MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN
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KHUSHMURODOVA MEKHRGIYO ALLAYAROVNA
MADJIDOVA YAKUTKHON NABIEVNA
ISKANDAROVA DILNOZAXON ERGASHEVNA
KHOLMUMINOV AZIZBEK ERKINOVICH
SAMATOV FARRUH FARHODOVICH

CLINICAL AND NEUROLOGICAL COMPLICATIONS OF BILIRUBIN ENCEPHALOPATHY IN INFANTS IN THE NEONATAL AND POSTNEONATAL PERIODS.

(Monograph)

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Authors:

M.A. Khushmurodova – dotsent, Department of Medical Psychology, Neurology and Psychiatry, Termez Branch of Tashkent State Medical University, PhD.

Y.N. Madjidova - Head of the Department of Neurology and Child Neurology, Medical Genetics, Tashkent State Medical University, Professor, Doctor of Medical Sciences.(DSc)

D.E. Iskandarova – Head of the Department of Medical Psychology, Neurology and Psychiatry, Termez Branch of Tashkent State Medical University, PhD.

A.E. Kholmuminov - Assistant Professor, Department of Medical Psychology, Neurology and Psychiatry, Termez Branch of Tashkent State Medical University.

F.F.Samatov - Assistant Professor, Department of Medical Psychology, Neurology and Psychiatry, Termez Branch of Tashkent State Medical University. PhD

Reviewers:

D.A. Khurmatova - Head of the Department of Obstetrics and Gynecology and Gynecology in Family Medicine, Termez Branch of Tashkent Medical Academy, Associate Professor.

G'afforova V.F. - Associate Professor of the Department of Neurology, Bukhara State Medical Institute named after Abu Ali ibn Sino, DSc

Monograph Abstract:

The monograph presents the results of clinical and neurological studies on the complications of bilirubin encephalopathy in infants during neonatal and postneonatal periods.

This monograph is intended as a practical guide for specialists including child neurologists, neonatologists, pediatricians, clinical residents, master's students, and senior medical undergraduates, as well as general practitioners and family physicians.

The monograph was approved for publication by the Central Scientific Advisory Committee of the Termez Branch of Tashkent State Medical Academy (Protocol No. 4 dated April 2026) and recommended for publishing by the Decision of the Ministry of Health of the Republic of Uzbekistan.

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INTRODUCTION

Neonatal jaundice represents one of the most prevalent clinical conditions encountered in newborns worldwide. During the first week of life, jaundice develops in approximately 60% of term infants and as many as 80% of preterm neonates. The mechanism by which bilirubin preferentially accumulates within the deep nuclei of the brain under hyperbilirubinemic conditions has yet to be fully elucidated. As bilirubin deposits progressively in cerebral tissues, characteristic yellow discoloration becomes evident in the basal ganglia, hypothalamus, brainstem nuclei - including the oculomotor, cochlear, and vestibular nuclei - as well as in the cerebellum. When complicated by acute bilirubin encephalopathy, neonatal jaundice may evolve into choreoathetoid cerebral palsy, thereby contributing to both morbid and premorbid clinical states. Despite its life-threatening potential, the pathophysiological cascade underlying this acute event, along with its progression toward kernicterus, remains incompletely understood.

According to data published by the World Health Organization (WHO), the global prevalence of severe neonatal jaundice and its associated complications among newborn populations ranges from 8.31% to 31.49%, with the highest rates observed in the African region. The burden of acute bilirubin encephalopathy reaches its peak in the Eastern Mediterranean countries (22.73%) and African nations (14.51%). Jaundice-related neonatal mortality has been reported at 13.02%, 7.52%, 2.01%, and 0.07% in the Eastern Mediterranean, African, South-East Asian, and European regions, respectively. The disabling sequelae of severe bilirubin encephalopathy continue to occur at elevated frequencies across populations worldwide.

In our country, comprehensive measures are being implemented to advance the national healthcare system, align medical services with international standards, and strengthen early diagnosis, treatment, and prevention of various

somatic disorders. In line with the seven priority directions of the Development Strategy of New Uzbekistan for 2022–2026, specific objectives have been established to elevate the quality of medical care provided to the population, including the goal of "...improving the quality of qualified medical-sanitary services delivered to citizens at the primary healthcare level..." In this context, conducting research aimed at the early detection of bilirubin encephalopathy in newborns and young children, preventing its complications, and enhancing therapeutic efficacy is both timely and warranted. Preventive measures targeting pathological jaundice and its complications are actively underway across the country, while the protection of maternal and child health remains one of the central priorities of the national healthcare agenda.

The present monographic investigation contributes - to a certain extent - to the implementation of objectives outlined in several key regulatory documents: Decree of the President of the Republic of Uzbekistan No. PD-60 of January 28, 2022, "On the Development Strategy of New Uzbekistan for 2022–2026"; Decree of the President of the Republic of Uzbekistan No. PD-134 of May 11, 2022, "On Approval of the National Program for the Development of School Education for 2022–2026"; Resolution No. PR-4063 of December 18, 2018, "On Measures for the Prevention of Non-Communicable Diseases, Support for Healthy Lifestyles, and Enhancement of Physical Activity Levels of the Population"; Resolution No. PR-296 of September 8, 2023, "On Measures for the Protection of Maternal and Child Health and the Strengthening of Reproductive Health of the Population"; as well as other normative-legal documents pertinent to this domain.

Current State of the Problem. Complications arising from pathological jaundice continue to rank among the leading causes of childhood disability and mortality in both developed and developing nations, persisting despite the implementation of routine neonatal screening programs. The clinical manifestations of pathological jaundice - particularly bilirubin encephalopathy

as one of its principal complications - together with the pathophysiological mechanisms underlying cerebral injury, have yet to be comprehensively characterized (Greco C., Arnolda G., Boo N.Y., Iskander I.F., Okolo A.A., Rohsiswatmo R., 2016). Although substantial progress has been achieved in elucidating the core pathophysiology of bilirubin toxicity and in refining available therapeutic modalities, cases of bilirubin encephalopathy continue to be reported globally. In Uzbekistan, this condition has likewise been documented and identified as a cause of long-term disability. By contrast, in developed countries, the incidence of kernicterus is estimated at approximately one case per 40,000 live births. A recently published Swedish report indicated that extreme hyperbilirubinemia requiring exchange transfusion affects roughly 50 per 100,000 newborns (Olusanya B.O., Osibanjo F.B., Slusher T., 2022). Delayed diagnosis and inadequate management of pathological, progressive indirect hyperbilirubinemia may result in persistent neurological deficits - a clinical entity defined as bilirubin encephalopathy (BE) (Cayabyab R., Ramanathan R., 2019). The principal clinical consequences of this disorder include damage to the central nervous system along with auditory, visual, dental, motor, and speech impairments. The progression from hyperbilirubinemia and its clinical sequelae to acute bilirubin encephalopathy (ABE), and subsequently to kernicterus, has been well documented in the literature (Gadzhizade G.Kh., 2020; Baranovskaya I.B., Boyko N.V., Samokhina O.F., Sysoyeva I.F., 2018).

A review of the published literature reveals that clinical and even neuropathological investigations related to bilirubin encephalopathy and kernicterus have been carried out. Neuronal injury attributable to bilirubin encephalopathy is typically observed when total bilirubin concentrations exceed 20 mg/dL, indicative of severe hyperbilirubinemia (Baranovskaya I.B., Boyko N.V., Samokhina O.F., Sysoyeva I.F., 2018).

In Uzbekistan, neonatal jaundice with a pathological course - and the bilirubin encephalopathy that frequently follows - continues to contribute to

disability among newborns. Investigations into the risk factors underlying this disorder have identified several contributing variables, including pathological conditions during pregnancy, intrauterine infection, low birth weight, hemolysis, sepsis, cephalohematoma, and perinatal asphyxia (Abdurakhmanova F.R., Salikhova K.Sh., Ishniyazova N.D., Agzamkhodjaeva B.U., Umarova L.N., 2022). Accordingly, the persistent occurrence of clinical-neurological complications of bilirubin encephalopathy in newborns and young children today underscores the need for further investigation into its risk factors and clinical course, as well as the development of strategies for early detection and prevention of its sequelae. These considerations have motivated ongoing scientific efforts directed at optimizing early diagnosis and therapeutic approaches (Abdurakhmonova G.E., Abdukadirova A.S., Aytbaeva F.A., 2016).

Further investigation is therefore warranted to clarify the factors driving the development of bilirubin encephalopathy, to characterize its clinical-neurological features, to evaluate its course and severity, to assess cerebral bioelectrical activity, and to deepen understanding of its pathogenesis and prevention.

CHAPTER I.

MODERN APPROACHES TO CLINICAL AND NEUROLOGICAL CHARACTERISTICS OF BILIRUBIN ENCEPHALOPATHY IN NEWBORNS AND INFANTS

Literature Review

§1.1. Clinical-Neurological Sequelae of Bilirubin Encephalopathy in Neonates and Children of Early Age

Across the majority of countries worldwide, pathologic jaundice in neonates continues to occur, and its sequelae account for substantial pediatric disability and mortality. The problem persists despite the implementation of universal neonatal screening. The pathologic trajectory of neonatal jaundice and its attendant neurological sequelae remain among the most pressing concerns in contemporary global health. Hyperbilirubinemia ranks among the conditions most frequently encountered during the first days and weeks of life. Delayed diagnosis and inadequate management of pathologic, progressive indirect hyperbilirubinemia can precipitate enduring neurological deficits — a clinical entity designated bilirubin encephalopathy (BE). The principal clinical concerns surrounding this disorder include central nervous system (CNS) injury together with auditory, visual, dental, neuromotor, and speech impairments. Active investigation is currently underway into the etiology, clinical presentation, diagnostic approaches, and sequelae of bilirubin encephalopathy in neonates and children of early age. Systematic analysis of the literature on bilirubin encephalopathy serves, in particular, to identify the causes that drive disability, elucidate the underlying risk factors, and refine therapeutic and preventive strategies in clinical practice.

Notwithstanding considerable progress in elucidating the core pathophysiology of bilirubin toxicity and in advancing currently available treatment modalities, bilirubin encephalopathy continues to be reported worldwide, with notably higher incidence in less developed countries than in their developed counterparts. Regrettably, the disorder has likewise been documented in our country and has been associated with long-term disability. A recently published Swedish report indicated that the incidence of extreme hyperbilirubinemia requiring exchange transfusion stands at approximately 50 cases per 100,000 live births. Additional clinical and neurological research is therefore needed to further characterize bilirubin encephalopathy and pathologic jaundice. Acute bilirubin encephalopathy (ABE) remains a significant cause of morbidity and mortality across the globe, with particular impact on neonates and children of early age [1; 366–367, 5; 437–438, 38; 292–293]. Cases of ABE continue to be reported worldwide and represent a notable cause of neonatal and infant death. The pathophysiologic mechanisms underlying this life-threatening acute event, together with its potential progression to kernicterus, remain insufficiently understood. The present review opens with an examination of the terminology surrounding hyperbilirubinemia and its clinical consequences, ABE, and the subsequent kernicterus spectrum disorder (KSD) [6; 8–22, 7; 31–40, 8; 12].

Although bilirubin encephalopathy and kernicterus remain relatively uncommon, their occurrence persists despite mass screening of neonates. Available sources indicate that both clinical and neuropathologic investigations of bilirubin encephalopathy have been documented in the literature [4; 131–142, 7; 31–40, 110; 26–39]. Neonatal jaundice is highly prevalent — observed in roughly 60% to 80% of newborns [2; 153–155, 5; 437–438, 34; 268]; severe hyperbilirubinemia (> 20 mg/dL), capable of precipitating kernicterus and neuronal injury, may likewise occur [4; 131–142, 6; 8–22, 101; 332–337].

Among the established risk factors are gestational pathology, intrauterine infection, low birth weight, hemolysis, sepsis, cephalohematoma, and perinatal asphyxia — all of which lay the groundwork for the development of bilirubin encephalopathy. Recent publications have illuminated the broad spectrum of clinical symptomatology and pathologic findings associated with bilirubin encephalopathy and kernicterus [3; 169, 7; 31–40, 18; 42–46].

The term *kernicterus* derives from the German *Kern* ("nucleus") and the Greek *icterus* ("jaundice"). It was originally introduced by Christian Georg Schmorl to describe the pathologic yellow staining observed in the basal ganglia of the brain and in the cerebellum [1; 366–367, 9; 189–195, 101; 332–337]. Over time, however, the term came to encompass both acute and chronic forms of bilirubin encephalopathy (BE). In 2004, with the aim of clarifying terminological usage, the National Institute for Child Health and Human Development (NICHD) recommended that the term ABE be reserved for the neurological manifestations emerging during the first few weeks of life, while *kernicterus* should designate the chronic sequelae of ABE. Despite these recommendations, long-standing inconsistencies have continued to surround the nomenclature, prompting Le Pichon and colleagues to propose replacing all previously employed terms for chronic BE — including kernicterus and bilirubin-induced neurologic dysfunction — with a unified terminology, while retaining ABE for the acute manifestations of the disorder [13; 119–123, 19; 78–80, 66; 8061–8072]. Under current usage, the acute clinical manifestation of bilirubin neurotoxicity occurring in the early neonatal period is referred to as acute bilirubin encephalopathy (ABE), whereas the persistent, chronic consequences of bilirubin toxicity are designated as kernicterus [11; 3–11, 78; 172–180, 98; 376].

It bears emphasis that not every episode of acute bilirubin encephalopathy progresses to kernicterus and, conversely, that not all patients with chronic

bilirubin encephalopathy will have manifested overt features of BE during the first days of life. In milder presentations, affected children may exhibit motor disturbances, isolated hearing loss, or impairments of auditory function — including isolated auditory nerve neuropathy [13; 119–123, 14; 24–28]. The more severe presentations, by contrast, are typically marked by cerebral palsy, dystonia, choreoathetosis, profound hearing impairment, upward gaze palsy, and dental enamel dysplasia [15; 48–51, 87; 32–33].

§1.2. Pathophysiology and Etiology of Bilirubin Encephalopathy in Neonates and Children of Early Age

The central pathophysiologic event underlying bilirubin encephalopathy is the accumulation of unconjugated bilirubin within cerebral cells [16; 267–270, 90; 163]. Several regions of the brain — including the globus pallidus, basal ganglia, substantia nigra, hippocampus, thalamic nuclei, and putaminal nuclei, together with the dentate and inferior olivary nuclei of the cerebellum — are symmetrically affected and constitute the structures most vulnerable to bilirubin-induced toxicity. The cranial nerves, particularly the third, fourth, and sixth, are also implicated in this pattern of injury [90; 163, 118; 1–11, 120; 1–13]. Of note, most of these structures share a common vascular supply with regions that are likewise susceptible to hyperbilirubinemia — a finding that points to an underlying genetic or biochemical mechanism responsible for their selective vulnerability to elevated bilirubin levels.

Imaging changes consistent with kernicterus on magnetic resonance imaging (MRI) include bilateral, asymmetric, high-intensity signals localized to the globus pallidus and subthalamic nuclei. During the acute phase of ABE, these enhanced signals are most clearly visualized on T1-weighted sequences. The cochlear nuclei and the oculomotor and vestibular systems are similarly involved. Destructive changes within the white matter and periventricular

infarcts have likewise been documented, while the cerebral hemispheres typically remain unaffected [15; 48–51, 111; 61–67]. Autopsy studies have confirmed yellow discoloration in the aforementioned cerebral regions, attributable to deposits of unconjugated bilirubin. Cellular-level analyses reveal disruption of glucose transport systems, impaired synthesis of DNA, proteins, and neurotransmitters, altered activity of numerous enzymes, abnormal iron transport, and activation of apoptotic pathways. Mitochondrial degeneration, together with alterations in neuronal membrane composition, gives rise to irreversible and permanent changes that ultimately lead to chronic bilirubin encephalopathy [18; 42–46, 112; 461–467].

Although delayed recognition and management of severe hyperbilirubinemia represent the principal cause of bilirubin encephalopathy in all neonates, numerous additional risk factors can pathologically elevate the concentration of unconjugated bilirubin within the central nervous system. Given that the disorder has a multifactorial etiology, several variables beyond bilirubin levels alone contribute to the likelihood of disease development [19; 78–80, 40; 91–94, 102; 291–295]. Conditions capable of elevating circulating bilirubin include hemolytic disease of the newborn (HDN), sepsis, hereditary spherocytosis, G6PD deficiency, and congenital or genetically determined disorders of bilirubin metabolism — such as Crigler-Najjar and Lucey-Driscoll syndromes. A particularly hazardous feature of HDN lies in its capacity to elevate indirect bilirubin levels in the bloodstream; once these lipophilic molecules cross into the cerebral nuclei, the circulating concentration becomes critically important for the development of kernicterus. Specifically, kernicterus has been reported in 30% of infants at indirect bilirubin levels of 428–496 μmol/L and in 70% at levels of 518–648 μmol/L. Hypoalbuminemia, acidosis, and hypoglycemia further predispose to the development of bilirubin encephalopathy [21; 243–253, 67; 285–302, 89; 699–704].

In view of the immaturity of the blood-brain barrier (BBB) in neonates and the requirement for unconjugated bilirubin to traverse this barrier, any condition that damages the BBB or augments its permeability may serve as a principal risk factor for bilirubin toxicity, ultimately allowing bilirubin to deposit within cerebral cells. The leading conditions exerting effects through this mechanism include hypoxic-ischemic encephalopathy (HIE), prematurity, sepsis, and meningitis [22; 86–93, 78; 172–180]. Additional risk factors encompass low birth weight, cephalohematoma, perinatal asphyxia, and the absence of hyperbilirubinemia screening programs for neonates. Kernicterus is considered more likely to develop in preterm infants given that their BBB is not yet fully formed. By the same token, neonates are particularly susceptible to severe jaundice and kernicterus because the enzymatic activity of their liver remains immature and their capacity to eliminate bilirubin from the bloodstream is correspondingly underdeveloped [25; 15–17, 78; 172–180]. Returning to the multifactorial nature of bilirubin encephalopathy, it is evident that — beyond bilirubin levels per se — several other factors predispose to the development of this condition [23; 62–65, 24; 67–73, 98; 172–180].

Preterm infants constitute the most vulnerable patient population with respect to this condition. The risk factors driving the development of bilirubin encephalopathy can be grouped into three principal categories:

1. Augmented permeability of the blood-brain barrier — influenced by gestational age; plasma hyperosmolarity (including hyperglycemia and the administration of hyperosmolar solutions); severe acidosis; the presence of infectious complications; intracerebral hemorrhage; and other contributing factors.
2. Heightened neuronal susceptibility to the toxic effects of unconjugated bilirubin — including prematurity, severe asphyxia, hypothermia, starvation, anemia, and hypoglycemia.

3. Reduced binding capacity of albumin to unconjugated bilirubin — attributable to hypoalbuminemia, acidosis, infections, intravascular hemolysis, the administration of certain pharmacologic agents (sulfonamides, furosemide, phenytoin, indomethacin, salicylates, oxacillin, cephalothin, and cefoperazone), and maternal alcoholism.

All of the factors enumerated above contribute to an elevated risk of bilirubin encephalopathy, and their coexistence may precipitate the disorder even at comparatively modest levels of hyperbilirubinemia [29; 47–49, 30; 23–24, 116; 12–17]. The icteric form represents the most frequently encountered manifestation of HDN. In some infants, jaundice is partially evident at birth (congenital jaundice form), while in the majority of cases it emerges during the first days of life. Early onset of jaundice typically signals a more severe clinical course of HDN. No strict correlation exists between indirect bilirubin levels and the degree of cutaneous icterus; nevertheless, yellow discoloration of the palms is generally considered indicative of unconjugated bilirubin levels exceeding 205 μmol/L [30; 23–24, 32; 146, 89; 699–704].

The simplest approach to gauging the severity of jaundice consists in determining the timing of its onset and the anatomic distribution of cutaneous icterus. When jaundice appears on any region of the body on the first day of life, on the upper and lower extremities by the second day, and on the palms and soles by the third day, it is regarded as a "high-risk" sign. Under such circumstances, phototherapy should be initiated without delay — without awaiting bilirubin laboratory results. In cases of ABO incompatibility, hyperbilirubinemia typically develops on the second or third day of life, and at times even later [56; 26–31, 99; 327–331].

Additional characteristic findings include hepatosplenomegaly and yellow discoloration of the sclerae and mucous membranes. In infants with elevated unconjugated bilirubin levels, signs of CNS depression syndrome —

linked to bilirubin intoxication — become progressively more pronounced. The congenital form of jaundice is often accompanied by immune deficiency, with attendant susceptibility to infectious processes. Hyperregenerative anemia of varying severity is likewise typical, manifesting alongside reticulocytosis, normoblastosis, and erythroblastosis. These features are reflected hematologically by an increased proportion of nucleated red blood cells (pseudoleukocytosis) and by thrombocytopenia [29; 47–49, 66; 8061–8072].

§1.3. Clinical-Neurological Features of Bilirubin Encephalopathy in Neonates and Children of Early Age

The clinical classification of bilirubin encephalopathy in neonates and children of early age encompasses three principal forms:

1. Acute bilirubin encephalopathy (ABE)
2. Chronic bilirubin encephalopathy (CBE)
3. Subacute bilirubin encephalopathy (SABE)

Acute Bilirubin Encephalopathy (ABE)

ABE constitutes an acute clinical condition arising from the toxic effects of bilirubin on the central nervous system. Its clinical features include lethargy, diminished sucking, hypotonia or hypertonia, monotonous high-pitched crying, opisthotonos, retrocollis, the setting-sun sign, fever, seizures, and — in some cases — death. Unless bilirubin levels are promptly lowered, ABE may progress to chronic bilirubin encephalopathy [31; 491–495, 83; 42–48]. Numerous questions surrounding the pathogenesis of ABE remain unanswered. It is unclear, for instance, why extreme hyperbilirubinemia (500–600 μmol/L, or 30–35 mg/dL) passes without apparent harm in some term and preterm infants, while in others kernicterus develops at total bilirubin levels well below the conventional exchange transfusion threshold [17; 45–53, 67; 112; 461–467].

Additional genetic factors are thought to play a role under such circumstances. Clinical manifestations of bilirubin encephalopathy are rarely detected within the first 36 hours of life; the condition is typically recognized between the third and sixth days. The clinical course of BE has been described as evolving through four sequential stages [33; 33–37, 113; 277–283]:

Stage 1 (Onset of ABE) generally manifests between the third and fifth days of life and is characterized by diminished responsiveness to environmental stimuli, poor feeding, hypotonia, and a weakened Moro reflex. Signs of bilirubin intoxication predominate during this stage, including CNS depression syndrome — monotonous high-pitched crying, reduced muscle tone, loss of appetite, regurgitation, vomiting, pathologic yawning, and a fixed staring gaze [37; 193, 38; 292–293, 91; 97–104].

Stage 2 (Moderate ABE) is variable in both onset and duration; it typically becomes evident during the first week and is subsequently accompanied by stupor. The clinical picture may include opisthotonos, retrocollis, high-pitched cry, and hypertonia of the extensor muscles alternating with hypotonia [23; 62–65, 40; 91–94, 56; 26–31]. The classical features of kernicterus emerge during this stage: rigidity of the cervical muscles, spasticity, opisthotonos, unresponsiveness to auditory stimulation, intermittent irritability with a piercing "cerebral" cry, bulging of the anterior fontanelle, facial muscle twitching or complete amimia, tremor of the extremities, convulsions, and ocular signs including the setting-sun sign, nystagmus, and Graefe's sign. Additional manifestations include apnea, cardiac rhythm disturbances, lethargy, and — occasionally — fever. Although apnea occurs only rarely, it may serve as a warning sign of impending seizure in a jaundiced neonate [113; 277–283, 118; 1–11].

Stage 3 (False Recovery Period) is characterized by an apparent reduction in clinical signs and may even create the impression of complete rehabilitation.

Stage 4 (Severe ABE) typically emerges after the first week and is most often characterized by hypotonia. Additional features include coma, pronator spasms of the proximal portions of the body, the setting-sun sign, fever, weakened sucking reflex, and apnea [53; 45–53, 56; 26–31, 97; 407–408]. Mortality may reach as high as 21%, generally as a consequence of respiratory failure or reflex seizure activity. The clinical sequelae of neurological involvement — cerebral palsy, athetosis, choreoathetosis, paresis, deafness, neurodevelopmental delay, and dysarthria — typically begin to manifest toward the end of the neonatal period or between the third and fifth months of life [47; 96–104, 102; 291–295, 112; 461–467]. Cerebral injury, respiratory or cardiac failure, and lethal outcomes — frequently against a background of hemorrhagic syndrome — may occur during the first two phases of bilirubin intoxication. The classical features of kernicterus are not invariably present in neonates, particularly in preterm infants, which is why early diagnostic methods for detecting the condition are currently under development [71; 24, 109; 12].

Chronic Bilirubin Encephalopathy (CBE, Kernicterus)

CBE represents a chronic state of neurological dysfunction arising from severe hyperbilirubinemia, in which subsequent reduction of bilirubin levels exerts no influence on the established sequelae. Clinically, CBE manifests through movement disorders — predominantly dyskinetic, often with a spastic component — severe motor disability in approximately 60% of cases, auditory neuropathy, visual impairment, and oculomotor disturbances (nystagmus, strabismus, upward or downward gaze palsy, or cortical visual impairment) [52; 554–556, 53; 45–53, 112; 461–467]. Blindness occurs only rarely. Other features include dental enamel hypoplasia, dysplasia of the deciduous teeth,

gastroesophageal reflux, and digestive dysfunction. Although intellectual function is diminished, most individuals with kernicterus (approximately 85%) demonstrate normal or borderline-normal cognitive function alongside psychomotor developmental delay. These disturbances are linked to involvement of the basal ganglia, auditory nuclei, and oculomotor nuclei. The cerebral cortex and white matter sustain only minimal injury, and epilepsy is uncommon [56; 26–31, 57; 67–74].

