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## Extrahepatic portal vein obstruction in children of the first year of life: diagnostic and treatment approaches

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Extrahepatic portal vein obstruction (EHPVO) is an important cause of symptomatic portal hypertension (PH) in pediatric population. PH may lead to serious complications including variceal bleeding and hypersplenism. Literature data on infants under 12 months old with EHPVO is poor.

**Aim** — to analyze our experience in treatment of children with symptomatic PH in children of the first year of life, the peculiarities of the course of EHPVO in them, and acknowledge readers with diagnostic algorithm of patients with EHPVO that ensures the timely start of treatment and reduce the risk of life-threatening complications.

**Materials and methods.** 11 patients who were diagnosed with EHPVO before age of 12 month are included into the study. All patients underwent in-hospital treatment in National Specialized Children's hospital «Okhmatdyt» in a period since 2006 to 2022.

**Results.** Among 11 patients of the group, 7 (63.6%) were males. Mean age at diagnosis was  $6.02 \pm 0.67$  months. 9 (83.8%) patients had umbilical catheter in anamnesis. 7 (63.6%) patients manifested bleeding episodes. Ultrasonography and enhanced computed tomography was performed in all patients. Endoscopically all patients had high grade varices. 8 (72.7%) patients underwent surgical interventions. Median hospital stay duration in children with bleeding was 36 (95% CI: 28–56) days, and 17 (95% CI: 14–22) days in children without bleeding ( $p < 0.003$ ).

The success of primary surgical interventions was assessed with Kaplan–Meyer test. Median overall survival was reached at 920 days after initial surgery; primary surgical intervention survival 0.417 (95% CI: 0.205–0.072).

There was zero mortality in the study group.

**Conclusions.** Newborns and infants with anamnesis of umbilical catheterization should be followed up closely by ultrasound imaging specialist. Patients with suspected PH are to be immediately referred to endoscopy and computed tomography in specialized center. Timely diagnosis, current endoscopic band ligation success in variceal bleeding primary prophylaxis would ensure further successful surgery and shorter hospital stay.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

**Keywords:** extrahepatic portal vein obstruction, children, variceal bleeding, Doppler ultrasound, computed tomography, portosystemic shunting.

### Допечінкова форма портальної гіпертензії в дітей першого року життя: діагностичні та лікувальні підходи

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Допечінкова форма портальної гіпертензії (ДПГ) є важливою причиною симптомної портальної гіпертензії (ПГ) у педіатричній популяції. ПГ може призводити до серйозних ускладнень, таких як кровотеча з варикозно розширених вен стравоходу та гіперспленізм. Літературних даних про пацієнтів віком до 12 місяців з ПГ недостатньо.

**Мета** — вивчити особливості перебігу симптомної ПГ в дітей першого року життя з ДПГ; ознайомити читачів із діагностичним алгоритмом клініки, який забезпечить своєчасний початок лікування та знизить ризик розвитку небезпечних ускладнень ПГ.

**Матеріали та методи.** До дослідження залучено 11 пацієнтів із ДПГ, яким діагноз встановлено у віці до 12 місяців і які перебували на стаціонарному лікуванні в НДСЛ «ОХМАТДИТ» у період 2006–2022 рр.

**Результати.** З 11 пацієнтів 7 (63,6%) осіб були чоловічої статі. Середній вік на момент встановлення діагнозу дорівнював  $6,02 \pm 0,67$  місяця. У 9 (83,8%) пацієнтів в анамнезі виявлено факт встановлення пупкового катетера. У 7 (63,6%) пацієнтів першим проявом ПГ був епізод кровотечі. Ультразвукове дослідження (УЗД) і комп'ютерна томографію (КТ) з внутрішньовенним контрастуванням проведено всім пацієнтам. Ендоскопічно в усіх пацієнтів виявлено варикоз високого ступеня. Оперативні втручання виконано 8 (72,7%) хворим. Медіана тривалості перебування в стаціонарі в дітей із кровотечею становила 36 (95% ДІ: 28–56) діб, а в дітей без кровотечі — 17 (95% ДІ: 14–22) діб ( $p < 0,003$ ).

Успішність первинних хірургічних оцінено за допомогою тесту Каплана–Меєра. Середню загальну виживаність досягнуто через 920 діб після початкової операції; виживаність після первинного хірургічного втручання становила 0,417 (95% ДІ: 0,205–0,072).

У групі дослідження смертність дорівнювала нулю.

