Idiopathic Neonatal Hepatitis: Clinical and Pathomorphological Analysis

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SUMMARY

Neonatal hepatitis is a rare but serious liver disease in infants during the first year of life. The term "neonatal hepatitis" refers to infectious liver damage that develops either in utero or during the first three months after birth. The timing of disease onset varies significantly depending on the etiology and is determined by the gestational period during which the fetus was infected as well as the incubation period. Therefore, in some cases, symptoms may appear almost immediately after birth, and in others – weeks or even months later.

Keywords: Neonatal hepatitis – infectious liver damage – infants

Idiopatická neonatálna hepatitída: klinická a patomorfologická analýza

SOUHRN

Novorodenecká hepatitída je zriedkavé a však závažne ochorenie pečeni u dojčiat v prvom roku života. Termín „neonatálna hepatitída" označuje infekčné poškodenie pečene, ktoré sa vyvinie buď in utero, alebo počas prvých troch mesiacov po narodení. Načasovanie nástupu hepatitídy sa výrazne líši v závislosti od etiológie a je určené gestačným obdobím, počas ktorého bol plod infikovaný, ako aj dĺžkou inkubačnej doby. Z tohto dôvodu sa v niektorých prípadoch príznaky NH objavia takmer okamžite po narodení, zatiaľ čo v iných - týždne alebo dokonca mesiace neskôr. Je jedným z najpálčivejších problémov u dojčiat počas prvého roku života.

Kľúčová slová: novorodenecká hepatitída – infekčné poškodenie pečene – dojčatá

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Neonatal hepatitis (NH) is one of the most significant problems in children during the first year of life. The term "neonatal hepatitis" refers to infectious liver damage that develops intrauterinely or during the first three months after birth. The time of hepatitis onset varies significantly depending on the etiology and is determined by the gestational age at which fetal infection occurred and by the length of the incubation period. For this reason, in some cases, symptoms of NH appear almost from birth, while in others – only after weeks or months. The causes leading to the development of NH are diverse (1,2,3,4).

Liver damage in newborns most often occurs due to viral infections caused by cytomegalovirus (CMV), herpes simplex virus, enteroviruses, parvovirus B19, hepatitis B and C viruses. Some viruses are not only infectious agents but also contribute to the development of malformations of various organs and systems. Currently, CMV is the most common cause of perinatal infection, detected in 1–2% of all newborns (3,5,6,7,8,9).

The main route of infection is hematogenous transplacental transmission, which occurs during a primary infection in the mother and concurrent placental damage impairing its barrier function. An ascending infection route is also possible – with CMV present in cervical and vaginal secretions or infected amniotic fluid. In 5–7% of cases, newborns are infected intranatally either through direct contact with infectious material or by aspiration of infected amniotic fluid containing CMV (10,11). In the postnatal period, 30% of newborns are infected through maternal secretions containing the virus – saliva, urine, genital discharge, breast milk, blood (11). Clinical manifestation of congenital CMV infection occurs in 10–15% of cases, with liver involvement in 40–63,3% of children (7,12,13,14). The likelihood of vertical transmission of herpes simplex virus (family Herpesviridae) ranges from 1:2,500 to 1:15,000 newborns. Neonatal herpes has a high mortality rate of 50–70% (8). Herpes simplex virus type 2 plays a dominant role in neonatal herpes and causes the disease in 70% of cases. Infection most often occurs intranatally (60–70%), though an ascending route is possible. Transplacental transmission of herpes simplex virus is rare and occurs during viremia in a pregnant woman due to primary infection. Liver damage in herpes infection is relatively common and occurs in both localized and generalized forms of the disease (3). Hepatitis B and C viruses also play an important role in the development of NH (15,16). Congenital hepatitis caused by these viruses is now rare due to various preventive measures.

Mechanisms of hepatocyte damage in infectious NH vary. Possible mechanisms include:

- Direct viral effect (e.g., in herpes infections) – viral cytolysis
- Indirect effect via the immune system (e.g., in hepatitis B) – immune cytolysis
- Combined mechanism (e.g., in hepatitis C) – viral-immune cytolysis

