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Clinical and laboratory study of premature infants with hypoxic-ischemic encephalopathy

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Abstract

We conducted a comprehensive clinical and laboratory study of 102 preterm infants with hypoxic-ischemic encephalopathy (HIE) of varying gestational ages. All preterm infants were born to mothers with a complicated obstetric history. Clinical manifestation of CNS hypoxic-ischemic injury was observed in 100% of this cohort. Intracranial hemorrhages (ICH) of grades I-IV were registered in 38 (37.2%) cases, while periventricular leukomalacia (PVL) was present in 5 (4.9%) cases. Intrauterine growth restriction (IUGR) was observed in 36 (35.3%) cases, and respiratory distress syndrome (RDS) in 65 (63.7%) cases. Mild cerebral ischemia was diagnosed in 51 (50%) cases, moderate-severity cases in 32 (31.4%) cases, and severe CI in 19 (18.6%) preterm infants.

The severity of clinical progression of HIE in preterm infants was shown to be dependent on gestational age, intrauterine hypoxia, and birth asphyxia. The health status of their mothers plays a crucial role in the development of CNS and other systemic injuries in preterm infants. Therefore, premature births remain a pertinent issue in modern society.

Keywords: Infant; Hypoxic-ischemic encephalopathy; Preterm infants; Perinatal central nervous system injury

1. Introduction

Perinatal lesions of the central nervous system (CNS) occupy a leading position in the structure of pathology among preterm infants; which is associated with a wide prevalence and a diverse spectrum of clinical manifestations [1;2;3]. Studies of the past decade indicate that perinatal pathology is more common among preterm and extremely low birth weight (ELBW) infants; often being the cause of their lethality [4;5;6]. In recent years; there has been a trend of increasing premature births. The frequency of preterm births is 9.6%. The mortality rate of infants weighing less than 2500 grams is 14 per 1000 live births (WHO data). Moreover; the majority consists of infants with a birth weight less than 1500 grams. It is known that perinatal lesions of the central nervous system can lead to the development of cerebral palsy (CP) in 60% of cases; occlusive hydrocephalus in 7.4% of cases; as well as retinopathy [3;4;7;8]. It is important to emphasize that retinopathy is often encountered in preterm infants and infants with ELBW; often complicating oxygen therapy. Due to the morphofunctional immaturity of the preterm infant's organism; the arising pathological conditions require effective medical intervention. Such newborns are at a high risk of developing psychoneurological complications at a later age; including intellectual disabilities; etc.[9;10;11]. Given the above; the aim of our study was to determine the features of the clinical course and the laboratory-diagnostic content in preterm infants with hypoxic-ischemic encephalopathy.

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2. Material and methods

We examined 102 premature newborns with perinatal CNS damage; who were divided into 2 main groups. Group I consisted of 56 premature infants with a gestational age of 35-37 weeks; and Group II consisted of 46 premature infants with a gestational age of <28-34 weeks. A control group (CG) included 30 conditionally healthy premature newborns. Chronic intrauterine hypoxia was observed in 41 (40.2%) premature children. Asphyxia was present in 20 (19.6%) premature infants; and umbilical cord entanglement was noted in 11 (10.8%) infants. Out of the mothers; 72 infants were born to women aged up to 35 years; accounting for 70.6% of the total. 30 (29.4%) infants were born to mothers over 35 years old. Repeat childbirth accounted for 65 (63.7%) cases; while primiparous women accounted for 37 (36.7%) cases. Male premature infants accounted for 53 (52%) cases; and female premature infants accounted for 49 (48%) cases. We used clinical-anamnestic; laboratory; and instrumental research methods. The examination of premature infants was conducted based on their functional systems. The clinical method included postnatal assessment of gestational age; morphofunctional immaturity parameters; and anthropometric features were taken into account. The severity of the clinical course of hypoxic-ischemic encephalopathy in infants was evaluated using the modified Sarnat H.B. scale. Instrumental research methods included radiological diagnostics of the chest organs; neurosonography of the brain; Doppler ultrasonography of brain and heart vessels; echocardiography; electroencephalography (if indicated); and abdominal ultrasound examinations. The diagnosis of perinatal central nervous system damage was based on anamnestic; clinical; laboratory; and instrumental data.

3. Results and discussion

We conducted a comprehensive study of 102 preterm infants of various gestational ages with hypoxic-ischemic encephalopathy. All preterm infants were born to mothers with a complicated obstetric history. Figure 1 shows that the highest percentage was represented by preterm infants with a gestational age of 36-37 weeks.

