HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2021.94759
Haydarpasa Numune Med J 2023;63(2):120–125

ORIGINAL ARTICLE

Long-Term Neurodevelopmental Outcomes of Newborns with High Bilirubin Levels

Derya Çolak[1], Münevver Kaynak Türkmen[1], Yelda Özsunar Dayanır[2], Hatice Aksu[3], Sema Başak[4], Ayşe Fahriye Tosun[5]

[1]Department of Neonatology, Adnan Menderes University, Aydın, Türkiye
[2]Department of Radiology, Adnan Menderes University, Aydın, Türkiye
[3]Department of Child and Adolescent Psychiatry, Adnan Menderes University, Aydın, Türkiye
[4]Department of Otolaryngology, Adnan Menderes University, Aydın, Türkiye
[5]Department of Pediatric Neurology, Adnan Menderes University, Aydın, Türkiye

Abstract

Introduction: The aim of this study is to evaluate the long-term neurodevelopmental outcomes of newborns who had exchange transfusion due to hyperbilirubinemia and presented with bilirubin values at the border of exchange transfusion and did not need exchange transfusion during the preparation period.

Methods: The study included 18 patients (n=18) who had exchange transfusion due to indirect hyperbilirubinemia (Group 1) and 10 patients (n=10) who applied with a bilirubin value at the border of exchange transfusion and decreased bilirubin during the preparation period (Group 2). Neurological examination, cranial magnetic resonance imaging (MRI), and auditory brainstem response test (BERA) results of the cases were evaluated through cross-sectional analysis. Ankara Developmental Inventory for children under the age of six and Wechsler intelligence scale-Revised for children over the age of six were performed.

Results: Sixty-seven percentage (n=12) of the patients in Group 1 were male, mean gestational week was 38.4±1.8 (34–42) and mean age was 8.8±2.1 years. 40% (n=4) of the patients in Group 2 were male, mean gestational week was 37.9±1.7 (36–40) and mean age was 8.2±2.2 years.The mean venous serum total bilirubin level of group 1 was 29.5±8.2 mg/dL and Group 2 was 22.8±3.9 mg/dL, which was statistically significant (p=0.024). Neurological examination was abnormal in four patients in Group 1 and one patient in Group 2. Two of the cranial MRIs (n=8) in Group 2 were pathological. There was no significant difference between the groups in terms of neurological examination, cranial MRI, BERA, and developmental tests.

Discussion and Conclusion: In this study, the fact that there was no neurodevelopmental difference between the cases who underwent exchange transfusion or whose bilirubin levels were lowered by phototherapy without the need for exchange transfusion, and the cases with neurodevelopmental abnormalities were very few, once again demonstrated the importance of intervening before bilirubin encephalopathy occurs.

Keywords: Exchange transfusion; hyperbilirubinemia; neurodevelopmental outcomes; newborn.

Jaundice is a common condition in newborns during the first week of life and often has a good course. However, high bilirubin levels can cause long-term cognitive retardation, sequelae with auditory and visual abnormalities, and kernicterus[1].

The mechanism of neurotoxicity due to hyperbilirubinemia has not yet been fully elucidated[2]. Bilirubin inhibits mitochondrial functions and oxidative phosphorylation, inhibits neurotransmitter synthesis-release-reuptake and protein synthesis. As a result, it causes excitoxicity, damage

Correspondence: Derya Çolak, M.D. Department of Neonatology, Adnan Menderes University, Aydın, Türkiye
Phone: +90 553 391 77 22 **E-mail:** colkdry@gmail.com
Submitted Date: 13.08.2021 **Revised Date:** 25.09.2021 **Accepted Date:** 30.10.2021

to the cell membrane, decrease the synthesis and replication of DNA, and ultimately cause neurotoxicity[3,4]. It has been shown in studies that bilirubin is neurotoxic by causing apoptosis in nerve cells[5-7].