**Висновки.** Новонароджені та немовлята з анамнезом катетеризації пупкової вени мають бути під ретельним наглядом спеціаліста з УЗД. Пацієнти з підозрою на ПГ повинні бути спрямовані на ендоскопію та КТ до спеціалізованого центру. Своєчасна діагностика, поточний успіх ендоскопічного лікування варикозних вен стравоходу в первинній профілактиці варикозної кровотечі забезпечать успіх подальшого хірургічного втручання.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

**Ключові слова:** допечінкова форма портальної гіпертензії, діти, кровотеча з варикозно розширених вен стравоходу, УЗД із доплерівським картуванням, комп'ютерна томографія, портосистемне шунтування.

## Background

Extrahepatic portal vein obstruction (EHPVO) is an important cause of symptomatic portal hypertension (PH) in pediatric population [5,12]. The etiology of EHPVO is not fully understood, but risk factors are determined, such as catheterization in anamnesis, dehydration, trauma, hypercoagulable state, local inflammatory conditions [4,7,9,12]. In different cohorts EHPVO accounts from 9% to 74% of children with PH [5]. PH may lead to serious complications such as variceal bleeding, hypersplenism, cholangiopathy, ascites, and even hepatopulmonary syndrome [4,8,10,12]. Many authors dedicate their research to study EHPVO in pediatric patients, but data on infants under 12 months old is poor, they are parts of cohorts or presented in case reports [7,8,10].

The *aim* of the study – to analyze our experience in treatment of children with symptomatic PH in children of the first year of life, to study the peculiarities of the course of EHPVO in them, and acknowledge readers with diagnostic algorithm of patients with EHPVO that ensures the timely start of treatment and reduce the risk of development of life-threatening complications, first of all, esophageal variceal bleeding.

## Materials and methods of the study

Patients' data was collected from case-records retrospectively. Out of 475 children, who had inpatient hospitalization for symptomatic portal hypertension from January 2010 to January 2022, in 11 (2.3%) the diagnosis of EHPVO was set at the age under 12 months after birth, that were included into the study group. The median follow-up period  $7.25 \pm 1.22$  years.

For all patients, the following criteria were analyzed: gender, age of disease debut, underlying pathology, basic laboratory and ultrasound symptoms and signs (bleeding episodes, hemoglobin level, thrombocytes count, spleen volume), endoscopic examinations and procedures, the type and the result of surgical treatment.

Examination was as follows: CBC with thrombocytes count, ultrasonography (US) in gray scale with spleen volume measurement (using the standard prolate ellipsoid formula:  $\text{length} \times \text{width} \times \text{depth} \times 0.523$ ), color Doppler, and spectral Doppler tracings, which were performed as initial screening to each patient and at later stages of treatment and follow-up using Samsung RS80A-UA, convex transducer (mean frequencies 1–7 MHz). Endoscopy was performed

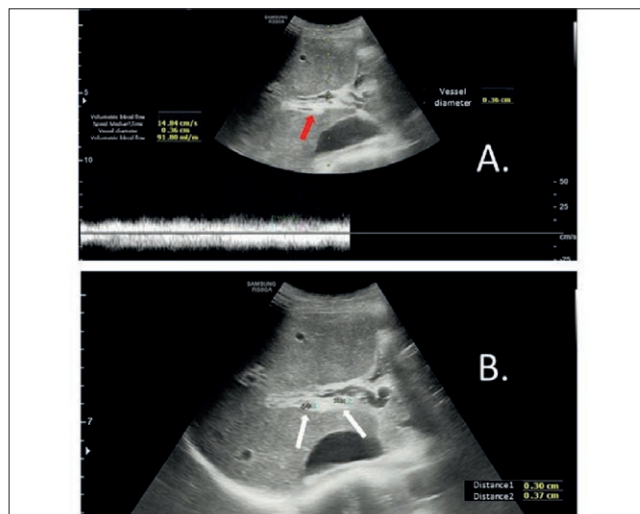
in all patients ( $n=11$ ; 100%) to assess the grade of esophageal varices and gastric mucosa, and to perform variceal band ligation when possible (Endoscope GIF-H190, Olympus LTD, Japan). Contrast-enhanced computed tomography (CT) was performed to all. Initial neurologist consult was performed at admission to all patients of the study group.

Statistical analysis was preformed using IBM SPSS for Windows version 24.0 (IBM Corp., Armonk, NY) and EZR (R-statistics). A P-value  $<0.05$  was considered statistically significant. Data distributions were compared (for different surgical methods) using the paired Student's t-test or Wilcoxon criteria. Kaplan–Meier estimator was used to assess the success of primary surgical treatment. 95% confidence interval (CI) was used to determine statistical significance.

