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O.S. Godik[1,2], D.S. Diehtiarova[2]

Extrahepatic portal vein obstruction in children. The diagnosis is established — what is next?

[1]Bogomolets National Medical University, Kyiv, Ukraine
[2]National Children's Specialized Hospital «OKHMATDYT», Kyiv, Ukrainea

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Extrahepatic portal vein obstruction (EHPVO) is the most common cause of portal hypertension in children, the most life-threatening manifestation of which is variceal bleeding, with a mortality rate of 4–19%.

The aim of the study is to determine the treatment tactics for children with symptomatic portal hypertension from the moment of diagnosis of EHPVO, indications for the endoscopic prevention and surgical procedures; to study the risk factors that influence the esophageal variceal bleeding to become the first sign of EHPVO.

Materials and methods. The data of patients, which was collected retrospectively from 245 case histories between January 2011 and January 2022, revealed 55 (22.4%) children with EHPVO, who had not undergone surgical procedures. The median follow-up period was 25 (95% CI 20–35) months. Statistical analysis was performed using IBM SPSS for Windows version 24.0 and EZR(R-statistics). A P-value<0.05 was considered statistically significant. Scheffe's method, Kruskal–Wallis and Dunn's tests were used to compare the follow-up results. Chi-square test was used to assess varices grade dynamics.

Results. The mean age of patients in the group was 5.1±0.54 years, 34 (61.8%) patients were males. 36 (65.5%) patients had complicated delivery with subsequent umbilical catheter insertion. 27 (47.1%) patients manifested bleeding episodes. Endoscopic ligation showed good results in improving varices grade (p<0.001). The logistic regression model identified factors connected to the bleeding risks: «way of delivery» (p=0.027) and «hemoglobin level» (p=0.0015). Indications for surgical intervention were failure to decrease the esophageal varices grade (n=4; 7.2%) and an increase in the volume of the spleen with thrombocytopenia progression (n=6; 10,9%).

Conclusion. The most careful medical attention to babies of the risk group is required. Endoscopic ligation has shown good results in variceal grade decrease. Indications for surgical treatment are failure to decrease the grade of esophageal varices, an increase in the volume of the spleen with thrombocytopenia progression.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research 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; bleeding esophageal varices; primary prevention; endoscopic variceal ligation; surgical treatment indications; children.

Допечінкова форма портальної гіпертензії в дітей. Діагноз встановлено — що далі?

О.С. Годік[1,2], Д.С. Дєгтярьова[2]

[1]Національний медичний університет імені О.О. Богомольця, м. Київ, Україна
[2]Національна дитяча спеціалізована лікарня «ОХМАТДИТ», м. Київ, Україна

Допечінкова форма портальної гіпертензії (ДфПГ) є найпоширенішою причиною портальної гіпертензії в дітей. Найбільш загрозливим проявом ДфПГ є кровотеча з варикозних вен стравоходу, смертність внаслідок якої є високою, становлячи 4–19%.

Мета дослідження: визначити тактику лікування дітей із симптомною портальною гіпертензією з моменту встановлення діагнозу ДфПГ, показання до ендоскопічної профілактики та хірургічного лікування; вивчити фактори ризику, що призводять до кровотечі як першого прояву ДфПГ.

Матеріали та методи. У ретроспективно зібраних даних із 245 історій хвороби в період із січня 2011 р. по січень 2022 р. виявлено 55 (22,4%) дітей із діагнозом ДфПГ, яким не проводилися хірургічні втручання. Медіана спостереження становила 25 (95% ВІ 20–35) місяців. Статистичний аналіз проведений IBM SPSS для Windows 24.0 та EZR (R-statistics). Значення p<0,05 вважалося статистично значущим. Для порівняння результатів спостереження використано метод Шеффе, тести Краскела–Уоліса та Данна. Для оцінки динаміки ступеня варикозного розширення вен застосовано критерій хі-квадрат.