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According to various authors, an infectious origin of the disease can be confirmed in 10–45.9% of newborns with NH (17). When the etiology of NH remains unclear, the term "idiopathic NH" is used (a group of undiagnosed infectious and non-infectious diseases). It is known that several inherited metabolic disorders can mimic NH, including disorders of amino acid metabolism (e.g., tyrosinemia), carbohydrates (e.g., galactosemia), bile acids (e.g., Byler syndrome), lipids (e.g., Gaucher disease, Niemann-Pick type C), as well as arginase deficiency, α1-antitrypsin deficiency, mucopolysaccharidoses, hemochromatosis, etc. (2,10). Since metabolic disorders can manifest in the neonatal period, it is important to consider both infectious and metabolic causes of liver pathology. Other potential non-infectious causes of NH include drug-induced liver injury. Hepatotoxicity may result from antibacterial agents (macrolides, antituberculotics, antifungals), non-steroidal anti-inflammatory drugs (paracetamol, diclofenac), and others. In neonates, immature functional systems – such as low levels of cytochrome P450, glutathione peroxidase, glutathione-S-transferase, and other liver enzymes – can contribute to the development of drug-induced hepatopathy (18).

Gathering the information from medical records of the infant, the extent to which the autopsies of premature or mature newborns and infants are conducted, and sometimes even the interpretation of the actual findings represent the most highlighted deficiencies.

CASE REPORT

A newborn girl from the third pregnancy was delivered at 36 weeks of gestation via cesarean section due to intrauterine growth restriction and breech presentation. The prenatal course was complicated by suspected gestational pemphigoid, treated with corticosteroids. Postnatal adaptation was adequate; however, on the 4th day of life, the patient was transferred to the neonatal clinic due to signs of congenital hepatopathy, hypocoagulation, and thrombocytopenia.

Laboratory tests confirmed severe liver dysfunction (hypoalbuminemia, hyperbilirubinemia, elevated ferritin, coagulopathy) as well as metabolic dysregulation (hypoglycemia, hypokalemia, lactic acidosis). Infectious causes were ruled out by PCR testing (CMV, EBV, HSV, Parvovirus B19, HCV – all negative). Screening for inherited metabolic diseases was inconclusive. Due to suspected GALD (gestational alloimmune liver disease), IVIG was administered and exchange transfusion was performed. Despite these interventions, hepatic failure, pancytopenia, and edema progressed.

Bone marrow examination confirmed hypocellularity without signs of malignancy. Liver ultrasound revealed hepatosplenomegaly with hyperechogenicity. Following a liver biopsy, the patient's condition suddenly deteriorated due to the development of intra-abdominal hemorrhage. CT imaging confirmed active subcapsular bleeding from the liver. Intensive resuscitation, coagulation support, surfactant therapy, and high-frequency oscillatory ventilation (HFOV) were unsuccessful. The infant died at the age of 26 days.

Autopsy Findings

An autopsy was performed on January 2, 2025.

External examination:

A live-born female infant, body length 52 cm, weight 4700 g. The anterior abdominal wall was enlarged and bulging above the chest level due to fluid accumulation in the abdominal cavity. There was pronounced swelling of the lower limbs (Figures 1, 2).

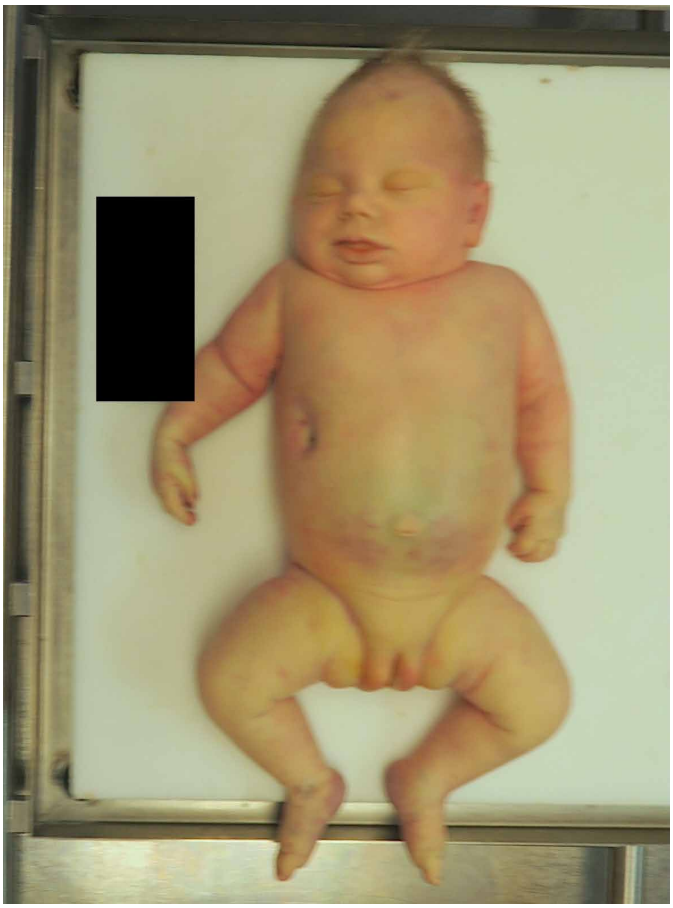

Figure 1. External view of the infant – front view.