Subacute Bilirubin Encephalopathy (SABE)

SABE represents a chronic clinical entity also referred to as bilirubin-induced neurologic dysfunction (BIND). Clinically, the disorder may give rise to neurological, cognitive, and motor disturbances, together with auditory impairment [60; 267–270, 81; 1239–1265]. Kernicterus is frequently associated with intellectual disability — most often arising as a consequence of hearing impairment that is typically detected on a standard audiogram. Kernicterus represents the more chronic and persistent clinical continuum of bilirubin toxicity in neonates who have recovered from ABE; it evolves gradually over several years in affected children. During the initial phase, occurring within the first year of life, hypotonia, hyperreflexia, and persistence of the tonic neck reflex are commonly observed. After the first year of life, clinical manifestations become more variable, with the classical symptom tetrad encompassing auditory, visual, and dental enamel impairment together with extrapyramidal disturbances [76; 176–182, 97; 407–408].

Auditory impairment typically presents as hearing loss — most often classified as sensorineural — although the auditory neuropathy spectrum disorder is likewise characteristic, since the underlying lesion involves the cranial nerve nuclei. These features may serve as early manifestations of both ABE and CBE and can occur even in the absence of other clinical signs of BE [69; 262–267, 70; 183–190]. Visual disturbances include upward gaze palsy and

horizontal nystagmus. The combination of upward gaze paresis and facial dystonia gives rise to a vacant stare, sometimes described as a "frightened look." Dental abnormalities consist of enamel hypoplasia and a green discoloration of the deciduous teeth. Extrapyramidal disturbances encompass dystonia, choreoathetosis, and athetosis; bulbar functions may also be affected [11; 3–11, 74; 1813, 75; 290–297]. Cognitive function remains relatively preserved. Although certain studies have suggested otherwise, such investigations may underestimate cognitive capacity in children who have experienced BE owing to limitations in their motor abilities. In milder presentations of bilirubin encephalopathy, auditory deficits may be associated with aphasia and additional neurodevelopmental disturbances, including central auditory processing impairment, deficits in sensory and sensorimotor integration, hypotonia, and ataxia [83; 42–48, 84; 443–454, 103; 33–44]. Kaplan and Hammerman reported the progression of ABE to CBE in 84% of affected infants. Other reports, however, have indicated that ABE did not progress to CBE in infants with moderate and severe disease following treatment. A review of the literature supports the view that genetic factors serve as relevant modulators of bilirubin neurotoxicity [67; 285–302, 90; 163].

The chronic course of bilirubin encephalopathy is influenced by elevated bilirubin levels, prolonged duration of the acute phase, the presence of comorbidities that predispose to hemolysis and amplify susceptibility to neuronal injury, factors that augment the permeability of the blood-brain barrier to bilirubin, and serum albumin concentration together with its bilirubin-binding capacity [7; 31–40, 88; 199–209, 89; 699–704]. Reliable theoretical evidence supports the role of variable gene expression as a critical determinant of bilirubin toxicity and the subsequent progression to kernicterus. This regional differential genetic expression may, at least in part, account for the selective pattern of cerebral injury observed. Although numerous genes have been implicated in the

development of hyperbilirubinemia, comparatively few studies have addressed those genes that are critical in determining a neonate's vulnerability to the toxic effects of bilirubin [10; 17–19, 45; 45–51, 93; 12]. Moreover, the precise toxic threshold of bilirubin cannot be reliably predicted — a finding borne out by multiple clinical investigations. Additional evidence points to environmental factors as significant contributors to disease development, including delayed feeding, exposure to teratogenic substances, and delayed access to timely and appropriate medical care — encompassing the failure to recognize the onset of severe hyperbilirubinemia and inadequate assessment of its severity [4; 131–144, 96; 1155]. In infants with mild BE, intensive treatment leads to complete recovery from neuronal injury. Stage 1 ABE is reversible with prompt and appropriate therapy, whereas the outcome of Stage 2 is more variable. Timely management of the disorder has been shown to prevent cerebral injury and to minimize the severity of sequelae once the disease has progressed to more advanced stages [23; 62–65, 99; 327–331, 103; 33–44].

§1.4. Clinical-Neurological Diagnosis of Bilirubin Encephalopathy in Neonates and Children of Early Age

In contemporary medical practice, the diagnosis of bilirubin encephalopathy is established through physical examination combined with instrumental investigations. Whereas the diagnosis was historically confirmed only at autopsy, current diagnostic strategies rely on targeted physical assessment, BIND scoring, and neurophysiologic and neuroimaging studies. The evaluation of bilirubin encephalopathy should be conducted on an individualized basis, with appropriate attention to the relevant risk factors [27; 15–17, 107; 947–953, 119; 1–13]. History taking holds particular importance — especially in identifying the underlying etiologic conditions. Of note, hemolytic disease of the newborn (HDN) — a frequent contributor to pathologic jaundice — can be detected in the antenatal period. All women with Rh-negative blood type should

undergo serial antibody-titer testing on three separate occasions: the first at the initial visit and upon registration at the women's consultation clinic. During the final three months of pregnancy, testing should be repeated on a monthly basis. When antibody titers reach 1:16 to 1:32 or higher, amniocentesis is indicated between 26 and 28 weeks of gestation, together with determination of bilirubin-like substance concentrations in the amniotic fluid. If clinically warranted, intrauterine exchange transfusion should be performed no later than the 32nd week of pregnancy. The edematous form of HDN may also be identified on ultrasound examination, and immunologic testing for HDN remains the most accessible and accurate diagnostic approach [6; 8–22, 32; 146, 101; 332–337, 103; 33–44, 107; 947–953].

Diagnostic Workup When HDN Is Suspected

When HDN is suspected, the recommended investigative protocol comprises the following components:

1. Blood typing — determination of blood group and Rh status in both mother and infant.
2. Peripheral blood analysis — including a reticulocyte count.
3. Serial bilirubin monitoring — measurement of bilirubin concentration in the infant's serum on a dynamic basis.
4. Hepatic enzyme assessment — determination of transaminase levels.
5. Immunologic testing. In cases of Rh incompatibility, this entails serial measurement of antibody titers in maternal blood and breast milk, an indirect Coombs test using infant erythrocytes, and an indirect Coombs test using maternal serum performed dynamically. In cases of ABO incompatibility, allohemagglutinin titers in maternal blood and breast milk are determined in both protein and saline media in order to distinguish natural agglutinins from immune agglutinins; the presence of

immune antibodies is indicated when the allohemagglutinin titer in the protein medium is at least two dilutions higher than that in the saline medium [3; 169, 53; 45–53, 104; 33–44, 119; 1–13]. When discrepancies between maternal and infant erythrocytes involve other antigenic factors, hemagglutination of the infant's erythrocytes upon the addition of maternal serum is documented (individual compatibility test) [51; 62–82, 78; 172–180, 105; 1–6].

Bilirubin concentrations should be interpreted on an hourly basis in accordance with the infant's postnatal age. The American Academy of Pediatrics (AAP) recommends that laboratory workup for all jaundiced neonates requiring phototherapy include blood group determination, direct antibody titer / Coombs test, total bilirubin and its fractions (free and conjugated bilirubin), liver enzyme levels, total protein measurement, and complete blood count (CBC) [23; 62–65, 107; 947–953].

During the first two weeks following birth, total bilirubin levels in neonates rise as a consequence of fetal erythrocyte breakdown, hepatic albumin insufficiency, and reduced conjugation capacity — together producing the clinical picture of physiologic jaundice. In some neonates, however, postnatal hepatic transport injury, impaired bilirubin conjugation, or accelerated hemolysis may give rise to a marked elevation of unconjugated bilirubin. Such jaundice is regarded as pathologic and can precipitate neonatal mortality or severe neurological sequelae [47; 96–104, 52; 554–556].

The Bilirubin-Induced Neurologic Dysfunction (BIND) score constitutes a 12-point scale that evaluates four clinical parameters: mental status, muscle tone, characteristics of the infant's cry, and ocular movements. A BIND score of 0 corresponds to normal status, while scores of 1–3, 4–6, and 7–9–12 indicate progressively greater severity. On the basis of these scores, acute bilirubin encephalopathy is classified as mild, moderate, or severe [37; 193, 63; 2, 108;

12, 113; 277–283]. El Houchi and colleagues (2017) examined the capacity of the BIND scale not only to detect neurological injury but also to predict its correlation with total bilirubin concentrations. A BIND score of 0 corresponds to a normal neonate, with low scores reflecting a favorable neurological outcome. By contrast, patients with elevated scores either succumb to the disease or are left with residual neurological sequelae [99; 327–331, 79; 57]. In the modified 12-point BIND scale, ocular movement abnormalities are assessed, including divergent gaze, upward gaze palsy, an anxious appearance, and nystagmus. The positive predictive value of this scoring system in the diagnosis and assessment of bilirubin encephalopathy reaches 98.2% [81; 1239–1265, 92; 610–620, 114; 111–116].

Instrumental Diagnostics

Among instrumental investigations, MRI holds considerable diagnostic value. MRI represents the most informative modality for diagnosing the acute and chronic neurological sequelae of bilirubin encephalopathy. The changes observed during the acute phase of BE are transient and ultimately subside. Pathologic alterations on MRI are documented in the globus pallidus in approximately 90% of cases, followed by the subthalamic region in roughly 40% [18; 42–46, 53; 45–53, 69; 262–267, 88; 199–209, 116; 12–17]. During the first several weeks of illness, MRI findings are most clearly visualized on T1-weighted sequences, whereas chronic bilirubin encephalopathy is better demonstrated on T2-weighted images. The acute phase of BE is characterized by generalized cerebral edema, bilateral asymmetric T2 hyperintensity, and — on FLAIR sequences during the chronic phase — hyperintensity in the globus pallidus and subthalamic nuclei [13; 119–123, 27; 15–17, 94; 204–208, 117; 1–13]. Signal abnormalities are classically observed in the globus pallidus, hippocampus, and cerebellum, although the nature of these changes evolves over time. During the days to weeks following the onset of acute bilirubin

encephalopathy — that is, during the subacute period — MRI studies in infants reveal enhanced T1 signal intensity in the globus pallidus and subthalamic nuclei. Additional MRI findings include restricted diffusion in the thalamus, hippocampus, substantia nigra, subthalamic nuclei, superior cerebellar peduncles, pontine nuclei, dentate nuclei of the cerebellum, superior thalamic radiations, and the periventricular and ventrolateral nuclei [98; 376].

§1.5. Treatment and Prevention of Bilirubin Encephalopathy in Neonates and Children of Early Age

During the acute phase of bilirubin encephalopathy, early intervention with phototherapy - together with exchange transfusion in cases of severe hyperbilirubinemia - may forestall the progression of bilirubin toxicity. To date, however, precise data regarding the duration of severe hyperbilirubinemia and the timing of bilirubin encephalopathy onset have yet to be firmly established [15; 48–51, 22; 86–93, 23; 62–65, 118; 1–11, 120; 1–13]. What is clear is that delaying treatment by more than a few hours in cases of markedly elevated hyperbilirubinemia - particularly in ill or preterm infants and in neonates with underlying hemolytic disease - substantially increases the likelihood of developing BE. Although effective therapeutic options exist for managing hyperbilirubinemia itself, no definitive treatment for the sequelae of bilirubin encephalopathy is currently available, and rehabilitation remains the sole therapeutic strategy. Timely diagnosis and prompt management of jaundice constitute the cornerstone of preventing severe hyperbilirubinemia [8; 12, 21; 245–253, 39; 42–47, 101; 332–337]. Cochlear implantation is indicated for children with auditory neuropathy and hearing loss.

In the icteric form of HDN, the infant is fed age-appropriate volumes of donor milk beginning 2–6 hours after birth, while breastfeeding is initiated from the second or third week of life - once alloantibody levels have declined.

Therapeutic strategies for hyperbilirubinemia are divided into conservative approaches (including exchange transfusion, plasmapheresis, and hemosorption) and operative measures. Phototherapy is currently the most widely employed conservative modality; its efficacy and safety profile have made it a mainstay of treatment [8; 12, 17; 45–53, 45; 45–51, 102, 120; 1–13].

A blue light source (wavelength 450 nm) is typically positioned 45–50 cm above the infant and should provide an illumination intensity of 5–30 μW/cm² per minute. In term infants, phototherapy is initiated by the end of the first day when serum indirect bilirubin reaches 145–205 μmol/L or above; in preterm infants, the threshold is 145 μmol/L or higher; and in neonates with very low birth weight, phototherapy is commenced once indirect serum bilirubin reaches 100 μmol/L. Ideally, phototherapy should be started within the first 24–48 hours of life and administered continuously. Although phototherapy exerts no harmful effects on the gonads, protective shielding of the eyes and genital area remains essential. The therapeutic benefit of phototherapy is attributed to enhanced urinary and fecal excretion of indirect bilirubin, together with a reduction in toxicity - and consequently in the risk of kernicterus - through photo-oxidation of indirect bilirubin. Phototherapy also demonstrates considerable efficacy in cases of breast-milk jaundice [11; 3–11, 19; 78–80, 78; 172–180, 90; 163].

Phototherapy may produce a range of adverse effects, which clinicians should monitor throughout treatment:

1. Inadequate hydration - fluid loss often exceeds physiologic norms; compensatory administration of an additional 25% fluid volume is therefore indicated.
2. Greenish discoloration of stools - commonly appears during treatment; reflects the formation of unconjugated bilirubin photoderivatives and resolves without intervention.
3. Transient skin rashes - have been reported.

4. CNS depression syndrome - may emerge.
5. Stretching of the abdominal musculature - occasionally observed and requires no treatment.
6. Bronze baby syndrome - occurs in infants with underlying hepatic injury; its prognosis is determined by the severity of liver damage.
7. Tendency toward thrombocytopenia - linked to accelerated platelet turnover; does not call for therapeutic intervention.
8. Growth deceleration - observed in neonates during the period of phototherapy.
9. Persistence of the patent ductus arteriosus (ductus Botalli) - noted in low-birth-weight infants.
10. Transient riboflavin deficiency - observed with prolonged phototherapy, though it does not appear to diminish therapeutic efficacy [1; 366–367, 15; 48–51, 70; 183–190, 90; 163, 104; 33–44, 120; 1–13].

The duration of phototherapy is dictated by the rate at which indirect bilirubin levels decline in the bloodstream. Therapeutic efficacy increases substantially when phototherapy is combined with infusion therapy, since this combination accelerates the elimination of water-soluble bilirubin derivatives. In term neonates during the first day of life, blood glucose levels must be carefully monitored, and 50–60 mL/kg of 5%–10% glucose solution is typically infused [58; 324–327, 64; 241–257, 78, 90; 163, 97; 407–408]. Daily increments of 20 mL/kg follow, with total fluid volume reaching 150 mL/kg per day by the fifth day. From the second day onward, calcium levels are corrected according to physiologic requirements - the normal value in term infants standing at 75 mg/kg. Correction is achieved using 10% calcium gluconate (9 mg/mL) or calcium chloride (36 mg/mL) solution. Beginning on the third day, 2 μmol/kg of sodium chloride (in isotonic solution) and 1 μmol/kg of potassium are added to

the infusion mixture. Hemodez and rheopolyglucin must not be administered to neonates, owing to their capacity to block the mononuclear phagocytic system and to reduce platelet aggregation [54; 89–97, 67; 285–302, 105; 1–6]. Phenobarbital is prescribed in the postnatal period; it promotes the formation of bilirubin glucuronide and enhances biliary secretion. On the first day of treatment, phenobarbital is administered at 20 mg/kg daily (divided into three doses); on subsequent days, the dose is 3.5–5 mg/kg.

Exchange Transfusion (ET)

Absolute indications for ET in term neonates include:

- Hyperbilirubinemia exceeding 342 μmol/L;
- A rise in total bilirubin at a rate of 9 μmol/L per hour;
- Umbilical-cord bilirubin concentration above 60 μmol/L.

From the first day of life, ET is indicated under the following circumstances:

(a) Jaundice or pronounced cutaneous pallor appearing within the first hours of life, accompanied by hepatomegaly or splenomegaly;

(b) Severe anemia on hematologic analysis (Hb < 100 g/L), normoblastosis, and documented ABO or Rh incompatibility between maternal and infant blood.

For exchange transfusion, the estimated bilirubin load is determined using a standardized calculation formula [39; 42–47, 64; 241–257, 73; 3390, 84; 443–453, 106; 166–178].

At present, no effective curative treatment exists for kernicterus. A small number of patients have shown reduction in neurological symptoms following deep brain stimulation (DBS). Pharmacologic agents such as clonazepam, gabapentin, and trihexyphenidyl (Artane) are frequently employed to manage

the movement disturbances associated with kernicterus. Therapeutic management of kernicterus targets the rehabilitation of motor impairments and addresses neurodevelopmental sequelae through physical, occupational, speech, and audiological therapies; concurrent attention is directed toward feeding difficulties, gastroesophageal reflux, sleep disturbances, muscular hypertonicity, and cramping [65; 241–257, 89; 699–704, 97; 407–408, 107; 947–953, 117; 1–13].

Conclusions to Chapter I

Drawing together the literature on the clinical-neurological sequelae of bilirubin encephalopathy in neonates and children of early age, several observations emerge concerning the relevance of this disorder. Elevated hyperbilirubinemia is encountered in 60% to 70% of term-born neonates during the neonatal period, and bilirubin levels exceeding 300–400 μmol/L drive the development of bilirubin encephalopathy. The sequelae of this condition are wide-ranging: hearing loss, lag in mental, speech, and motor developmental milestones, the emergence of seizure syndrome, pathology of the extrapyramidal system, and — in 5.5% to 6.2% of cases — the dyskinetic form of cerebral palsy. Systematic analysis of the available literature has revealed a marked paucity of definitive data on the pathophysiologic theories underlying bilirubin encephalopathy and on the precise threshold at which bilirubin reaches toxic concentrations within the central nervous system.

A survey of literature originating within the Republic of Uzbekistan indicates that, while the progression from hyperbilirubinemia to bilirubin encephalopathy has been examined by numerous neonatologists, sources addressing its clinical-neurological sequelae remain limited. The available statistical analyses nonetheless confirm that CNS injury arising from hyperbilirubinemia continues to be reported within the territory of Uzbekistan. According to the World Health Organization (WHO), the frequency of

complicated bilirubin encephalopathy is concentrated predominantly in low-income and developing countries — where the incidence runs roughly tenfold higher than in developed nations. Unconjugated bilirubin is neurotoxic. The precise mechanism underlying its neurotoxic action has yet to be fully elucidated, and no scientific consensus has been reached regarding the threshold concentration at which unconjugated bilirubin exerts its neurotoxic effect.

According to the consensus view, kernicterus - the nuclear form of jaundice - presents along a continuum ranging from comparatively mild symptomatology to clinically devastating manifestations. In children with severe clinical expression, the picture comprises grave neurological disturbances including cerebral palsy, dystonia, choreoathetosis, hearing loss, upward gaze palsy, and dental enamel dysplasia; however, the transition from acute bilirubin encephalopathy to its chronic form - or to overt kernicterus - has yet to receive comprehensive coverage in the scientific literature.

Examination of theoretical frameworks and primary sources addressing the prognostication and therapeutic optimization of bilirubin encephalopathy in neonates and children of early age has confirmed the importance of disease etiology and the contributing risk factors. Yet the literature reveals fragmented and divergent views regarding which stage of the disease corresponds to which severity of bilirubin encephalopathy, and at which stage therapeutic intervention should be optimized. This state of affairs, in turn, underscores the need to refine and optimize the clinical management strategy for bilirubin encephalopathy.

CHAPTER II.

CHARACTERISTICS OF CLINICAL MATERIALS AND DIAGNOSTIC METHODS OF BILIRUBIN ENCEPHALOPATHY IN NEWBORNS AND INFANTS

§2.1. Clinical Characterization of the Study Material

To carry out a clinical-neurological investigation of bilirubin encephalopathy in neonates and children of early age, 100 hyperbilirubinemic infants were recruited from the Surkhandarya Regional Perinatal Center and from the neonatal pathology and neonatal intensive care unit (NICU) of the Regional Multidisciplinary Pediatric Medical Center. Eligible participants were term-born infants whose biochemical blood analysis demonstrated a total bilirubin (TB) concentration exceeding 200 μmol/L, whose icterus persisted for 2 weeks or longer, and whose Kramer scale score was 4–5 points. The recruited infants were stratified into subgroups according to the degree of hyperbilirubinemia and the duration of icterus. To support therapeutic optimization of BE, the cohort was further partitioned into a study group, a comparison group, and a control group of healthy children. Physiological development of the neonates was evaluated using the standardized "Percentile Chart for Neonatal Development." To identify the etiologic factors and developmental determinants of bilirubin encephalopathy, the following parameters were examined: maternal age, hereditary disorders, epidemiologic history, maternal somatic comorbidities, obstetric-gynecologic history, the course and complications of pregnancy, and the course of labor. A total of 100 patients diagnosed with neonatal jaundice were investigated. Among the 100 neonates and children of early age who had either developed or recovered from bilirubin encephalopathy, hemolytic disease of the newborn (HDN) was identified in 62 cases.

The severity of bilirubin encephalopathy was graded according to the BIND (Bilirubin-Induced Neurologic Dysfunction) score, on the basis of which each neonate was assigned to one of three clinical categories:

Group 1 — mild bilirubin encephalopathy (n = 17), BIND score 1–3;

Group 2 — moderate bilirubin encephalopathy (n = 62), BIND score 4–6;

Group 3 — severe bilirubin encephalopathy (n = 21), BIND score 7–10.

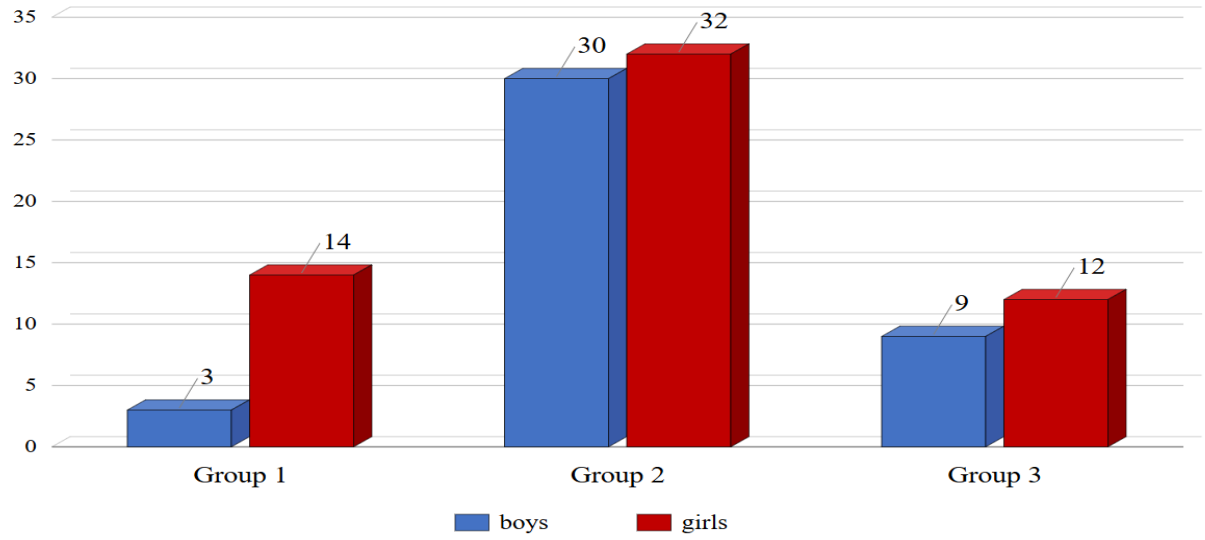

Figure 2.1. *Sex distribution of the children across the study groups.*

Table 2.1

Anthropometric Characteristics of the Children Across the Study Groups

Group	Sex	Age (days)	Body weight (g)	Length (cm)
Group 1 (n = 17)	Boys 3 / Girls 14	10.2 ± 14.0	3734.1 ± 734.6	51.5 ± 3.4
Group 2 (n = 62)	Boys 30 / Girls 32	18.3 ± 17.6	3060.0 ± 706.6	52.8 ± 3.8
Group 3 (n = 21)	Boys 9 / Girls 12	15.7 ± 13.4	2924.3 ± 546.0*	50.3 ± 3.4
Control group	Boys 10 / Girls 20	10.7 ± 6.4	3789.3 ± 46.0	51.3 ± 3.1

Note: **Differences between the mean anthropometric values of the children across the groups are statistically significant (P < .05).*

The following examination protocol was implemented for both mothers and their infants:

Preconception assessment — maternal hereditary disorders, hepatobiliary pathology, parental blood group incompatibility, and concomitant somatic diseases occurring prior to pregnancy were identified.

Antenatal evaluation — the obstetric history during the current pregnancy, chronic genital tract pathology, iron-deficiency anemia, gestosis (preeclampsia spectrum), chronic fetoplacental insufficiency, and factors predisposing to intrauterine infection and fetal hypoxia were investigated using standard clinical methods.

Objective neonatal assessment — general clinical status, anthropometric parameters, and adaptation to the extrauterine environment were evaluated.