BERA test can be used to evaluate acute neurotoxicity of bilirubin in the peripheral and central auditory pathway[8]. Abnormal MRI findings and clinical findings have been found to be associated in hyperbilirubinemia. In the acute phase, signal changes are seen in T1-weighted sequences in the globus pallidus and subthalamic nuclei, and in T2-weighted sequences in the subacute and chronic phases[9].

In this study, it was aimed to evaluate and compare the long-term neurodevelopmental outcomes of babies who had high bilirubin levels and had exchange transfusion, and babies whose bilirubin levels were decreased by phototherapy during the preparation process for exchange transfusion.

Materials and Methods

In this study, 18 (group 1) of 51 patients who underwent exchange transfusion with the diagnosis of indirect hyperbilirubinemia in the Neonatal Intensive Care Unit of our hospital between 1999 and 2012, and 10 (group 2) out of 55 patients who applied at or above the exchange transfusion limit and whose bilirubin level fell below the exchange transfusion limits with phototherapy during the transfusion preparation process, were evaluated. Clinical Research Ethics Committee Approval and informed consent from the families were obtained. Etiologies of hyperbilirubinemia and socio-demographic characteristics of the cases were learned retrospectively from hospital records. Maternal and infant blood groups, direct Coombs test, complete blood count, reticulocyte count, peripheral smear, total serum bilirubin (TSB), indirect and direct serum bilirubin levels, and glucose-6-phosphate dehydrogenase (G6PD) results were evaluated at the admission of the patients to the hospital. For the indications of exchange transfusion and phototherapy, bilirubin levels in the indirect hyperbilirubinemia treatment table of the Turkish Neonatology Society were taken as basis. Cases with a history of congenital malformation, congenital heart disease, hereditary metabolic and genetic disease, sepsis, intrauterine growth retardation, hypoxic-ischemic encephalopathy, were not included in the study. Cross-sectional neurological examinations of the cases, cranial MRI, BERA test, Ankara Developmental Screening Inventory (AGTE) under the age of six and Wechsler Intelligence Scale for Children — Revised (WISC-R) developmental tests for children over the age of six were performed. Neurological examinations were performed by an experienced pediatric neurologist. Cranial MRIs were performed with the Philips Acheiva 1.5T MRI machine and were evaluated by the same radiologist, unaware of the infants' clinical history. Audiological evaluation was performed with the BERA test in the Audiology Department of the Otorhinolaryngology Department of our hospital. In order to evaluate the effect of hyperbilirubinemia on mental and motor functions, AGTE developmental tests under the age of six and WISC-R developmental tests were performed on children above the age of six by a clinical psychologist.

This study was supported by the Scientific Research Projects Unit (BAP) with the decision numbered 31 on 14/4/2014 with the project code 04636, and Ethics committee approval was obtained. It was performed in accordance with the Principles of the Declaration of Helsinki.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. For descriptive statistics; mean, standard deviation, minimum and maximum were given for numerical variables, and numbers and percentages were given for categorical variables. Comparisons of numerical variables in two independent groups were analyzed with Student's t test, since the condition of normal distribution was met. Conformity of continuous variables to normal distribution was tested with the Kolmogorov-Smirnov test. The ratio of the categorical variable between the groups was compared with chi square test. Statistical significance level was accepted as $p<0.05$.

Results

67% of the patients in Group 1 (n=18) included in the study were male, with a mean age of 8.8±2.1 (6-14) years. Their mean gestational week was 38.4±1.8 (34-42) weeks and mean birth weight was 3396±574 (2160-4350) grams. The mean age at presentation due to jaundice in Group 1 was 3.8±2.9 (1-13) days and the mean TSB was 29.5±8.2 (17-51) mg/dl (Table 1).