Результати. Середній вік пацієнтів групи був 5,1±0,54 років, 34 (61,8%) пацієнти були чоловічої статі. У 36 (65,5%) пацієнтів були ускладнені пологи з подальшим встановленням пупкового катетера. У 27 (47,1%) хворих першим проявом ДфПГ був епізод кровотечі. Ендоскопічне лігування показало хороші результати щодо зменшення ступеня варикозу (p<0,001). Модель логістичної регресії виявила фактори, пов'язані з ризиком кровотечі: «шлях пологів» (p=0.027) та «рівень гемоглобіну» (p=0.0015). Показаннями до хірургічного лікування стали відсутність зменшення ступеня варикозу (n=4; 7,2%), збільшення об'єму селезінки з прогресуванням тромбоцитопенії (n=6; 10,9%).

Висновки. Немовлятам із групи ризику потрібний найпильніший медичний нагляд. Ендоскопічне лігування показало хороші результати у зменшенні ступеня варикозу. Показаннями до хірургічного лікування є відсутність зменшення ступеня варикозних вен стравоходу, збільшення об'єму селезінки з прогресуванням тромбоцитопенії.

Дослідження виконано відповідно до принципів Гельсінської Декларації. Протокол дослідження ухвалено Локальним етичним комітетом установи. На проведення досліджень отримано інформовану згоду батьків, дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: допечінкова форма портальної гіпертензії, кровотеча з варикозних вен стравоходу, первинна профілактика, ендоскопічне лігування варикозних вен стравоходу, показання до оперативного лікування, діти.

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Introduction

Extrahepatic (prehepatic) portal vein obstruction (EHPVO), or thrombosis if proven, is the most common cause of portal hypertension in children [14] and can count up to 74% of pediatric patients with portal hypertension [7]. Esophageal and gastric varices are detected in up to 90% of children with EHPVO [8], the most life-threatening manifestation of which is variceal bleeding [4,5,7], which can occur in a child with no apparent past medical history. Despite the rapid evolution in endoscopic procedures and surgical technologies, as methods of bleeding control, the mortality rate from variceal bleeding remains high, counting 4–19% [5]. The opinion on primary prophylaxis of bleeding is controversial and varies in different countries [6], there is no generally accepted protocol for management of children with EHPVO.

The aim of the study is to analyze our experience and determine the treatment tactics for children with symptomatic portal hypertension from the moment of diagnosis of EHPVO, indications for the endoscopic primary prophylaxis and for the following surgical procedures; to study the risk factors that may lead the esophageal variceal bleeding to become the first sign of EHPVO.

Materials and methods of the study

The data of patients was collected retrospectively from case records. 245 case histories were analyzed in the period from January 2011 to January 2022, in 55 (22.4%) patients the diagnosis of EHPVO was established and they had not undergone surgical procedures yet. The follow up period was 6–185 months, median 25 (95% CI 20–35).

For all patients, the following criteria were analyzed: gender, age of onset, variceal bleeding as the initial symptom, underlying pathology, basic laboratory and ultrasound results (hemoglobin level, leucocyte count, thrombocyte count, spleen volume), endoscopic examinations and procedures (initial and following varices grade, variceal band ligation procedures and the quantity of used bands), the result of endoscopic primary prophylaxis, indications for surgical treatment.

The examination was as follows: complete blood count (CBC) with thrombocyte count, gray-scale ultrasonography (US) with spleen volume measurement (using the standard prolate ellipsoid formula: length × width × depth × 0.523), color Doppler, and Spectral Doppler tracings, using Samsung RS80A-UA, convex transducer (mean frequencies 1–7 MHz). Endoscopy was performed in all patients (n=55) to assess the grade of esophageal varices and gastric mucosa, and to perform variceal band ligation, if necessary, using endoscopes GIF-H185, GIF-Q150, GIF-XQ260, Olympus LTD, Japan, and ligation devices Boston Scientific, Cook Medical Incorporated, Mar Flow, Micro-Tech with capacity of 6–7 ligature rings per cassette. The esophageal varices grade was assessed according to the Japanese Research Society for Portal Hypertension [13], gastric varices were graded according to the Sarin classification [12]. Contrast-enhanced computed tomography (CT) was performed to all patients, using Siemens Somatom Definition AS. The contrast agent was calculated according to the patient's weight: 2 ml of water-soluble contrast (Ultravist, Vizipak) per 1 kg of body weight at an injection speed of 2 ml/sec: arterial phase — at 20–25 sec, portal phase — at 60 sec, with following multiplanar and 3-D reconstruction. All endoscopic examinations and CT-scans in children of younger age were performed under general anesthesia. A neurologist consult was performed to all patients of the study group to differentiate the cause of encephalopathy.