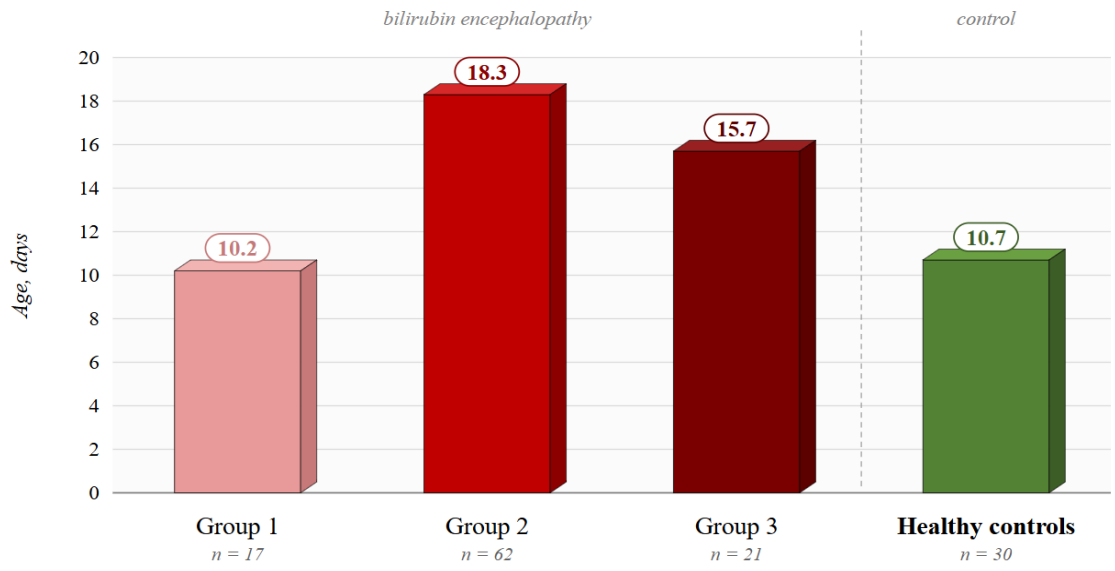

Figure 2.2. *Age distribution of the children across the study groups.*

All neonates underwent comprehensive clinical-anamnestic and laboratory evaluation. Establishing an accurate diagnosis in the neonatal period is notably more challenging than in other age categories, given the nonspecific clinical presentation and the limited communicative capacity of the patient. In

accordance with the predetermined examination protocol, a thorough history was obtained for each neonate and child of early age, with particular attention to the obstetric history — which served as the primary source of information regarding both the direct causative factors of the pathologic condition and the contributing risk factors for disease progression.

The Apgar score was used to evaluate the general condition of the newborn at birth. This rapid clinical scoring system grades neonatal status at standardized time points, yielding a composite value on a scale from 0 to 10. Together with birth weight and length, the Apgar score is one of the three principal parameters routinely communicated to the parents immediately after delivery.

Table 2.2

The Five Parameters of the Apgar Score

Parameter	0 points	1 point	2 points
Skin color	Generalized pallor or generalized cyanosis	Pink body, cyanotic extremities	Entire body and extremities pink
Respiration	Absent	Weak (hypoventilation)	Active crying, rhythmic breathing
Heart rate (beats/min)	< 60 or absent	< 100	≥ 100
Reflex irritability	Absent	Grimace in response to stimulation	Vigorous cry, active movement
Muscle tone	Absent	Partial flexion of the extremities	Active motion

Score interpretation. Assessment is routinely performed at 1 and 5 minutes after birth, with repeat evaluation indicated when the initial findings are unfavorable. A score below 3 reflects a severely compromised neonatal condition, whereas a score above 7 is regarded as normal. The Apgar score was developed to help clinicians identify which neonates require more intensive

monitoring: an infant scoring 5 needs closer observation than one scoring 7–10. A neonate with a 1-minute score of 5–6 who reaches 7–10 by 5 minutes is considered healthy. By contrast, infants who score 5 at birth and remain at 5 after 5 minutes require resuscitative support. A maximum score of 10 is rarely encountered in clinical practice.

Kramer scale. Visual assessment of neonatal jaundice severity was performed using the Kramer dermal zoning system, which correlates the cephalocaudal progression of skin discoloration with approximate serum bilirubin concentrations:

Area I — jaundice limited to the face and neck (bilirubin ≈ 80 μmol/L);

Area II — jaundice extending to the umbilicus (bilirubin ≈ 150 μmol/L);

Area III — jaundice reaching the knees (bilirubin ≈ 200 μmol/L);

Area IV — jaundice spreading to the face, upper and lower extremities, sparing the palms and soles (bilirubin ≈ 300 μmol/L);

Area V — generalized jaundice involving the entire body, including the palms and soles (bilirubin ≈ 400 μmol/L).

BIND scale.

The clinical-neurological manifestations of encephalopathy arising from bilirubin intoxication were evaluated using the Bilirubin-Induced Neurologic Dysfunction (BIND) score. This instrument serves to objectify and streamline the clinical diagnosis of acute bilirubin encephalopathy (ABE), while also providing a structured framework for monitoring neurological status in neonates with progressive hyperbilirubinemia at risk of encephalopathy. The BIND scale grades neonates across four domains — mental status, muscle tone, character of the cry, and ocular movements — thereby stratifying the clinical progression into three severity categories: subtle, moderate, and advanced.

In accordance with the clinical course of the disease, each evaluated parameter is assigned a score ranging from 0 to 3. A score of 0 corresponds to normal neurological status. Scores of 1–3 indicate mild bilirubin encephalopathy; scores of 4–6 reflect moderate encephalopathy; and scores of 7–9 or 10–12 denote advanced ABE, for which urgent, prompt, and individually tailored intervention is recommended — to prevent cerebral injury, minimize the severity of long-term sequelae, and potentially reverse the acute clinical course.

A score of 4–6 points corresponds to moderate ABE; within this range, complications may still be averted through immediate and aggressive bilirubin-lowering strategies.

A score of 1–3 points is consistent with the neurological features of a mild course of ABE in neonates with hyperbilirubinemia.

Table 2.3

Grading of Acute Bilirubin Encephalopathy Using the BIND Scale

(adapted from Johnson et al., 2009)

	Clinical sign	BIND score
1	**Mental status**	
1.1	Normal	0
1.2	Drowsy but irritable; poor feeding	1
1.3	Lethargy, weak sucking or irritability/jitteriness with strong sucking	2
1.4	Pre-coma, inability to feed, seizures, coma	3
2	**Muscle tone**	
2.1	Normal	0
2.2	Mild to moderate persistent hypotonia	1
2.3	Hypertonia alternating with hypotonia; arching of the neck and trunk on stimulation	2
2.4	Persistent retrocollis and opisthotonos; involuntary movements of the arms and legs	3

3	**Cry pattern**	
3.1	Normal	0
3.2	Shrill cry on arousal or stimulation	1
3.3	High-pitched cry, difficult to console	2
3.4	Inconsolable high-pitched cry, or cry weak or absent	3
4	**Eye movements**	
4.1	Normal	0
4.2	Divergent gaze	1
4.3	Upward gaze palsy	2
4.4	Anxious appearance and nystagmus	3
	TOTAL	**12 points**

The neurological status of the neonates was assessed using a standardized neurological examination protocol [Badalyan LO, 1980; Palchik AB].

Criteria for Assessing Psychomotor Development in Neonates and Children of Early Age Using the Bayley Scales

Clinical-neurological assessment in the study cohort was performed on a regular basis. General neurological examinations were repeated several times each day in the neonates. Infants who had sustained bilirubin encephalopathy were re-evaluated in the outpatient setting at 1, 6, and 12 months of life, with concurrent assessment of their psychomotor development. Interpretation of the Bayley test results begins with the computation of the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). For each age group, the mean value of both indices is set at 100, with a standard deviation (SD) of 15. A score of 100 on either scale indicates that the child's development corresponds to the established age-specific norm. Values of 85 or 115 represent ±1 SD from the mean, while scores of 70 or 130 correspond to a deviation of ±2 SD. In a normally distributed sample, approximately two-thirds of children score

between 85 and 115, 95% fall within the range of 70 to 130, and nearly all children show results between 55 and 145 (±3 SD).

Interpretation of the **Behavior Rating Scale (BRS)** — a component of the Bayley Scales of Infant Development — begins with evaluation of the total raw score, which provides a numerical expression of the examiner's overall impression of the child's performance during testing. The maximum attainable total score is 18 points for infants aged 1–5 months, 28 points for those aged 6–12 months, and 26 points for children aged 13–42 months. The total score reflects the child's neuropsychic development and additionally captures adaptive capacity. Results may be assigned to one of three classification categories: *within normal limits* — a score that meets or exceeds the 26th percentile for the corresponding age group.

§2.2. Complete Blood Count and Biochemical Parameters

Among the laboratory investigations performed, the complete blood count (CBC) together with total bilirubin and its fractions served as the principal indicators of the severity of bilirubin intoxication and the trajectory of the disease. For each participant, bilirubin and its fractions were measured serially over the course of clinical follow-up, since these parameters reflect both the acute or chronic course of the disease and the status of associated neurological dysfunction. Total bilirubin (TB) concentrations in the study group and the comparison group were re-evaluated prior to treatment initiation and subsequently reassessed dynamically across the 7- to 10-day therapeutic interval.

In parallel, the concentrations of the neuron-specific proteins NSE and S100 — biomarkers of central nervous system injury — were determined. These analyses were carried out at the Biomedical Research Center of Tashkent State Medical University. When TB in neonates and children of early age exceeded 200 μmol/L during the acute phase of disease, a 1-mL venous blood sample was

collected and centrifuged to separate the plasma fraction. Specimens were stored in dedicated containers in a laboratory freezer for up to three months and transported to the analytical facility under controlled frozen conditions.

Laboratory analysis was performed by enzyme-linked immunosorbent assay (ELISA) on the MAGLUMI 800 (Snibe) chemiluminescence analyzer, which permits simultaneous loading of up to 40 samples and 9 reagent positions within a 17-minute run cycle, with a throughput of 180 tests per hour. Detection relied on the low-molecular-weight, non-enzymatic ABEI chemiluminescent label, and the corresponding results were subsequently retrieved. The reference ranges applied in this study were NSE < 17 ng/mL and S100 protein 0.080–0.15 ng/mL; substantial deviations from these values were documented among the examined infants. Quantification of total bilirubin, its fractions, and the neuron-specific proteins was performed during the acute phase of disease — namely, when hyperbilirubinemia exceeded 256 μmol/L — corresponding to day 7 ± 3 of life in infants presenting with jaundice. In the study group, neuron-specific protein concentrations were subsequently re-evaluated dynamically on days 7–10 of treatment.

§2.3. Cerebral Neurosonographic Examination

Neurosonography (NSG) was employed for the assessment of cerebral status in cases of bilirubin encephalopathy, selected as a noninvasive and readily accessible imaging modality suitable for both neonates and children of early age. Each participant underwent an initial NSG examination during the first week of hospital admission; in severely affected neonates the study was repeated dynamically, while infants with chronic bilirubin encephalopathy (CBE) were additionally evaluated at 1 month and 6 months of age. In all patients, NSG was complemented by Doppler sonography. Examinations were performed on Vivid GE, Mindray M7, and Siemens Acuson S2000 systems using sector probes at 5–10 MHz and linear probes at 7–14 MHz.

NSG findings enabled the evaluation of the following parameters: maturity of cerebral structures; sequelae of intraventricular hemorrhage; parenchymal hemorrhages; dilatation of the external and internal cerebrospinal fluid spaces; periventricular hemorrhagic changes; elevation or reduction of blood-flow velocity in the anterior cerebral artery; and alterations in the resistive index within the anterior, middle, and posterior cerebral arteries together with their corresponding venous outflow tracts.

§2.4. Recording and Analysis of Cerebral Bioelectrical Activity

Electroencephalography (EEG) was used to assess cerebral bioelectrical activity in patients with bilirubin encephalopathy. Recordings were carried out in the EEG suite of the Diagnostic Department of the Termez City Multidisciplinary Central Polyclinic, using a second-generation Neuron-Spectrum-2 device (Neurosoft) operated through the Neuron-Spectrum 19+1 software package. EEG acquisition was performed in the sleep state, with 19 cup electrodes positioned according to the international 10–20 system and bilateral auricular reference electrodes (A1, A2) attached.

Recordings were obtained predominantly during a 1-hour sleep period at 46–48 weeks of postmenstrual age in infants whose total bilirubin had exceeded 200 μmol/L during the hyperbilirubinemic phase. Cup-type electrode systems were employed throughout the EEG monitoring procedure, and the detected electrographic changes were interpreted in accordance with the 2017 ILAE classification of epilepsies and seizures.

§2.5. Statistical Analysis

Statistical processing of the study data was carried out using the Excel 2019 statistical package on a personal computer of the corresponding generation. The following parameters were computed: arithmetic mean (M), standard deviation (δ), standard error of the mean (±m), reliability coefficient (t),

between-group differences (t and P), and chi-square (χ^2) values — together enabling the determination of nonparametric indicators across the study groups. Qualitative differences between paired groups were assessed using the Mann-Whitney U test and the Wilcoxon signed-rank test, and correlational relationships between variables were examined using the Pearson correlation coefficient (r), defined as the coefficient of linear correlation. Results were considered statistically significant at $P \leq .05$.

Conclusions to Chapter II

To investigate the clinical-neurological manifestations of bilirubin encephalopathy in neonates and children of early age, a cohort of 100 hyperbilirubinemic infants was recruited from the neonatal pathology department and the NICU of the Surkhandarya Regional Perinatal Center together with the Regional Multidisciplinary Pediatric Medical Center. Eligible participants were term-born infants whose biochemical blood analysis demonstrated a TB concentration exceeding 200 μmol/L, in whom icterus had persisted for 2 weeks or longer, and whose Kramer scale score was 4–5 points. The enrolled infants were stratified into subgroups by the degree of hyperbilirubinemia and the duration of icterus; for the purpose of therapeutic optimization, the cohort was further partitioned into a study group, a comparison group, and a control group of healthy children. Severity grading of bilirubin encephalopathy was performed using the BIND (Bilirubin-Induced Neurologic Dysfunction) score, on the basis of which three severity-defined groups were established.

All neonates underwent meticulous clinical-anamnestic surveillance and laboratory examination. Achieving a precise diagnosis in the neonatal period is notably more demanding than in older age categories, owing to the nonspecific clinical presentation and the limited communicative capacity of the patient. In accordance with the study protocol, a comprehensive history was obtained for

each neonate and child of early age, with detailed attention to the obstetric history — which captured both the immediate precipitating factors of the pathologic condition and the risk factors contributing to disease progression.

Clinical-neurological assessment of the study cohort was conducted on a regular basis. Infants who had sustained bilirubin encephalopathy were referred for outpatient neurological examination at 1, 6, and 12 months of life, and their psychomotor development was evaluated accordingly. Interpretation of the Bayley Scales of Infant Development (BSID) began with the computation of the Mental Development Index (MDI) and the Psychomotor Development Index (PDI).

Among laboratory parameters, the complete blood count (CBC) together with serum bilirubin and its fractions were monitored serially in line with disease dynamics; in the study group and the control group, TB values were re-measured prior to treatment and again over a 7- to 10-day therapeutic interval. In parallel, the concentrations of the neuron-specific proteins reflecting CNS injury — namely neuron-specific enolase (NSE) and S100 protein — were determined. These assays were performed at the Biomedical Research Center of Tashkent State Medical University.

Cerebral structural changes were assessed by means of neurosonography (NSG). Each enrolled neonate underwent an initial NSG examination during the first week of hospitalization; in severely affected infants and in those who had developed chronic bilirubin encephalopathy (CBE), repeat neurosonographic studies were performed at 1 and 6 months of age. To characterize cerebral bioelectrical activity in bilirubin encephalopathy, electroencephalography (EEG) was employed. EEG recordings were obtained in the EEG suite of the Diagnostic Department of the Termez City Multidisciplinary Central Polyclinic, using a second-generation Neuron-Spectrum-2 device (Neurosoft) operated through the Neuron-Spectrum 19+1 software package.

Statistical processing of the results was carried out by means of the Excel 2019 statistical package on a personal computer of the corresponding generation. The computed parameters included the arithmetic mean (M), standard deviation (δ), standard error of the mean (±m), reliability coefficient (t) for assessing the precision of indicators, the level of significance for between-group differences (t and P), and the linear correlation coefficient. Differences were regarded as statistically significant at $P \leq .05$.

CHAPTER III.
CLINICAL-NEUROLOGICAL FEATURES OF BILIRUBIN ENCEPHALOPATHY IN IN NEWBORNS AND INFANTS

In neonates and children of early age, bilirubin encephalopathy emerges as a consequence of hyperbilirubinemia. The prenatal, antenatal, and intranatal contributors implicated in its pathogenesis were systematically examined and evaluated.

§3.1. The Significance of Perinatal Risk Factors Leading to Bilirubin Encephalopathy in Neonates and Children of Early Age

In the course of analyzing perinatal risk factors across the study groups, the obstetric history emerged as a parameter of considerable importance. The maternal history during pregnancy for the children in each group is summarized below. It warrants particular emphasis that, in the cohort of neonates with severe bilirubin encephalopathy, risk factors operating during the gestational period were notably predominant. Elevated uterine tone was registered in 61.9% of cases, fetoplacental insufficiency in 57.1%, meconium-stained amniotic fluid in 57.1%, placental abruption in 47.6%, and double nuchal cord entanglement in 71%. Within the moderate-BE cohort, the same constellation of factors prevailed, though at comparatively lower frequencies — 46.8%, 50%, 50%, 17.7%, and 56.5%, respectively. In the mild-BE cohort, fetoplacental insufficiency (47.1%) and nuchal cord entanglement (52.9%) predominated when contrasted with Groups 2 and 3. Taken together, these findings substantiate that hypoxic fetal injury sustained during the gestational period constitutes a principal risk factor underlying the development of severe and moderate forms of bilirubin encephalopathy (see Table 3.1).

Table 3.1

Characteristics of the obstetric history during pregnancy of mothers of children with bilirubin encephalopathy across the study groups

Indicator	Group 1 (n=17)			Group 2 (n=62)			Group 3 (n=21)		
	n	%	χ^2; p	n	%	χ^2; p	n	%	χ^2; p
Threatened miscarriage	1	5.9	χ^2=1.92 p>0.05	14	22.6	χ^2=0.05 p>0.05	8	38.1	χ^2=1.14 p>0.05
Low-lying placenta	3	17.6	χ^2=0.05 p>0.05	8	12.9	χ^2=0.1 p>0.05	4	19.0	χ^2=0.15 p>0.05
Elevated uterine tone	5	**29.4***	χ^2=3.87 p<0.05	29	**46.8***	χ^2=3.41 p<0.05	13	**61.9***	χ^2=4.49 p<0.05
Anterior placentation	3	17.6	χ^2=0.02 p>0.05	9	14.5	χ^2=0.05 p>0.05	4	19.0	χ^2=0.08 p>0.05
Fetoplacental insufficiency	8	**47.1***	χ^2=5.03 p<0.05	31	**50.0***	χ^2=5.01 p<0.05	12	**57.1***	χ^2=4.12 p<0.05
History of abortion and miscarriage	2	11.8	χ^2=0.01 p>0.05	4	6.5	χ^2=0.8 p>0.05	5	23.8	χ^2=1.77 p>0.05
Oligohydramnios	0	0.0	—	5	8.1	χ^2=0.54 p>0.05	2	9.5	χ^2=0.07 p>0.05
Polyhydramnios	4	23.5	χ^2=0.7 p>0.05	6	9.7	χ^2=0.52 p>0.05	4	19.0	χ^2=0.25 p>0.05
Premature rupture of membranes	3	17.6	χ^2=0.21 p>0.05	11	17.7	χ^2=0.58 p>0.05	10	**47.6***	χ^2=3.41 p<0.05
Contamination of amniotic fluid	4	23.5	χ^2=1.4 p>0.05	38	**60.0***	χ^2=5.05 p<0.05	12	**57.1***	χ^2=4.24 p<0.05
History of children with hemolytic disease	7	**41.2***	χ^2=3.11 p<0.05	42	**67.7***	χ^2=5.44 p<0.05	13	**61.9***	χ^2=4.56 p<0.05
Double nuchal cord entanglement	9	**52.9***	χ^2=5.06 p<0.05	35	**56.5***	χ^2=5.03 p<0.05	15	**71.4***	χ^2=3.26 p<0.05

Note: **Differences in the prevalence of risk factors contributing to the development of BE compared with other factors are statistically significant within the groups (*p<0.05).*

A maternal history of a previously affected child with hemolytic disease of the newborn (HDN) was identified across all study groups, with markedly elevated frequencies registered in Groups 2 and 3 ($P < .05$).

Maternal morbidities during the gestational period may also constitute a precipitating factor for the development of bilirubin encephalopathy in the offspring. Notably, the highest prevalence of maternal illness during pregnancy was registered among neonates with severe BE.

Table 3.2

Maternal morbidities during pregnancy in children affected by bilirubin encephalopathy across the study groups

Indicator	Group 1 (n=17)			Group 2 (n=62)			Group 3 (n=21)		
	n	**%**	**χ^2; p**	**n**	**%**	**χ^2; p**	**n**	**%**	**χ^2; p**
Grade 1 and 2 anemia	6	35.3	χ^2=0.06 p>0.05	24	38.7	χ^2=0.49 p>0.05	3	14.3	χ^2=4.16 p<0.05
Grade 3 anemia	9	**52.9***	χ^2=3.1 p<0.05	35	**56.5***	χ^2=3.9 p<0.05	19	**90.5****	χ^2=7.2 p<0.01
Acute respiratory infection (ARI)	5	29.4	χ^2=0.84 p>0.05	29	46.8	χ^2=0.01 p>0.05	14	66.7	χ^2=0.72 p>0.05
Pyelonephritis	4	23.5	χ^2=0.4 p>0.05	21	33.9	χ^2=0.07 p>0.05	9	42.9	χ^2=0.27 p>0.05
Diffuse goiter	8	**47.1***	χ^2=4.1 p<0.05	31	**50.0***	χ^2=3.0 p<0.05	8	38.1	χ^2=0.22 p>0.05
Stress	4	23.5	χ^2=0.21 p>0.05	25	**40.3***	χ^2=3.7 p<0.05	9	**42.9***	χ^2=4.0 p<0.05
Cystitis	1	5.9	χ^2=0.11 p>0.05	2	3.2	χ^2=0.06 p>0.05	1	4.8	χ^2=0.02 p>0.05
Diabetes mellitus	2	11.8	χ^2=0.11 p>0.05	4	6.5	χ^2=0.29 p>0.05	3	14.3	χ^2=0.43 p>0.05
TORCH infection	1	5.9	χ^2=1.8 p>0.05	33	58.7	χ^2=4.1* p<0.05	14	66.7	χ^2=3.6* p<0.05
COVID-19	3	17.6	χ^2=2.1 p>0.05	32	51.5	χ^2=4.3* p<0.05	12	57.1	χ^2=4.1* p<0.05

Indicator	Group 1 (n=17)			Group 2 (n=62)			Group 3 (n=21)		
	n	**%**	**χ^2; p**	**n**	**%**	**χ^2; p**	**n**	**%**	**χ^2; p**
Mild toxicosis	5	29.4	χ^2=0.6 p>0.05	10	16.1	χ^2=0.15 p>0.05	4	19.0	χ^2=0.01 p>0.05
Severe toxicosis	3	17.6	χ^2=0.03 p>0.05	38	**61.3***	χ^2=4.5* p<0.05	10	47.6	χ^2=3.7* p<0.05
Pre-eclampsia	3	17.6	χ^2=1.43 p>0.05	21	33.9	χ^2=0.13 p>0.05	14	66.7	χ^2=5.0* p<0.05
Eclampsia	0	0.0	—	6	9.7	χ^2=0.32 p>0.05	2	9.5	χ^2=2.75 p>0.05
Seizures	1	5.9	χ^2=0.33 p>0.05	1	1.6	χ^2=0.29 p>0.05	1	4.8	χ^2=0.16 p>0.05
Genital diseases	3	17.6	χ^2=0.05 p>0.05	10	16.1	χ^2=0.23 p>0.05	8	38.1	χ^2=0.22 p>0.05
Cardiovascular diseases	0	0.0	—	2	3.2	χ^2=0.06 p>0.05	3	14.3	χ^2=0.43 p>0.05

Note: **Differences in the prevalence of maternal morbidities contributing to the development of BE compared with other factors are statistically significant within the groups (*p<0.05; **p<0.01).*

Grade 3 anemia was documented in 90.5% of mothers of Group 3 neonates, while 56.5% of mothers in Group 2 — whose infants exhibited moderate BE — likewise presented with this condition ($P < .01$). TORCH infection was particularly noteworthy, occurring in 58.7% of mothers in Group 2 and 66.7% of mothers in Group 3 ($P < .05$). Infants born to TORCH-positive mothers tended to manifest more severe forms of bilirubin encephalopathy. Furthermore, the coexistence of Grade 3 anemia (52.9%) and diffuse goiter (47.1%) was identified among pregnant women in Group 3 ($P < .05$). Children delivered under such maternal conditions exhibited prolonged hyperbilirubinemia.

Severe gestosis (preeclampsia spectrum) was recorded in 17.6% of mothers in Group 1, 61.3% in Group 2, and 47.6% in Group 3 ($P > .05$). Within Group 3, encompassing infants with severe BE, TORCH infection affected 66.7% of mothers, whereas in Group 2 the corresponding rate was 58.7%. The

maternal coexistence of TORCH infection, Grade 3 anemia, severe gestosis, and diffuse goiter was substantively associated with prolonged hyperbilirubinemia and elevated serum bilirubin concentrations in the affected offspring. Diffuse goiter predominated among mothers of Group 1 and Group 2 neonates — at 47.1% and 50%, respectively — whereas in Group 3 the condition was identified in 38% of mothers.

Recurrent episodes of acute respiratory viral infections likewise prevailed in Groups 3 (66.7%) and 2 (46.8%). Pyelonephritis was registered in 43% of mothers in Group 3, 34% in Group 2, and 23% in Group 1. Preeclampsia was observed across all study groups, reaching its highest frequency (67%) among mothers in Group 3 — a factor that itself influenced the severity grade of bilirubin encephalopathy in the neonates. In addition, gestational stress was prominent in 43% of Group 3 mothers.

Offspring born to mothers with the combination of Grade 3 anemia (56.5%; n = 35), diffuse goiter (50%; n = 31), TORCH infection (37.1%; n = 23), cystitis and genital tract disease (18.1%), and preeclampsia (33.9%; n = 23) registered a mean BIND score of 6.5 ± 0.9 points — these factors having exerted a more potent influence on the intensification and progression of the clinical-neurological features of BE than any others identified. It is equally noteworthy that, in offspring of mothers who contracted SARS-CoV-2 infection during pregnancy, serum total bilirubin (TB) concentrations ranged between 250 and 280 μmol/L, with BE developing to a moderate-to-severe degree, advancing rapidly, and following a prolonged course ($P < .05$).

