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CLINICAL MARKERS OF HYPERTENSION IN THE LEFT RENAL VEIN SYSTEM

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Abstract. Introduction. Hypertension in the left renal vein (LRV) system is usually a consequence of aorta mesenteric clamp (the so-called “nutcracker syndrome”) and leads not only to venous stasis of the left kidney, but also to the development of pelvic congestion syndrome. The frequency and severity of the “nutcracker syndrome” (NS) symptoms varies from asymptomatic microhematuria to severe forms of pelvic venous congestion. Some patients indicate distinct and constant clinical symptoms, some patients, especially children, note an asymptomatic course

The objective was to study the prevalence and degree of hypertension clinical symptoms manifestations in the LRV system.

Materials and methods. The study included 248 patients (156 men and 92 women, an average age constituted 28.24±2.74) with suspicion of NS who underwent examination and treatment from 1999 to 2022. All patients were interviewed for specific complaints, pain syndrome in particular (questionnaire according to VAS) and underwent laboratory diagnostic tests, color Doppler ultrasound of the reno-caval segment, kidneys, pelvis, and CT angiography, if necessary.

Results. According to the conducted patient questionnaire, one third of patients with AMC without critical LRV stenosis did not have a pain syndrome, and when present, mild and moderate pain prevailed. However, pain syndrome was indicated by 93.1% of respondents in the group of patients with critical LRV stenosis (II group) and the structure of its intensity also changed.

Apparently, macrohematuria lasting more than 2 years with a frequency of more than 2 times in 2 months (32.84%) prevailed in the patients with critical LRV stenosis (group II), whereas this indicator in the patients of groups I and III constituted 4.26% and 4.56%, respectively.

Evidently, a significant decrease in BMI was observed in the patients with critical LRV stenosis (16.2±1.08 vs. 23.8±1.12 and 24.7±2.38 in the patients of groups I and III, respectively). As a result of the examination, a distinct correlation was established between the decrease in BMI and the pain syndrome intensity according to VAS in the patients of group II: Spearman’s rank correlation coefficient was 0.948, $P < 0.0001$, CI 95% for R_s from -0.972 to -0.906 constituted 18.2% in group I, 46.3% in group II, 12.4% in group III, respectively.

Left sided varicocele was diagnosed in 48 (54.5%) examined men of groups I and II: stage I was diagnosed in 12 (25%) cases, stage II was observed in 31 (64.5%) cases, stage III was found in 5 (10.5%) patients and in 12 (13.4%) patients of group III (control).

However, analysis of the varicocele frequency, taking into account its stage, found no connection between the degree of varicocele and the presence of LRV critical stenosis.

Conclusions. NS is characterized by distinct polymorphism of clinical manifestations and a variety of clinical forms. The main hypertension markers in the LRV system are pain syndrome and hematuria. Color Doppler ultrasound of the reno-caval segment is recommended to the patients with left sided varicocele / left sided pudendal varicose veins, hematuria, proteinuria, with a diagnosis of pelvic congestion; with dyspareunia, algodysmenorrhea, the appearance of blood during coitus / hemospermia, with chronic epigastric pain of unknown etiology, with anorexia, idiopathic infertility, in order to exclude pathology of the reno-caval segment.

Keywords: “the nutcracker syndrome”, aorta mesenteric clamp, critical stenosis of the left renal vein, pelvic congestion syndrome.

Introduction and justification of the research.

Hypertension in the left renal vein (LRV) system is usually a consequence of aorta mesenteric clamp (the so-called “nutcracker syndrome”) and leads not only to venous stasis of the left kidney, but also to the development of pelvic congestion syndrome.

The frequency and severity of the “nutcracker syndrome” (NS) symptoms varies from asymptomatic

microhematuria to severe forms of pelvic venous congestion [2,3,7,10,12,13,15]. Some patients indicate distinct and constant clinical symptoms, some patients, especially children, note an asymptomatic course [5].

Essential hematuria is the most specific NS symptom resulting from the rupture of the thin-wall venules of the left kidney due to increased venous pressure in renal collecting system, varying from microhematuria to severe

persistent macrohematuria with anemia development [1,5,12].