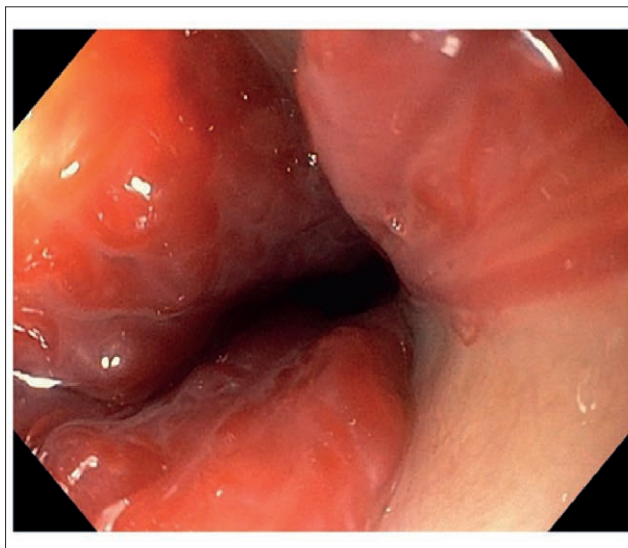
The Committee on Clinical Investigation of Bogomolets National Medical University approved this study (Protocol № 141, 27.01.2021). All the studies were conducted according to implemented guidelines in consideration of GCP-ICH and Declaration of Helsinki [14]. The written informed consent of all participants' parents/guardians was achieved.

## Results of the study

Among 11 patients of the group, 7 (63.6%) were males. Mean age at diagnosis was  $6.02 \pm 0.67$  months. 9 (83.8%) patients had umbilical catheter in anamnesis, 8 of them underwent long-term treatment in the neonatal intensive care department for following reasons: complicated labor and delivery with hypoxic ischemic encephalopathy and its consequences ( $n=4$ ; 36.3%), multiple congenital anomalies ( $n=1$ ; 9%), congenital heart defect ( $n=1$ ; 9%), congenital kidney anomaly ( $n=1$ ; 9%), pneumonia and sepsis ( $n=1$ ; 9%). In ( $n=1$ ; 9%). EHPVO was considered as idiopathic. 2 infants had surgeries in anamnesis: 1 – cardiac congenital anomaly correction, 1 – colostomy for anal atresia at the rural hospital. 7 (63.6%) patients manifested bleeding episodes as the first sign of PH, 4 of them were admitted to our center with signs of acute bleeding. Others ( $n=4$ , 36.3%) were directed to examination for accidentally splenomegaly. Despite all patients had anemia and thrombocytopenia before initial admission, in most cases being followed by medical specialists laboratory changes were attributed to the main diagnosis and a long period of recovery and rehabilitation. At admission in all patients



**Fig. 1.** Ultrasound appearance of *patient T.*, 10 months old. Grayscale ultrasound, convex introducer. **A:** Hyperechogenous liver hilum — fibrosis (red arrow), the diameter of main branch of the portal vein is 36 mm, volumetric portal blood flow is decreased to 91 ml per minute. **B:** Numerous collaterals of portal vein (white arrows)



**Fig. 2.** Endoscopic appearance of *patient M.*, 4 months old. Esophageal varices grade III, varicose veins protrude into the lumen covering more than 1/3 of it, do not collapse after air insufflation, with red wales and hematocystic spots

detected anemia with mean hemoglobin level of  $67.4 \pm 8.1$  g/l regardless of current or previous acute bleeding in anamnesis, thrombocytopenia with mean thrombocytes count of  $84.3 \pm 13.9 \times 10^9/l$ . In 3 (27.2%) patients leucocytes count was less than  $1.5 \times 10^9/l$ . US was performed in all patients (Figure 1). Typical signs of PH were detected: thin and crimped main portal vein branch, either impossibility to detect in cavernoma developed in and splenomegaly. Median spleen volume was measured  $108 \text{ cm}^3$  (95% CI: 66–300).

Endoscopy was performed in all patients ( $n=11$ ; 100%). According to endoscopy data, all patients had grade II – grade III varices (Figure 2). In 7 (63.6%) of patients the procedure of endoscopic band ligation was performed, both for acute bleeding and as prophylaxis. 4 (36.3%) patients of the group went on their course of Endoscopic band ligation and were not operated yet by the time the study was completed.

Enhanced CT was performed in all ( $n=11$ ; 100%) patients, to confirm the diagnosis of EHPVO. In 5 (45.4%) patients cavernoma of portal vein was found, in 6 (54.5%) – ascites, in all – the absence of intrahepatic portal vein branches and splenomegaly (Figure 3).