40% of the patients in Group 2 (n=10) were male, their mean age was 8.2±2.2 (6-12) years. Their mean gestational week was 37.9±1.7 (36-40) weeks and birth weight was 3110±453 (2450-3720) grams. The mean age at presentation due to jaundice in Group 2 was 6.7±2.9 (1-11) days and the mean TSB was 22.8±3.9 (14-27) mg/dl (Table 1).

In Group 1, 33% of the patients had ABO and 5.5% had Rh incompatibility, and 5.5% had G6PD deficiency. ABO incompatibility was detected in 10% of the patients in Group 2 and Rh incompatibility in 20%. The mean admission day

Table 1. Demographic and clinical characteristics of the cases in the groups

	Group 1 (n=18)	Group 2 (n=10)	p
Sex n (%)			
Female	6 (33)	6 (60)	0.364
Male	12 (67)	4 (40)	
Average age (years)[a]	8.8±2.1 (6-14)	8.2±2.2 (6-12)	0.470
Gestational week	38.4±1.8 (34-42)	37.9±1.7 (36-40)	0.437
Birth weight (g)[a]	3396±574 (2160-4350)	3110±453 (2450-3720)	0.187
Type of birth n (%)			
NSVD	15 (83)	6 (60)	0.207
C/S	3 (17)	4 (40)	
Age at Application (days) [a]	3.8±2.9 (1-13)	6.7±2.9 (1-11)	0.023
TSB (mg/dl) [a]	29.5±8.2 (17-51)	22.8±3.9 (14-27)	0.024
ABO Incompatibility n (%)	6 (33)	1 (10)	0.150
Rh Incompatibility n (%)	1 (5.5)	2 (20)	0.248
G6PD deficiency n (%)	1 (5.5)	0 (0.0)	0.453
Unknown n (%)	10 (56)	7 (70)	0.391
Breastfeeding	18 (100)	9 (90)	0.135

[a]Mean±SS (min-max); NSVD: Normal Spontaneous Vaginal Delivery), C/S : Cesarean section.

in Group 2 was statistically significantly higher than Group 1 (p=0.023). The mean TSB of Group 1 was statistically significantly higher than Group 2 (p=0.024). No statistically significant difference was found in the other demographic characteristics of the cases in the groups (Table 1).

Neurological examination of the four patients in Group 1 was abnormal. Dysmetria, lateral gaze palsy, hearing loss and hypoactive deep tendon reflexes were detected in one case each. Cranial MRI was performed in 14 of 18 patients in Group 1 and all were normal. Three children in Group 1 had abnormal developmental tests (WISC-R). BERA test was performed on 9 children in Group 1, the result was abnormal in one case and exchange transfusion had been performed three times in this case. Cranial MRI and developmental tests were normal in patients with pathological neurological examination in Group 1 (Table 2).

Table 2. Distribution of patients with abnormal findings in group 1 and group 2

Group 1 (n=18)	TSB (mg/dl)	Hemolytic Diseasea	Neurological examination	Cranial MRI	Developmental test	Hearing test
Patient 1	23	Absent	Abnormal (dysmetria)	Normal	Normal	Normal
Patient 2	29	Absent	Abnormal (lateral gaze paralysis)	Normal	Normal	Normal
Patient 3	28	Absent	Abnormal (decreased deep tendon reflexes)	Normal	Normal	Normal
Patient 4	29	Absent	Abnormal (hearing loss)	Normal	Normal	Abnormal
Patient 5	51	Absent	Normal	Normal	Abnormal (WISC-R)	Normal
Patient 6	17	Absent	Normal	Normal	Abnormal (WISC-R)	Normal
Patient 7	35	Absent	Normal	Normal	Abnormal (WISC-R)	Normal
Group 2 (n=10)						
Patient 1	22	Absent	Abnormal (nystagmus)	Normal	Normal	Normal
Patient 2	14	ABO incompatibility	Normal	Abnormal (right frontal lobe signal pathology)	Normal	Normal
Patient 3	24	Absent	Normal	Abnormal (signal pathology in the brain stem)	Normal	Normal

[a]:Rh, ABO incompatibility, G6PD deficiency.