Statistical analysis was performed 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. Scheffe's method, Kruskal–Wallis multiple comparison and Dunn's test were used to compare the follow-up results. Chi-square test was used to assess nonparametric data analysis for varices grade dynamics assessment. The logistic regression model was built to identify factors that may influence the risk of variceal bleeding as the initial manifestation of EHPVO.

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

This study is a fragment of the Department of Pediatric Surgery research «Development and implementation of modern methods for diagnosis and treatment of congenital defects and acquired diseases of the digestive tract in children», state registration number 0118U100562, 12.21.2018.

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Table 1

Characteristics of patients in the study group

Characteristic	Total (n)	Percent, %
Gender:		
male	34	61.8
female	21	38.2
Etiology:		
umbilical catheter	36	65.5
idiopathic	18	32.7
portal vein thrombosis as complication of pancreatitis	1	1.8
Anamnesis at admission:		
complicated labor and delivery	36	65.5
body weight at birth lower than 2500 g	17	30.9
delivery by C-section	16	29.1
mechanical ventilation in nICU	17	30.9
Previous surgeries	3	5.4
Clinical presentation:		
Bleeding episode as a debut sign	27	49.1
Hemotransfusion	11	20.0
Splenomegaly	55	100
Hypersplenism	49	89.1
Ascites	12	21.8
Esophageal varices at admission:		
no varices (0)	2	3.6
Grade I	14	25.4
Grade II	19	34.5
Grade III	20	36.6

Results of the study

Among 55 patients of the study group, 34 (61.8%) were males. Patients age at initial admission ranged from 6 months to 15 years, the mean age was 5.1±0.54 years. In 14 (25.4%) patients only the labor and delivery were on time and uneventful. Other 5 (9.1%) were delivered premature, but without complications.

36 (65.5%) patients had complicated labor and delivery, of which 16 (29.1%) were delivered by emergency C-section. All mentioned 36 (65.5%) patients had umbilical catheter in anamnesis. 17 (30.9%) patients had low birth weight under 2500 g. In other children following complications were registered: hypoxic ischemic encephalopathy and its consequences (10 (18.2%) patients), multiple congenital anomalies (2 (3.6%) patients), congenital heart defect (n=2; 3.6%), respiratory distress syndrome (7 (12.7%) patients), pneumonia and sepsis (5 (9.1%) patients), meconium aspiration (4 (7.2%) patients), head trauma at birth and limb trauma (4 (7.2%) patients), necrotizing enterocolitis (1 (1.8%) patients), Rhesus incompatibility (1 (1.8%) patient). 3 (5.4%) infants had surgeries in anamnesis: 1 — the correction of cardiac congenital anomaly, 1 — colostomy for anal atresia, 1 — the closure of tracheoesophageal fistula. In (1 (1.8%) patient) with uneventful birth in term and insignificant medical history until the age of 10 years old, familial pancreatitis manifested at mentioned age, which was complicated by portal vein thrombosis by the age of 14 years old. In other (18 (32.7%) patients) EHPVO was considered idiopathic. All patients after complicated delivery underwent treatment in the neonatal intensive care unit (nICU) with (17 (30.9%) children) required mechanical ventilation.

The clinical presentation at initial admission alongside with summarized patients' characteristics are presented in Table 1.

27 (49.1%) patients manifested bleeding as the first sign of portal hypertension, developed as a result of EHPVO, 11 (50.7%) of them were admitted with signs of acute bleeding and required hemotransfusion. All (55 (100%) cases) patients had splenomegaly and almost all patients presented hypersplenism (49 (89.1%) children). According to the CBC results, hemoglobin level lower than 100 g/l was found in 14 (25.4%) patients, and only 7 (12.7%) children had hemoglobin level higher than 120 g/l due to the current or previous acute bleeding in anamnesis. Thrombocytopenia was found in the majority of patients, whereby (n=20;36,6%) patients had thrombocyte count lower than 100 per mm^3.