According to Table 3.3, delivery by cesarean section was less frequently observed in neonates with mild bilirubin encephalopathy than in those of Groups 2 and 3. In Group 1, the majority of cases — 82.4% — were delivered through physiological vaginal labor. The observations indicated that both physiological delivery and labor complicated by obstetric intervention occurred more

frequently among children with severe BE. The study established that 66.1% of neonates in Group 2 and 61.9% in Group 3 were born through physiological labor ($P > .05$). Cephalohematoma was likewise documented in 17.7% of Group 2 newborns — twice as frequently as in the remaining groups — among infants delivered with obstetric intervention ($P > .05$).

Table 3.3

Characteristics of intranatal factors in children with bilirubin encephalopathy across the study groups

Indicator	Group 1 (n=17)			Group 2 (n=62)			Group 3 (n=21)		
	n	**%**	**χ^2; p**	**n**	**%**	**χ^2; p**	**n**	**%**	**χ^2; p**
Physiological labor	14	**82.4**	χ^2=0.24 p>0.05	42	**66.1***	χ^2=4.0 p<0.05	13	**61.9***	χ^2=3.0 p<0.05
Cesarean section	3	17.6	χ^2=1.8 p>0.05	20	32.3	χ^2=0.01 p>0.05	8	38.1	χ^2=0.2 p>0.05
Breech presentation	0	0.0	—	1	1.6	χ^2=0.11 p>0.05	1	4.8	χ^2=1.12 p>0.05
Obstetric intervention (vacuum extraction, obstetric forceps)	2	11.8	χ^2=0.05 p>0.05	11	17.7	χ^2=0.3 p>0.05	10	**47.6***	χ^2=1.4 p>0.05
Drug-induced labor	0	0.0	—	1	1.6	χ^2=0.11 p>0.05	5	27.8	χ^2=0.2 p>0.05

§3.2. Clinical-Neurological Features of Bilirubin Encephalopathy in Neonates and Children of Early Age

The evaluation of the clinical-neurological status in bilirubin encephalopathy is inseparably linked to grading disease severity, establishing the diagnosis and — most critically — formulating the prognosis and instituting preventive measures against its sequelae. Within the present section, the clinical-neurological status of bilirubin encephalopathy is assessed across cohorts stratified on the basis of the BIND score.

According to the data presented in Table 3.4, the principal symptom registered across all affected infants was jaundice. Accompanying manifestations included poor sucking in 58.8% (n = 10), vomiting in 64.7% (n = 11), retrocollis — that is, backward extension of the head — in 52.9% (n = 9), and restlessness in 41.2% of the examined children. The anamnestic data derived from maternal reports demonstrated that the intensification and progression of the principal symptoms in these infants correlated with the manifestations of jaundice, serum bilirubin concentrations, and the reactive state of the organism ($P < .05$). The tabulated findings further revealed that poor sucking — a cardinal symptom observed across the entire cohort — was registered in 58.8% of Group 1 patients, 61.3% in Group 2, and 71.4% in Group 3 (the latter corresponding to severe jaundice), with the between-group differences attaining statistical significance ($P < .01$).

Table 3.4

Principal complaints reported by mothers concerning neonates and infants of early age across the study groups

Indicator	Group 1 (n=17)			Group 2 (n=62)			Group 3 (n=21)		
	n	%	χ^2; p	n	%	χ^2; p	n	%	χ^2; p
Poor sucking	10	**58.8***	χ^2=5.02 p<0.05	38	**61.3***	χ^2=4.01 p<0.05	15	**71.4****	χ^2=7.1 p<0.01
Restlessness	7	41.2	χ^2=3.8 p<0.05	40	**64.5***	χ^2=3.5 p<0.05	16	**76.2****	χ^2=6.2 p<0.01
Retrocollis (backward extension of the head)	5	29.4	χ^2=1.37 p>0.05	16	58.6	χ^2=3.8 p<0.05	16	**76.1****	χ^2=7.2 p>0.05
Trembling of the jaw	8	**47.1***	χ^2=4.12 p<0.05	44	**71.0***	χ^2=4.51 p<0.05	19	90.5	χ^2=5.47 p<0.05
Seizures	2	11.8	χ^2=0.09 p>0.05	6	9.7	χ^2=0.39 p>0.05	7	33.3	χ^2=2.47 p>0.05
Twitching of the limbs	1	5.9	χ^2=2.49 p>0.05	12	19.4	χ^2=0.76 p>0.05	14	**66.7***	χ^2=5.1 p<0.05

Sleep disturbance	2	11.8	χ^2=0.38 p>0.05	25	40.1	χ^2=0.15 p>0.05	17	**80.3***	χ^2=4.27 p<0.05
Excessive sleep	4	23.5	χ^2=1.46 p>0.05	30	**48.3***	χ^2=4.2 p>0.05	0	0.0	—
Vomiting	11	64.7	χ^2=0.05 p>0.05	33	**53.2***	χ^2=4.14 p<0.05	15	**71.4**	χ^2=3.26 p>0.05
Fever	0	0.0	—	7	11.3	χ^2=0.19 p>0.05	7	33.3	χ^2=2.9 p>0.05

*Note: *Differences in the prevalence of complaints reported by mothers across the study groups are statistically significant (*p<0.05, **p<0.01).*

The complaint of restlessness predominated in 76.2% of neonates with severe bilirubin encephalopathy, while the corresponding rates in Group 1 and Group 2 stood at 41% and 64%, respectively. Trembling of the jaw was registered in 90.5% of infants in Group 3, 71% in Group 2, and 47% in Group 1. Seizures were documented in 33% of cases in Group 3, 9.7% in Group 2, and 11.8% in Group 1. Twitching of the limbs proved more characteristic of Group 3 infants (66.7%), with reliable between-group differences ($P < .05$). Vomiting, by contrast, was reported across all study groups; poor sucking and excessive somnolence predominated chiefly in Group 2, whereas backward extension of the head was observed in essentially all infants of Group 3.

Table 3.5

Characteristics of physiological reflexes in neonates and infants of early age across the study groups

Indicator	Group 1 ($\mathbf{n = 17}$)			Group 2 ($\mathbf{n = 62}$)			Group 3 ($\mathbf{n = 21}$)		
	N	%	$\boldsymbol{\chi^2; p}$	n	%	$\boldsymbol{\chi^2; p}$	n	%	$\boldsymbol{\chi^2; p}$
Diminished palmomental (Babkin) reflex	5	29.4	$\chi^2 = 0.75$ $p > 0.05$	15	23	$\chi^2 = 4.7^*$ $p < 0.05$	15	71.4*	$\chi^2 = 4.7$ $p < 0.05$

Diminished snout reflex	7	41.2	$\chi^2 = 0.01$ $p \gg 0.05$	38	66.2*	$\chi^2 = 2.0$ $p < 0.05$	16	76.2*	$\chi^2 = 3.5$ $p < 0.05$
Diminished Kussmaul rooting (search) reflex	5	29.4	$\chi^2 = 0.32$ $p > 0.05$	25	46	$\chi^2 = 0.32$ $p > 0.05$	17	81*	$\chi^2 = 4.5$ $p < 0.05$
Diminished sucking reflex	1	29.4	$\chi^2 = 0.75$ $p \gg 0.05$	38	49.6	$\chi^2 = 3.9^*$ $p \ll 0.0$	16	76.2*	$\chi^2 = 3.8$ $p < 0.8$
Weakness of palmomental (Babkin) reflex	4	34	$\chi^2 = 0.01$ $p \gg 0.05$	18	27	$\chi^2 = 0.01$ $p > 0.05$	11	40.7	$\chi^2 = 0.01$ $p > 0.01$
Defense reflex	5	29.4	$\chi^2 = 0.32$ $p > 0.05$	30	48.7	$\chi^2 = 3.32$ $p > 0.05$	15	71.4*	$\chi^2 = 5.3$ $p < 0.05$
Diminished support reflex and automatic walking	5	29.4	$\chi^2 = 3.75$ $p > 0.05$	35	60.5*	$\chi^2 = 3.7$ $p < 0.05$	18	85.7**	$\chi^2 = 7$ $p < 0.01$
Altered Bauer crawling reflex	7	41.2	$\chi^2 = 0.01$ $p > 0.05$	34	56.7*	$X^2 = 4.7$	16	76.7*	$\chi^2 = 4.1$ $p < 0.05$
Altered grasping (Robinson) reflex	5	29.4	$\chi^2 = 0.32$ $p > 0.05$	18	29.4	$\chi^2 = 0.32$ $p > 0.05$	12	57.2*	$\chi^2 = 5.3$ $p < 0.05$
Altered Galant reflex	5	29.4	$\chi^2 = 0.32$ $p > 0.05$	18	29.4	$\chi^2 = 0.75$ $p > 0.05$	8	47.3	$\chi^2 = 1.75$ $p > 0.05$
Diminished Perez reflex	7	41.2*	$\chi^2 = 2.4$ $p < 0.05$	15	41.2	$\chi^2 = 3.9$ $p > 0.05$	5	31.4	$\chi^2 = 1.4$ $p > 0.05$
Diminished Moro reflex	5	29.4	$\chi^2 = 1.32$ $p < 0.05$	32	51.2*	$\chi^2 = 5.1$ $p < 0.05$	13	61.9*	$\chi^2 = 5.3$ $p < 0.05$

Diminished asymmetric tonic neck reflex	2	29.4	$\chi^2 = 0.75$ $p > 0.05$	12	29.4	$\chi^2 = 0.75$ $p > 0.05$	8	38.1	$\chi^2 = 0.75$ $p > 0.05$
Diminished symmetric tonic neck reflex	7	41.2	$\chi^2 = 0.01$ $p > 0.05$	17	41.2	$\chi^2 = 0.01$ $p > 0.05$	6	28.6	$\chi^2 = 0.01$ $p > 0.05$
Diminished tonic labyrinthine reflex	5	29.4	$\chi^2 = 0.32$ $p > 0.05$	16	29.4	$\chi^2 = 0.32$ $p > 0.05$	7	33.3	$\chi^2 = 0.32$ $p > 0.05$

Note: *Differences in the prevalence of altered reflexes among newborns across the study groups are statistically significant ($^{*}p < 0.05$; ** $p < 0.01$).

According to the data presented in Table 3.5, the principal neurological alterations registered in the examined children reflect the intensified impact of hyperbilirubinemia upon the central nervous system, particularly against the backdrop of concomitant pathologic conditions. Neurological examination revealed diminished elicitation of the unconditioned neonatal reflexes — namely the Bauer, Moro, Robinson, and stepping support reflexes. As demonstrated in Table 3.5, the attenuation of these reflexes in Group 3 differed reliably from the corresponding indices in Groups 1 and 2 ($P < .01$). Diminution of the oral automatism reflexes attained its peak frequency in Group 3, reaching 76.2% ($P < .05$); the suppression of these reflexes became progressively more pronounced in parallel with rising hyperbilirubinemia levels ($\chi^2 = 4.75$; $P < .05$). The attenuated elicitation of neonatal reflexes was inseparably linked to alterations in muscle tone — muscle dystonia was registered in 29.4% of cases (n = 5), which in turn accounted for the observed modifications of the spinal automatism reflexes. Diminution of the placing reflex and automatic walking reflex, together with alteration of the Moro reflex, was particularly conspicuous in Group 3 and

yielded markedly higher indices than those documented in Groups 1 and 2 ($P <$ .01) — a phenomenon arising as a consequence of disturbed muscle tone.

Table 3.6

Indicators of movement disorders in neonates and infants of early age across the study groups

Indicator	Group 1 (**n = 17**)			Group 2 (**n = 62**)			Group 3 (**n = 21**)		
	N	%	χ^2; **p**	n	%	χ^2; **p**	n	%	χ^2; **p**
Retrocollis	0	0.0	-	7	11.3	$\chi^2 = 2.82$	12	66.7**	$\chi^2 = 7.22$ $p < 0.01$
Opisthotonos	0	0.0	-	4	6.5	$x^2 = 3.44$ $p < 0.05$	9	42.9*	$\chi^2 = 6.2$ $p < 0.05$
Backward extension of the head	6	35.8	$\chi^2 = 0.05$ $p > 0.05$	46	74.2*	$\chi^2 = 5.28$ $p < 0.05$	16	76.9**	$\chi^2 = 6.6$ $p < 0.05$
Muscle hypotonia	5	29.4	$\chi^2 = 0.75$ $p > 0.05$	36	63.7*	$\chi^2 = 4.15$ $p < 0.05$	5	23.8*	$\chi^2 = 3.69$ $p < 0.05$
Muscle hypertonia	7	41.2	$\chi^2 = 0.01$ $p > 0.05$	10	16.3*	$\chi^2 = 2.84$ $p > 0.05$	9	42.9*	$\chi^2 = 6.76$ $p < 0.01$
Muscle dystonia	5	29.4	$x^2 = 3.32$ $p < 0.05$	16	26.7*	$\chi^2 = 3.65$ $p < 0.05$	7	33.3	$\chi^2 = 5.77$ p < 0.05
Hyperreflexia of deep tendon reflexes	11	64.7*	$\chi^2 = 5.13$ $p < 0.05$	28	43.5	$\chi^2 = 5.61$ $p < 0.05$	19	90.5**	$\chi^2 = 7.01$ $p < 0.01$
Anisoreflexia of deep tendon reflexes	0	0.0	-	1	1.6	$\chi^2 = 0.69$ $p > 0.05$	3	14.3	$\chi^2 = 2.82$ $p > 0.05$

Note: *Differences in the prevalence of movement disorders among children across the study groups are statistically significant (*p<0.05; ** $p < 0.01$).

The data set forth in Table 3.6 indicate that movement disorders were prominently expressed in children across the study groups, with the magnitude of these disturbances varying in step with the serum concentration of

unconjugated bilirubin and the extent of nervous system injury. Severe motor derangements — specifically retrocollis and opisthotonos — were registered exclusively in Groups 2 (11% and 6.5%) and 3 (68% and 43%, respectively). Muscle hypotonia was documented in 67.3% of Group 2 patients, demonstrating a statistically reliable difference from the remaining cohorts ($P < .05$). Muscle hypertonia was registered in 41% of Group 1 newborns and 43% of Group 3 infants. Hyperreflexia of the deep tendon reflexes was identified across all three groups. Among children manifesting severe BE with BIND scores of 6.7 ± 2.8, the constellation of movement disturbances — encompassing retrocollis, opisthotonos, muscle hypertonia, and restricted motor activity — proved statistically reliable ($P < .01$).

Table 3.7

Characteristics of clinical-neurological signs in neonates and infants of early age across the study groups

Signs	Group 1 ($\mathbf{N = 17}$)			Group 2 ($\mathbf{N = 62}$)			Group 3 ($\mathbf{N = 21}$)		
	N	%	χ^2; p	n	%	χ^2; p	n	%	χ^2; p
Cranial nerves									
Graefe's sign	0	0.0	-	8	12.9	$\chi^2 = 0.01$ $p > 0.05$	5	23.8*	$\chi^2 = 4.6$ $p < 0.05$
Strabismus	0	0.0	-	2	3.2	$\chi^2 = 0.57$ $p > 0.05$	3	19.0	$\chi^2 = 1.07$ $p > 0.05$
Diminished corneal reflexes	0	0.0	-	1	1.6	$\chi^2 = 0.11$ $p > 0.05$	4	19.0	$\chi^2 = 2.12$ $p > 0.05$
Diminished conjunctival reflexes	0	0.0	-	2	3.2	$\chi^2 = 0.11$ $p > 0.05$	3	14.3	$\chi^2 = 1.97$ $p > 0.97$
Diminished sucking reflex	7	41.2*	$\chi^2 = 5.4$ $p < 0.05$	29	46.8*	$\chi^2 = 5.9$ $p < 0.05$	19	91.0*	$\chi^2 = 8.6$ $p < 0.01$

Congenital stridor	3	17.6	$\chi^2 = 3.2$ $p < 0.05$	13	21.0	$\chi^2 = 3.22$ $p < 0.05$	9	42.9*	$\chi^2 = 4.4$ $p < 0.05$
Hearing impairment	0	0.0	-	2	3.2	$X^2 = 0.06$ $p > 0.05$	5	23.5	$\chi^2 = 3.98$ $p < 0.05$
Autonomic nervous system									
Acrocyanosis of the lips and limbs	16	94.1*	$\chi^2 = 5.0$ $p < 0.05$	58	93.5*	$\chi^2 = 3.0$ $p < 0.05$	20	95.2*	$\chi^2 = 8.32$ $p < 0.01$
Marbling of the skin	11	64.7*	$\chi^2 = 4.8$ $p < 0.05$	38	61.3*	$\chi^2 = 3.2$ $p < 0.05$	20	95.2*	$\chi^2 = 7.12$ $p < 0.01$
Apnea	0	0.0	-	2	3.2	$\chi^2 = 4.2$ $p < 0.05$	6	27.4*	$\chi^2 = 5.4$ $p < 0.05$
Higher cortical activity									
Disturbed sleep	12	70.6*	$\chi^2 = 4.51$ $p < 0.05$	21	33.8	$\chi^2 = 5.02$ $p < 0.05$	15	71.4*	$\chi^2 = 6.12$ $p < 0.01$
Restlessness	12	70.6*	$\chi^2 = 4.3$ $p < 0.05$	46	74.2*	$\chi^2 = 5.05$ $p < 0.05$	18	85.7*	$\chi^2 = 7.21$ $p < 0.01$
Somnolence	5	29.4	$\chi^2 = 4.0$ $p < 0.05$	33	53.2*	$\chi^2 = 0.08$ $p > 0.05$	1	4.8	$\chi^2 = 0.96$ $p > 0.05$
High-pitched cry	2	11.8	$\chi^2 = 1.5$ $p > 0.05$	13	21.1	$\chi^2 = 3.9$ $p < 0.05$	15	71.4*	$\chi^2 = 4.9$ $p < 0.05$
Diminished auditory and visual reactivity	6	35.3	$\chi^2 = 0.04$ $p > 0.05$	18	29.0	$\chi^2 = 0.81$ $p > 0.81$	15	71.4*	$\chi^2 = 5.4$ $p < 0.05$

Note: *Differences in the prevalence of clinical-neurological signs in newborns across the study groups are statistically significant (*p<0.05; **p<0.01).

According to the data set forth in Table 3.7, the principal neurological alterations included the following manifestations of cranial nerve involvement in Group 3 newborns: restriction of upward eye movement in 71% of cases and strabismus in 19% and 23%, respectively. A diminished sucking reflex was documented in 90.1% of Group 3, 48% of Group 2, and 41% of Group 1; the studies established that suppression of the sucking reflex correlated with the

severity of BE, with the between-group differences attaining a high degree of statistical reliability ($P < .01$). Children belonging to Group 1 - beyond manifestations of mild irritability - likewise exhibited focal signs, inasmuch as infants in whom hyperbilirubinemia coexisted with intrauterine infection or with congenital heart disease (CHD) displayed signs of cranial nerve dysfunction. Specifically, a diminished sucking reflex was registered in 41.2% (n = 7) and congenital stridor in 17.6%, while attenuated auditory and visual responsiveness together with high-pitched cry predominated among Group 3 neonates - at 71%, 29%, and 21%, respectively - whereas in Group 1 the corresponding rates were 35.3% and 11%.

Autonomic disturbances were registered across all three groups: perioral acrocyanosis in 94.1%, 93%, and 95%, respectively; and marbling of the skin in 64.7%, 61.3%, and 95.2%. Apnea in neonates was confined to Group 3 (52.4%) and Group 2 (9.7%), with its emergence in severe BE distinguished by statistically reliable between-group separation.

Table 3.8

Scale-based indicators for assessing the severity of bilirubin encephalopathy in patients across the study groups

Groups	APGAR scale (mean score)		BIND scale (mean score)	Kramer scale (mean score)	CSD scale (mean score)
	1st minute	5th minute			
Group 1 (**n = 17**)	6.94 ± 0.24	8.94 ± 0.24	3.0 ± 0.0	4.6 ± 0.6	3.4 ± 0.7*
Group 2 (**n = 62**)	6.01 ± 0.89	7.01 ± 0.44	6.7 ± 0.8*	4.5 ± 0.6	4.5 ± 1.9
Group 3(n = 21)	5.2 ± 0.5	6.71 ± 0.46	7.7 ± 1.2*	4.7 ± 0.7	8.8 ± 1.7**
Control group	7.94 ± 0.24	8.94 ± 0.24	-	-	-

Note: *Differences in the scale-based indicators used for evaluating bilirubin encephalopathy in newborns across the study groups are statistically significant (*$p<0.05$; **$p<0.01$).

According to the data presented in Table 3.8, the severity of bilirubin encephalopathy was graded using the Kramer, BIND, and KSD scales. The Kramer scale yielded near-identical values across all groups when used to assess severity and was therefore deemed of limited discriminatory utility in clinical grading. The BIND scale — the principal instrument for evaluating the severity of acute bilirubin encephalopathy — registered its peak indices in Group 3 (7.7 ± 1.2). The KSD scale, by contrast, captures the chronic evolution of BE: among Groups 1 and 2 patients who had sustained mild BE according to the BIND scale, the corresponding KSD score (4.5 ± 1.9) reflected the absence of progression toward chronic bilirubin encephalopathy. (A KSD score below 5 signifies the absence of clinical features indicative of kernicterus development.) Conversely, in Group 3 children who had endured severe BE, the BIND scale registered 7.7 ± 1.2 while the KSD scale attained 8.8 ± 1.7, with concomitant manifestation of the neurological hallmarks of kernicterus.

§3.3. Characteristics of Psychomotor Development in Children of Early Age According to the Bayley Scales

Clinical-neurological evaluation of the infants enrolled in the study cohort was conducted on a regular basis. During the neonatal period, a comprehensive neurological examination was performed several times daily; subsequently, infants who had sustained bilirubin encephalopathy underwent outpatient neurological follow-up at 1, 6, and 12 months of life, with concurrent assessment of their psychomotor development. Interpretation of the Bayley test commenced with the computation of the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). For each age group, the mean value of both indices was set at 100, with a standard deviation (SD) of 15.

Table 3.9

Quantitative indicators of psychomotor development in neonates and infants of early age according to the Bayley Scales

Groups	MDI and PDI values at 1 month of age	MDI and PDI values at 6 months of age	MDI and PDI values at 1 year of age
Group 1	92.5 ± 6	108.5 ± 9.6	111.5 ± 9.6
Group 2	$67.3 \pm 10.8^{*}$	$75.3 \pm 10.8^{*}$	$100.3 \pm 7.8^{*}$
Group 3	$60.6 \pm 11.6^{*}$	$72.6 \pm 8.6^{*}$	$75.6 \pm 11.6^{*}$
Control group	105.5 ± 1.6	111.5 ± 1.6	113.2 ± 1.6

Note: *Differences in the Bayley Scales indicators between the study groups of neonates and infants of early age are statistically significant* ($p < 0.05$).

According to Table 3.9, a Bayley score of 100 indicates that the child's development conforms to the established normative range. Scores of 85 or 115 correspond to one SD below or above the mean, while values of 70 or 130 denote two SD from the mean. By definition, in a normative sample two-thirds of children attain scores between 85 and 115; the results of 95% of children fall within the range of 70 to 130, and the indices of virtually all children lie between 55 and 145 (±3 SD).

Psychomotor development of children who had sustained bilirubin encephalopathy was tracked across the first year of life using the Bayley scales. Among Group 1 infants assessed at outpatient examinations conducted between 1 and 6 months, MDI and PDI values averaged 92.5 ± 9.6 - indicating mild motor developmental lag. At the 12-month follow-up, however, both indices returned to within the normal range at 111.5 ± 9.6.

In Group 2 infants (n = 62), substantive psychomotor developmental delay was registered. At the 1-month outpatient evaluation, all (100%) registered MDI and PDI values of 83.3 ± 10.8, attesting to lagging psychomotor development. A depressed MDI was identified in 70% of Group 2 infants at the 1-month

examination; at the 6-month assessment, 36.9% of these children had attained normal MDI values, and by 12 months a developmental lag persisted in only 16.9% of cases. Motor developmental delay was documented in 77% of Group 2 infants and likewise registered at the 12-month follow-up ($P < .05$). Of these, 30% manifested pronounced developmental delay (MDI and PDI < 70 points), whereas 70% predominantly exhibited reduced PDI values. At the 6- and 12-month evaluations, 50% of these children attained normal MDI and PDI values (95.3 ± 10.8 and 100.3 ± 7.8, respectively).

In Group 3 infants under follow-up, mean MDI and PDI values reached 69.6 ± 11.6, with pronounced psychomotor developmental delay registered across the cohort. At 6 months, attenuation of the MDI was documented in 70% of Group 3 infants. Within this group, mild-to-moderate psychomotor developmental delay persisted up to the 1-year mark (75.6 ± 11.6).

Correlational analysis revealed interdependence among the scales evaluating the severity of bilirubin encephalopathy (BIND), identifying chronic bilirubin encephalopathy (KSD), and assessing psychomotor development (Bayley).

Table 3.10

Correlational interrelations between serum bilirubin concentration and the indices of the Bayley, BIND, and KSD scales

Variables	Pearson correlation (p-value)	Interpretation
Bilirubin + BIND	r-Pearson = 0.61; p<0.01	Moderate positive correlation
Bilirubin + KSD	r -Pearson = 0.55; p < 0.01	Moderate positive correlation
Bilirubin + Bayley	r -Pearson = 0.35; p < 0.01	Weak correlation

KSD + Bayley	r -Pearson = −0.74; p < 0.01	Strong negative correlation

Interpretation of correlation coefficient values

Coefficient value	Interpretation
≤ 0.2	Very weak correlation
< 0.5	Weak correlation
< 0.7	Moderate correlation
< 0.9	Strong correlation
0.9 <	Very strong correlation

The study findings established correlational interrelations among several parameters: the BIND and KSD scales - instruments that determine the severity of BE in the study groups - serum bilirubin concentration, and the Bayley scales reflecting the psychomotor development of the affected children. Specifically, a rise in serum bilirubin concentration was paralleled by a corresponding elevation in BIND scale indices (Pearson $r = 0.61$; $P < .01$) - a correlation of moderate magnitude. A correlation of comparable strength was registered between serum bilirubin concentration and the KSD scale (Pearson $r = 0.55$; $P < .01$). These patterns indicate that, as serum bilirubin rises, the severity of the disease likewise progresses. Between the Bayley scales - reflecting psychomotor development - and bilirubin concentration, a weaker correlation was detected (Pearson $r = 0.35$; $P < .01$). Of particular note, observations disclosed a strong inverse correlation between the KSD and Bayley scales (Pearson $r = −0.74$; $P < .01$) - an interrelation that makes manifest that, in children who have sustained severe BE (that is, kernicterus or chronic bilirubin encephalopathy), psychomotor developmental delay emerges in pronounced form.