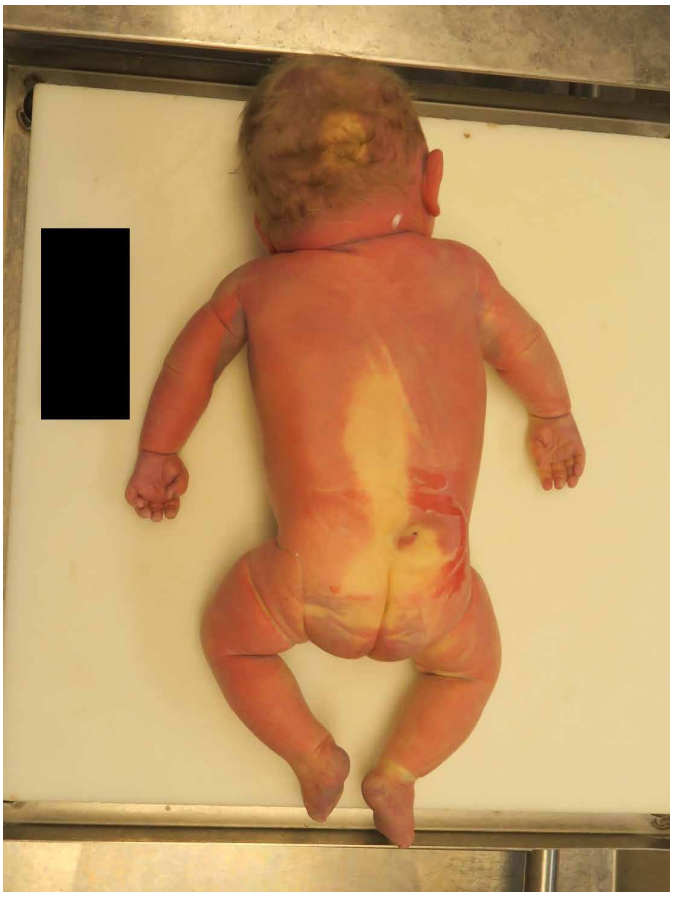

Figure 2. External view of the infant – rear view.

Internal examination:

Both pleural cavities contained 30 ml of transudate. The lungs (right – 44 g, left – 41g) were compact and pale. The abdominal cavity contained 250 ml of fresh blood and 25 g of coagulated blood. The liver (10 × 5.5 × 2 cm, 90 g) was age-appropriate in size, with adequate consistency, preserved vascular network, normal anatomical structure, and rounded edges. The surface was nodular. On section, the liver tissue showed multiple gray-white round lesions measuring 0.1–0.4 cm in diameter, interspersed with visible necrotic foci (Figure 3). The spleen (8 × 5.5 × 2 cm, 50 g) was pathologically enlarged, with a smooth, shiny, soft dark purple surface and firm consistency; the edges were rounded and did not adhere to surrounding tissues. On section, the tissue appeared edematous.

Other organs and systems showed no macroscopic changes.

Interpretation of Autopsy Findings and Conclusion

Microscopic examination of internal organs using Gram staining revealed the following:

- Lungs: Large and small bronchi lined with flat epithelium; bronchial mucosa preserved but infiltrated with lymphocytes. Bronchial and respiratory bronchiole lumens contained exudates. Alveoli showed hemosiderin deposits and desquamated alveolocytes. Pulmonary vessels had typical histological structure; fibrin deposits with signs of organization were found in the lumens.
- Liver: Giant cell transformation, focal necrosis with hepatocellular cholestasis, alternating portal mononuclear inflammatory infiltrates. Extramedullary hematopoiesis was also present (Figure 4, 5).
- Brain: Pericellular and perivascular edema, numerous blood vessels, areas of periventricular leukomalacia, and extravascular hemorrhages.

Based on the results of the autopsy (both macroscopic and microscopic findings), the diagnosis was: Idiopathic neonatal hepatitis.

The immediate cause of death was a perinatal hematological disorder resulting in hemorrhagic shock.