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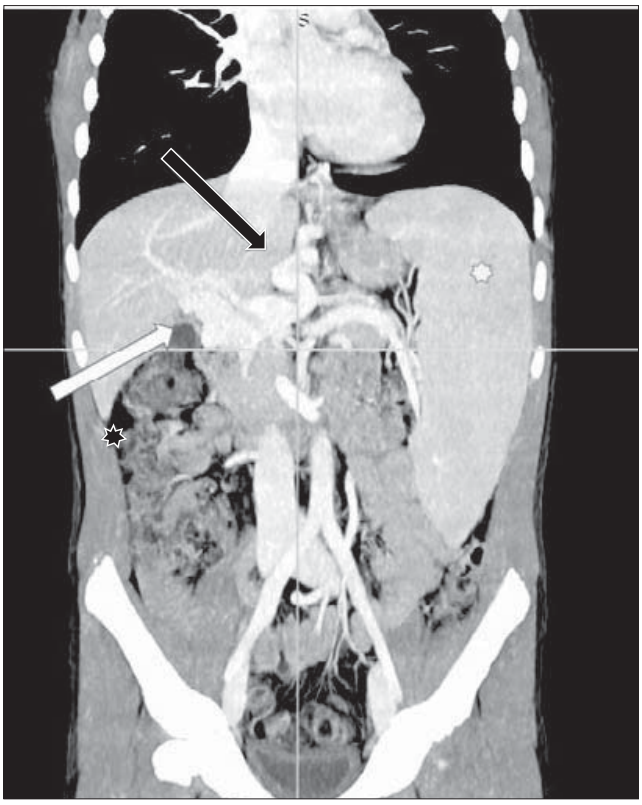
US was performed in all patients and detected signs of portal hypertension resulted from EHPVO: thin and crimped main portal vein branch, fibrosis of the liver hilum, low volumetric intrahepatic portal vein flow, and splenomegaly. CT was performed to all patients to confirm the diagnosis. Typical imaging findings are presented at Figure1, where initial enhanced CT of a patient without any significant previous medical history, no umbilical catheter in anamnesis, no confirmed bleeding episodes are presented.

Endoscopy was performed in all 55 (100%) patients. According to the endoscopy data, 39 (70.9%) patients had high grade (II–III) varices (Figure 2A). In 2 (3.6%) patients no varices were identified initially and within the whole follow up period. Out of the study group, 45 (81.8%) patients required endoscopic band ligation for high grade varices. In general, they have required 1–6 (mean 2.5±0.16) procedures with 2–23 (median 7(95% CI 4–6)) bands used in each patient (Figure 2B).

By the time the study was completed, the decrease in varices grade was observed in most patients, in 2 (3.6%) cases eradication of varices was reached. The dynamics in laboratory tests, spleen volume, and varices grade between initial admission and the end of the study period are shown in Table 2.

The procedure of endoscopic band ligation showed good results in improving varices grade, decreasing it to Grade I (p=0.0000082), and increasing hemoglobin level (p<0.001), however was accompanied with spleen volume increase (p<0.001). Platelet and leucocyte counts did not change significantly.

For multifactorial analysis logistic regression model was constructed (Figure 3A) to identify factors that could prognose the risk of bleeding as the first sign of EHPVO. The factors investigated were as follows: age at initial diagnosis (months), gender (male/female), umbilical catheter in anamnesis (yes/no), way of delivery of the baby (natural birth/C-section), complications at birth (yes/no), birth weight lower than 2500 g (yes/no), mechanical ventilation in nICU (yes/no), spleen volume (median cm^3). The results of the multifactorial analysis are represented in Table 2.



Notes: delayed venous phase, enhanced CT, maximum intensity imaging regimen. Liver hilum cavernoma was found (white arrow), gastric and esophageal collaterals (black arrow), splenomegaly (white star) and moderate ascites (black star).