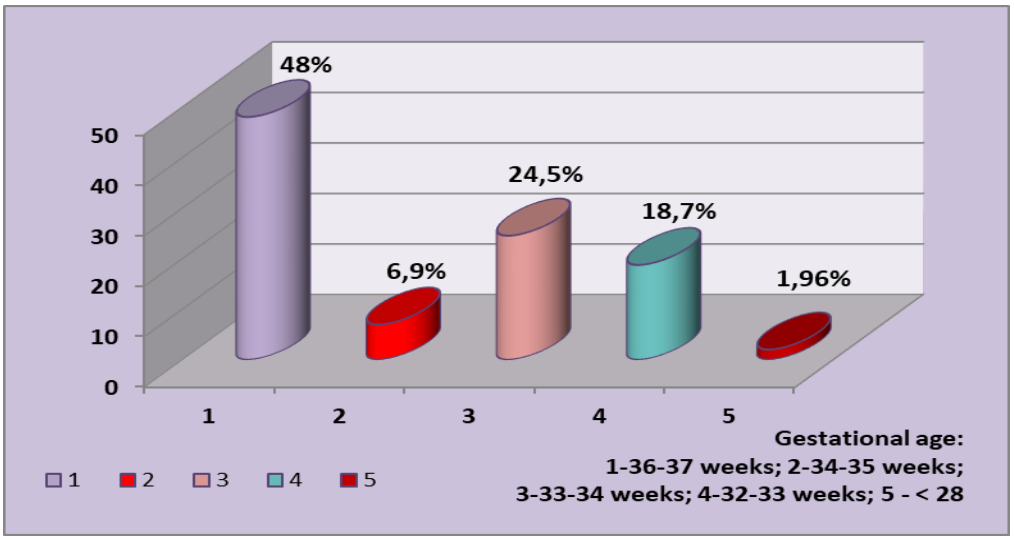

Figure 1 Distribution diagram of infants according to gestational age

The general condition of preterm infants with a gestational age of 35-37 weeks at birth; assessed using the Apgar scale at 1 minute; was rated at 4.37±0.06 points; and at 5 minutes; it was rated at 6.04±0.1 points.

We divided the infants into two groups. Group I consisted of 56 infants with a gestational age of 35-37 weeks; diagnosed with hypoxic-ischemic encephalopathy. Group II included 46 infants with a gestational age ranging from <28 to 34 weeks; presenting the same pathology. In Group I; the gestational age of 36-37 weeks was registered in 87.5% of infants; 34-35 weeks in 12.5%. In Group II; the distribution was as follows: 33-34 weeks in 54.4% and 32-33 weeks in 41.3%. Gestational age of 28 weeks or less was observed in 4.3% of cases; respectively.

Table 1 General characteristics of preterm infants with Hypoxic-Ischemic Encephalopathy (HIE)

General ccharacteristics		**I group n=56**	**II group n=46**
		abs.	**abs.**
Gestational Age (in weeks)		35;5±1;5	30;5±3;5
Infant's Body Weight (g)		2112;5±362;5	1207;5±292;5
Gender	male	31	22
	female	25	24
Apgar Score (in points)	at 1 min	4;37±0;06	3;58±0;07
	at 5 min	6;04±0;1	5;45±0;07
pH		7.27±0;005	7;15±0;01
CPAP (Constant Positive Airway Pressure)		14 (25%)	13(28;2%)
Mechanical Ventilation		8 (4;3%)	9(19;6%)
Parenteral nutrition		12(21;4%)	16(34;8%)

The overall profile of preterm infants with HIE revealed that the body weight of preterm infants with a gestational age of 35-37 weeks was recorded within the range of 2112.5±362.5 grams; while for infants with a gestational age of less than 28 to 34 weeks; the weight was in the range of 1207.5±292.5 grams (Table 1). In infants with a gestational age of less than 28 to 34 weeks; the Apgar score at 1 minute after birth was assessed as 3.58±0.07 points; and at 5 minutes; it was 5.45±0.07 points; respectively. In Group I; parenteral nutrition was provided to 12 (21.4%) infants; and in Group II; to 16 (34.8%) infants (see Table 1).