In addition to hematuria, the following clinical manifestations are peculiar to the “nutcracker syndrome”: left sided pain in the abdomen and lumbar region, left sided varicocele in men and left sided pudendal varicose veins in women. However, the non-specificity and polymorphism of clinical symptoms greatly complicates the diagnosis making [11].

The objective of the research was to study the prevalence and degree of hypertension clinical symptoms manifestations in the LRV system.

Materials and methods. The study included 248 patients (156 men and 92 women, an average age constituted 28.24 ± 2.74) with suspicion of NS who underwent examination and treatment from 1999 to 2022. All patients were interviewed for specific complaints, pain syndrome in particular (questionnaire according to VAS) and underwent laboratory diagnostic tests (complete blood count, urinalysis, Nechiporenko urine test), color Doppler ultrasound of the reno-caval segment, kidneys, pelvis, and CT angiography, if necessary.

Pain syndrome was assessed using the Visual Analog Scale (VAS). The main symptoms of the disease, the intensity of which was studied in the examined patients according to VAS, were as follows: 1) pain in the left half of the abdomen; 2) pain in the left lumbar region; 3) abdominal discomfort; 4) pain in the epigastrium; 5) manifestations of pudendal varicose veins / varicocele on the left; 6) algodismenorrhea / erectile dysfunction; 7) dyspareunia.

VAS is designed to assess the intensity of the studied symptom and is a continuous scale in the form of 10 cm horizontal lines with the values “0” on the left and “10” on the right below it.

The above-mentioned values mean the following: 0 denotes a complete absence of the symptom, 10 is the strongest manifestation of the symptom. Pain could be characterized as mild, moderate, severe, terminal, unbearable. Having acquainted with the rules of the questionnaire filling in, the respondent filled in the form independently with the direct participation of the interviewer who controlled the correctness of the questionnaire filling in by communicating with the patient.

Quantitative results were summed in order to obtain a final score in the form of the VAS integrative index. The higher the obtained score, the more severe the disease symptom. A dynamic comparison of the obtained results provided an opportunity to conduct a clinical assessment of the disease course and the treatment results.

Statistical processing of the obtained data was conducted using Microsoft Excel spreadsheets (Windows XP), the MedCalc for Windows program (version 11.4.2). Average indicators between the groups of patients were compared with the use of the nonparametric Mann-Whitney U-test (the distribution was not close to normal). Correlations between the indicators were determined by means of Spearman’s rank correlation coefficient (R_s). Average values with a 95% confidence interval were determined in selected groups of patients. STATISTICA 10 program was used to compare correlation coefficients. The critical level of significance (p) was considered equal to 0.05 when testing statistical hypotheses in this research.

Results of the research. The patients were randomized into three groups on the basis of the performed color Doppler ultrasound results. Group I (116 people, the average age constituted 29.42 ± 0.78 years) included patients with varying degrees of aorta mesenteric clamp (AMC) without critical LRV stenosis. Group II (54 people, the average age constituted 23.65 ± 1.87 years) consisted of patients with critical LRV stenosis. Group III (78 people, the average age was 31.66 ± 0.94 years) included patients without AMC signs (control group).

According to observations, clinical manifestations of severe forms of AMC syndrome occurred in case of an increase in the diameter of LRV distal (prestenotic) part by 3-6 times (by 4.3 times on average) compared to its proximal (aorta mesenteric) segment, as well as an increase in peak systolic velocity in the stenosed proximal (aorto-mesenteric) segment by 6-14 times (by 8.7 times on average) compared to the LRV distal segment. Indicators of the ratio of LRV distal and proximal segments diameters ≥ 3 and the ratio of peak systolic velocities in the proximal and distal segments ≥ 6 were considered as critical LRV stenosis [1,7,12].

According to the conducted patient questionnaire, one third of patients with AMC without critical LRV stenosis did not have a pain syndrome, and when present, mild and moderate pain prevailed.