Table 3. Neurological examination, cranial magnetic resonance imaging, developmental test and auditory brainstem response results in group 1 and group 2

	Group 1 (n=18)		Group 2 (n=10)		
	n	%	n	%	p
Neurological examination					
Normal	14	78	9	90	0.626
Abnormal	**4**	22	**1**	10	
Cranial MRI					
Normal	14	100	6	75	0.121
Abnormal	0	0,0	2	25	
Developmental test					
Normal	15	83	8	100	0.529
Abnormal	**3**	17	0	0	
BERA test					
Normal	8	89	3	100	1.000
Abnormal	**1**	11	0	0,0	

Nystagmus was detected in the neurological examination of one patient in Group 2. Cranial MRI, developmental and hearing tests of this case were normal. Cranial MRI was performed in eight of 10 patients in Group 2, and T2 signal increase was detected in the right frontal lobe in one patient and in the brainstem in the second patient, and these were reported as abnormal. Neurological examination was normal in two cases with abnormal MRI findings (Table 2). Eight of the 10 cases in Group 2 underwent a developmental test, and all were evaluated as normal. BERA test could be performed in three patients in Group 2 and all were found to be normal (Table 3).

There was no statistically significant difference in the rates of neurological examination, pathology in cranial MRI, developmental test and BERA test abnormality of the groups (p=0.626, p=0.121, p=0.529, p=1.000; respectively) (Table 3).

Discussion

Neonatal hyperbilirubinemia is seen at a rate of 50-60% in term babies and 80% in preterm babies in the first week of their lives. Despite advances in neonatal care, neurotoxicity due to hyperbilirubinemia remains a major problem[10].

Babies affected by high bilirubin levels may develop dystonic and athetoid movement disorder, hearing loss, upward gaze paralysis, dental enamel dysplasia, and ataxia and hypotonia due to cerebellar involvement in the late period[11]. Rose et al.[12] stated that a moderate level of bilirubin elevation may affect the developing central nervous system, especially the basal ganglia and cerebellum, and that cerebral lesions can be identified on MRI in dyskinetic cerebral palsy due to hyperbilirubinemia. In a study investigating the etiology and poor prognosis criteria of high bilirubin levels, abnormal cranial MRI findings were detected in only 4 of 15 patients with bilirubin encephalopathy, and it was reported that cranial MRI is indispensable in evaluating the severity and prognosis of hyperbilirubinemia, but cranial MRI is not always a good marker in demonstrating abnormal clinical findings[13]. In this study, findings of cranial nerve involvement and cerebellar involvement were found in four (22%) patients in Group 1; however, the developmental test and cranial MRI results of these patients were normal. Nystagmus was detected in the neurological examination of one patient in the second group and it was thought to be associated with cerebellar involvement. Cranial MRI and developmental test of this patient were evaluated as normal. Cranial MRI results of patients with abnormal neurological findings in both groups were found to be normal, and when evaluated with the literature, it was thought that patients with abnormal neurological examination findings were not always associated with MRI results.

In Group 2, in two patients whose bilirubin levels were found to be 14 mg/dl and 24 mg/dl on days 1 and 5, respectively, at the time of admission to the hospital, pathological signal changes were detected in the right frontal lobe and brain stem, respectively, outside the expected localizations in cranial MRI. However, neurological examination, developmental tests and hearing tests of these two patients were normal. There was no statistically significant difference between the two groups in terms of abnormal neurological examination, developmental test and MRI findings.

In a study where Heimler et al.[14] compared patients with serum bilirubin levels between 20-30 mg/dl with a healthy control group, they found no significant difference in terms of neurosensory hearing loss and neurological deficit. In this study, the mean TSB level was found to be 29.5±8.2 (17-51) mg/dl in the first group, and the mean venous TSB level was 22.8±3.9 (14-27) mg/dl in the second group. Although the hearing test was found to be normal and the developmental test abnormal in a patient with a total serum bilirubin level of 51 mg/dl, hearing loss was detected in a patient with a lower total bilirubin level (29 mg/dl), and no pathology was detected in the cranial MRI and developmental test of this patient.