Fig. 1. Enhanced CT of *patient K.*, 11 years old

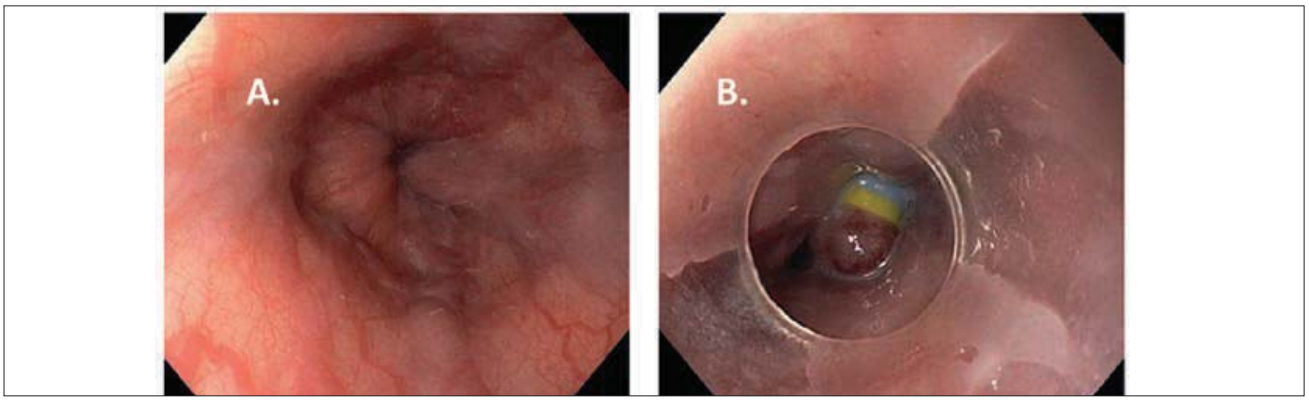


Fig. 2. Endoscopic appearance of *patient B.*, 2 years old, no umbilical catheter in anamnesis, variceal bleeding episode as a debut: A — initial endoscopic appearance: esophageal varices grade III, varicose veins protrude into the lumen covering more than 1/3 of it; B — band on the esophageal varicose vein

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Table 2

Comparison of primary and final clinical, US, laboratory and endoscopic data in experimental groups

Variable	Primary results	Final results	p-value
Spleen volume, cm^3 (median (Q1÷Q3))	**231 (95% CI 188–327)**	**356 (95% CI 291-442)**	**<0.001[1]**
Hemoglobin, g/l (median (Q1÷Q3)) (mean±SD)	**108 (95% CI 105–111)**	**113±1.51**	**<0.001[1]**
Platelet count per mm^3 (median (Q1÷Q3))	120 (95% CI 101-143)	118 (95% CI 103-140)	0.127[1]
Leukocyte count per mm^3 (median (Q1÷Q3)) (mean±SD)	4,6 (95% CI 0.44-5.3)	4.8±0.23	0.293[1]
Esophageal varices grade, number of patients (%): 0 I II III	 2 (3.6%) 14 (25.4%) 19 (34.5%) 20 (36.6%)	 4 (7.2%) 38 (69.1%) 12 (21.8%) 1 (1.8%)	 0,679[2] **0.0000082[2]** 0.203[2] **0.000003[2]**

Notes: [1] — Wilcoxon W-test, [2] — Fisher's exact test.

Table 2

Risk factors included into the logistic regression model of variceal bleeding as the first risk factor for developing EHPVO

Risk factors	OR (95% CI)	p-value
Age	1.010 (0.7390–1.39e+00)	0.94
Gender	0.426 (0.0816–2.22e+00)	0.31
Umbilical catheter in anamnesis	0.661 (0.0820–5.33e+00)	0.69
Way of delivery of the baby	**0.207 (0.0512–0.0873)**	**0.027**
Complications at birth	1.510 (0.8400–4.49e+01)	0.74
Low birth weight	0.9840 (0.9480000–9.82e+00)	0.43
Mechanical ventilation in nICU	3.740 (0.8100–17.30)	0.09
Spleen volume	0.997 (0.9930–1.00e+00)	0.16
Hemoglobin level	**0.919 (0.872–0.968)**	**0.0015**
Leucocyte count	1.100 (0.7470–1.63e+00)	0.62
Thrombocyte count	0.993 (0.9820–1.010)	0.26

Using a stepwise method, two factors were revealed that are connected to the bleeding as the first sign of EHPVO risks: «way of delivery of the baby» and «hemoglobin level». Based on these two factors, a logistic prognosing model was constructed (Figure 3B).