Conclusions to Chapter III

Perinatal risk factors exert a discernible influence upon the extent to which bilirubin encephalopathy develops. Within the cohort of neonates presenting with severe BE, gestational risk factors clearly predominated: elevated uterine tone (61.9%), fetoplacental insufficiency (57.1%), meconium-stained amniotic fluid (57.1%), placental abruption (47.6%), and double nuchal cord entanglement (71%) were each prominently registered. The same constellation of factors prevailed in the moderate-BE cohort, albeit at comparatively lower frequencies - 46.8%, 50%, 50%, 17.7%, and 56.5%, respectively. Among neonates with mild BE, fetoplacental insufficiency (47.1%) and nuchal cord entanglement (52.9%) predominated when contrasted with Groups 2 and 3. Taken together, these findings substantiate that hypoxic fetal injury sustained during the gestational period constitutes a principal risk factor underlying the genesis of severe and moderate forms of bilirubin encephalopathy. A maternal history of a previously affected child with HDN was identified across all study groups, with elevated frequencies in Groups 2 and 3 ($P < .05$).

Maternal morbidities during the gestational period likewise constitute a precipitating factor for BE in the offspring. Of particular emphasis, the highest prevalence of maternal illness during pregnancy was registered among neonates with severe BE. Grade 3 anemia was documented in 90.5% of mothers of Group 3 neonates, while in 56.5% of Group 2 mothers - whose infants exhibited moderate BE - this condition was likewise registered ($P < .01$). TORCH infection proved particularly noteworthy, occurring in 58.7% of Group 2 mothers and 66.7% of Group 3 mothers; its association with disease progression was confirmed on correlational analysis ($P < .05$). Infants born to TORCH-positive mothers tended toward more severe forms of bilirubin encephalopathy. Furthermore, the coexistence of Grade 3 anemia (52.9%; $P < .05$) and diffuse goiter (47.1%) was identified among pregnant women in Group 3 ($P < .05$);

children delivered under such maternal conditions exhibited prolonged hyperbilirubinemia.

Severe gestosis (preeclampsia spectrum) was registered in 61.3% of pregnant women in Group 2 and 47.6% in Group 3 ($P > .05$). The combined occurrence of TORCH infection, Grade 3 anemia, severe gestosis, and diffuse goiter among the mothers was distinguished by prolonged hyperbilirubinemia and elevated bilirubin concentrations in their offspring. Diffuse goiter predominated among mothers of Group 1 and Group 2 neonates - at 47.1% and 50%, respectively - while in Group 3 it was identified in 38% of mothers.

Recurrent episodes of acute respiratory viral infections similarly predominated among Group 3 (66.7%) and Group 2 (46.8%) mothers. Pyelonephritis was documented in 43% of Group 3 mothers, 34% in Group 2, and 23% in Group 1. Preeclampsia was registered across all study groups, reaching its highest frequency (67%) among Group 3 mothers - a factor that itself influenced the severity grade of BE in the offspring. In addition, gestational stress was prominent in 43% of Group 3 mothers. Offspring born to mothers with the combination of Grade 3 anemia (56.5%; n = 35), diffuse goiter (50%; n = 31), TORCH infection (37.1%; n = 23), cystitis and genital tract disease (18.1%), and preeclampsia (33.9%; n = 23) attained a mean BIND score of 6.5 ± 0.9 points - these factors having exerted a more potent influence on the intensification and progression of the clinical-neurological features of BE than any other contributors. It is equally noteworthy that, in offspring of mothers who contracted SARS-CoV-2 infection during pregnancy, serum total bilirubin concentrations ranged between 250 and 280 μmol/L, with BE developing to a moderate-to-severe degree, advancing rapidly, and following a prolonged course ($P < .05$).

With respect to intranatal risk factors, delivery by cesarean section was less frequently registered among neonates with mild BE than among those in

Groups 2 and 3. The observations indicate that both physiological labor and delivery complicated by obstetric intervention proved more prevalent in children manifesting severe bilirubin encephalopathy.

The principal neurological alterations registered in neonates and children of early age affected by BE reflect the intensified impact of hyperbilirubinemia upon the central nervous system, particularly against the backdrop of concomitant pathologic conditions. In Group 3, attenuation of the oral automatism reflexes reached its peak frequency, accounting for 76.2% of cases ($P < .05$); the suppression of these reflexes became progressively more pronounced in parallel with rising hyperbilirubinemia levels. The diminished elicitation of neonatal reflexes was inseparably linked to alterations in muscle tone - muscle dystonia was registered in 29.4% of cases (n = 5), which in turn accounted for the observed modifications of the spinal automatism reflexes. Diminution of the placing reflex and automatic walking reflex, together with alteration of the Moro reflex, was conspicuously manifested in Group 3, yielding markedly higher indices than those documented in Groups 1 and 2 ($P < .01$) - a phenomenon arising as a consequence of disturbed muscle tone.

The expression of movement disorders varied in step with serum bilirubin concentration and the extent of nervous system injury. Severe motor derangements - retrocollis and opisthotonos - were registered exclusively in Groups 2 (11% and 6.5%) and 3 (68% and 43%, respectively). Muscle hypotonia was documented in 67.3% of Group 2 patients, demonstrating reliable between-group differences ($P < .05$). Muscle hypertonia was identified in 41% of Group 1 newborns and 43% of Group 3 infants. Hyperreflexia of the deep tendon reflexes was registered across all three groups. Among children with severe BE attaining a BIND score of 6.7 ± 2.8, the differences in retrocollis, opisthotonos, muscle hypertonia, and restricted motor activity proved statistically reliable ($P < .01$).

Within the spectrum of principal neurological alterations registered in the children of Groups 2 and 3, cranial nerve involvement manifested as restriction of upward eye movement in 71% of cases ($P < .01$) and strabismus in 19% and 23%, respectively. Diminution of the sucking reflex was documented in 90.1% of Group 3, 48% of Group 2, and 41% of Group 1; the investigations established that suppression of the sucking reflex correlated with the severity of BE, with the between-group differences attaining a high degree of statistical reliability ($P < .01$).

Beyond manifestations of mild irritability, focal signs were also registered in Group 1 children, inasmuch as infants in whom hyperbilirubinemia coexisted with intrauterine infection or with congenital heart disease (CHD) displayed signs of cranial nerve dysfunction. Specifically, diminished sucking reflex (41.2%; n = 7) and congenital stridor (17.6%) demonstrated statistically reliable between-group differences. Attenuated auditory and visual responsiveness together with high-pitched cry predominated among Group 3 neonates (71%), whereas in Groups 1 and 2 the corresponding rates were 35.3% and 11%. Autonomic disturbances were registered across all three groups: perioral acrocyanosis in 94.1%, 93%, and 95%, respectively, and marbling of the skin in 64.7%, 61.3%, and 95.2%. Apnea was confined to Group 3 (52.4%) and Group 2 (9.7%), with its emergence in severe BE distinguished by statistically reliable between-group differences.

The severity of BE in neonates and children of early age was graded using the Kramer, BIND, and KSD scales. The Kramer scale yielded near-uniform values across all groups when employed for severity grading and was therefore deemed of limited utility for evaluative purposes. The BIND scale - the principal instrument for grading the severity of acute bilirubin encephalopathy - registered its peak indices in Group 3, attaining 7.7 ± 1.2 points. The KSD scale, by contrast, reflects the chronic evolution of BE: in Groups 1 and 2 patients who

had sustained mild BE according to the BIND scale, the corresponding KSD value (4.5 ± 1.9) indicated the absence of progression toward chronic bilirubin encephalopathy (a KSD score below 5 signifies the absence of clinical features indicative of kernicterus development). Conversely, in Group 3 children who had endured severe BE, the BIND scale registered 7.7 ± 1.2 while the KSD scale attained 8.8 ± 1.7 points, with concomitant manifestation of the neurological hallmarks of kernicterus.

A Bayley score of 100 indicates that the child's development conforms to the established normative range. Scores of 85 or 115 correspond to ±1 SD from the mean, whereas values of 70 or 130 denote ±2 SD. Psychomotor development of children who had sustained BE was tracked across the first year of life using the Bayley scales. Among Group 1 infants assessed at outpatient examinations conducted between 1 and 6 months, MDI and PDI values averaged 92.5 ± 9.6 - indicating mild motor developmental lag; however, the 12-month follow-up examination revealed the recovery of both indices to the normal range at 111.5 ± 9.6.

In Group 2 infants (n = 62), substantive psychomotor developmental delay was registered. During outpatient evaluation at 1 month, all (100%) registered MDI and PDI values of 83.3 ± 10.8, attesting to lagging psychomotor development. A depressed MDI was identified in 70% of Group 2 infants at the 1-month examination; at 6 months, 36.9% of these children had attained normal MDI values, and by 12 months a developmental lag persisted in only 16.9% of cases. Motor developmental delay was documented in 77% of Group 2 infants and likewise registered at the 12-month follow-up ($P < .05$). Of these, 30% manifested pronounced developmental delay (MDI and PDI < 70 points), whereas 70% predominantly exhibited reduced PDI values. At the 6- and 12-month evaluations, 50% of these children attained normal MDI and PDI values (95.3 ± 10.8 and 100.3 ± 7.8, respectively). In Group 3 infants under follow-up,

mean MDI and PDI values reached 69.6 ± 11.6, with pronounced psychomotor developmental delay registered across the cohort. At 6 months, attenuation of the MDI was documented in 70% of Group 3 infants; in this group, mild-to-moderate psychomotor developmental delay persisted up to the 1-year mark (75.6 ± 11.6).

Correlational interrelations were established among the scale evaluating the severity of bilirubin encephalopathy (BIND), the scale detecting chronic bilirubin encephalopathy (KSD), and the scale assessing children's psychomotor development (Bayley). The findings of the present investigation revealed correlational interrelations between several parameters across the study groups: the BIND and KSD scales - which determine the severity of BE - serum bilirubin concentration, and the Bayley scales reflecting psychomotor development. Specifically, elevation of serum bilirubin concentration was paralleled by a corresponding rise in BIND scale indices (Pearson $r = 0.61$; $P < .01$) - a correlation of moderate magnitude. A correlation of comparable strength was registered between serum bilirubin concentration and the KSD scale (Pearson $r = 0.55$; $P < .01$). The correlational pattern indicates that, with the rise in serum bilirubin concentration, disease severity progresses concomitantly. Between the Bayley scales - reflecting children's psychomotor development - and bilirubin concentration, a weaker correlation was detected (Pearson $r = 0.35$; $P < .01$). However, observations disclosed a strong inverse correlation between the KSD and Bayley scales (Pearson $r = -0.74$; $P < .01$) - an interrelation that makes manifest that, in children who have sustained severe BE (namely kernicterus, or chronic bilirubin encephalopathy), psychomotor developmental delay emerges in pronounced form.

CHAPTER IV.
CLINICAL-LABORATORY AND INSTRUMENTAL DIAGNOSTIC CRITERIA FOR BILIRUBIN ENCEPHALOPATHY IN IN NEWBORNS AND INFANTS

§4.1. Clinical-Laboratory Diagnostic Criteria for Bilirubin Encephalopathy in Neonates and Children of Early Age

In the development of bilirubin encephalopathy among neonates and children of early age, the complete blood count (CBC), biochemical blood analysis, and quantitative determination of neuromarkers in the bloodstream together constitute the cardinal criteria for establishing the diagnosis, monitoring the dynamics of disease evolution, and formulating the prognosis. The clinical-laboratory criteria were appraised on the basis of analyses performed across the study groups.

Table 4.1

Complete blood count and serum bilirubin concentrations in bilirubin encephalopathy across the study groups

Indicator	Group 1	t-value	Group 2	t-value	Group 3	t-value	Control group
	(n = 17)		(n = 62)		(n = 21)		
Hemoglobin, g/L	131.1 ± 17.3	t = 2.45 p>0.05	95.0 ± 19.2**	t = 18.8p < 0.01	90.8 ± 20.5**	t = 17.7p < 0.01	156.3 ± 12.8
Color index	0.88 ± 0.08*	t = 11.0p < 0.05	0.79 ± 0.11*	t = 8.6p < 0.05	0.76 ± 0.19*	t = 9.8p < 0.05	0.98 ± 0.05
Erythrocytes, $\times 10^{12}$/L	3.71 ± 0.42	t = 1.6 p>0.05	3.04 ± 0.45	t = 1.7 p>0.05	4.04 ± 1.7*	t = 5.0p < 0.05	4.93 ± 0.37
Leukocytes, $\times 10^{9}$/L	7.82 ± 4.07	t = 0.8 p>0.05	7.49 ± 2.38*	t = 8.0p < 0.05	9.24 ± 3.14*	t = 11.2p < 0.05	6.56 ± 1.6

ESR, mm/h	8.21 ± 1.48	t = 5.6p < 0.05	8.37 ± 1.14	t = 0.05 p>0.05	9.17 ± 2.76*	t = 3.1p < 0.05	4.93 ± 2.2
Total bilirubin, μmol/L	292.3 ± 59.2*	t = 10.1 p<0.05	318.3 ± 85.3**	t = 34.0 p<0.01	446.3 ± 148.1**	t = 33.5 p<0.01	107.5 ± 16.4

Note: *Differences in CBC parameters and bilirubin values among newborns with bilirubin encephalopathy across the study groups are statistically significant ($p < 0.05$;** $p < 0.01$).*

According to the data presented in Table 4.1, blood analysis of the children across the study groups demonstrated that, as bilirubin concentration rose, hemoglobin values in the affected infants progressively diminished ($P <$ .01). Erythrocyte counts and color-index values likewise attained their lowest levels in Group 3 children, while leukocyte counts simultaneously rose. These observations indicate that severe bilirubin encephalopathy was registered predominantly among children with pronounced anemia ($P <$ .01). The elevated leukocyte counts seen in Group 3 attest to the reactive state of the organism, to the presence of inflammatory and hypoxic processes, and to the unfolding of severe bilirubin encephalopathy against the background of concomitant pathological conditions. A progressive elevation of bilirubin concentration across the study groups was likewise documented ($P <$ .01). In neonates and children of early age, comorbid conditions predisposing to bilirubin encephalopathy were accompanied by substantial alterations of the laboratory parameters.

Table 4.2

Characteristics of bilirubin, NSE, and S100 indicators in group 1 children with comorbid conditions

№	Comorbid condition	No. of patients	%	TB, μmol/mL	NSE	S100
1	Prolonged neonatal jaundice	5	29.4	249.3 ± 65.0	35.0 ± 0.0	0.876 ± 0.0*

2	Jaundice of hemolytic disease of the newborn (HDN)	13	70.6	310.2 ± 48.6**	31.2 ± 8.0	0.78 ± 0.09
3	ABO blood group incompatibility	4	23.5	285.3 ± 20.5	25.0 ± 2.8	0.73 ± 0.04
4	Rh factor incompatibility	9	52.9	320.6 ± 51.6 *	34.4 ± 7.1*	0.82 ± 0.09*
5	Grade 1 hypotrophy	0	0	-	-	-
6	Hypoxic-ischemic CNS injury (HIE)	1	5.9	200.0 ± 0.0	-	-
7	Intrauterine infection	3	17.6	260.8 ± 52.6 *	-	-
8	Neonatal sepsis	0	0	-	-	-
9	DIC syndrome	0	0	-	-	-
10	Hyperthermic syndrome	0	0	-	-	-
11	Pylorospasm	1	5.9	200.0 ± 0.0	-	-
12	Grade 2-3 anemia	10	53.0	235.6 ± 66.2*	-	-
13	Cephalohematoma	1	5.9	290.0 ± 0.0	-	-
14	Hepatic disease	0	0	-	-	-
15	Hereditary disorders	1	5.9	306.8 ± 0.0	32.0 ± 0.0	0.786 ± 0.0
16	Enzymopathy	1	5.9	304.0 ± 0.0	35.0 ± 0.0	0.786 ± 0.0
17	Jaundice of unclear etiology	0	0	-	-	-
18	Asphyxia	0	0	-	-	-

Note: *Differences in bilirubin, NSE, and S100 indicators in newborns with comorbid conditions across the study groups are statistically significant (*$p<0.05$; **$p<0.01$).

Table 4.3

Characteristics of bilirubin, NSE, and S100 indicators in concomitant diseases in children of Group 2 (n=62)

№	Concomitant disease	Number of patients	%	TB (μmol/mL)	NSE	S100
1	Prolonged neonatal jaundice	20	32.0	304.9±85.8	**39.1±10.5***	**0.92±0.25***
2	HDN-type jaundice	42	67.7	**445.3±71.4***	**31.7±8.7***	**0.79±0.11***
3	ABO incompatibility	12	19.7	362.8±71.5	33.0±10.1	0.79±0.12
4	Rh-factor incompatibility	30	48.3	**321.9±62.1***	40.0±4.7	0.77±0.09
5	Grade 1 anemia	10	16.1	307.7±94.8	35.5±8.5	0.82±0.11
6	I.T.N.K.A.T.N.	5	8.1	297.5±98.3	36.9±15.4	0.87±0.16
7	Intrauterine infection	33	53.2	**316.4±90.5***	**41.2±10.8****	**0.93±0.27****
8	STP	6	9.7	269.5±113.1	35±0	0.874±0.0
9	Neonatal sepsis	10	16.8	312.2±195.5	**47.5±9.2****	**1.293±0.7****
10	DIC syndrome	1	1.6	350.0±0.0	41.0±0.0	0.932±0.0
11	Hyperthermic syndrome	1	1.6	267.0±0.0	--	--
12	Pyloric spasm	5	8.1	313.6±71.3	36.0±8.7	0.85±0.09
13	Grade 2–3 anemia	32	51.7	316.0±32.6	39.7±10.9	0.87±0.11
14	Cephalohematoma	6	9.7	276.9±58.3	43.0±0.0	0.876±0.0
15	Liver disease	1	1.6	297.0±0.0	--	--
16	Hereditary diseases	2	3.2	477.6±71.6	50.0±5.7	1.336±0.7
17	Enzymopathies	3	4.8	338.7±158.1	47.4±24.9	0.83±0.09
18	Jaundice of unclear etiology	0	0.0	--	--	--
19	Asphyxia	5	8.1	**381.5±89.3***	27.7±3.8	0.73±0.09

Note: **Differences in bilirubin, NSE, and S100 indicators in concomitant diseases in newborns across groups are statistically significant (*p<0.05, **p<0.01).*

The pathogenetic impact of comorbid conditions upon the development of bilirubin encephalopathy in neonates is likewise discernible through laboratory parameters. As set forth in Tables 4.2 and 4.3, the severe clinical course of bilirubin encephalopathy was registered at elevated frequencies among children manifesting pronounced anemia.

This pattern was documented in 58.5% of Group 3 children (TB 435.8 ± 207.9 μmol/L; NSE 54.2 ± 20.0 ng/L; S100 protein 1.31 ± 0.67 ng/L; $P < .05$). Among children with established bilirubin encephalopathy, the icteric form of hemolytic disease of the newborn (HDN) was identified in 70% of Group 1, 67.7% of Group 2 (TB 310.2 ± 48.6 μmol/L; NSE 31.2 ± 8.0 ng/L; S100 protein 0.78 ± 0.09 ng/L; $P < .01$), and 77% of Group 3. In children who had sustained the icteric form of HDN, elevated NSE and S100 values were documented predominantly in those manifesting its severe clinical form. The peak NSE and S100 values in Group 3 HDN cases, however, were registered chiefly among children with concomitant Grade 2–3 anemia and intrauterine infection: NSE 45.5 ± 9.0 ng/L; S100 protein 1.10 ± 0.28 ng/L ($P < .01$).

The neurotoxic action of bilirubin on the developing brain is inseparably tied to its circulating concentration; nonetheless, in children with antecedent intrauterine infection, asphyxia, or anemia, bilirubin encephalopathy was triggered even at total bilirubin (TB) values of 260.8 ± 52.6 μmol/L ($P < .05$). In parallel, the severe form of bilirubin encephalopathy was documented in the setting of intrauterine infection at TB 351.9 ± 180 μmol/L, neuron-specific enolase (NSE) 54.0 ± 15.5 ng/L, and S100 protein 1.42 ± 0.59 ng/L ($P < .01$), whereas in the severe icteric form of HDN the corresponding values reached TB 567.9 ± 90.5 μmol/L, NSE 45.5 ± 9.0 ng/L, and S100 protein 1.10 ± 0.28 ng/L ($P < .05$).

Table 4.4

Characteristics of bilirubin, NSE, and S100 indicators in group 3 children ($\mathbf{n = 21}$) with comorbid conditions

№	Comorbid condition	n	%	TB, **μmol/mL**	NSE	S100
1	Prolonged neonatal jaundice	5	23.7	405.0 ± 158.7	47.4 ± 16.6 *	1.22 ± 0.60*
2	Jaundice of hemolytic disease of the newborn (HDN)	16	76.6	**567.9 ± 90.5**	**45.5 ± 9.0** *,*	**1.10 ± 0.28** *,*
3	ABO blood group incompatibility	5	23.8	451.4 ± 56.9	47.2 ± 11.8	1.00 ± 0.15
4	Rh factor incompatibility	11	52.3	494.9 ± 117.8	**51.3 ± 6.5** **	**1.21 ± 0.36** **
5	Grade 1 hypotrophy	4	19.1	357.0 ± 113.4	41.3 ± 18.3	1.02 ± 0.1
6	Hypoxic-ischemic CNS injury (HIE)	3	14.3	391.6 ± 210.9	46.0 ± 23.9	1.32 ± 0.5
7	Intrauterine infection	12	57.1	351.9 ± 180.0	54.0 ± 15.5 **	1.42 ± 0.59**
8	Congenital heart disease (CHD)	0	0	-	-	-
9	Neonatal sepsis	7	33.3	491.6 ± 63.4	73.0 ± 12.2**	2.26 ± 0.42**
10	DIC syndrome	2	9.5	510.0 ± 353.6	69.0 ± 25.5	1.95 ± 0.78
11	Hyperthermic syndrome	0	0	-	-	-
12	Pylorospasm	0	0	-	-	-
13	Grade 2-3 anemia	11	58.5	435.8 ± 207.9	54.2 ± 20.0 **	1.31 ± 0.67**
14	Cephalohematoma	1	4.8	309.0 ± 0.0	34.0 ± 0.0	0.987 ± 0.0
15	Hepatic disease	0	0	-	-	-

16	Hereditary disorders	0	0	-	-	-
17	Jaundice of unclear etiology	7	33.8	427.1 ± 68.8	44.5 ± 6.5	1.06 ± 0.2
18	Asphyxia	4	19.1	353.7 ± 66.7	37.9 ± 5.4	0.96 ± 0.14

Note: *Differences in bilirubin, NSE, and S100 indicators in newborns with comorbid conditions across the study groups are statistically significant (*p<0.05; **p<0.01).

Observations indicated that circulating bilirubin levels of TB 351.9 ± 180 μmol/L in children affected by intrauterine infection and TB 567.9 ± 90.5 μmol/L in those with the severe form of HDN were sufficient to precipitate kernicterus. The gap between these two TB values amounted to 217 μmol/L - a substantial divergence. NSE and S100 protein concentrations were likewise elevated in both subgroups, although the magnitude of the rise was approximately 20% greater in children with a history of intrauterine infection ($P < .01$). It follows that bilirubin-mediated injury to the brain is shaped not by the serum bilirubin burden alone but also by the immunologic and reactive status of the organism, together with factors that augment permeability of the blood–brain barrier (BBB). Of particular note, among children in whom asphyxia - a recognized trigger of severe CNS injury - was documented (19.1% of the cohort), TB reached 353.7 ± 66.7 μmol/L, NSE 67.9 ± 5.4 ng/L, and S100 protein 1.96 ± 0.14 ng/L; in neonatal sepsis (14.3%), the corresponding values were TB 491.6 ± 63.4 μmol/L, NSE 73.0 ± 12.2 ng/L, and S100 protein 2.26 ± 0.42 ng/L, with the neuron-specific proteins peaking at their highest measured concentrations ($P < .05$).

In the majority of acute and chronic neurological disorders that manifest with focal or diffuse neurodestruction, neuron-specific proteins, enzymes, and their isoenzymes are released from injured cerebral cells into the interstitial space and ultimately reach the body's biological fluids. At present, NSE stands

as the sole universal marker shared by all differentiated neurons and functions as an intracellular enzyme of the central nervous system (CNS) [25; 47; 78; 90; 105].

When neural tissue sustains injury of varied origin - hypoxic-ischemic, traumatic, or infectious - heightened permeability of the BBB permits neuron-specific proteins to enter the bloodstream. This marker remains the only common signature presently recognized across all differentiated neurons. Detection of elevated NSE in neonates therefore signals involvement of the CNS. In children with intrauterine infection, high NSE values reflect not merely a compromised BBB but, in conjunction, the deeper character of the underlying injury - hypoxia, intoxication, and inflammation acting together. Because differential diagnosis of CNS injury in neonates affected by diverse pathologies remains clinically difficult, this biomarker may serve as a criterion of perinatal injury severity and, alongside other parameters, inform the selection of therapeutic strategy. Increased synthesis of S100 protein has been documented in response to chronic or severe acute hypoxic exposure. Within our study cohorts, we analyzed serum NSE and S100 protein concentrations in neonates; the findings are presented in Table 4.5.