Bilirubin is particularly sensitive to the auditory system and can lead to abnormal neurological conditions ranging from speech disorders to profound hearing loss[15]. In a study evaluating 77 patients with neurological damage due to severe hyperbilirubinemia, it was stated that ABR test was the best predictor of neurotoxicity due to high bilirubin levels[16]. However, bilirubin-related hearing loss requires a window period, this is because the sensory pathway completes myelination before the motor pathway and premature babies under 34 weeks are at higher risk for hearing loss. On the contrary, motor system disorders seen in classical kernicterus are reported to be more common in term babies[15]. Similarly, in this study, no pathology was found in the BERA test results of patients with abnormal neurological examination findings. Wong et al.[8] similarly showed that there was no significant relationship between BERA and abnormal neurological outcomes, and they also stated that the pathology in the auditory brainstem pathways may be temporary thanks to early intervention in the patients. Although BERA is a method that can be used for monitoring neurological complications, they stated that it is not an adequate indicator to show neurological outcomes in the long term[10].

Cognitive dysfunction may develop in some of the cases followed up due to hyperbilirubinemia. In a study by Hızel et al.[17] in which they evaluated babies with hyperbilirubinemia who underwent exchange transfusion, they found that the rate of abnormal results in the Denver Developmental Screening Test increased as the serum indirect bilirubin level increased. In a study in which 128 cases with high bilirubin levels or exchange transfusion were examined, it was stated that at least one neurobehavioral disorder was found in 45% of the cases in the late period, and this was considered statistically significant. Conversely, in a large prospective study investigating the long-term neurotoxicity of severe hyperbilirubinemia, no statistically significant difference was found in cognitive scores. They stated that no direct relationship was found between hyperbilirubinemia and abnormal cognitive functions. They stated that cognitive dysfunction may be associated with conditions affecting unconjugated bilirubin level or other accompanying risk factors. In our study, WISC-R test results were found to be abnormal in three of the cases in Group 1 and all WISC-R tes at results were found to be normal in Group 2, and the developmental test results of the two groups showed no statistically significant difference. This study supports that there is no direct relationship between hyperbilirubinemia and cognitive functions, similar to the literature[18].

The limitations of this study are that it was a large patient group whose etiology of hyperbilirubinemia could not be determined, the number of patients that could be reached in the groups and the number of cranial MRI and BERA performed were low. Considering these factors, studies are needed involving larger patient groups with a long follow-up period in order to demonstrate neurotoxicity in hyperbilirubinemia.

Conclusion

Although many studies have reported that hyperbilirubinemia adversely affects neurodevelopmental outcomes, no serious long-term neurological sequelae were found in our study. This was attributed to the early admission of infants to the hospital and the initiation of intensive phototherapy from the time of admission, or the appropriate treatment of severe hyperbilirubinemia by exchange transfusion.

Ethics Committee Approval: This study was supported by the Scientific Research Projects Unit (BAP) with the decision numbered 31 on 14/4/2014 with the project code 04636, and Ethics committee approval was obtained. It was performed in accordance with the Principles of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.K.T., D.Ç.; Design: D.Ç.; Supervision: D.Ç.; Fundings: Y.Ö.D., S.B.; Materials: S.B., Y.Ö.D., H.A.; Data Collection or Processing: A.T., H.A.; Analysis or Interpretation: D.Ç., A.T.; Writing: D.Ç.; Critical Review: M.K.T.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Çoban A, Türkmen M, Gürsoy T. Türk neonatoloji derneği, yenidoğan sarılıklarında yaklaşım, izlem ve tedavi rehberi. 2014. p.3–36.

