American Journal of Medicine and Medical Sciences 2026, 16(4): 2109-2111
DOI: 10.5923/j.ajmms.20261604.111

The Role of Prognostic Biomarkers for Neurological Complications in Hyperbilirubinemia in Newborns VEGF and BDNF as Prognostic Markers of Neurological Complications in Hyperbilirubinemia

Salikhova K. Sh., Bakhramova Sh. M.

Republican Specialized Scientific and Practical Medical Center of Pediatrics, Uzbekistan

Abstract **Objectives:** Neonatal hyperbilirubinemia is a significant risk factor for bilirubin-induced damage to the central nervous system. Disruptions in neurovascular homeostasis, accompanied by an imbalance of angiogenic and neurotrophic factors, including vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), play an important role in the pathogenesis of this condition. **The aim of the study** was to assess the prognostic significance of serum VEGF and BDNF levels in the development of neurological complications in newborns with hyperbilirubinemia. **Methods:** A total of 135 newborns were included in this prospective study. VEGF and BDNF concentrations were determined using ELISA. A correlation analysis was performed to assess the relationship between these biomarkers and bilirubin levels as well as clinical neurological abnormalities. **Results:** It was found that elevated VEGF and decreasd BDNF were significantly associated with the severity of hyperbilirubinemia and adverse neurological outcomes. VEGF correlated positively with unconjugated bilirubin levels ($r = 0.61$; $p < 0.01$), whereas BDNF demonstrated a negative correlation ($r = –0.68$; $p < 0.01$). **Conclusions:** The data confirm that VEGF and BDNF are promising prognostic biomarkers for the risk of bilirubin-induced neurotoxicity.

Keywords Hyperbilirubinemia, Newborn, Neurotoxicity, Bilirubin, Biomarkers

1. Introduction

Hyperbilirubinemia is one of the most common conditions of the neonatal period and can lead to bilirubin-induced damage to the central nervous system [1,2]. Unconjugated bilirubin is capable of crossing the blood-brain barrier, causing neurotoxic effects accompanied by damage to neurons, glial cells, and disruption of synaptic connections [3,4].

Current understanding points to a multifactorial pathogenesis involving oxidative stress, inflammation, mitochondrial dysfunction, and endothelial dysregulation [2,5]. Disruption of the neurovascular unit plays a particular role. Among the molecular mediators involved in the regulation of neurovascular homeostasis, vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) play key roles [6–9]. VEGF regulates angiogenesis, vascular permeability, and endothelial activation, facilitating adaptive responses to hypoxia and tissue damage [6,7]. However, its overexpression may contribute to disruption of the blood-brain barrier and exacerbation of neuroinflammatory processes [7]. BDNF, in turn, is one of the most important neurotrophins, regulating neuronal survival, differentiation, synaptic plasticity, and neurogenic processes [8,9]. Decreased BDNF levels are associated with increased vulnerability of neural tissue to toxic and ischemic effects [9,12]. An imbalance between angiogenic and neurotrophic factors may reflect the degree of disruption in compensatory mechanisms during hyperbilirubinemia and be associated with the risk of neurological complications. However, the prognostic significance of changes in VEGF and BDNF levels in hyperbilirubinemia remains insufficiently studied to date.

Objective. To investigate the prognostic significance of vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) in the development of neurological complications in hyperbilirubinemia in newborns.

2. Materials and Methods

A prospective observational study was conducted in the Department of Neonatal Pathology at the Republican Specialized Scientific and Practical Medical Center of Pediatrics. A total of 135 newborns were examined, including: the main group —115 full-term newborns with prolonged unconjugated

Received: Apr. 8, 2026; Accepted: Apr. 23, 2026; Published: Apr. 28, 2026
Published online at http://journal.sapub.org/ajmms

hyperbilirubinemia aged 14 days to 1.5 months; and the control group—20 essentially healthy full-term newborns without jaundice.