Table 4.5

Neuron-specific protein concentrations in the blood of neonates and children of early age

Indicator	Group 1	t	Group 2	t	Group 3	t	Control group
NSE	31.7 ± 7.48**	t = 13.0; P < .01	36.4 ± 10.6**	t = 27.2; P < .01	48.1 ± 14.9**	t = 21.1; P < .01	12.2 ± 3.3
S100	0.8 ± 0.09**	t = 33.5; P < .01	0.86 ± 0.21**	t = 7.8; P < .01	1.24 ± 0.51**	t = 31.1; P < .01	0.11 ± 0.03

Note. Statistically significant between-group differences in neuron-specific protein concentrations in the blood of neonates: * P < .05; ** P < .01.

It deserves emphasis that NSE and S100 protein concentrations diverged from those of the control group and rose progressively as bilirubin encephalopathy advanced in severity. Whereas the control group registered an NSE value of 12.2 ± 3.3 ng/mL, neonates with mild BE showed 31.7 ± 7.48; Group 2, classified as moderate-grade BE, reached 36.4 ± 10.6; and children with severe BE recorded 48.1 ± 14.9 — a shift of marked magnitude relative to the control cohort. A parallel elevation was documented for S100 protein. Against a control value of 0.11 ± 0.03, Groups 1 and 2 — corresponding to mild and moderate BE — yielded 0.8 ± 0.09 and 0.86 ± 0.21, respectively, while Group 3 climbed reliably to 1.24 ± 0.51, a trajectory that points to entrenched toxic and hypoxic-ischemic disturbances in children affected by BE. Taken together, these findings indicate that neuronal-level injury is more pronounced in children with severe BE, which in turn accounts for the lag in normal psychomotor developmental milestones and the emergence of neurological sequelae in this subgroup.

§4.2. Neurosonographic Changes in Bilirubin Encephalopathy in Neonates and Children of Early Age

Early identification of the various forms of CNS injury in neonates continues to rank among the most pressing diagnostic challenges. The difficulty stems from the limited yield of topical diagnosis, the anatomical and functional immaturity of the central nervous system, and the brain's nonspecific polymorphic response to a wide range of intracranial pathologic processes [15; 3; 52]. Contemporary medicine commands a range of high-yield, informative diagnostic modalities for detecting perinatal pathology. Among them, neurosonography (NSG) currently stands out as the most accessible and noninvasive option. Investigative findings indicate that bilirubin encephalopathy in neonates and children of early age arises within the perinatal window. It may evolve concurrently with perinatal injury of the nervous system or emerge in its

wake. Neurosonography holds substantial value in the workup of perinatal pathologies. Although bilirubin encephalopathy lacks a pathognomonic neurosonographic signature, the modality permits evaluation and characterization of the CNS — and it warrants mention that structural alterations are indeed detectable on NSG in cases of BE.

Table 4.6

Principal Neurosonographic Findings of Structural Brain Changes in Bilirubin Encephalopathy Among Neonates and Children of Early Age

Neurosonographic finding	Group 1			Group 2			Group 3		
	n	%	TB (μmol/L)	n	%	TB (μmol/L)	n	%	TB (μmol/L)
Grade 1 ventriculomegaly	3	17.6	314.6 ± 22.8	23	37.1	326.4 ± 83.4	8	38.1	**498.7 ± 135.9***
Grade 2 ventriculomegaly	0	0	0.0 ± 0.0	2	3.2	361.9 ± 77.6	6	28.6	**459.4 ± 174.3***
Grade 3 ventriculomegaly	0	0	0.0 ± 0.0	0	0	0.0 ± 0.0	7	34.8	381.3 ± 0.0
Periventricular leukomalacia	0	0	0.0 ± 0.0	5	8.1	301.5 ± 130.3	8	38.1	**473.8 ± 134.3***
Intraventricular hemorrhage	0	0	0.0 ± 0.0	12	19.4	**313.5 ± 95.4***	8	38.1	**471.1 ± 107.*0**
Widening of the interhemispheric fissure	0	0	0.0 ± 0.0	11	17.7	292.8 ± 63.4	5	23.8	494.3 ± 214.3
Echogenic changes of the subcortical nuclei (basal ganglia)	0	0	0.0 ± 0.0	22	34.2	**378.5 ± 0.1***	15	71.4	**487.4 ± 138.1****
Altered echogenicity of the cerebral cortex	0	0	0.0 ± 0.0	3	4.8	334.5 ± 86.4	1	4.8	452.0 ± 0.0
Multicystic echogenicity	0	0	0.0 ± 0.0	2	3.2	283.8 ± 32.2	1	4.8	309.0 ± 0.0
Altered echogenicity of the cerebral vascular pattern	16	94.1	**291.0 ± 60.8***	52	83.9	**320.1 ± 88.9****	14	66.7	**487.6 ± 164.6***
Subarachnoid space changes	9	52.9	**276.7 ± 73.9***	34	54.8	**299.8 ± 87.2****	13	61.9	**440.3 ± 163.9***

Neurosonographic finding	Group 1			Group 2			Group 3		
	n	%	TB (μmol/L)	n	%	TB (μmol/L)	n	%	TB (μmol/L)
Calcifications	0	0	0.0 ± 0.0	9	14.5	324.1 ± 117.2	11	52.4	**510.8 ± 148.0***
Doppler sonographic changes	8	47.1	**304.2 ± 31.0***	45	72.6	**334.6 ± 92.4***	15	71.4	**482.8 ± 145.4***
Cephalohematoma	0	0	0.0 ± 0.0	2	3.2	265.0 ± 105.3	0	0	0.0 ± 0.0
Periventricular hemorrhage	0	0	0.0 ± 0.0	9	14.5	343.1 ± 86.5	7	33.3	423.4 ± 52.1

Note: **Statistical significance of differences in the principal neurosonographic findings of structural brain changes in bilirubin encephalopathy among neonates and children of early age between the study groups (*P < .05; **P < .01).*

Structural alterations in cerebral tissue, in turn, scaled in step with both the severity of bilirubin encephalopathy and the degree of CNS injury. In Group 1, altered echogenicity of the choroid plexus was registered in 16 patients (94.1%) at TB 291.0 ± 60.8 μmol/L, while widening of the subarachnoid space was identified in 52.9% of the children at TB 276 ± 73.9 μmol/L; in Groups 2 and 3 these same findings appeared in combination with additional neurosonographic features. Disturbances of cerebral circulation were detected across all three groups: on Doppler sonographic examination, altered flow within the cerebral vessels tracked with quantitative shifts in serum bilirubin, and the changes were especially pronounced in neonates born with a history of intrauterine infection or asphyxia ($P < .05$).

Among the NSG features regarded as characteristic of bilirubin encephalopathy, echogenic alterations in the thalamus, basal ganglia, and cerebellum were absent in Group 1; in Group 2, corresponding to a moderate clinical course, these changes were demonstrable in 22.2% of children, whereas in the severe-course cohort they were identified in 15 children (71.4%) ($P < .01$). The findings were particularly striking in children with marked hyperbilirubinemia, protracted icteric duration, neonatal sepsis, or a history of

intrauterine infection — in whom involvement of the brainstem regions emerged with unmistakable clarity. Such alterations expose the pathoanatomic substrate underlying one of the principal sequelae of bilirubin encephalopathy in children: the dyskinetic form of cerebral palsy. Widening of the interhemispheric fissure and intracerebral calcifications, in turn, were most conspicuous in Group 2. Across all cohorts, the severity grade of bilirubin encephalopathy found expression in the spectrum of neurosonographic findings within the brain. In Group 3, the co-occurrence of intraventricular hemorrhage, Grade 3 ventriculomegaly, subarachnoid hemorrhage, and altered echogenicity of the thalamus, basal ganglia, and cerebellar region was documented alongside the highest quantitative elevations of NSE and S100 protein recorded in the study — a constellation that stands as one of the diagnostic indicators for gauging the depth of neuronal injury.

§4.3. Features of the Impact of Bilirubin Encephalopathy on Cerebral Bioelectrical Activity in Neonates and Children of Early Age

Table 4.7

Features of Cerebral Bioelectrical Activity in Children of Early Age With Bilirubin Encephalopathy

Electroencephalographic finding	Group 1			Group 2			Group 3		
	n	%	TB (µmol/L)	n	%	TB (µmol/L)	n	%	TB (µmol/L)
Maturation of neurophysiologic rhythms	14	82.3	**279.0 ± 21.7***	37	60	**288.9 ± 68.58***	6	28.5	298.0 ± 0.0
Disturbance in the formation of sleep spindles and vertex sharp waves	3	17.6	326.9 ± 60.6	17	27.4	338.6 ± 93.3	15	71.2	**447.3 ± 151.9****
Focal epileptiform activity	0	0	0.0 ± 0.0	1	1.6	360.0 ± 93.1	4	19.1	**453.7 ± 119.5***

Electroencephalographic finding	Group 1			Group 2			Group 3		
	n	%	TB (μmol/L)	n	%	TB (μmol/L)	n	%	TB (μmol/L)
Presence of diffuse slow waves	0	0	0.0 ± 0.0	12	19.3	333.3 ± 78.0	9	42.8	**643.9 ± 108.5***
Predominance of focal slow-wave activity	0	—	326.9 ± 60.6	9	14.5	338.6 ± 93.3	6	28.5	467.3 ± 108.5
Alteration in the formation of the posterior dominant rhythm	3	17.6	266.8 ± 76.1	25	43.4	**339.0 ± 69.6***	15	71.2	**360.5 ± 151.9****

Note: **Statistical significance of differences in the features of cerebral bioelectrical activity in children of early age with bilirubin encephalopathy between the study groups (*P < .05; **P < .01).*

The study findings registered cerebrocortical electrical activity as an indicator of bilirubin neurotoxicity. Bilirubin exerts a particular affinity for the thalamus and the cerebral cortex. Because rhythmic shifts on EEG arise from the interplay between cortex and thalamus, the influence of bilirubin on cerebral bioelectrical rhythms - together with its long-term electrophysiologic consequences across postnatal age - was the focus of dedicated investigation. To characterize cerebral bioelectrical activity in the setting of hyperbilirubinemia, EEG recordings were obtained in each study cohort.

Among children in the early-age period, alterations linked to age-dependent features of cerebral rhythm development were apparent. Between gestational weeks 46 and 48, neurophysiologic maturation of the brain manifests as the emergence of sleep spindles and vertex sharp waves and the consolidation of the posterior dominant rhythm. In children who had sustained bilirubin encephalopathy, however, EEG recordings revealed shifts that scaled with the clinical severity of the disease. In Group 1, altered formation of sleep spindles, vertex sharp waves, and the posterior dominant rhythm was registered in 17.6% of patients; the corresponding figures rose to 27.4% in Group 2 and 71.2% in Group 3. Diffuse slow-wave activity appeared in Groups 2 and 3 at rates of

19.3% (TB 333.3 ± 78.0 μmol/L) and 42.8% (TB 643.9 ± 108.5 μmol/L), respectively. Focal slow-wave activity was likewise documented in 28.5% of Group 3 patients. Within Group 3, motor-tonic seizures accompanied by autonomic paroxysms were observed in 19.1% of children. Across the hyperbilirubinemia cohort, delta-frequency activity ran high while theta-frequency activity ran low; the regional contrasts between groups extended throughout all cerebral territories and reached their starkest expression in Group 3. In the subgroups marked by prolonged hyperbilirubinemia, TB values of 400–500 μmol/L, and BIND scores of 7–10 points, delta activity and sharp-and-slow-wave complexes were recorded over the frontal and parietal lobes. Within Group 2, high-amplitude delta rhythms and focal slow-wave activity were captured in 10 children whose hyperbilirubinemia was complicated by sepsis or intrauterine infection.

Analysis of the frequency-domain distribution of cerebral bioelectrical activity in neonates with bilirubin encephalopathy revealed substantive departures from the standard deviations of normal values established in healthy children. Of note, although the EEG yielded a sizeable number of conventional frequency-presentation variants, the most prevalent pattern of deviation across nearly all study groups consisted of an increase and reorganization of delta-band activity coupled with reduced maturation of the posterior dominant rhythm ($P < .01$).

Chapter IV — Conclusions

The trajectory, clinical presentation, and tempo of bilirubin encephalopathy are gauged in large measure against the backdrop of laboratory data. Analysis of complete blood counts across the cohorts demonstrated that, as bilirubin levels climbed, hemoglobin (Hb) concentrations fell in tandem ($P < .01$). Erythrocyte counts and the color index likewise registered their lowest values in Group 3 children, while leukocyte counts moved in the opposite

direction. These patterns confirmed that severe bilirubin encephalopathy developed preferentially among children with high-grade anemia ($P < .01$). The elevated leukocyte burden seen in Group 3 reflected the reactive state of the organism — its engagement with inflammatory and hypoxic processes — together with the susceptibility to severe BE that accompanies a comorbidity-laden clinical background. A graded rise in bilirubin concentrations was documented across the groups ($P < .01$). In sum, laboratory parameters in neonates and children of early age underwent appreciable shifts in the presence of concomitant disorders that predispose to bilirubin encephalopathy.

The pathogenetic contribution of concomitant illnesses to the unfolding of bilirubin encephalopathy in the neonatal period is itself legible in laboratory findings. Among children with anemia of higher severity, a correspondingly severe clinical course of BE was observed at elevated frequency — registered in 58.5% of Group 3 children (TB 435.8 ± 207.9 μmol/L; NSE 54.2 ± 20.0 ng/L; S100 protein 1.31 ± 0.67 ng/L; $P < .05$). Among children who developed BE, hemolytic disease of the newborn (HDN) was identified in 70% of Group 1, in 67.7% of Group 2 (TB 310.2 ± 48.6 μmol/L; NSE 31.2 ± 8.0 ng/L; S100 protein 0.78 ± 0.09 ng/L; $P < .01$), and in 77% of Group 3. Within the HDN cohort, the highest NSE and S100 protein concentrations were captured in children whose HDN ran a severe course. The peak values, however, emerged in Group 3 HDN children whose course was further complicated by Grade 2–3 anemia or intrauterine infection: NSE 45.5 ± 9.0 ng/L; S100 protein 1.10 ± 0.28 ng/L ($P < .01$).

The neurotoxic action of bilirubin on the developing brain remains tied to its circulating concentration; nevertheless, in children with antecedent intrauterine infection, asphyxia, or anemia, BE was triggered even at TB values of 260.8 ± 52.6 μmol/L ($P < .05$). The severe form of BE was likewise documented against a backdrop of intrauterine infection at TB 351.9 ± 180

μmol/L, NSE 54.0 ± 15.5 ng/L, and S100 protein 1.42 ± 0.59 ng/L ($P < .01$), and in the severe icteric form of HDN at TB 567.9 ± 90.5 μmol/L, NSE 45.5 ± 9.0 ng/L, and S100 protein 1.10 ± 0.28 ng/L ($P < .05$). Observations indicated that serum bilirubin values of TB 351.9 ± 180 μmol/L in children with intrauterine infection and TB 567.9 ± 90.5 μmol/L in those with severe HDN were sufficient to precipitate kernicterus — a separation of 217 μmol/L between the two contexts that marked a substantial divergence. NSE and S100 protein were elevated in both settings, with the magnitude of the rise in children carrying a history of intrauterine infection exceeding the comparator by 20% ($P < .01$). Bilirubin-driven cerebral injury, then, hinges not on serum bilirubin alone but on the immunologic and reactive status of the organism and on the array of factors that augment permeability of the blood–brain barrier. Of particular note, among children in whom asphyxia — a recognized trigger of severe CNS injury — was documented (19.1% of the cohort), the values reached TB 353.7 ± 66.7 μmol/L, NSE 67.9 ± 5.4 ng/L, and S100 protein 1.96 ± 0.14 ng/L; in neonatal sepsis (14.3%), TB 491.6 ± 63.4 μmol/L, NSE 73.0 ± 12.2 ng/L, and S100 protein 2.26 ± 0.42 ng/L were recorded, and neuron-specific protein concentrations peaked at their highest measured levels ($P < .05$).

NSE and S100 protein concentrations diverged from those of the control group and rose in step with the worsening of BE. The control group registered an NSE value of 12.2 ± 3.3 ng/mL, while neonates with mild BE reached 31.7 ± 7.48; moderate-grade patients (Group 2) reached 36.4 ± 10.6; and the severe-BE cohort reached 48.1 ± 14.9 — a marked shift relative to the control. A parallel pattern was traced for S100 protein. Against a control level of 0.11 ± 0.03, Groups 1 and 2 — mild and moderate BE — registered 0.8 ± 0.09 and 0.86 ± 0.21, respectively; Group 3 climbed to 1.24 ± 0.51, a reliable rise that points to entrenched toxic and hypoxic-ischemic disturbances in BE-affected children. Neuronal-level injury is therefore more pronounced in severely affected

children, which accounts for the lag behind normal psychomotor developmental milestones and the emergence of neurological dysfunction in this subgroup.

Cerebral tissue alterations, in their own right, tracked the severity of BE and the depth of CNS injury. In Group 1, altered echogenicity of the choroid plexus was registered in 16 children (94.1%) at TB 291.0 ± 60.8 μmol/L, while widening of the subarachnoid space appeared in 52.9% at TB 276 ± 73.9 μmol/L; both findings recurred in Groups 2 and 3 in combination with further neurosonographic features. Disturbances of cerebral circulation were detected across all three cohorts; Doppler sonography revealed shifts in intracranial vascular flow that correlated with quantitative changes in bilirubin and grew particularly pronounced in children with a history of intrauterine infection or asphyxia ($P < .05$). Among the NSG features regarded as characteristic of BE, echogenic alterations of the thalamus, basal ganglia, and cerebellum were absent in Group 1; in Group 2 (moderate clinical course) they were identified in 22.2% of patients, and in the severe-course cohort they appeared in 15 children (71.4%) ($P < .01$). Such findings were particularly conspicuous in children with marked hyperbilirubinemia, protracted icteric duration, neonatal sepsis, or a history of intrauterine infection — populations in whom involvement of the brainstem regions emerged with unmistakable clarity. These changes lay bare the pathoanatomic substrate of one of the principal sequelae of BE in children: the dyskinetic form of cerebral palsy.

Children in the early-age period likewise displayed age-dependent shifts in cerebral rhythm features. Between gestational weeks 46 and 48, neurophysiologic maturation of the brain manifests in the emergence of sleep spindles and vertex sharp waves and in the consolidation of the posterior dominant rhythm. In children who had sustained BE, EEG recordings exhibited graded alterations that scaled with the clinical severity of the disease. Altered formation of sleep spindles, vertex sharp waves, and the posterior dominant

rhythm was registered in 17.6% of Group 1 patients, in 27.4% of Group 2, and in 71.2% of Group 3. Diffuse slow-wave activity appeared in Groups 2 and 3 at 19.3% (TB 333.3 ± 78.0 μmol/L) and 42.8% (TB 643.9 ± 108.5 μmol/L), respectively. Focal slow-wave activity was likewise captured in 28.5% of Group 3 children. Within Group 3, motor-tonic seizures accompanied by autonomic paroxysms were documented in 19.1% of children. In subgroups marked by prolonged hyperbilirubinemia, TB values of 400–500 μmol/L, and BIND scores of 7–10 points, delta activity together with sharp-and-slow-wave complexes was recorded over the frontal and parietal lobes. In Group 2, high-amplitude delta rhythms and focal slow-wave activity were observed in 10 children whose hyperbilirubinemia was complicated by sepsis or intrauterine infection. It bears emphasis that — alongside an appreciable number of conventional EEG frequency-presentation variants — the most widespread pattern of deviation across nearly all study groups consisted of an increase and reorganization of delta-band activity coupled with attenuated maturation of the posterior dominant rhythm ($P < .01$).

CHAPTER V.
OPTIMIZATION OF THE TREATMENT OF BILIRUBIN ENCEPHALOPATHY IN NEONATES. CRITERIA FOR THE CLINICAL-NEUROLOGICAL FOLLOW-UP OF CHILDREN OF EARLY AGE

§5.1. Assessment of the Dynamics of the Clinical-Neurological Status During the Treatment of Bilirubin Encephalopathy

For the management of bilirubin encephalopathy in neonates and children of early age, baseline therapy was supplemented with levocarnitine (L-carnitine) — a pharmacologic agent administered to enhance the neurometabolic activity of the brain and to counter hypoxic injury. To track the therapeutic dynamics, patients were allocated to a study group and a comparison group. The study group received baseline therapy plus levocarnitine and comprised all Group 3 patients together with low-birth-weight children from Group 2 whose premorbid background was severe. The comparison group encompassed Group 1 children with mild BE and those Group 2 children who exhibited moderate BE features but lacked a severe premorbid background; this group received baseline therapy alone.

Baseline therapy consisted of phototherapy, detoxification measures, and - guided by the underlying etiology - antibiotic therapy and hepatoprotectors, with plasma transfusion or exchange transfusion reserved for severe clinical

courses. Baseline therapy was delivered to every group. Dosing of levocarnitine was titrated to body weight and age. For neonates, the daily dose was set within the 40–75 mg/day range, with the maximum dose selected in proportion to the severity of bilirubin encephalopathy. Children presenting with prolonged neonatal jaundice combined with intrauterine infection received 75 mg/day, delivered intravenously by drip in physiological saline over 5 to 7 days, followed by oral levocarnitine drops (300 mg/mL) at 2 drops twice daily, administered 30 minutes before meals for 20 days.

The dynamics of the treatment course were tracked through serial assessment of the clinical-neurological status during the neonatal period. Evaluation extended over a 5- to 10-day inpatient stay, after which follow-up continued in the outpatient setting at scheduled polyclinic visits. According to these observations, the post-treatment clinical-neurological status exhibited substantial change.

Table 5.1

Dynamics of the Clinical-Neurological Status During the Treatment of Bilirubin Encephalopathy in Neonates and Children of Early Age

Neurological sign	Study group (n = 50)		Comparison group (n = 50)	
	Before treatment (%)	After treatment (%)	Before treatment (%)	After treatment (%)
Restriction of upward eye movement	23	17	8	8
Graefe's sign	13	10	13	11
Strabismus	9	9	2	2
Diminished sucking reflex	57	**16****	35	**11****
Weakened swallowing reflex	13	**10***	0	0
Congenital stridor	25	**12***	20	15
Hearing impairment	30.5	30.5	0	0

Neurological sign	Study group (n = 50)		Comparison group (n = 50)	
	Before treatment (%)	After treatment (%)	Before treatment (%)	After treatment (%)
Retrocollis	21	12	0	0
Opisthotonos	13	10	0	0
Head retraction (arching backward)	65	**21***	40	**20***
Muscle hypotonia	18	**5***	40	**25***
Muscle hypertonia	41	**17***	20	15
Muscle dystonia	40	**23***	10	10
Hyperreflexia of the deep tendon reflexes	94	**59****	80	**36****
Weakened neonatal reflexes	72	51	38	**11****
Elicitability of neonatal reflexes	28	**49***	17	**39***
Autonomic disturbances	—	—	—	—
Perioral acrocyanosis	94	**48****	54	**18****
Bradypnea	1	0	0	0
Marbling of the skin	69	**28****	39	**11****
Apnea	17	**5***	0	0
Restlessness	76	**38****	39	**18****
Drowsiness	13	**4***	38	**8****
High-pitched cry	30	**5****	10	**2****
Diminished auditory-visual response	39	**5****	38	**6****

Note: **Statistical significance of differences between the study and comparison groups in the dynamics of the clinical-neurological status during the treatment of bilirubin encephalopathy in neonates and children of early age (*P < .05; **P < .01).*

According to the observations summarized in Table 5.1, dynamic assessment of the clinical-neurological status across the course of treatment revealed substantial improvement in neurological findings. In both the study group and the comparison group, the most conspicuous shifts during treatment

registered in the domain of motor function. Within the study group, the pathologic motor signs subsided as follows: retrocollis declined from 21% to 12%, opisthotonos from 13% to 10%, head retraction from 65% to 21% ($P < .01$); muscle hypotonia decreased from 32% to 10% ($P < .05$); muscle hypertonia from 41% to 27% ($P < .05$); muscle dystonia from 40% to 23% ($P > .05$); and hyperreflexia of the deep tendon reflexes from 94% to 59% ($P < .05$). Comparable, statistically meaningful gains in motor function were registered in the comparison group as well. Restoration of neonatal reflexes was particularly clear-cut in the comparison group ($P < .05$). The therapeutic yield in both groups was likewise reflected in maternal-reported complaints and in indices of higher cortical function: disturbed sleep declined from 68% to 28% over the treatment course ($P < .01$), restlessness fell from 76% to 38% ($P < .01$), and drowsiness contracted from 13% to 4% of patients ($P < .05$). High-pitched crying persisted in 5% of patients, down from 30.5% ($P < .01$); diminished auditory and visual responsiveness improved in 8 of the 39 affected patients ($P < .01$). The attenuation of cranial nerve dysfunction in the study group manifested chiefly in the normalization of the sucking, conjunctival, and corneal reflexes. Children in the study group exhibited a steeper reduction in features of the autonomic-visceral syndrome than their comparison-group counterparts ($P < .01$).

§5.2. Clinical and Laboratory Indicators of the Treatment of Bilirubin Encephalopathy

In neonates and children of early age, the evaluation was conducted over a 5- to 10-day inpatient stay; during this interval, complete blood counts (CBC) and serum bilirubin with its fractions were obtained on repeated occasions, and neuron-specific proteins were assayed between days 7 and 10 of treatment. The observations recorded substantive shifts following treatment.