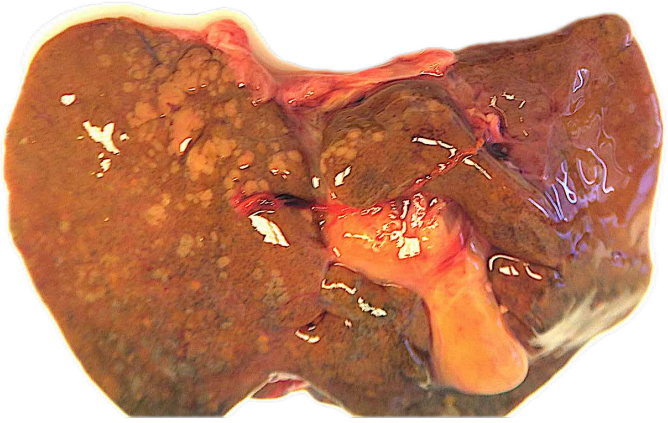

Figure 3. Macroscopic view of the liver.

CONCLUSION

Risk factors for the development of neonatal hepatitis include: advanced maternal age, history of spontaneous or medical abortions, various inflammatory diseases of the urogenital system, anemia of varying severity, and low birth weight of the newborn.

The source of infection leading to the development of neonatal hepatitis is usually the mother, particularly in the presence of urogenital inflammatory diseases and various infections confirmed by ELISA test results.

The main diagnostic criteria for neonatal hepatitis are: hemorrhagic syndrome with liver involvement (confirmed by clinical, laboratory, and imaging studies), hepatolienal syndrome, and anemia of varying degrees – particularly moderate to severe anemia.

Collecting data from infants' medical records, the frequency and thoroughness of autopsies performed on premature or full-term newborns and infants, as well as the interpretation of the findings, often reveal the most significant shortcomings in the practice of newborn autopsy. (19).