Inclusion criteria:
Full-term newborns
Unconjugated hyperbilirubinemia >220 μmol/L
Exclusion criteria
Intrauterine infections
Congenital anomalies
ABO, Rh

The mean level of unconjugated bilirubin in the main group by the end of the second week of life was 256.9 ±21.7 μmol/L. Serum concentrations of VEGF and BDNF were determined by quantitative enzyme-linked immunosorbent assay (ELISA) using standard commercial kits in accordance with the manufacturer's instructions. Student's t-test was used for statistical analysis. Correlations were calculated using Pearson's correlation coefficient. Prognostic value was assessed using ROC analysis with AUC calculation.

3. Results and Discussion

The study found that newborns with prolonged unconjugated hyperbilirubinemia exhibited significant changes in neuromolecular markers. The levels of bilirubin and VEGF over the course of observation are presented in Table 1.

The serum vascular endothelial growth factor (VEGF) level in children of the main group was significantly higher compared to the control group ($p < 0.01$). As the concentration of unconjugated bilirubin decreased, a gradual and statistically significant decrease in VEGF levels was observed. Elevated VEGF levels were recorded predominantly in newborns with higher concentrations of unconjugated bilirubin, indicating the severity of vascular dysfunction and the activation of angiogenic mechanisms under conditions of bilirubin-induced stress. The identified relationship indicates a dose-dependent nature of endothelial activation with increasing hyperbilirubinemia. Clinically, children in the main group more frequently exhibited signs of central nervous system depression, decreased physiological activity, changes in muscle tone, and delayed development of early neonatal reflexes, which may reflect a disturbance in neurovascular homeostasis. The obtained data allow us to consider an increase in VEGF as one of the early markers of an unfavorable course of hyperbilirubinemia and a potential prognostic indicator of the risk of developing neurological complications [6,7,11].

The level of brain-derived neurotrophic factor (BDNF) in the main group was significantly lower compared to the control group ($p<0.05$) (Table 2), indicating a reduction in the neuroplastic and neuroprotective potential of the brain in newborns with hyperbilirubinemia [8,9,12]. Clinically, the decrease in BDNF was associated with a less favorable neurological profile, including delayed development of motor and sensory responses, such as motor and cognitive developmental delays, as well as an increased risk of residual neurological deficits, underscoring its prognostic significance.

The observed changes in VEGF and BDNF levels reflect disturbances in neurovascular homeostasis and indicate the activation of angiogenic mechanisms and the suppression of neurotrophic mechanisms in hyperbilirubinemia.

Table 1. VEGF levels (ng/mL) in newborns with hyperbilirubinemia

Indicator	Day 14	1 month	1.5 months
Indirect bilirubin level (mmol/L)	265.7 ±34.5	201.7 ±19.4	145.9 ±21.7
VEGF levels in children with hyperbilirubinemia (ng/mL)	198.4 ±27.6	162.9 ±21.3*	128.7 ±18.9*
VEGF levels in children in the control group (ng/mL)	121.6 ±16.4	118.9 ±15.8	120.3 ±17.1

*differences are statistically significant compared to the control group.

Table 2. Brain-Derived Neurotrophic Factor (BDNF) Level (pg/mL)

Group	Day 14	1 month	1.5 months
Indirect bilirubin level	265.7±34.5	201.7 ±19.4	145.9 ±21.7
BDNF levels in hyperbilirubinemia	8.6 ±1.4**	12.3 ±1.9*	16.8 ±2.1*
BDNF levels in children in the control group	21.4 ±2.6	23.1 ±2.8	24.6 ±3.1

* p compared to the control

Table 3. Correlational relationships between VEGF, BDNF, and unconjugated bilirubin

Parameter	BDNF	VEGF	Unconjugated bilirubin
BDNF	1,00	–0,52 (p < ,005) *	-0,68 (p < 0,01)*
VEGF	–0,52 (p < 0,05)	1,00	+0,61 (p < 0,01)*
Unconjugated bilirubin	–0,68 (p < 0,01)*	+0,61 (p < 0,01)	1,00

* - p difference is significant

Correlation analysis (Table 3) revealed a statistically significant positive correlation between VEGF levels and unconjugated bilirubin concentration in newborns of the main group ($r = 0.57$; $p < 0.05$), reflecting an increase in vascular activation and endothelial response as the bilirubin load increases. The identified correlation indicates a dose-dependent nature of the activation of angiogenic mechanisms in hyperbilirubinemia and underscores the clinical significance of monitoring VEGF alongside bilirubin to assess the risk of neurovascular homeostasis disturbances and potential neurological complications in the early postnatal period.