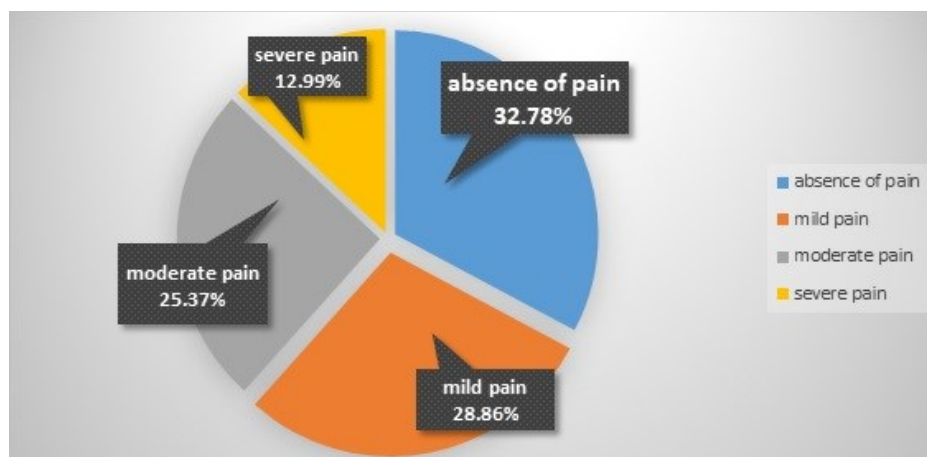


Fig. 1. Intensity of pain syndrome in the patients with AMC according to VAS.

However, pain syndrome was indicated by 93.1% of respondents in the group of patients with critical LRV stenosis (II group) and the structure of its intensity also changed.

Therefore, 54.5% of patients of group II characterized the pain syndrome as severe pain.

Hematuria was assessed taking into account the following parameters.

Duration: up to 2 years / over 2 years, micro- or macrohematuria, frequency (more than 2 times in 2 months/ < 2 times in 2 months).

The prevalence of hematuria in patients of the 3 groups constituted 18.2% in group I, 46.3% in group II, 12.4% in group III, respectively.

The structure of hematuria in the patients of 3 groups is presented in Fig. 3.

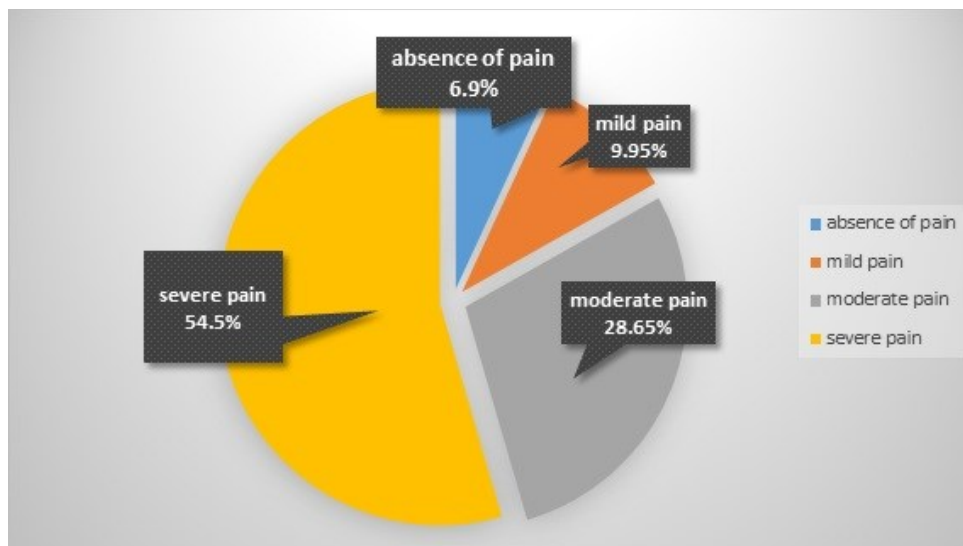


Fig. 2. Intensity of pain syndrome in the patients with critical LRV stenosis according to VAS