2. Silva RF, Rodrigues CM, Brites D. Rat cultured neuronal and glial cells respond differently to toxicity of unconjugated bilirubin. Pediatr Res 2002;51:535–41. [CrossRef]
3. Shapiro SM. Bilirubin toxicity in the developing nervous system. Pediatr Neurol 2003;29:410–21. [CrossRef]
4. Watchko JF. Neonatal indirect hyperbilirubinemia and kernicterus. In: Gleason CA, Juul SE, editors. 10th ed. Avery's diseases of the newborn. Philadelphia: Elsevier Saunders; 2018. p.1198–218. [CrossRef]
5. Grojean S, Koziel V, Vert P, Daval JL. Bilirubin induces apoptosis via activation of NMDA receptors in developing rat brain neurons. Exp Neurol 2000;166:334–41. [CrossRef]
6. Silva RF, Rodrigues CM, Brites D. Bilirubin-induced apoptosis in cultured rat neural cells is aggravated by chenodeoxycholic acid but prevented by ursodeoxycholic acid. J Hepatol 2001;34:402–8. [CrossRef]
7. Fernandes A, Vaz AR, Falcão AS, Silva RF, Brito MA, Brites D. Glycoursodeoxycholic acid and interleukin-10 modulate the reactivity of rat cortical astrocytes to unconjugated bilirubin. J Neuropathol Exp Neurol 2007;66:789–98. [CrossRef]
8. Wong V, Chen WX, Wong KY. Short- and long-term outcome of severe neonatal nonhemolytic hyperbilirubinemia. J Child Neurol 2006;21:309–15. [CrossRef]
9. Campistol J, Galvez H, Cazorla AG, Málaga I, Iriondo M, Cusí V. Neurological dysfunction induced by bilirrubin. Neurologia [Article in Spanish] 2012;27:202–11. [CrossRef]
10. Chen WX, Wong VC, Wong KY. Neurodevelopmental outcome of severe neonatal hemolytic hyperbilirubinemia. J Child Neurol 2006;21:474–9. [CrossRef]
11. Kaplan M, Bromiker R, Hammerman C. Severe neonatal hyperbilirubinemia and kernicterus: Are these still problems in the third millennium? Neonatology 2011;100:354–62. [CrossRef]
12. Rose J, Vassar R. Movement disorders due to bilirubin toxicity. Semin Fetal Neonatal Med 2015;20:20–5. [CrossRef]
13. Yu C, Li H, Zhang Q, He H, Chen X, Hua Z. Report about term infants with severe hyperbilirubinemia undergoing exchange transfusion in Southwestern China during an 11-year period, from 2001 to 2011. PLoS One 2017;12:e0179550. [CrossRef]
14. Heimler R, Sasidharan P. Neurodevelopmental and audiological outcome of healthy term newborns with moderately severe non-haemolytic hyperbilirubinemia. J Paediatr Child Health 2010;46:588–91. [CrossRef]
15. Campbell Wagemann S, Mena Nannig P. Severe hyperbilirubinemia in newborns, risk factors and neurological outcomes. Rev Chil Pediatr [Article in Spanish] 2019;90:267–74. [CrossRef]
16. Yuan X, Song J, Gao L, Cheng Y, Dong H, Zhang R, et al. Early Amplitude-integrated electroencephalography predicts long-term outcomes in term and near-term newborns with severe hyperbilirubinemia. Pediatr Neurol 2019;98:68–73. [CrossRef]
17. Hızel S, Tanyer G, Serdaroğlu A, Dallar Y, Genç D. Kan değişimi uygulanmış hiperbilirubinemili bebeklerin uzun dönem risk faktörleri yönünden izlenmesi. T Klin Pediatri 1998,7:159–65.
18. Wusthoff CJ, Loe IM. Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. Semin Fetal Neonatal Med 2015;20:52–7. [CrossRef]