Table 2 Clinical Characteristics of the Studied Preterm Infants

Clinical manifestations and syndromes	**I group n=56**		**II group n=46**		**Total n=102**	
	abs.	**rel.%**	**abs.**	**rel. %**	**abs.**	**rel. %**
Intrauterine Growth Restriction (IUGR)	17	30;3%	19	41;3%	36	35;3%
Respiratory Distress Syndrome (RDS)	29	51;8%	36	78;2%	65	63;7%
Perinatal Post-Hypoxic CNS Injury	56	100%	46	100%	102	100%
Hypertensive Syndrome	13	23;2%	11	23;9%	24	23;5%
Seizure Syndrome	12	21;4%	19	41;3%	31	30;4%
Hydrocephalic Syndrome	2	3;6%	3	6;5%	5	4;9%
Intracranial Hemorrhages (ICH) I-IV degree	17	30;3%	21	45;6%	38	37;2%
Periventricular Leukomalacia (PVL)	3	5;3%	2	4;3%	5	4;9%
Brain edema	2	3;6%	3	6;5%	5	4;9%
Cerebral Palsy (CP)	0	0	1	2;2%	1	0;9%
Conjugated Jaundice	17	30;3%	19	41;3%	36	35;2%
Gastrointestinal Tract (GIT) Functional Disorders	9	16;1%	8	17;4%	17	16;6%
Hemodynamic disturbances	11	19;6%	12	26;1%	23	22;5%
Patent Foramen Ovale (PFO)	13	23;2%	21	45;6%	34	33;3%
Patent Ductus Arteriosus (PDA)	12	21;4%	16	34;7%	28	27;4%

The neonatal period for these infants in the respective groups was characterized by the involvement of various organs and systems (see Table 2).

As shown in Table 2; hypoxic-ischemic CNS injury was observed in all 102 preterm infants; accounting for 100% of cases. Seizure syndrome was recorded in 31 (30.4%) cases; hypertensive syndrome in 24 (23.5%) cases; and hydrocephalic syndrome in 5 (4.9%) cases. Intracranial hemorrhages (ICH) of I-IV degree were diagnosed in 38 (37.2%) cases; and periventricular leukomalacia (PVL) in 5 (4.9%) cases. Among the clinical symptoms observed in preterm infants were hyperesthesia in 11.2% of cases; restlessness in 28.2%; hand and chin tremors in 33.7% of cases; and the syndrome of depression in 53.7% of cases. There were also observed changes in muscle tone; such as dystonia in 38.2% of cases; hypotonia in 11.2%; and hypertonia in 13.5% of cases. In terms of reflexes; the Moro and Babinski reflexes were strengthened in 48.3% and weakened in 19.2% of cases; while the ROA reflexes were weakened in 34% of cases. Neurological symptoms affecting the eyes were also noted: Greffe's positive sign in 19% of cases; horizontal nystagmus in 7.9% of cases; and exophthalmos in 37.2% of cases. Hydrocephalic syndrome was present in 15.2% of cases and was characterized by an increase in head circumference by 1-2 cm; sagittal suture divergence in 8.2%; and pronounced bulging of the fontanelle in 39.2% of cases. Seizures with clonic characteristics; altered consciousness; and monotonic crying were observed in some infants. Neurosonographic images (NSG) of preterm infants revealed enhanced vascular pulsation; increased echogenicity in the periventricular area; and enlargement or dilation of the lateral ventricles. Doppler ultrasound studies showed an increased resistance index in 6.2% of preterm infants with hydrocephaly. Specifically; an increase in blood flow velocity in cerebral vessels was noted. Ventricular dilation occurred due to the stretching of arteries and constriction of the vascular lumen in the brain.

Premature infants with periventricular hemorrhagic infarction (PVHI) showed a decrease in blood flow through the anterior cerebral artery and an increase in the cerebral vascular resistance index. In 14 cases (13.7%) of posthypoxic encephalopathy; an acceleration of blood flow velocity was observed on the affected side.

In children with low body weight and infants born with extremely low birth weight (ELBW); respiratory distress syndrome (RDS) was diagnosed in 63.7% of cases. It is important to note that respiratory insufficiency was a characteristic manifestation of the clinical course of RDS. These infants exhibited hypothermia; shortness of breath; hypoxemia observed from the first minutes or within the first hours after birth. Hypothermia is indicative of the immaturity of the thermoregulatory center of the brain. Characteristic features included reduced partial pressure of oxygen (PaO2 < 40 mmHg); secondary apnea; sinking of the chest; xiphoid process; acro- and perioral cyanosis. Auscultatory findings indicated weakened breath sounds in the lungs and the presence of crepitating rales. Radiographic images ranged from slight pneumatisation reduction to the appearance of "white lungs" (Figure 2). It is important to note that these infants were in an incubator environment; with vital systems being monitored including SpO_2; pCO_2; respiratory rate; and heart rate. Blood electrolyte levels were determined; including sodium; potassium; calcium; and magnesium; as well as protein; glucose; albumin; and anion gap as indicated. Intensive therapy was employed as treatment; and respiratory support for the respiratory system was provided through methods such as CPAP (Continuous Positive Airway Pressure); mechanical ventilation; and surfactant therapy. CPAP treatment was administered to 14 (25%) preterm newborns at 35-37 weeks of gestation and 13 (28.2%) infants at <28-34 weeks for RDS management. Mechanical ventilation was applied to 8 (4.3%) infants in Group I and 9 newborns in Group II; comprising 19.6% of cases. In assessing the overall condition of preterm infants at birth using the Apgar scale (4-6 points); infants receiving CPAP were subjected to respiratory ventilation through intranasal cannulas or endotracheal mask to alleviate symptoms of moderate to severe RDS. As mentioned earlier; surfactant therapy was employed; with the chosen drug being curasurf. The dosage used was 200 mg/kg of the preterm infant's body weight. For severe cases of RDS; mechanical ventilation was utilized as part of the respiratory therapy.