Clinically, this group of newborns more frequently exhibited signs of central nervous system depression, decreased physiological activity, changes in muscle tone, and delayed development of early neonatal reflexes. Correlation analysis revealed a significant negative correlation between BDNF levels and unconjugated bilirubin concentration ($r = -0.68$; $p < 0.01$), as well as between BDNF and VEGF levels ($r = -0.52$; $p < 0.05$) [9]. These data indicate that the progression of neuronal damage and bilirubin load is accompanied by an imbalance between angiogenic activity and neurotrophic support**,** which disrupts the processes of neural tissue repair. In newborns with such changes, clinical signs of bilirubin-induced central nervous system damage were more frequently observed, suggesting that the combination of VEGF and BDNF levels may serve as potential biomarkers for the early diagnosis and risk stratification of bilirubin encephalopathy. Elevated VEGF and decreased BDNF were accompanied by clinical signs of CNS depression, impaired muscle tone, and delayed development of early neonatal reflexes, underscoring their prognostic significance. The negative correlation between VEGF and BDNF ($r = -0.52$ ($p < 0.05$)) indicates an imbalance between the angiogenic and neurotrophic components, which is a key mechanism of bilirubin-induced neurotoxicity [5,7].

4. Conclusions

Thus, the obtained data allow us to consider bilirubin-induced brain damage in newborns as a multilevel pathological process [2,5]. A comprehensive assessment of these biomarkers allows not only for the detection of early signs of subclinical central nervous system damage but also for the stratification of the risk of adverse neurological outcomes in newborns with severe hyperbilirubinemia. Thus, the obtained data allow us to consider bilirubin-induced brain damage in newborns as a multilevel pathological process, including: direct toxic damage to neurons, reactive activation of glial cells, disruption of the blood-brain barrier, and suppression of neurotrophic support and neuroplasticity.

A comprehensive assessment of these biomarker data allows not only for the identification of early signs of subclinical central nervous system damage but also for the identification of risk factors for adverse neurological outcomes in newborns with severe hyperbilirubinemia [6–9].

REFERENCES

[1] Bhutani VK, Johnson LH, Keren R. Diagnosis and management of hyperbilirubinemia in the term neonate. *Clin Perinatol*. 2004; 31(3): 555–574.

[2] Watchko JF. Bilirubin-induced neurotoxicity in the preterm neonate. *Clin Perinatol*. 2016; 43(2): 297–311.

[3] Shapiro SM. Chronic bilirubin encephalopathy: diagnosis and outcome. *Semin Fetal Neonatal Med*. 2010; 15(3): 157–163.

[4] Hansen TW. Mechanisms of bilirubin toxicity: clinical implications. *Clin Perinatol*. 2002; 29(4): 765–778.

[5] Ostrow JD, Pascolo L, Shapiro SM, Tiribelli C. New concepts in bilirubin encephalopathy. *Eur J Clin Invest.* 2003; 33(11): 988–997.

[6] Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev*. 2004; 25(4): 581–611.

[7] Rosenstein JM, Krum JM. New roles for VEGF in nervous tissue. *J Cereb Blood Flow Metab*. 2004; 24(12): 1289–1300.

[8] Binder DK, Scharfman HE. Brain-derived neurotrophic factor. *Growth Factors*. 2004; 22(3): 123–131.

[9] Numakawa T, Odaka H, Adachi N. Actions of brain-derived neurotrophic factor in the brain. *Biochem Biophys Res Commun*. 2018; 501(4): 972–978.

[10] Leviton A, Dammann O. Brain damage markers in the neonate. *Clin Chim Acta*. 2002; 315(1–2): 1–8.

[11] Aly H, Hammad TA, Nada A, et al. Vascular endothelial growth factor in neonates with hypoxic conditions. *Pediatrics*. 2004; 113(5): e503–e509.

[12] Zhou X, et al. BDNF and neonatal brain injury: a review. *Neurosci Lett*. 2019; 712: 134–146.