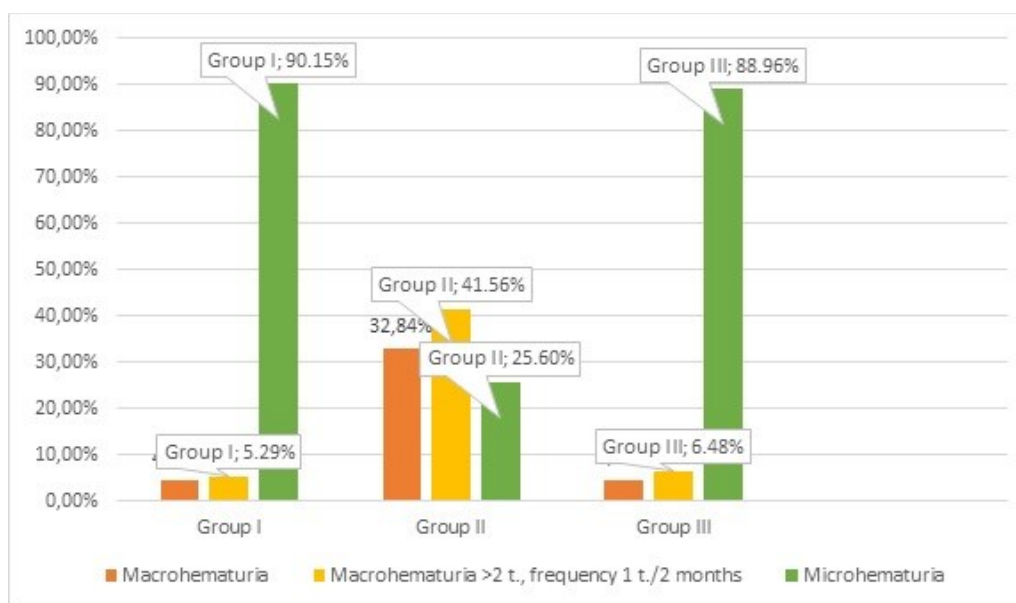


Fig. 3. Hematuria structure in the patients of 3 groups.

Apparently, macrohematuria lasting more than 2 years with a frequency of more than 2 times in 2 months (32.84%) prevailed in the patients with critical LRV stenosis (group II), whereas this indicator in the patients of groups I and III constituted 4.26% and 0.56%, respectively.

Mild anemia (degree I) was detected in 5 patients with macrohematuria (hemoglobin level was 90-110 g/l).

Proteinuria was diagnosed in 6 patients (6.8%), its combination with hematuria was observed in 2 of them.

Body mass index (BMI) was also determined for all patients.

The BMI distribution in the patients of the 3 groups is presented in Table 1.

Table 1
Distribution of BMI in the patients of 3 groups (M±m)

Parameters	Group I (n=116) M±m	Group II (n=54) M±m	Group III (n=78) M±m
BMI	23.8±1.12	16.2±1.08	24.7±2.38

Evidently, a significant decrease in BMI was observed in the patients with critical LRV stenosis

(16.2 ± 1.08 vs. 23.8 ± 1.12 and 24.7 ± 2.38 in the patients of groups I and III, respectively) which confirmed the hypothesis of a connection between a decrease in body weight and, accordingly, visceral fat in the patients with NS performing a cushioning role in case of an acute angle of superior mesenteric artery origin from the aorta.

As a result of the examination, a distinct correlation was established between the decrease in BMI and the pain syndrome intensity according to VAS in the patients of group II: Spearman's rank correlation coefficient was 0.948, $P < 0.0001$, CI 95% for R_s from -0.972 to -0.906 (Fig. 4)

Left sided varicocele was diagnosed in 48 (54.5%) examined men of groups I and II: stage I was diagnosed in 12 (25%) cases, stage II was observed in 31 (64.5%) cases, stage III was found in 5 (10.5%) patients (Fig. 5.) and in 12 (13.4%) patients of group III (control).

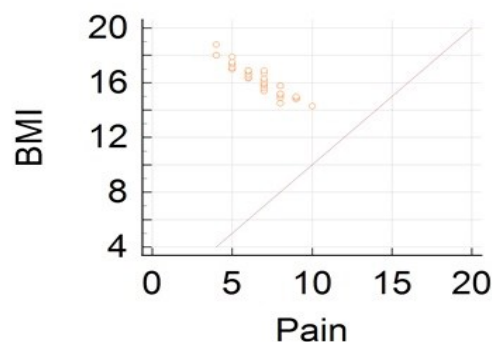


Fig. 4. Correlation dependence between pain syndrome severity according to VAS and BMI in the patients of group II (n=54).