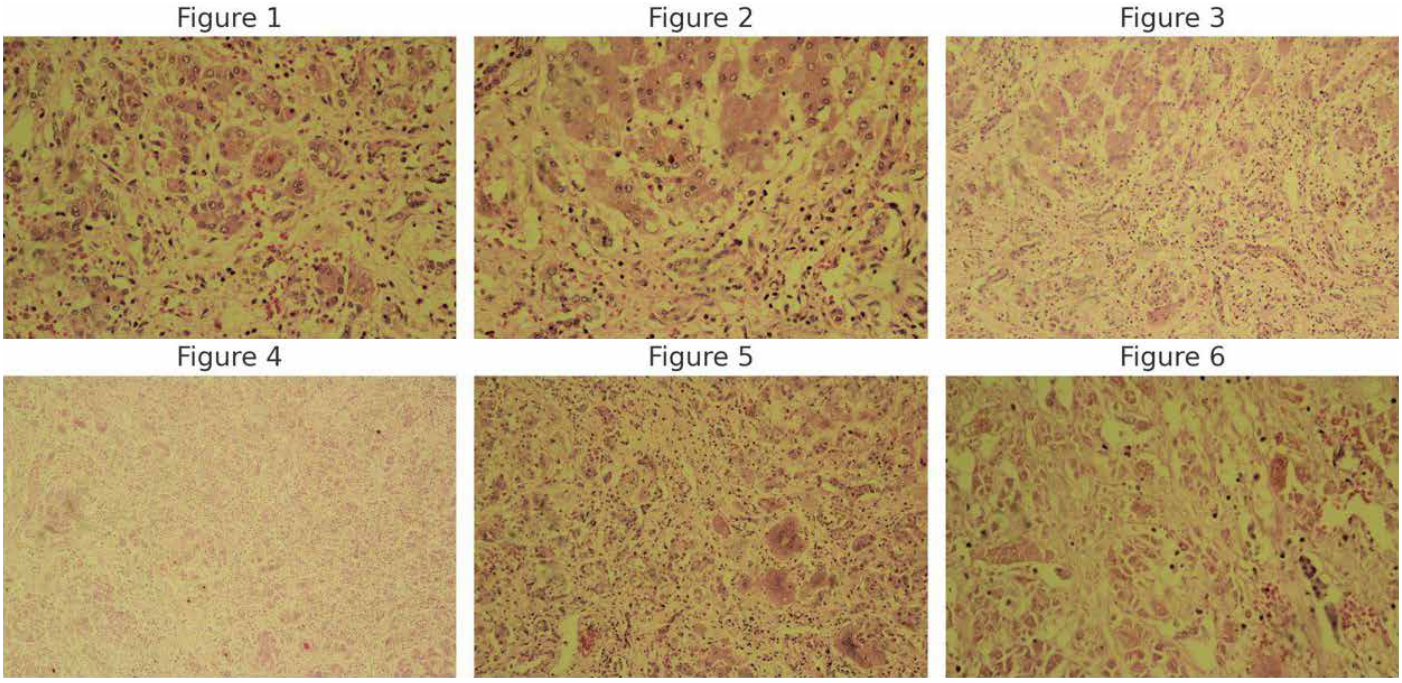

Figure 4. Microscopic view of the liver. Grid 1 (Figures 1–6): demonstrates giant cell transformation, necrotic foci, and inflammatory infiltrates.

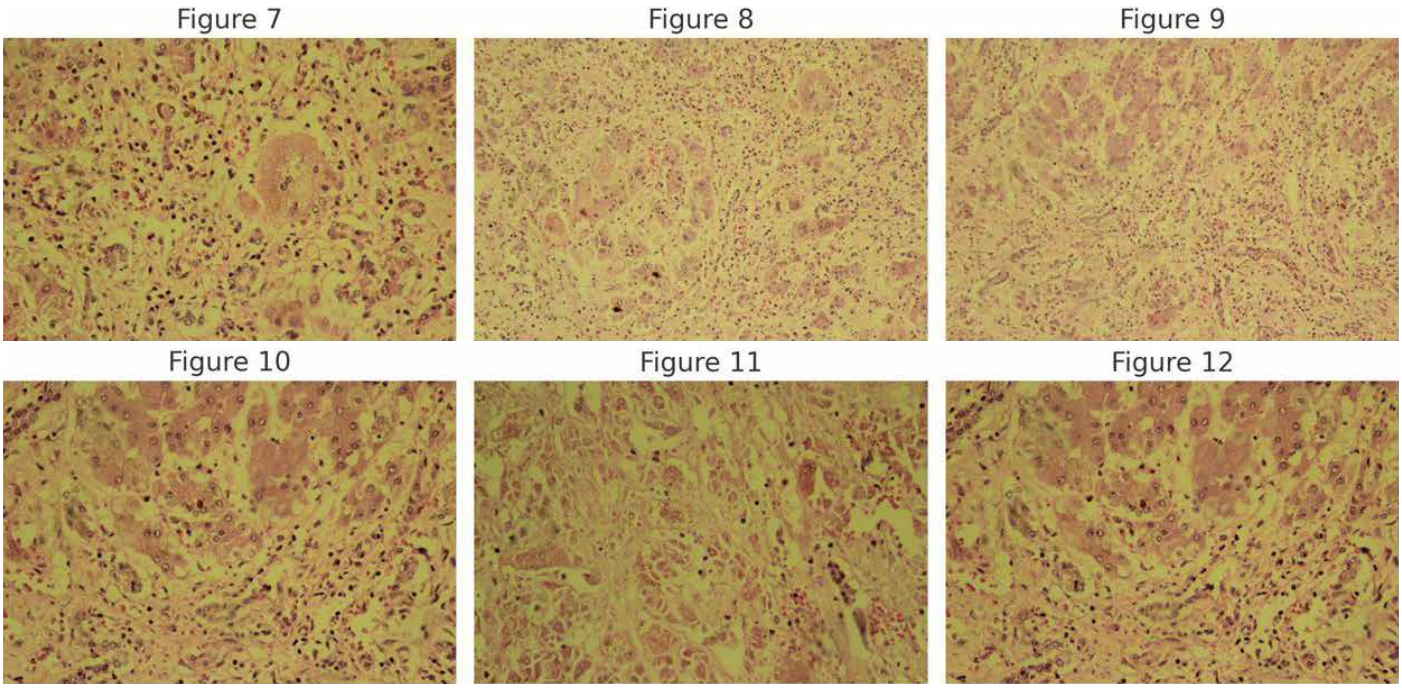

Figure 5. Microscopic view of the liver. Grid 2 (Figures 7–12): shows prominent areas of cholestasis, extramedullary hematopoiesis, and periportal changes.

When parents are provided with a clear explanation of the autopsy results in cases where the diagnosis is established but the exact cause of death remains uncertain, it often helps them come to terms with the loss of their infant. The findings should be communicated in language that parents can comprehend, illustrating how these results contribute to clarifying the cause of death. Moreover, the forensic pathologist ought to take the time to answer parents' questions with compassion, respect, and sensitivity to their grief and dignity (20).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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