the difference was significant for groups B and D.

The postnatal dynamics of the CoD-score in the groups is shown in Figure 1.

There was a significant developmental delay in group D, as compared to the other three groups for all the studied age periods.

As mentioned above, we found a significant difference between groups B and D regarding domicile. Therefore, we examined the significance of this sign for the psycho-motor development of the studied cohort (Figure 2).

Of the 92 infants we followed up, 78 resided in urban areas and 14 - in rural areas. However, we did not find a significant difference in the CoD-score dynamics for all followed-up age periods of both groups.

**Table 2.** Summarized data of the groups –number of observed newborns by groups, gender, body weight, gestation age at birth, delivery mode, Apgar score of newborns, age of mother, level of education of the mother, residence of the mother.

| Indicators | Groups | | | | p |
|---|---|---|---|---|---|
| | A | B | C | D | |
| **n** | 25 | 25 | 20 | 22 | - |
| **Gender (girls / boys)** | 36/64 | 44/56 | 35/65 | 32/68 | NS |
| **BW (body weight (g))** | 3255±380 | 3252±293 | 3405±439 | 3366±503 | NS |
| **GA at birth (Gestation age)** | 38.6±1.0 | 38.4±1.1 | 38.4±1.2 | 38.7±1.0 | NS |
| **Delivery mode PN/SC(Partus Normalis / Cesarean section)** | 56/44 | 48/52 | 35/65 | 41/59 | NS |
| **Apgar score** | | | | | |
| **1st min.** | 8.4±1.0 | 8.6±1.6 | 8.4±1.4 | 8.7±0.8 | NS |
| **5th min.** | 9.7±0.6 | 9.6±0.7 | 9.4±0.9 | 9.7±0.6 | NS |
| **Age of mother (years)** | 29.7±4.1 | 29.0±5.2 | 31.3±5.0 | 30.3±4.8 | NS |
| **Level of education of the mother (higher / secondary / primary)** | 28/72/0 | 24/72/4 | 40/60 /0 | 18/82/0 | NS |
| **Residence of the mother (town / village)** | 88/12 | 96/4 | 85/15 | 68/32 | 0.06* |