8 (72.7%) patients underwent surgical interventions, 3 (27.2%) after urgent endoscopic band ligation procedure. Median age at initial surgery was 6 (95% CI: 3–72) months. 5 (45.4%) of surgical procedures were urgent. Esophagogastric devascularization procedure ( $n=3$ ; 37.5%), splenorenal shunting ( $n=3$ ; 37.5%), distal splenorenal shunting ( $n=1$ ; 12.5%), mesoportal shunting

( $n=1$ ; 12.5%) were among initial surgical procedures. Initial median hospital stay duration in children with or after acute bleeding was 36 (95% CI: 28–56) days, and 17 (95% CI: 14–22) days in children without acute bleeding ( $p < 0.003$ ).

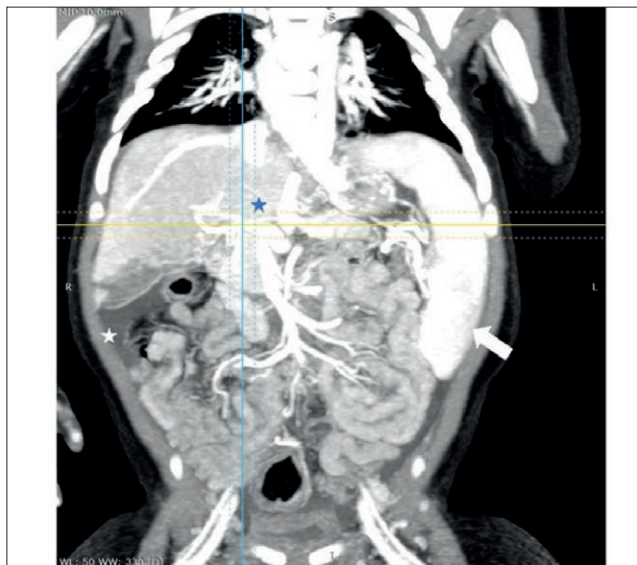
In 4 (36.3%) patients initial surgery was not successful: mesoportal shunt child developed thrombosis on the first postoperative day, and the splenorenal shunting was performed in this patient, in which thrombophilia was confirmed in late follow-up period. Initial splenorenal shunt in 5 month old patient clotted 1 month after initial surgery, splenectomy and esophagogastric devascularization procedure were performed. Sugiura procedure was performed in a patient with distal splenorenal shunting in 1 year after initial surgery. Patient with initial esophagogastric devascularization procedure underwent splenorenal shunting in 3 years after initial surgery. The last two developed recurrent variceal bleeding.

Kaplan–Meyer survival analysis was performed to estimate the success of primary surgical interventions. Median overall survival was reached by the patients of the study group at 920 days after initial surgery (Figure 4).

There was zero mortality in the study group. All patients, who underwent surgical treatment, resolved the symptoms PH by the end of the follow-up period.

## Discussion

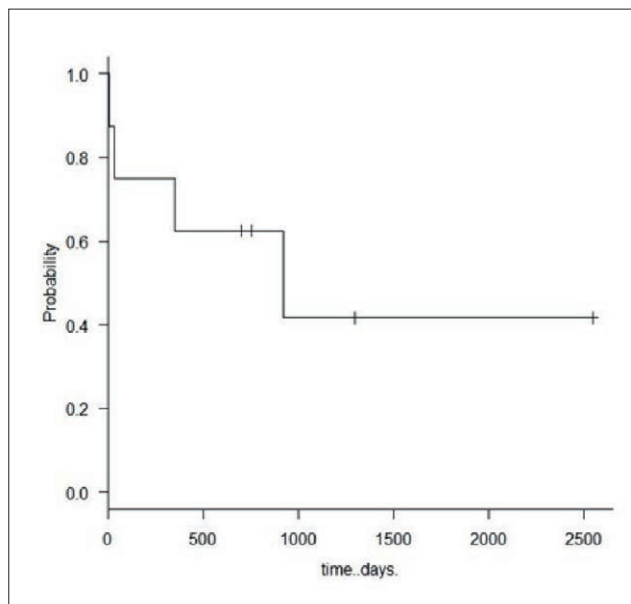
PH is a clinical syndrome characterized by an increase of the pressure gradient between the portal vein and the inferior vena cava above 5 mmHg



**Fig. 3.** Enhanced CT of patient S., 5 months old. Venous phase, enhanced CT, maximum intensity imaging regimen. Liver hiatum cavernoma is found (blue star) with portal vein thrombosis, splenomegaly (white arrow) and ascites (white star)

and develops when there is a resistance in the portal-venous system exacerbated by an increased splanchnic and portal-collateral blood flow. In children EHPVO dominates as the main reason of PH [4,5,12], causing life-threatening bleedings from esophageal varices, and other complications, such as splenomegaly, hypersplenism, ascites [7–9,12,13]. Upper gastrointestinal bleeding in children with EHPVO is assessed up to 70% in some reports [2]. In our study group variceal bleeding as the first symptom of EHPVO developed in 63.7% (n=7) patients.