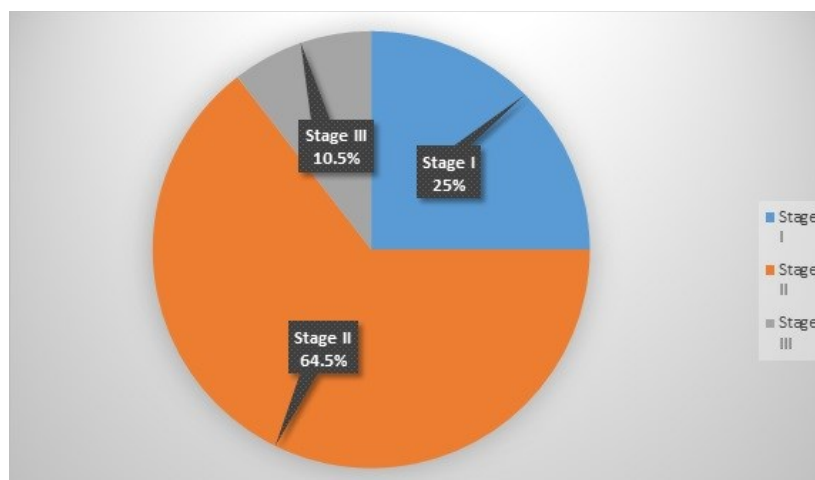


Fig. 5. Distribution of the patients with AMC (groups I and II) according to varicocele degree.

However, analysis of the varicocele frequency, taking into account its stage, found no connection between

the degree of varicocele and the presence of LRV critical stenosis (Fig. 6.)

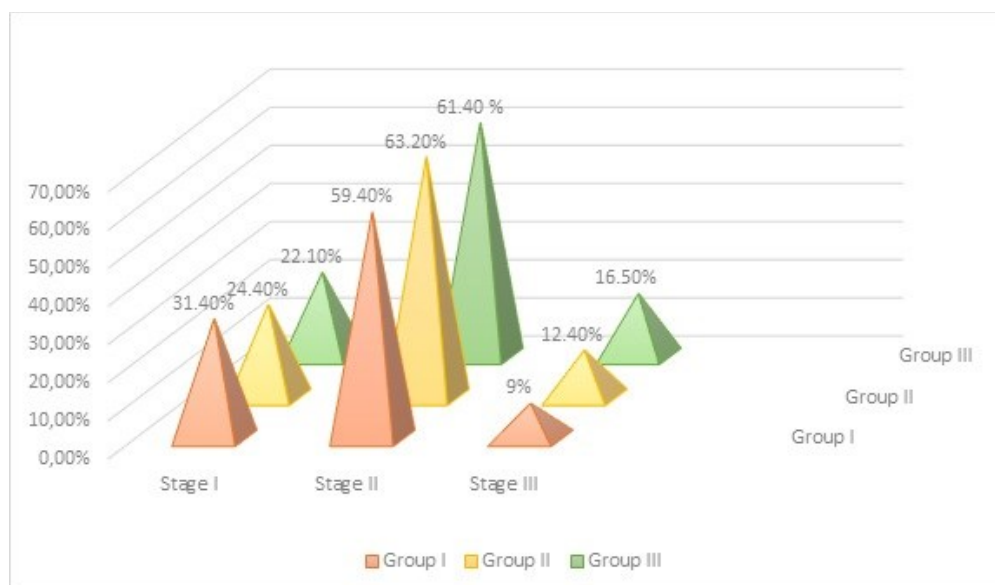


Fig. 6. Distribution of the patients of groups I, II and III according to varicocele degree.

Left sided pudendal varicose veins was found in 10.7% of women (n=7).

31.8% of men with AMC (n=28) indicated erectile dysfunction, 86.3% of them were diagnosed with

varicocele. Hemospermia was detected in 3.4% (n=3) of the group with critical LRV stenosis.

Dysmenorrhea was detected in 38 patients (58.5%) and dyspareunia was observed in 6 patients

(9.2%) with AMC, two of them indicated blood appearance during coitus.