** significant difference between groups B and D*

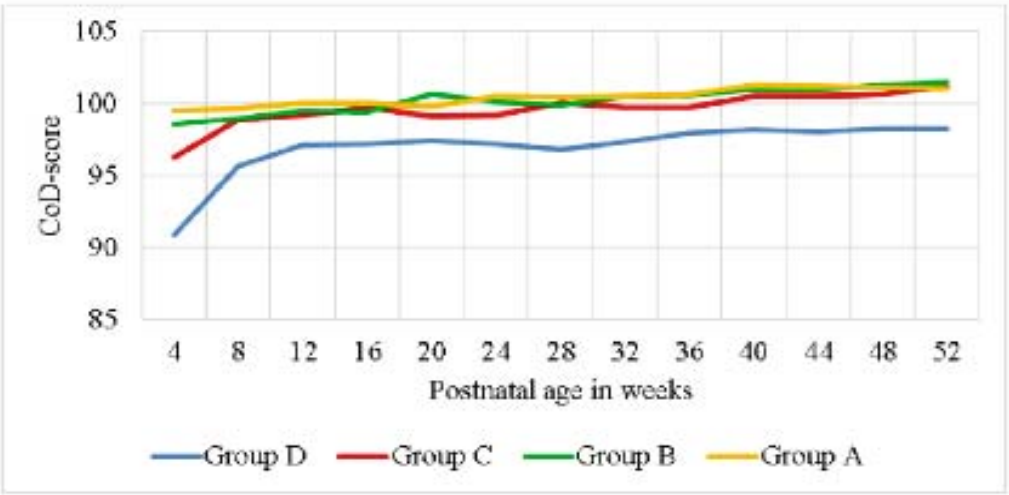


**Figure 1.** postnatal dynamics of the CoD-score in the groups

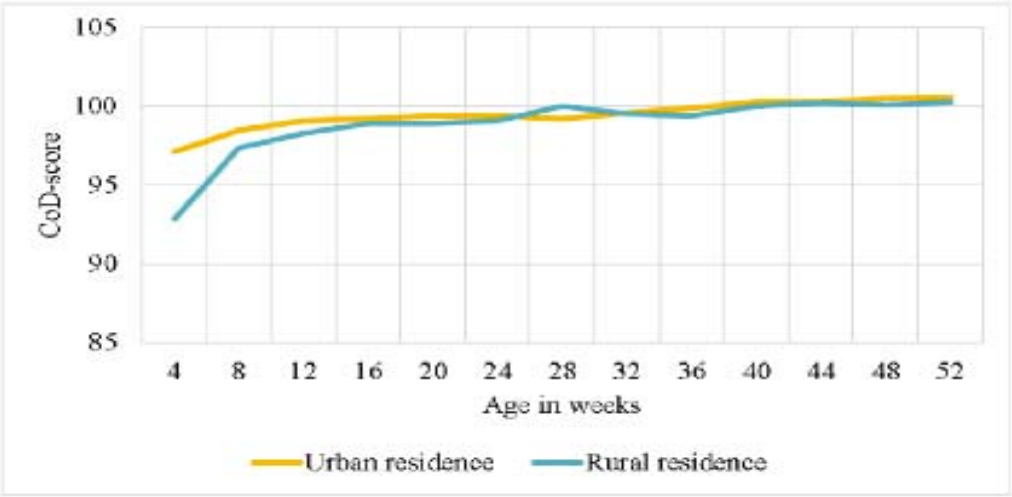


**Figure 2.** CoD-score dynamics according to the domicile

## Discussion

Despite the presence of neonatal jaundice diagnostic and therapeutic algorithms, the problem is still not resolved. On the average, about 140 million of newborns on the planet annually, 84-112 million of them have from neonatal jaundice, and 1 out of 10 newborns with neonatal jaundice require extensive diagnostic procedures and treatment [7]. The importance of neonatal hyperbilirubinemia should not be neglected. Neonatal jaundice is one of the most common causes of neonatal mortality in some regions of the world, and current migration patterns aggravate this problem (Table 3) [7].

The late severe and irreversible consequences of extreme hyperbilirubinemia – kernicterus and kernicterus-associated disorders, are well known and described [8]. They result from pathomorphological cerebral damages, which lead to long-term neurological impairment [9]. An auditory analyzer is affected [10].

Investigators have focused on searching for a relationship between the history of neonatal hyperbilirubinemia and cognitive and behavioral disorders [11], autistic spectrum disorders [12], childhood asthma [13], among others.

The cases of mild and moderate hyperbilirubinemia requiring only conservative treatment are usually neglected.

In a large-scale 30-year follow-up of children who had neonatal hyperbilirubinemia in Finland [11], cognitive impairment continuing in adulthood was demonstrated in 45% of the patients. Reading, writing, and mathematical skills impairments were described. These impairments continue at a higher level of education (secondary and tertiary education). The degree of life satisfaction is lower in affected patients.

On the other hand, the treatment of neonatal jaundice may also have side effects. Phototherapy today is the most commonly used therapeutic method. Several studies describe side effects such as DNA damage in mononuclear cells depending on irradiation duration [14], enhancement of apoptosis in peripheral lymphocytes [15], degenerative damage in the testicles [16]. Phototherapy leads to an increase in the frequency of sister chromatid exchange regardless of irradiation and may have some genotoxic adverse effects on chromosomes [17].

Our study included only the newborns with a good Apgar score, without underlying clinical and cardiorespiratory adaptation problems, and no significant difference in such factors as education and environment that may affect their development. The observed bilirubin levels during the neonatal period and up to the third month did not reach extreme values suggestive of risk for encephalopathy and requiring an exchange transfusion. Only phototherapy was administered and, in the cases of prolonged jaundice – deoxycholic urea acid for promoting bile flow. Bilirubin levels were well controlled in all four groups. Nevertheless, we established a statistically significant difference in the coefficient of development in the first year of life

**Table 3.** Newborn jaundice and its place in neonatal mortality structure by 2016 in some regions of the world.

| Geographic region | Postnatal period | |
|---|---|---|
| | Early neonatal | Late neonatal |
| **Asia** | 7 | 7 |
| **Sub-Saharan Africa** | 8 | 12 |
| **North America** | 13 | 21 |
| **Western Europe** | 9 | 15 |

in children with prolonged jaundice. As a result, there was a lag in the development of motor skills and emotional and social activity and, to a lesser extent, speech and sensory activity. Their neuro-motor development was compromised, which was seen at the age of 12 weeks. The final CoD was also lower, as compared to the other groups.

## Conclusions

According to our data, prolonged neonatal jaundice significantly affects the neuro-psychological development of children during their first year of life. This finding proves the existence of mechanisms other than direct cytotoxic action of bilirubin, compromising neuronal metabolism. The children with prolonged neonatal jaundice need a long-term follow-up of their mental and cognitive functions. It is also necessary to expand the Neonatal Jaundice Diagnostic Panel for proper diagnosis and prevention of its prolonged course.

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