In the diagnostic assessment of severe clinical course of Respiratory Distress Syndrome (RDS) with an Apgar score of 6; mechanical ventilation (MV) was applied to infants. The use of MV is currently widely discussed due to the frequent occurrence of postventilation complications in clinical practice. As shown in Figure 2; in a preterm infant with RDS; the X-ray revealed linear lucencies - "air bronchograms".

According to the obtained data; 68 (67.7%) infants experienced intrauterine hypoxia. Asphyxiated births accounted for 34 (33.3%) infants. The extent of central nervous system (CNS) damage depends on the degree of experienced hypoxia; cerebral ischemia (CI); and the maturity of the infant. During the observation period; mild cerebral ischemia was diagnosed in 51 (50%) cases; moderate-severity cases were observed in 32 (31.4%) cases. Severe CI was identified in 19 (18.6%) premature infants. The severity of Hypoxic-Ischemic Encephalopathy (HIE) in premature infants was assessed using a modified Sarnat scale. In cases of mild HIE; the clinical picture exhibited hypercapnia; acidosis; hypoxemia; and moderately pronounced hypertensive syndrome. Depending on the morphofunctional immaturity of the premature infant; the CNS depression syndrome lasted for 6-10 days. The Dopplerographic picture was as follows:

an increase in blood flow velocity in the central brain vessels was noted; a decrease in the resistance index was observed; and hypoperfusion was visualized in the anterior cerebral artery. In cases of grade III cerebral ischemia in infants; the clinical presentation was characterized by respiratory insufficiency; neurological ocular symptoms; seizure syndrome; and brain edema.

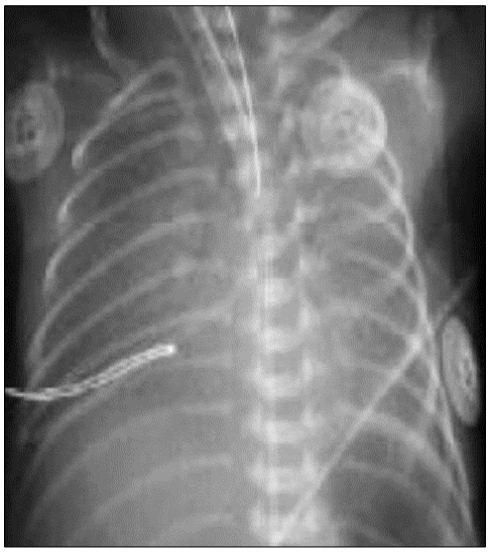

Figure 2 RDS. Radiographic Image: lung field opacities - "ground glass" appearance. (own research)

When assessing the acid-base status in infants with grade III cerebral ischemia; metabolic acidosis was noted in 33% of cases; with a pH of 7.2±0.1. In 7% of infants with grade I cerebral ischemia; pH was 7.2±0.1; and metabolic acidosis was also observed. Cerebral changes in premature infants depended on the severity of asphyxia during childbirth. Intrauterine growth restriction was characteristic of preterm infants with grade III cerebral ischemia. From a clinical symptomatic perspective; there were also observed suppressed reflexes of oral or innate automatism; apnea; absence or weakened sucking and swallowing reflexes; bradycardia; regurgitation; and occasional vomiting. When assessing the acid-base status in infants with grade III cerebral ischemia; metabolic acidosis was noted in 33% of cases; with a pH of 7.2±0.1. In 7% of infants with grade I cerebral ischemia; the pH was 7.2±0.1; and metabolic acidosis was also observed. Cerebral changes in premature infants depended on the severity of asphyxia during childbirth.

Thus; the issue of premature births remains a significant healthcare concern despite the utilization of cutting-edge medical technologies and methods for the care of preterm infants. Premature births entail significant medical and social consequences; particularly among preterm infants born with gestational ages earlier than 33-32 weeks of pregnancy.

4. Conclusion

- Antenatal; intranatal; and postnatal risk factors play a pivotal role in the development of Hypoxic-Ischemic Encephalopathy (HIE) in preterm infants.
- The clinical course of HIE and the formation of long-term consequences are directly influenced by the gestational age of the preterm infant and the severity of intrauterine hypoxia and birth asphyxia.
- Infants with extremely low birth weight exhibit the most severe course of HIE; attributed to the anatomical and physiological immaturity of both structural and functional aspects of organs and systems

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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