11.3% of men (n=10) and 6.2% of women (n=4) in the group with AMC indicated pain in the epigastrium in combination with the impossibility of taking large amounts of food. All patients were previously consulted by a gastroenterologist and underwent gastroscopy. According to the results of the latter, no pathological changes in the mucous membrane of the stomach and duodenum, or minor changes were found: 4 patients were diagnosed with gastroduodenitis. The patients did not notice any improvement in the course of the treatment by gastroenterologists. Critical LRV stenosis with duodenal obstruction was diagnosed in all patients with these symptoms.

Thus, clinical symptoms indicating the presence of hypertension in the LRV system can be conditionally divided into specific and non-specific.

The specific ones include hemospermia, the appearance of blood during coitus, pain in the epigastrium combined with the impossibility of taking large amounts of food. Critical LRV stenosis was confirmed in all patients with the above-mentioned symptoms.

We considered pain syndrome in the left lumbar region and left half of the abdomen, hematuria, proteinuria, erectile dysfunction, dyspareunia, dysmenorrhea as non-specific symptoms, i.e. the symptoms that may indicate hypertension in LRV system with a high probability and are the basis for conducting color Doppler ultrasound of the reno-caval segment.

Discussion. Venous hypertension, as a result of LRV compression, is diagnosed in patients with varicocele from 30-53% to 80-90.8% of cases according to various data [4,5,8,10]. This explains the ineffectiveness of surgical interventions that do not eliminate hypertension in LRV.

Pelvic varicose veins are the consequence of hypertension in the LRV system in women. Its frequency has not been sufficiently studied yet and ranges from 5.4 to 80.0% according to various data [9].

The relevance and importance of this problem is emphasized by the fact that pelvic congestion syndrome is a pathology that occurs mainly in women of reproductive age. However, the data on its effect on the occurrence of idiopathic forms of infertility, carrying of a pregnancy, the course of childbirth, the occurrence and course of gynecological pathology is absent so far [4,6]. Pelvic varicose veins are known not only to accompany various gynecological diseases, but also to cause chronic pelvic pain (pelvic congestion syndrome) [7]. Dilatation of true pelvic veins has been considered an incidental diagnostic finding till present.

At a young age, asymptomatic forms of the disease are more often diagnosed. In such case, organic changes in the venous system of the true pelvis are detected only when additional research methods are used [5,12].

At the same time, approximately 10% of gynecological patients suffer from chronic pelvic pain [7]. For years, these female patients have been unsuccessfully examined and treated for chronic inflammatory processes of the appendages, genital endometriosis [7,10,12].

According to the Mayo Clinic data, one in five women seeks medical advice with pain syndrome on the background of pelvic varicose veins. Meanwhile, the

correct diagnosis is made only in 2% of cases, up to 40% of unsubstantiated hysterectomies are associated with undiagnosed pelvic congestion syndrome (Annual medical bulletin Mayo Clinic, 1999).

According to various data, the causes of pelvic congestion are NS in 74% of cases, May-Thurner syndrome in 17% of cases, a combination of these two causes in 9% of cases [9,10,14].

A violation of venous outflow from the left adrenal gland is also AMC consequence leading to fluctuations in blood pressure, the appearance of syncope and orthostatic intolerance [6].

Some patients also indicate distinct epigastric pain that worsens after eating, nausea, periodic vomiting, the inability to consume large amounts of food due to increased pain syndrome because of duodenal obstruction syndrome known also as Wilkie's Syndrome, or superior mesenteric artery syndrome [10,12].

Duodenal obstruction syndrome development is caused by the compression of the descending horizontal part of the duodenum by the upper mesenteric artery as a result of the acute angle of the origin of the latter, usually 9-16° [10, 14].

In addition to NS anatomical classification into anterior, posterior, and a combined one, AMC syndrome is classified according to clinical manifestations into typical (with renal manifestations) and atypical (with urological symptoms) variant [12].