Table 5.2

Dynamics of laboratory indicators in study-group patients following treatment

Indicator	Pre-treatment	Post-treatment	W (Wilcoxon)	P
Total bilirubin	318.3 ± 85.3	124.5 ± 31.8	6.8	< .01
NSE	36.6 ± 10.8	26.3 ± 9.4	3.7	< .05
S100 protein	1.1 ± 0.2	0.5 ± 0.2	4.3	< .05
Kramer scale	6.5 ± 0.6	3.4 ± 0.6	7.3	< .01
BIND score	4.7 ± 0.8	2.1 ± 0.8	6.9	< .01

According to Table 5.2, laboratory indicators in study-group children registered demonstrable shifts. Total bilirubin in the peripheral blood declined by 195.8 μmol/L ($P < .01$). A change of this magnitude in TB drove correspondingly meaningful shifts on the BIND and Kramer scales. Concomitantly, neuron-specific protein concentrations contracted: NSE (reference < 17 ng/mL) fell by 10.1 ± 4.3 ng/mL in patients receiving baseline therapy plus levocarnitine ($P < .05$), while the S100 protein marker shifted by 0.4 ± 0.2 ng/mL (reference 0.080–0.15 ng/mL) — a reduction in neuron-specific proteins that signals attenuation of neuronal injury.

According to Table 5.3, the concentrations of neuron-specific proteins in the peripheral blood of the study group diverged substantively from those of the comparison group. NSE in the comparison group exceeded that of the study group by 12.61 ± 7.5 ng/mL ($P < .05$), while the S100 protein marker showed a difference of 0.3 ± 0.1 ng/mL (reference 0.080–0.15 ng/mL) ($P < .05$). The quantitative gap between the two groups reflects more robust post-treatment recovery from neuronal injury in the study group ($P < .05$). No meaningful between-group difference, however, was registered on the Kramer scale.

Table 5.3

Differences in laboratory indicators between study-group and comparison-group children

Indicator	Study group	Comparison group	U (Mann–Whitney)	P
Total bilirubin	112 ± 28.0	109.8 ± 29.9	117.0	> .05
NSE	25.4 ± 7.9	38.3 ± 21.9	114	< .05

S100 protein	0.5 ± 0.2	0.8 ± 0.2	97.5	< .05
Kramer scale	2.6 ± 0.5	2.3 ± 0.6	6.4	> .05
BIND score	1.4 ± 0.9	2.0 ± 0.6	123.62	< .05
Length of stay (days)	8.4 ± 2.4	5.4 ± 2.0	362	> .05

§5.3. Clinical-Neurological Features During the Early-Age Period in Children Who Had Sustained Bilirubin Encephalopathy

Children from Groups 1, 2, and 3 who had experienced bilirubin encephalopathy during the neonatal period exhibited substantive differences in clinical-neurological features over the first year of life. Outpatient evaluations conducted at 6 and 12 months of postnatal age documented these changes.

Table 5.4

Features of the Dynamics of Neurological Status at 6 Months of Age in Children Across the Study Groups

Neurological sign	Group 1	%	Group 2	%	Group 3	%
Muscle dystonia	3	17.6	20	32	12	57.1
Muscle hypertonia	—	—	10	16	9	42.8
Muscle hypotonia	2	11.7	5	8	4	19
Diminished hearing	0	0	2	3.2	7	30.5
Altered eye movement	0	0	5	8	5	23.8
Psychomotor developmental delay	2	11.2	18	29	12	57.1
Mental-emotional developmental delay	3	17.6	11	17.7	3	14.3
Motor developmental delay	4	23.5	17	27.4	6	28.6
Seizure syndrome	1	11.7	3	4.8	5	23.8
Risk of developing cerebral palsy	0	0	7	11.3	12	57.1

Neurological sign	Group 1	%	Group 2	%	Group 3	%
Children who recovered without sequelae	10	59	16	25.8	—	—

According to the data in Table 5.4, disturbances of motor function were prominently expressed across all three groups. Notably, alterations in muscle tone were registered in 29.3% of Group 1 patients, 58% of Group 2, and 90% of Group 3; psychomotor developmental delay was documented in the same groups at 11.2%, 29%, and 57.2%, respectively.

Hearing impairment was identified in 30.5% of Group 3 children, and abnormalities of eye movement in 10%. Recovery without sequelae was achieved in 59% of Group 1 and 25.8% of Group 2, while no such outcomes were registered in Group 3. In summary, the clinical-neurological status of children in the postnatal period proved to be closely tied to the severity of bilirubin encephalopathy.

Table 5.5

Features of the Dynamics of Neurological Status at 12 Months of Age in Children Across the Study Groups

Neurological sign	Group 1 (n=17)	%	Group 2 (n=62)	%	Group 3 (n=21)	%
Muscle dystonia	0	0	9	14.5	12	57.1
Muscle hypertonia	—	—	4	6.4	4	19.8
Diminished hearing	0	0	2	3.2	7	30.5
Altered eye movement	0	0	4	6.4	5	23.8
Psychomotor developmental delay	0	0	11	17.7	12	57.1

Neurological sign	Group 1 (n=17)	%	Group 2 (n=62)	%	Group 3 (n=21)	%
Mental-emotional developmental delay	1	5.8	6	9.6	3	14.3
Motor developmental delay	2	11.6	12	19.3	6	28.6
Seizure syndrome	0	0	2	3.2	4	19.1
Risk of developing cerebral palsy	0	0	4	6.5	12	57.1
Children who recovered without sequelae	14	82.3	37	60	0	0

According to the data in Table 5.5, distinctions among children in Groups 1, 2, and 3 were readily apparent. Comparison of clinical features at 6 months with those at 12 months likewise disclosed shifts within each cohort. The principal between-group differences emerged in the domains of psychomotor development and motor function.

Children at risk of developing cerebral palsy were absent in Group 1, while the figure stood at 6.5% in Group 2 and 57.1% in Group 3. Among Group 3 children, the prevalence of psychomotor developmental delay held steady at 57.1% between the 6-month and 12-month assessments. By 12 months, 82.3% of Group 1 children and 60% of Group 2 children were free of sequelae. The pattern indicates that complicated bilirubin encephalopathy unfolded preferentially in children whose BIND score fell in the upper range.

Chapter V — Conclusions

In summary, the management of bilirubin encephalopathy in neonates and children of early age combined baseline therapy with levocarnitine — a pharmacologic agent administered to enhance the neurometabolic function of the brain and to counter hypoxic injury. To track therapeutic dynamics, patients were

allocated to a study group and a comparison group. The study group received baseline therapy plus levocarnitine and comprised all Group 3 patients together with low-birth-weight children from Group 2 - those whose body weight was disproportionately low for their age and whose premorbid background was severe. The comparison group encompassed Group 1 children with mild BE and Group 2 children who displayed moderate BE features but lacked a severe premorbid background; this group received baseline therapy alone.

Baseline therapy consisted of phototherapy, detoxification measures, and - guided by the underlying etiology - antibiotic therapy, choleretic agents, and hepatoprotectors, with plasma transfusion or exchange transfusion reserved for severe clinical courses. Baseline therapy was administered to every cohort. Dosing of levocarnitine was titrated to body weight and age. For neonates, the daily dose was set within the 40–75 mg/day range, with the maximum dose selected in accordance with the severity of bilirubin encephalopathy. Children presenting with prolonged neonatal jaundice combined with intrauterine infection received 60 mg/day, delivered intravenously by drip in physiological saline over 5 to 7 days, followed by oral levocarnitine drops (300 mg/mL) at 2 drops twice daily, administered 30 minutes before meals for 20 days.

The dynamics of the treatment course were tracked through serial assessment of the clinical-neurological status during the neonatal period. Evaluation extended over a 5- to 10-day inpatient stay, after which follow-up continued in the outpatient setting at scheduled polyclinic visits. According to the observations, the post-treatment clinical-neurological status registered substantive shifts.

Dynamic assessment of the clinical-neurological status across the treatment course revealed marked improvement in neurological findings. In both the study group and the comparison group, the most striking changes registered

in the domain of motor function. Within the study group, the pathologic motor signs subsided as follows: retrocollis declined from 21% to 12%, opisthotonos from 13% to 10%, head retraction from 65% to 21% ($P < .01$); muscle hypotonia decreased from 32% to 10% ($P < .05$); muscle hypertonia from 41% to 27% ($P < .05$); muscle dystonia from 40% to 23% ($P > .05$); and hyperreflexia of the deep tendon reflexes from 94% to 59% ($P < .05$). Comparable, statistically meaningful gains in motor function were registered in the comparison group as well. Restoration of neonatal reflexes was particularly conspicuous in the comparison group ($P < .05$).

The therapeutic yield in both groups was likewise reflected in maternal-reported complaints and in indices of higher cortical function: disturbed sleep declined from 68% to 28% over the treatment course ($P < .01$), restlessness fell from 76% to 38% ($P < .01$), and drowsiness contracted from 13% to 4% of patients ($P < .05$). High-pitched crying persisted in 5% of patients, down from 30.5% ($P < .01$); diminished auditory and visual responsiveness improved in 31 of 39 affected patients ($P < .01$). The attenuation of cranial nerve dysfunction in the study group manifested chiefly in the normalization of the sucking, conjunctival, and corneal reflexes. Children in the study group exhibited a steeper reduction in features of the autonomic-visceral syndrome than their comparison-group counterparts ($P < .01$).

Post-treatment laboratory parameters in the study group registered substantive shifts. Total serum bilirubin declined to 195.8 μmol/L ($P < .01$). Reductions of this magnitude in total bilirubin produced corresponding shifts in BIND and Kramer scale readings. Likewise, concentrations of the neuron-specific proteins dropped: NSE (reference < 17 ng/mL) fell to 10.1 ± 4.3 ng/mL among recipients of baseline therapy plus levocarnitine ($P < .05$), and S100 protein reached 0.4 ± 0.2 ng/mL (reference 0.080–0.15 ng/mL) — a pattern

indicating that the reduction in neuron-specific protein concentrations mirrored attenuation of neuronal injury.

Within the study group, serum neuron-specific protein concentrations differed appreciably from those in the comparison group. NSE in the comparison group exceeded the study-group value by 12.61 ± 7.5 ng/mL ($P < .05$), and S100 protein shifted by 0.3 ± 0.1 ng/mL (reference 0.080–0.15 ng/mL) ($P < .05$). The differential between the two cohorts reflected greater post-treatment recovery of neuronal injury in the study group ($P < .05$). No appreciable difference, however, emerged in Kramer scale readings.

Among children of early age — those in Groups 1, 2, and 3 who had sustained bilirubin encephalopathy during the neonatal period — substantive between-group differences in clinical-neurological features were registered across the first year of life. Outpatient evaluations conducted at 6 and 12 months of postnatal age documented these shifts.

Motor-sphere disturbances were prominent across all three groups. Muscle tone alterations were registered in 29.3% of Group 1, 58% of Group 2, and 90% of Group 3 patients; psychomotor developmental delay reached 11.2%, 29%, and 57.2%, respectively. Hearing impairment was documented in 30.5% of Group 3 children and ocular movement disturbances in 10%. Complication-free recovery was achieved in 59% of Group 1 and 25.8% of Group 2 patients, with none in Group 3. In summary, postnatal clinical-neurological status in children proved contingent on the severity of bilirubin encephalopathy.

Differences across Groups 1, 2, and 3 became apparent at the 12-month outpatient evaluation in children of early age. Comparison of these groups' clinical profiles between the 6-month and 12-month time points revealed clear shifts. The principal differences were captured in psychomotor development and motor-sphere function.

Children at risk of developing cerebral palsy were not encountered in Group 1; the corresponding figures stood at 6.5% in Group 2 and 57.1% in Group 3. Among Group 3 patients, psychomotor developmental delay remained unchanged at 57.1% between the 6-month and 12-month assessments. By 12 months, 82.3% of Group 1 children and 60% of Group 2 children were free of complications. The data therefore confirm that complicated bilirubin encephalopathy unfolded in children carrying the highest BIND scores.

DISCUSSION

In reviewing the literature on the clinical-neurological sequelae of bilirubin encephalopathy in neonates and children of early age, the relevance of the topic emerges with unmistakable clarity: severe hyperbilirubinemia is encountered in 60% to 70% of term-born neonates during the neonatal period. Once hyperbilirubinemia exceeds the 300–400 μmol/L threshold, the trajectory tilts toward bilirubin encephalopathy. The disorder, in its turn, drives hearing loss, lag in mental, speech, and motor developmental milestones, the emergence of seizure syndrome, and pathologies of the extrapyramidal system; in 5.5% to 6.2% of cases, it culminates in the dyskinetic form of cerebral palsy. The literature review further established that theories addressing the pathophysiology of bilirubin encephalopathy and definitive data on the threshold concentration at which bilirubin becomes toxic to the central nervous system remain in short supply.

Analysis of the national literature indicates that the evolution from hyperbilirubinemia to bilirubin encephalopathy has been examined by a number of neonatologists in Uzbekistan; while sources addressing its clinical-neurological sequelae remain limited, the available statistical data confirm that CNS injury arising from hyperbilirubinemia continues to occur within the country. According to the World Health Organization (WHO), the frequency of complicated bilirubin encephalopathy in low-income and developing countries runs roughly tenfold higher than in developed nations. The scarcity of data and practical recommendations concerning the prevention and prognostication of bilirubin encephalopathy as a complication of hyperbilirubinemia therefore reinforces the timeliness of the present work. Unconjugated bilirubin is neurotoxic. The mechanism by which it inflicts that neurotoxicity has yet to be fully elucidated, and the question of the "critical" threshold at which unconjugated bilirubin damages the nervous system remains a subject of ongoing debate. According to the consensus view, kernicterus presents along a continuum that ranges from comparatively mild symptoms to clinically devastating manifestations. In children with severe clinical expression, the picture comprises cerebral palsy, dystonia, choreoathetosis, severe neurological hearing impairment, upward gaze palsy, and dental enamel dysplasia; the transition from acute bilirubin encephalopathy (ABE) to chronic bilirubin encephalopathy (CBE) — or to overt kernicterus — has not, to date, been fully delineated in the scientific literature.

Examination of theories and primary sources addressing the prognostication and therapeutic optimization of BE in neonates and children of early age established the importance of disease etiology and the factors that drive its progression. Yet the literature review revealed that current sources offer only fragmented, often divergent views on which stage of disease begets which severity of bilirubin encephalopathy and at which stage treatment should be

optimized — a state of affairs that itself calls for further refinement and optimization of therapeutic strategy in bilirubin encephalopathy. To carry out a clinical-neurological investigation of bilirubin encephalopathy in neonates and children of early age, 100 hyperbilirubinemic infants were recruited from the Surkhandarya Regional Perinatal Center and from the neonatal pathology and neonatal intensive care unit (NICU) of the Regional Multidisciplinary Children's Medical Center. Eligible participants were term-born infants whose biochemical analysis demonstrated a total bilirubin concentration above 200 μmol/L, whose icterus persisted for 2 weeks or longer, and whose Kramer scale score was 4–5 points. The recruited infants were stratified into subgroups by the degree of hyperbilirubinemia and the duration of icterus. To support therapeutic optimization of BE, the cohort was further partitioned into a study group, a comparison group, and a control group of healthy children. Severity of bilirubin encephalopathy was graded according to the BIND score, and on this basis the cohort was apportioned across three groups. All neonates underwent meticulous clinical-anamnestic and laboratory evaluation. Accurate diagnosis and workup in neonates stand apart from those in older patient populations by virtue of their inherent complexity. According to the examination protocol, each neonate and child of early age was characterized by a comprehensive history-taking together with an obstetric history that captured both the direct causative factors of the pathologic state and the risk factors driving disease progression. Clinical-neurological assessment in the study cohort was performed systematically. In neonates, general neurological examinations were repeated several times each day. Infants with a history of bilirubin encephalopathy were re-evaluated in the outpatient setting at 1, 6, and 12 months of life, with psychomotor development concurrently assessed. Interpretation of the Bayley Scales of Infant Development (BSID) results began with computation of the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). Laboratory workup included complete blood counts (CBC) and measurements of serum bilirubin and its

fractions, performed serially in accordance with the dynamics of disease and tracked over time — both bilirubin levels and the distribution of its fractions enable appraisal of whether the clinical course is acute or chronic and of the status of neurological dysfunction. In the study group and the control group, TB was reassessed prior to treatment and again over a 7- to 10-day interval to capture therapeutic dynamics. The concentrations of the neuron-specific proteins NSE and S100, which gauge the extent of CNS injury, were likewise determined. The laboratory analyses were carried out at the Biomedical Research Center of Tashkent State Medical University.

Cerebral neurosonographic examination was employed. Each enrolled neonate underwent NSG during the first week of admission to the inpatient unit; in neonates with a severe clinical trajectory, and in those who had sustained chronic bilirubin encephalopathy (CBE), repeat neurosonography was performed at 1 month and 6 months of age. To characterize cerebral bioelectrical activity in bilirubin encephalopathy, electroencephalography (EEG) was employed. EEG recordings were obtained in the Diagnostic Department of the Termez City Multidisciplinary Central Polyclinic, in a dedicated EEG suite equipped with a Neurosoft Neuron-Spectrum 2 system running the Neuron-Spectrum 19+1 software package. Statistical handling of the numerical data was performed on a personal computer of the corresponding generation using the Excel 2019 statistical software designed for this class of computer technology. The following parameters were computed: arithmetic mean (M), standard deviation (δ), standard error of the mean (±m), reliability coefficient (t) and of between-group differences (t and P), and the linear correlation coefficient. Results were considered statistically significant at $P \leq .05$.

Perinatal risk factors shaped the trajectory toward bilirubin encephalopathy. In the severe-BE neonatal cohort, gestational-period risk factors held clear dominance: elevated uterine tone (61.9%), fetoplacental insufficiency (57.1%),

meconium-stained amniotic fluid (57.1%), placental abruption (47.6%), and double nuchal cord entanglement (71%). The same set of factors prevailed in the moderate-BE cohort but at attenuated proportions - 46.8%, 50%, 50%, 17.7%, and 56.5%, respectively. In the mild-BE cohort, fetoplacental insufficiency (47.1%) and nuchal cord entanglement (52.9%) led in frequency relative to Groups 2 and 3. The findings therefore confirm that gestational hypoxic injury constitutes a defining risk factor in the origin of moderate and severe bilirubin encephalopathy. A maternal history of a prior child affected by hemolytic disease of the newborn (HDN) was identified across all cohorts, with the highest figures recorded in Groups 2 and 3 ($P < .05$). Maternal disorders, in turn, exert influence on the gestational period and may set the stage for bilirubin encephalopathy in the offspring. Notably, the highest frequencies of maternal disease during gestation were registered in mothers of neonates with severe BE. Grade 3 anemia was documented in 90.5% of mothers of Group 3 neonates and in 56.5% of mothers of Group 2 neonates (moderate-BE cohort) ($P < .01$). TORCH infection, in particular, was identified in 58.7% of Group 2 mothers and 66.7% of Group 3 mothers, and a correlational link with disease progression was demonstrable ($P < .05$). The pattern indicates that infants born to TORCH-positive mothers were prone to shift toward a more severe form of bilirubin encephalopathy. The combined occurrence of Grade 3 anemia (52.9%; $P < .05$) and diffuse goiter (47.1%) was likewise documented in Group 3 mothers during pregnancy ($P < .05$). Infants born under such circumstances exhibited prolonged hyperbilirubinemia. Mild and severe forms of gestosis (preeclampsia spectrum) were observed in pregnant women across the cohorts; the severe form was registered in 17.6% of Group 1 mothers, 61.3% of Group 2, and 47.6% of Group 3 ($P > .05$). Within the severe-BE cohort (Group 3), TORCH infection was identified in 66.7% of mothers; in Group 2 the corresponding figure stood at 58.7%. The combined presence of TORCH infection, Grade 3 anemia, severe gestosis, and diffuse goiter in mothers was reflected in their offspring by

prolonged hyperbilirubinemia and notably elevated bilirubin concentrations. Diffuse goiter was more prevalent among the mothers of Group 1 and Group 2 neonates - 47.1% ($P < .05$) and 50% ($P < .05$), respectively - whereas among Group 3 mothers it appeared in 38%.

Recurrent episodes of acute respiratory viral infections likewise dominated in Group 3 mothers (66.7%) and Group 2 mothers (46.8%). Pyelonephritis was identified in 43% of Group 3 mothers, 34% of Group 2 mothers, and 23% of Group 1 mothers. Preeclampsia was registered across all groups but reached its highest prevalence among Group 3 mothers at 67% - a finding that itself influenced the severity grade of bilirubin encephalopathy in their neonates. Furthermore, gestational stress was prominent among 43% of Group 3 mothers. Offspring born to mothers with the combination of Grade 3 anemia (56.5%; n = 35), diffuse goiter (50%; n = 31), TORCH infection (37.1%; n = 23), cystitis and genital tract disease (18.1%), and preeclampsia (33.9%; n = 23) registered a mean BIND score of 5.5 ± 0.9 points - these factors having exerted a more potent influence on the intensification and progression of the clinical-neurological features of BE than any others identified. It should likewise be noted that neonates of mothers infected with SARS-CoV-2 during pregnancy exhibited BE of moderate-to-severe grade, with a brisk tempo of evolution and prolonged duration, at TB values in the 250–280 μmol/L range ($P < .05$). Among the intranatal risk factors, delivery by cesarean section was less frequently observed in mild-BE neonates than in those of Groups 2 and 3. In Group 1, physiological vaginal delivery accounted for the majority - 82.4% of cases. The observations indicated that both physiological delivery and delivery requiring obstetric intervention occurred more often among children with severe-grade bilirubin encephalopathy ($P > .05$). The principal neurological alterations registered in neonates and children of early age with bilirubin encephalopathy reflected an amplification of the CNS impact of hyperbilirubinemia against the backdrop of

concomitant disease. Diminished oral automatism reflexes reached their highest frequency in Group 3 - 76.2% ($P < .05$). As hyperbilirubinemia advanced, the prominence of this finding intensified accordingly ($\chi^2 = 4.75$; $P < .05$). Diminished elicitation of neonatal reflexes was inseparably linked to alterations in muscle tone: muscle dystonia was registered in 29.4% of cases ($\chi^2 = 3.32$; $P < .05$). For the same reason, alterations were also observed in the spinal automatism reflexes. Diminished placing reflex and automatic walking reflex, together with alteration of the Moro reflex, were most clearly expressed in Group 3 and exceeded the figures recorded in Groups 1 and 2 ($P < .01$) patterns that arose as a direct consequence of disturbed muscle tone.

The intensity of motor disturbances shifted in step with circulating unconjugated bilirubin and the extent of nervous-system injury. Severe motor signs - retrocollis and opisthotonos - were confined to Groups 2 (11% and 6.5%) and 3 (68% and 43%). Muscle hypotonia was registered in 67.3% of Group 2 patients, a frequency that diverged reliably from the other cohorts ($P < .05$). Muscle hypertonia appeared in 41% of Group 1 and 43% of Group 3 neonates. Hyperreflexia of the deep tendon reflexes was documented across all three groups. Among children with severe-grade BE (BIND 6.7 ± 2.8), retrocollis, opisthotonos, muscle hypertonia, and restriction of motor activity emerged with statistical reliability ($P < .01$). Among the principal neurological findings, Group 3 neonates exhibited cranial nerve dysfunction in the form of restricted upward eye movement in 71% ($P < .01$), with strabismus in 19% and 23%. Diminished sucking reflex was recorded in 90.1% of Group 3, 48% of Group 2, and 41% of Group 1 patients. The data confirm that diminished sucking is tied to the severity grade of BE, with cross-group reliability holding to a high standard ($P < .01$). In Group 1, alongside mild irritability symptoms, focal symptoms were also captured. In children with combined hyperbilirubinemia and intrauterine infection or combined hyperbilirubinemia and congenital heart

disease (CHD), cranial nerve dysfunction signs - diminished sucking reflex (n = 7; 41.2%; $\chi^2 = 0.46$; $P > .05$) and congenital stridor (17.6%; $\chi^2 = 3.2$; $P < .05$) - distinguished these subgroups with statistical reliability. Diminished auditory and visual responses, together with high-pitched crying, occurred more frequently in Group 3 - 71%, 29%, and 21% - whereas in Group 1 the corresponding figures stood at 35.3% and 11%. Autonomic disturbances were observed across all three groups: perioral acrocyanosis in 94.1%, 93%, and 95%; marbling of the skin in 64.7%, 61.3%, and 95.2% ($\chi^2 = 8.62$; $P < .01$). Apnea was confined to Group 3 (52.4%) and Group 2 (9.7%) neonates, and its emergence in severe BE was distinguished by statistically reliable separation.

To grade the severity of bilirubin encephalopathy in neonates and children of early age, three instruments were applied: the Kramer scale, the BIND score, and the KSD scale. The Kramer scale produced near-identical readings across all groups and proved to be of limited discriminative value in capturing severity gradients. The BIND score, by contrast, established itself as the principal instrument for grading acute bilirubin encephalopathy: its highest values registered in Group 3 (7.7 ± 1.2 points), in alignment with the most severe clinical manifestations. The KSD scale, in turn, served to flag chronic progression of the disorder. Among Group 1 and Group 2 patients - those who had sustained mild BE according to the BIND score - KSD readings averaged 4.5 ± 1.9 points, indicating that chronic bilirubin encephalopathy had not taken hold (a KSD value below 5 reflects the absence of clinical signs pointing to kernicterus). In Group 3, however, where BIND values reached 7.7 ± 1.2, the corresponding KSD score climbed to 8.8 ± 1.7, and the neurological hallmarks of kernicterus were manifest.

The Bayley Scales of Infant Development (BSID) frame interpretation as follows: a score of 100 points reflects developmental conformity with the age norm; 85 or 115 points corresponds to 1 SD below or above the mean; 70 or 130

points marks a 2 SD deviation. Psychomotor development of children who had sustained bilirubin encephalopathy was evaluated by the Bayley scale across the first year of life. On outpatient assessment in Group 1, between 1 and 6 months of age, the Mental Development Index (MDI) and Psychomotor Development Index (PDI) averaged 92.5 ± 9.6 points - a finding that signaled mild motor developmental lag; on repeat outpatient evaluation at 12 months, however, MDI and PDI values had reverted to normal ranges (111.5 ± 9.6). Group 2 (n = 62) presented a markedly different trajectory: substantial psychomotor developmental delay was registered, with 100% of these infants exhibiting MDI and PDI values of 83.3 ± 10.8 at the 1-month visit. Reduced Mental Development Index was identified in 70% of Group 2 patients at the 1-month examination; by 6 months, 36.9% of this subset had recovered to normal MDI values; and at 12 months, MDI lag persisted in 16.9%. Motor developmental delay in Group 2 was registered in 77% of cases at both the early and the 12-month examinations ($P < .05$), with 30% displaying pronounced developmental lag (MDI and PDI < 70 points); in the remaining 70%, reduction of the PDI predominated. At the 6- and 12-month assessments, MDI and PDI fell within normal limits in 50% of these patients (95.3 ± 10.8 and 100.3 ± 7.8, respectively). In Group 3, MDI and PDI averaged 69.6 ± 11.6 points - a finding consistent with profound psychomotor developmental delay; at 6 months, reduced MDI was documented in 70% of Group 3 patients, and through the first year of life, mild-to-moderate psychomotor developmental delay (75.6 ± 11.6) was sustained without resolution.