Since a significant proportion of patients with PH remain asymptomatic and therefore are not likely to undergo invasive diagnosing techniques, noninvasive diagnosing methods are thus paid special attention to. US is one of them, as a cheap, time saving, and widely applied method, simple and widespread [5,11,15]. Despite known limitations of ultrasound elastography in PH diagnosing, this method such, is fast, and changes such as splenomegaly, normal liver echotexture with periportal fibrosis, and portal blood flow violation are to be easily identified by ultrasound imaging specialist [15]. US potential role in predicting gastro-esophageal varices is weak, but after initial changes are identified, such patient is to be referred to specialized center to undergo endoscopy. None of the patients of the study group, who developed variceal bleeding (n=7; 63.4%) was referred to US before bleeding episode, despite close observation for underlying pathologies by other medical specialists. In 4 (36.3%) patients splenomegaly was revealed



**Fig. 4.** Survival (Kaplan–Meier curve) for primary surgery (uniform line). Primary surgical intervention survival 0.417 (95% CI: 0.205–0.072)

by ultrasound, which became a reason for further examination.

Endoscopy is a key visualization method to access esophageal varices, and with band ligation development it became an effective treatment method as long as the method of prophylaxis of variceal bleeding in pediatric patients with EHPVO. According to M. Duche et al. [3], high-risk varices were found in 96% of children who bled spontaneously and in 11% of children who did not bleed without primary prophylaxis. Authors consider variceal band ligation to be effective as a primary bleeding prophylaxis, as it is already mentioned in our earlier publications [3,6,13]. Band ligation is widely used in our center since 2017, therefore all patients who underwent treatment before 2017, which were included into the study group, were prescribed to urgent surgery when admitted with acute bleeding. 7 (63.6%) patients of our study underwent band ligation successfully.

Enhanced CT is to be performed as the last step of examination, considering the risks of irradiation under all the rules of radiologic safety. CT provides accurate data on liver texture, cavernous transformation of portal vein, its, thrombosis, splenomegaly, splenic hilar collaterals, gastric, esophageal, and rectal collaterals, ascites [1]. In our study all patients underwent enhanced CT for strict indications.

Surgical procedures in children vary: it depends on the favorable anatomy in mesoportal shunting, and the appropriateness of the vessels for shunting as is [1,5,7,12]. Esophagogastric devascularization



procedures are performed when shunting surgeries are not feasible. Considering the age of the patients of the study group, esophagogastric devascularization procedures were the option of the first choice in 3 (27.2%) cases, and the secondary choice in 1 (9%) case.

The occurrence of rebleeding after surgical treatment in different cohorts is reported from 3% up to 53% [4]. In our study group actual recurrence of bleeding took place in 5 (45.4%) patients, which correlate with literature data. Authors consider the urgent surgery for acute bleeding in weakened by the underlying pathology and the sequences of bleeding organisms pay role in the future unsuccessful result of primary operation, as it was shown by Kaplan–Meyer test with primary surgery survival of 0.417 (95% CI: 0.205–0.747). Children who underwent planned surgeries, after the course of band ligation, with full varices eradication, had no major complications, and their postoperative period was uneventful.

Absence of regular physical examination in asymptomatic children, and low awareness of PH in pediatricians and other specialists, who closely examined children for concurrent pathology were key causes of late EHPVO diagnosis with symptomatic PH identification, and variceal bleeding development, which deteriorated the patients' condition dramatically, resulting also into a long hospital stay.

## Conclusions

EHPVO and symptomatic portal hypertension remain a significant cause of morbidity and mortality of pediatric patients of young age. Kaplan–Meiersurvivalanalysis showed primary surgical procedure survival was 0.417 (95% CI: 0.072–0.747); bleeding recurrences developed in patients who had underwent urgent operations after initial critical bleedings. Newborns and infants with anamnesis of umbilical catheterization, neonatal intensive care unit for various reasons should be followed up closely by ultrasound imaging specialist, with focus on portal vein anatomy and blood flow, collaterals development, and spleen volume. In case of revealed pathologic changes such patients are to be immediately referred to endoscopy and CT in specialized center. Timely diagnosis, current endoscopic band ligation success in variceal bleeding primary prophylaxis would ensure further successful surgery and shorter hospital stay.

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