There was zero mortality in the study group. By the end of the follow-up period, the indications for planned surgical intervention were set to 10 (18.1%) patients, from which 4 (7.2%) failed to decrease the grade of esophageal varices despite repetitive band ligation procedures, and 6 (10.9%) had a critical increase in spleen volume up to 1000 cm^3 together with thrombocytopenia progression. All patients would be assessed for the installation of a mesoportal (Rex) shunt.

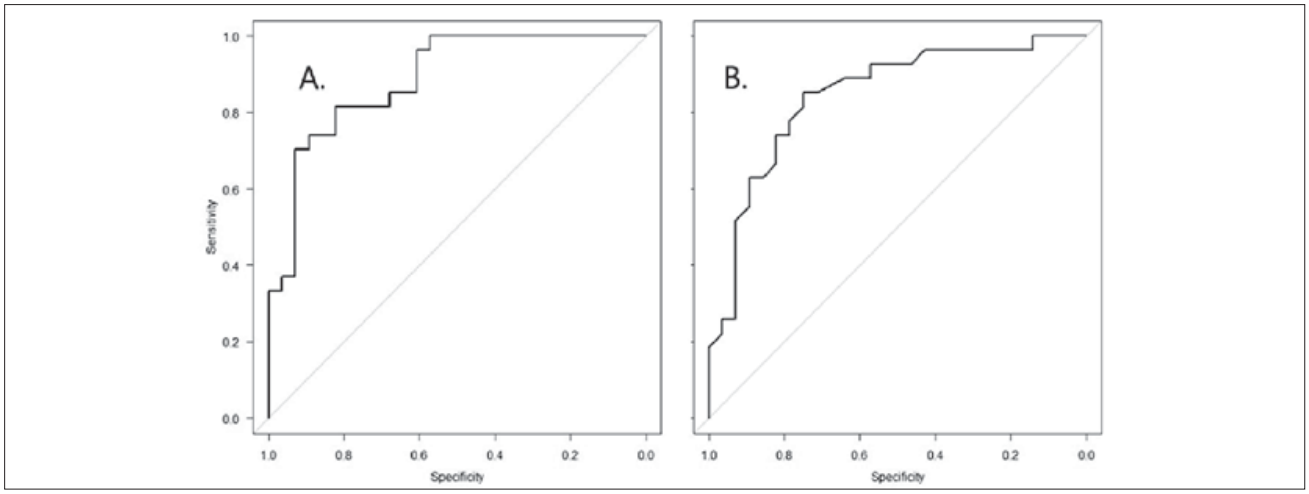

Fig. 3. **A** — ROC-curve of the 11-factor logistic regression model of variceal bleeding as the first risk factor for the development of EHPVO: AUC= 0.886 (95% CI 0.801-0.972): **B** — final 2-factor logistic regression model of variceal bleeding as the first EHPVO risks: AUC=0.843 (95% CI 0.736-0.95)

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Discussion

EHPVO in pediatric patients is the main cause of portal hypertension [11,14]. The highest rate of varices registered in a group of patients with EHPVO found by the authors was 90% [8], which, when ruptured, causes the life-threatening bleedings from esophageal varices, and other complications, such as splenomegaly, hypersplenism, ascites [5,7,8,11,13]. Upper gastrointestinal bleeding in children with EHPVO is assessed up to 70% in some reports [3], while the mortality from variceal bleeding remains high at up to 19% [5].