A correlational analysis was carried out between the scales gauging severity of bilirubin encephalopathy (BIND), the instrument indexing chronic disease (KSD), and the assessment of psychomotor development (Bayley).

According to the findings, the BIND score and KSD scale - together with circulating bilirubin and the Bayley index of psychomotor development

exhibited mutual correlational links. Rising serum bilirubin tracked an increase in BIND values (r = .61; P < .01), a moderate correlation. A moderate correlation likewise emerged between serum bilirubin and the KSD scale (r = .55; P < .01). Taken together, these correlations indicate that as circulating bilirubin climbs, severity grade advances in step. Between the Bayley scale of psychomotor development and serum bilirubin, a weak correlational link was identified (r = .35; P < .01). Notably, however, a strong inverse correlation surfaced between the KSD and Bayley scales (r = −.74; P < .01), indicating that in children who had sustained severe bilirubin encephalopathy - kernicterus (chronic bilirubin encephalopathy) psychomotor developmental lag becomes unmistakably evident.

The trajectory, clinical presentation, and tempo of bilirubin encephalopathy are appraised through the lens of laboratory findings. Across the study cohorts, as circulating bilirubin climbed, hemoglobin levels in the affected children declined in parallel (P < .01). Erythrocyte counts and color index reached their lowest values in Group 3 patients, while leukocyte counts moved in the opposite direction. These observations confirm that severe-grade anemia in children was paralleled by the emergence of severe bilirubin encephalopathy (P < .01). The elevated leukocyte counts encountered in Group 3 reflected the body's reactive state, inflammatory and hypoxic processes, and the development of severe BE against the backdrop of additional concurrent disease. Bilirubin concentrations rose progressively across groups (P < .01).

Marked alterations in laboratory parameters were registered in neonates and children of early age with bilirubin encephalopathy whose course was complicated by coexisting disease. The pathogenetic contribution of comorbid conditions to BE in the neonatal period is mirrored in laboratory readings. As reflected in the data, severe-grade anemia in children was associated with the highest frequency of severe BE: this pattern was observed in 58.5% of Group 3

patients (TB 435.8 ± 207.9 μmol/L; NSE 54.2 ± 20.0 ng/L; S100 1.31 ± 0.67 ng/L; $P < .05$). Among children who developed BE, hemolytic disease of the newborn (HDN) was identified in 70% of Group 1, 67.7% of Group 2 (TB 310.2 ± 48.6 μmol/L; NSE 31.2 ± 8.0; S100 0.78 ± 0.09; $P < .01$), and 77% of Group 3 cases. Children who had sustained HDN exhibited elevated NSE and S100 readings, with the highest values clustering in those with the severe form of HDN. Peak NSE and S100 concentrations, however, were registered in Group 3 patients with HDN who also presented with Grade 2–3 anemia and intrauterine infection: NSE 45.5 ± 9.0 ng/L; S100 1.10 ± 0.28 ng/L ($P < .01$).

Bilirubin's toxic impact on the brain is intimately tied to circulating concentrations; nonetheless, in children burdened by intrauterine infection, asphyxia, or anemia, BE took hold even at TB values of 260.8 ± 52.6 μmol/L ($P < .05$). Severe BE in the setting of intrauterine infection corresponded to TB 351.9 ± 180 μmol/L; NSE 54.0 ± 15.5 ng/L; S100 1.42 ± 0.59 ng/L ($P < .01$), while severe icteric-form HDN registered TB 567.9 ± 90.5 μmol/L; NSE 45.5 ± 9.0 ng/L; S100 1.10 ± 0.28 ng/L ($P < .05$). The observations indicate that kernicterus emerged in children with intrauterine infection at TB values of 351.9 ± 180 μmol/L and in those who had sustained severe HDN at TB values of 567.9 ± 90.5 μmol/L; the differential between these TB values reached 217 μmol/L — a substantive gap. NSE and S100 concentrations climbed in both settings, with intrauterine infection yielding the larger 20% differential ($P < .01$). Bilirubin-related cerebral injury is therefore tied not only to circulating bilirubin but also to the body's immune-reactive status and to factors that heighten blood–brain barrier (BBB) permeability. It should likewise be noted that among children with asphyxia — a recognized cause of severe CNS injury — 19.1% exhibited TB 353.7 ± 66.7 μmol/L, NSE 67.9 ± 5.4 ng/L, and S100 1.96 ± 0.14 ng/L, while in cases of neonatal sepsis (14.3%) the corresponding values reached TB 491.6 ±

63.4 μmol/L, NSE 73.0 ± 12.2 ng/L, and S100 2.26 ± 0.42 ng/L — the highest neuron-specific protein readings on record ($P < .05$).

It bears emphasis that NSE and S100 concentrations diverge appreciably from control-group values and climb in step with the intensification of bilirubin encephalopathy. Thus, while NSE registered 12.2 ± 3.3 in the control group, the values reached 31.7 ± 7.48 in neonates with mild BE, 36.4 ± 10.6 in the moderate-grade second cohort, and 48.1 ± 14.9 in the severe-BE group — figures that mark a striking departure from control values. Comparable upward shifts were captured for S100: 0.11 ± 0.03 in the control group versus 0.8 ± 0.09 and 0.86 ± 0.21 in the Group 1 and Group 2 (mild and moderate BE) cohorts, respectively, climbing to a statistically reliable 1.24 ± 0.51 in Group 3. Neuronal-level injury is therefore more pronounced in children with severe BE — a finding that accounts for the lag in normal psychomotor developmental indices in this patient population.

Structural changes within cerebral tissues, in their turn, tracked the severity of bilirubin encephalopathy and the extent of CNS injury. In Group 1 patients, altered echogenicity of the choroid plexus was registered in 16 cases (94.1%) at TB 291.0 ± 60.8 μmol/L, and widening of the subarachnoid space was documented in 52.9% of patients at TB 276 ± 73.9 μmol/L; in Groups 2 and 3, these findings coexisted with additional neurosonographic abnormalities. Alterations in cerebral blood flow were registered across all groups: Doppler examination identified disturbances in cerebral vascular flow patterns that paralleled fluctuations in bilirubin concentration, with the most pronounced shifts seen in infants burdened by intrauterine infection or asphyxia ($P < .05$). Among the neurosonographic alterations specific to bilirubin encephalopathy — echogenic changes of the thalamus, basal ganglia, and cerebellum — no such findings were identified in Group 1; in Group 2 they emerged in 22.2% of cases with moderate-grade BE, and in Group 3 they were documented in 15 patients

(71.4%) with severe-grade disease ($P < .01$). The brainstem-region alterations grew most pronounced in children with overt hyperbilirubinemia, protracted icterus, neonatal sepsis, or intrauterine infection. These changes provide the pathoanatomic substrate for the dyskinetic form of cerebral palsy - a recognized sequel of bilirubin encephalopathy.

Among children of early age, age-dependent characteristics of cerebral rhythms were captured along with disease-related shifts. Between 46 and 48 weeks of gestational age, the neurophysiological maturation of the brain proceeds along recognizable lines - formation of sleep spindles and vertex waves and consolidation of the posterior dominant rhythm. In children who had sustained bilirubin encephalopathy, EEG tracings registered alterations that varied with disease severity. Disturbed formation of sleep spindles, vertex waves, and the posterior dominant rhythm was documented in 17.6% of Group 1, 27.4% of Group 2, and 71.2% of Group 3 patients. Diffuse slow-wave activity was registered in Groups 2 and 3 at 19.3% (TB 333.3 ± 78.0 μmol/L) and 42.8% (TB 643.9 ± 108.5 μmol/L), respectively. Focal slow-wave activity surfaced in 28.5% of Group 3 patients. Within Group 3, 19.1% of children exhibited motor-tonic seizures accompanied by autonomic paroxysms. In children who had sustained mild BE, delta-band activity declined across all cerebral regions while theta-band activity rose with advancing age. In the hyperbilirubinemia cohort, by contrast, delta activity ran high and theta activity remained suppressed, with the cross-group differences spanning all cerebral regions and reaching their sharpest expression in Group 3. In children with protracted hyperbilirubinemia, total bilirubin in the 400–500 μmol/L range, and a BIND score of 7–10 points, delta activity together with sharp–slow-wave complexes were recorded over the frontal and parietal regions. Among Group 2 patients with hyperbilirubinemia complicated by sepsis or intrauterine infection, high-amplitude delta rhythms and focal slow-wave activity were captured in 10 children.

The investigation into the frequency-distribution characteristics of cerebral bioelectrical activity in neonates with bilirubin encephalopathy identified appreciable departures from the standard deviations of healthy-child normative values. Notably, alongside the considerable spectrum of typical EEG frequency-representation variants, the most widespread deviation across nearly all study cohorts comprised reduced maturation of the posterior dominant rhythm coupled with a rise in delta-band activity and associated shifts ($P < .01$).

In the treatment of bilirubin encephalopathy in neonates and children of early age, baseline therapy was complemented by levocarnitine - a pharmacological agent directed at enhancing neurometabolic function in the brain and providing antihypoxic protection. To monitor therapeutic dynamics, patients were apportioned across a study group and a comparison group. The study group received baseline therapy plus levocarnitine and comprised all Group 3 patients along with the underweight-for-age Group 2 patients carrying a heavy premorbid burden. The comparison group consisted of Group 1 patients with mild bilirubin encephalopathy and Group 2 patients exhibiting moderate-grade BE without a heavy premorbid background; these patients received baseline therapy alone. Baseline therapy encompassed phototherapy, detoxification measures tailored to the etiological factor, antibiotic therapy, choleretic agents and hepatoprotectors, and - in severe presentations - plasma or blood transfusion. Baseline therapy was administered across all groups. Levocarnitine dosing accounted for body weight and age. For neonates, a daily dose of 40–60 mg was prescribed, with the maximum dose selected on the basis of BE severity grade. In children with protracted neonatal icterus combined with intrauterine infection, a daily dose of 60 mg was administered intravenously by drip in physiological saline over 5–7 days, followed by oral levocarnitine drops 300 mg/mL - 2 drops twice daily, 30 minutes before meals, for 20 days.

Therapeutic dynamics were tracked through serial appraisal of the clinical-neurological status during the neonatal period. The evaluation spanned 5 to 10 days on the inpatient ward and continued thereafter at outpatient visits in the polyclinic setting. The observations established that post-treatment clinical-neurological status underwent substantive change.

Within the study group and the comparison group, the most striking treatment-related shifts involved the motor sphere. In the study group, motor-sphere pathology evolved as follows: retrocollis dropped from 21% to 12%; opisthotonos from 13% to 10%; backward head tilting from 65% to 21% ($P < .01$); muscle hypotonia from 32% to 10% ($P < .05$); muscle hypertonia from 41% to 27% ($P < .05$); muscle dystonia from 40% to 23% ($P > .05$); and hyperreflexia of the deep tendon reflexes from 94% to 59% ($P < .05$). The comparison group likewise registered substantive shifts in motor-sphere disturbances. Restoration of neonatal reflexes emerged with striking clarity in the comparison group ($P < .05$). The effectiveness of therapy across both the study group and the comparison group was further reflected in maternal report and in alterations of higher cortical function: restless sleep in the child dropped from 68% to 28% over the treatment course ($P < .01$); irritability declined from 76% of patients to 38% ($P < .01$); somnolence retreated from 13% to 4% ($P < .05$). Strident high-pitched crying persisted in 5% of patients (down from 30.5%; $P < .01$), and reduced auditory and visual responsiveness improved in 31 of 39 patients ($P < .01$). Within the study group, signs of vegetative-visceral syndrome receded to a greater degree than in the comparison group ($P < .01$).

Post-treatment laboratory parameters in the study group registered substantive shifts. Total serum bilirubin declined to 195.8 μmol/L ($P < .01$). Reductions of this magnitude in total bilirubin produced corresponding shifts in BIND and Kramer scale readings. Likewise, concentrations of the neuron-specific proteins dropped: NSE (normal range < 17 ng/mL) fell to 10.1 ± 4.3

ng/mL among recipients of baseline therapy plus levocarnitine ($P < .05$), and S100 reached 0.4 ± 0.2 ng/mL (normal range 0.080–0.15 ng/mL) — a pattern indicating that the reduction in neuron-specific protein concentrations mirrored attenuation of neuronal injury. Within the study group, serum neuron-specific protein concentrations differed appreciably from those in the comparison group. NSE in the comparison group exceeded the study-group value by 12.61 ± 7.5 ng/mL ($P < .05$), and S100 shifted by 0.3 ± 0.1 ng/mL (normal range 0.080–0.15 ng/mL) ($P < .05$). The differential between the two cohorts reflected greater post-treatment recovery of neuronal injury in the study group ($P < .05$). No appreciable difference, however, emerged in Kramer scale readings. Motor-sphere disturbances were prominent across all three groups. Muscle tone alterations were registered in 29.3% of Group 1, 58% of Group 2, and 90% of Group 3 patients; psychomotor developmental delay reached 11.2%, 29%, and 57.2%, respectively. Hearing impairment was documented in 30.5% of Group 3 patients and ocular movement disturbances in 10%. Complication-free recovery was achieved in 59% of Group 1 and 25.8% of Group 2 patients, with none in Group 3. In summary, postnatal clinical-neurological status in children proved contingent on the severity of bilirubin encephalopathy. Differences across Groups 1, 2, and 3 became apparent at the 12-month outpatient evaluation in children of early age. Comparison of these groups' clinical profiles between the 6-month and 12-month time points revealed clear shifts. The principal differences were captured in psychomotor development and motor-sphere function.

Children at risk of developing cerebral palsy were not encountered in Group 1; the corresponding figures stood at 6.5% in Group 2 and 57.1% in Group 3. Among Group 3 patients, psychomotor developmental delay remained unchanged at 57.1% between the 6-month and 12-month assessments. By 12 months, 82.3% of Group 1 children and 60% of Group 2 children were free of

complications. The data therefore confirm that complicated bilirubin encephalopathy unfolded in children carrying the highest BIND scores.

Criteria for the Early Diagnosis of Bilirubin Encephalopathy in Neonates

The criteria for the early diagnosis of bilirubin encephalopathy in neonates have been refined to encompass the identification of perinatal risk factors, the application of the BIND score in delineating the clinical stages of disease, and the serial determination of laboratory parameters to prognosticate the trajectory of disease and to forestall progression to severe stages.

Diagnostic algorithm. Neonates:

— Icterus persisting beyond 72 hours.

— Measurement at 2 hours: total bilirubin, conjugated bilirubin, free bilirubin, and total protein.

— Reappraisal of TB every 6 hours.

— Reframing of the working diagnosis with respect to pathological icterus.

— Icterus emerging within the first 24 hours: monitoring and workup; icterus persisting beyond 72 hours: monitoring and workup.

Risk-factor profile: gestational age below 38 weeks; siblings with a history of icterus; hereditary disorders; asphyxia; sepsis; hypothyroidism; Gilbert syndrome; Crigler–Najjar syndrome.

Working classification of jaundice: unconjugated hyperbilirubinemia - hemolytic versus non-hemolytic. Internal causes: G6PD deficiency, hereditary spherocytosis. External causes: pharmacological agents, isoimmune disorders (ABO, Rh), sepsis.

Severity stratification by BIND score: 1–3 points - healthy infant; 4–6 points - bilirubin encephalopathy with TB > 200–256 μmol/L; 8–12 points - severe bilirubin encephalopathy, with neuron-specific protein readings of NSE > 17 ng/mL and S100 > 0.15 ng/mL. The Kramer scale 4–5 zone corresponds to bilirubin encephalopathy in development.

Concurrent comorbidity: Grade 3 anemia and intrauterine infection.

Therapeutic algorithm: for healthy infants - phototherapy and active breastfeeding; for bilirubin encephalopathy - phototherapy, infusion therapy, exchange transfusion, neurometabolic and symptomatic therapy.

Diagnostic Criteria for Bilirubin Encephalopathy in Children of the Neonatal Period

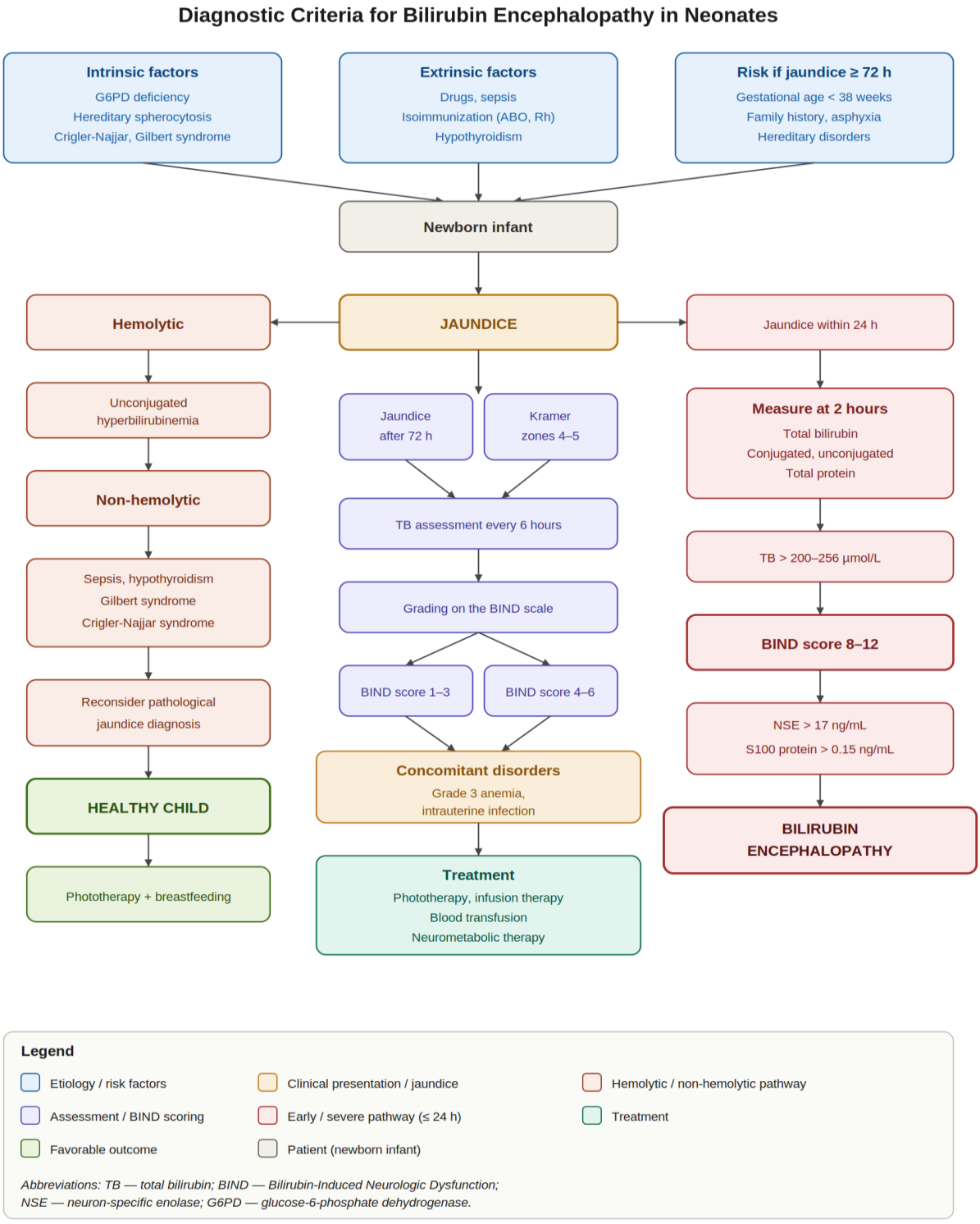

Figure 3. Clinical pathway and BIND-based diagnostic algorithm.

CONCLUSIONS

On the basis of the findings obtained in the dissertation work completed in pursuit of the academic degree of Doctor of Philosophy (PhD) in Medical Sciences on the topic "*Clinical-Neurological Sequelae of Bilirubin Encephalopathy in Neonates and Children of Early Age*," the following conclusions are formulated:

1. Among the drivers that prefigured the development of bilirubin encephalopathy during the prenatal period, the concurrent occurrence of maternal disorders — Grade 3 anemia (56.5%), gestosis (33.9%), and COVID-19 (24%) — together with gestational pathology, including fetoplacental insufficiency (60%), neonatal-period HDN (62%), and intrauterine infection (48%), tracked with severe and protracted bilirubin encephalopathy.

2. The clinical-neurological signature of BE in neonates was defined by the predominance of the following syndromes: vegetative-visceral syndrome (90.2%), neuro-reflex hyperexcitability (57%), diminished oral automatism reflexes (53.7%), altered muscle tone (46%), CNS depression syndrome (41%), and affective-respiratory syndrome (19%); in severe BE, these syndromes presented in combination.

3. On Bayley assessment of psychomotor development, mild BE corresponded to a PDI of 92.5 ± 9.6 — a value reflecting mild psychomotor developmental lag — whereas severe BE produced a PDI of 72.6 ± 8.6, indicating profound psychomotor developmental delay. Within this framework, a strong inverse correlation emerged between the KSD scale (which grades severe-form BE) and the Bayley scale ($r = -.74$).

4. EEG alterations principally took the form of arrested maturation of neurophysiological biorhythms, registered in 17.6% of Group 1, 27.4% of Group 2, and 71.2% of Group 3 patients. Diffuse slow-wave activity was identified in Groups 2 and 3 at 19.3% (TB 333.3 ± 78.0 μmol/L) and 42.8% (TB 643.9 ±

108.5 μmol/L), respectively; in Group 3, focal slow-wave activity reached 28.5%, and in 4% of Group 3 patients it appeared together with focal-tonic and autonomic paroxysms.

5. In severe BE, elevation of the neurotrophic markers NSE (36.6 ± 10.8 ng/mL) and S100 (0.9 ± 0.2 ng/mL) was registered as a consequence of hypoxic-ischemic CNS injury — a pattern carrying the risk of progression to cerebral palsy and the development of CNS injury polysyndromes; in mild BE, NSE and S100 concentrations remained comparatively lower, with a positive correlational relationship demonstrable between them (r = .61).

6. On follow-up of treatment dynamics in the neonatal period, combination therapy incorporating a neurometabolic agent produced — relative to the comparison group receiving baseline therapy alone — greater attenuation in the study-group patients across multiple domains: neuro-reflex hyperexcitability declined by 15%, restoration of physiological neonatal reflexes advanced by 18%, vegetative-visceral syndromes receded by 20%, and serum concentrations of the neuron-specific proteins NSE and S100 fell by more than 25%.

PRACTICAL RECOMMENDATIONS

— In children with bilirubin encephalopathy, identification of prenatal and postnatal risk factors for nervous-system injury enables appraisal of disease severity.

— Given the risk of neurological sequelae in bilirubin encephalopathy, the determination of the neuron-specific proteins NSE and S100 — alongside the standard workup (CBC, biochemical blood analysis, EEG, NSG) — should be incorporated to support timely diagnosis.

— For early detection of psychomotor developmental delay in children with bilirubin encephalopathy, severity of disease, duration of the disorder, and anamnestic data should be taken into account, and psychomotor development should be appraised by means of the Bayley scale.

— To optimize the management of bilirubin encephalopathy in children, the application of criteria for the early diagnosis of neurological sequelae, together with the incorporation of neurometabolic therapy into the treatment regimen, affords a means of attenuating complications.

¶

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LIST OF ABBREVIATIONS

ABE – Acute Bilirubin Encephalopathy (Ўткир билирубин энцефалопатияси)

BE – Bilirubin Encephalopathy (Билирубин энцефалопатияси)

BBB – Blood-Brain Barrier (Гематоэнцефалик тўсик)

BIND – Bilirubin-Induced Neurologic Dysfunction (Билирубин таъсиридаgi неврологик бузилишлар)

CBF – Bioelectric Activity [of the brain] (Биоэлектрик фаоллик)

CBE – Chronic Bilirubin Encephalopathy (Сурункали билирубин энцефалопатияси)

CB – Conjugated Bilirubin (Боғланган билирубин)

CNS – Central Nervous System (Марказий нерв тизими)

CN – Cranial Nerves (Бош мия нервлари)

CP – Cerebral Palsy (Болалар церебрал фалажи)

CT – Computed Tomography (Компьютер томография)

EEG – Electroencephalography (Электроэнцефалография)

HDN – Hemolytic Disease of the Newborn (Чақалоқлар гемолитик касаллиги)

KSD – Kernicterus Spectrum Disorders (Керниктерус спектри бузилиши)

MDI – Mental Development Index (Руҳий ривожланиш индекси / РРИ)

MRI – Magnetic Resonance Imaging (Магнит-резонанс томографияси)

MREDI – Mental-Emotional Development Index (Руҳий-эмоционал ривожланиш индекси / РЭРР)

NSE – Neuron-Specific Enolase (Нейронспецифик энолаза)

NSG – Neurosonography (Нейросонография)

PDI – Psychomotor Development Index (Психомотор ривожланиш индекси / ПМРИ)

PPICNS – Perinatal Hypoxic-Ischemic Injury of the Central Nervous System (Марказий нерв тизимининг перинатал зарарланиши / МНСПЗ)

TB – Total Bilirubin (Умумий билирубин)

UB – Unbound Bilirubin (Эркин билирубин)