A typical variant is characterized by macro- or microhematuria, orthostatic proteinuria with present or absent pain in the left half of the abdomen. An atypical variant of the course includes general weakness, pain in the left half of the abdomen and left lumbar region, dysmenorrhea, dyspareunia and left sided pudendal varicose veins in women, left sided varicocele in men, as well as orthostatic intolerance.

Some scientists consider that NS should be divided into three subtypes: with idiopathic hematuria, with orthostatic proteinuria, if urine protein levels are over 400 mg/dL, and with orthostatic intolerance, which significantly reduces the quality of life [10].

Such systemic clinical symptoms as headache, abdominal pain, general fatigue and tachycardia are also observed in the patients with orthostatic intolerance [10].

Although systemic hypertension is not one of NS clinical markers, some researchers describe the presence of renin-dependent hypertension in patients with this pathology [12].

Similarly, NS is also associated with various other clinical disorders such as IgA nephropathy, membranous nephropathy, idiopathic hypercalciuria, Henoch-Schönlein purpura, and familial Mediterranean fever [10].

A description of NS complete clinical picture is almost not found in the literature due to the symptoms non-specificity and the varying intensity of clinical manifestations. However, according to Basile A., clinical symptoms severity clearly correlates with the hypertension level in LRV and with the degree of its compression [1].

Conclusions:

1. NS is characterized by distinct polymorphism of clinical manifestations and a variety of clinical forms.
2. The main hypertension markers in the LRV system are pain syndrome and hematuria.

3. Color Doppler ultrasound of the reno-caval segment is recommended to the patients with left sided varicocele / left sided pudendal varicose veins, hematuria, proteinuria, with a diagnosis of pelvic congestion; with dyspareunia, algodysmenorrhea, the appearance of blood during coitus / hemospermia, with chronic epigastric pain of unknown etiology, with anorexia, idiopathic infertility, in order to exclude pathology of the reno-caval segment.

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КЛІНІЧНІ МАРКЕРИ ФЛЕБОГІПЕРТЕНЗІЇ В СИСТЕМІ ЛІВОЇ НИРКОВОЇ ВЕНИ

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Резюме. Флебогіпертензія в системі лівої ниркової вени (ЛНВ) зазвичай є наслідком аорто-мезентеріальної компресії (т.зв. синдрому «лускунчика») і призводить не лише до явищ венозного застою лівої нирки, але і до розвитку тазового флебостазу.

Частота і важкість симптомів синдрому «лускунчика» (СЛ) варіює від асимптомної мікрогематурії до важких форм тазової венозної конгестії. Одні пацієнти вказують на виражену та постійну клінічну симптоматику, інші, особливо діти, відзначають асимптомний перебіг.

Мета: вивчити поширеність та ступені прояву клінічних симптомів флебогіпертензії в системі ЛНВ.

Матеріали і методи: у дослідженні брали участь 248 пацієнтів (156 чоловіків і 92 жінки, середній вік 28,24±2,74) з підозрою на СЛ, що проходили обстеження та лікування з 1999 по 2022 рр. Всі пацієнти були опитані щодо специфічних скарг, зокрема больового синдрому (анкетування за шкалою ВАШ), проведено лабораторну діагностику (загальний аналіз крові, загальний аналіз сечі, аналіз сечі за Нечипоренко), ультразвукову кольорову доплерографію (УЗДГ) рено-кавального сегменту, нирок, малого тазу та, за потреби, КТ – ангиографію.

Результати. Відповідно до проведеного анкетування пацієнтів виявлено, що у третини пацієнтів з АМК без критичного стенозу ЛНВ больовий синдром відсутній, а при наявності – переважав слабкий та помірний біль. У групі пацієнтів із критичним стенозом ЛНВ (II група) на больовий синдром вказували 93,1% опитаних. Поширеність гематурії у пацієнтів 3-

х груп становила: у I групі – 18, 2%, у II групі – 46,3%, у III групі – 12,4% відповідно.

Висновки. СЛ характеризується вираженим поліморфізмом клінічних проявів та різноманітністю клінічних форм. Основними маркерами флебогіпертензії в системі ЛНВ є больовий синдром та гематурія.

Ключові слова: синдром «лускунчика», аорто–мезентеріальна компресія, критичний стеноз лівої ниркової вени, тазовий флебостаз.

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