In our study group, variceal bleeding as the first symptom of EHPVO developed in 27(49.1%) patients. This brought the authors an idea that before considering the method of prophylaxis, there must be a reason found underlying such type of debut.

The initial idea of multifactorial analysis of logistic regression model construction was to identify such a risk factor, and as a result — two were identified: way of delivery of the mother (p=0.027) and hemoglobin level (p=0.0015). It must be stated that most patients after complicated birth had persistent low hemoglobin level, which was considered by pediatricians as the consequence of weaning and accompanying pathology.

The authors propose an easy diagnostic algorithm: US, followed by endoscopy, then CT. The US is a cheap and noninvasive method, and despite its known limitations, it provides to detect the most significant for EHPVO changes — fibrosis of the liver hilum and splenomegaly [3,13]. All patients of the study group (n=55; 100%) had splenomegaly. None of the 9 (16.3%) patients of the study group, who developed variceal bleeding without previous significant medical history, was referred to US before the bleeding episode, which may indicate the low quality of physical examination by primary care medical specialists.

Endoscopy is a key visualization method to access esophageal varices, and together with band ligation, it is the effective method for primary bleeding prophylaxis in pediatric patients with EHPVO [6]. The authors consider variceal band ligation to be effective as a primary bleeding prophylaxis, as it is already mentioned in our earlier publications as band ligation has been widely used in our center since 2017 [10]. In the current study, band ligation resulted into decrease of the grade of varices (p=0.0000082).

Enhanced CT should be performed as the last step of examination, according to the rules of radiologic safety, to confirm the diagnosis and plan the future surgery. CT shows the cavernous transformation of the portal vein, gastric, esophageal, splenic hilar collaterals, splenomegaly, ascites, if present [2]. In our study, all 55 (100%) patients underwent enhanced CT.

Surgical procedures as a secondary prophylaxis in children vary: they depend on the appropriateness of the vessels for shunting and, as all authors agree, on favorable anatomy for the mesoportal shunt, which is the golden standard of surgical treatment in children with symptomatic portal hypertension caused by EHPVO [1,9]. As in the previous study authors proved that umbilical catheter was not a contradiction for mesoportal shunting, after appropriate evaluation all children from the current study group, who were directed to surgical treatment, will all be assessed for mesoportal shunting. The suitability of vessels for shunting depends on favorable anatomy for mesoportal shunting. [1,2,9].

The absence of close medical attention to the children from the risk group, including those after C-section with persistently low hemoglobin level, absence of regular physical examination in asymptomatic children which could reveal splenomegaly and low awareness of portal hypertension among pediatricians and other primary care specialists, results into that bleeding is the first sign of EHPVO, when timely diagnosis could prevent further deterioration of the child's condition.

Conclusion

Symptomatic portal hypertension resulted from EHPVO remains a significant cause of morbidity and mortality in pediatric patients. Closest medical attention to babies and toddlers of the risk group with persistently low hemoglobin level (p=0.0015), born via C-section (p=0.027), and, probably, ventilated (p=0.09) within neonatal ICU should include regular ultrasound examination, with focus on fibrosis of portal hilum and spleen volume. When pathologic changes are revealed, patients should immediately be referred to CT and endoscopy to the specialized center. The procedure of endoscopic band ligation showed good results in improving varices grade (p=0.0000082) and increasing the hemoglobin level (p<0.001), however was accompanied with an increase in spleen volume (p<0.001). Indications for surgical treatment should include failure

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to decrease the grade of esophageal varices, increase in spleen volume together with thrombocytopenia progression. All patients should be assessed for the possibility of installing a mesoportal (Rex) shunt.

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The authors have no competing interests to declare that are relevant to the content of this article.

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Відомості про авторів:
Годік Олег Святославович — к.мед.н., доц. каф. дитячої хірургії НМУ ім. О.О. Богомольця; лікар-трансплантолог, лікар-хірург дитячий відділення ургентної хірургії НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1. https://orcid.org/0000-0002-1084-9484.
Дєгтярьова Дар'я Сергіївна — PhD, лікар-хірург дитячий відділення ургентної хірургії НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1. https://orcid.org/0000-0002-2356-0874.
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