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Effect of undifferentiated connective tissue dysplasia on clinical course of varicose disease and thrombophlebitis of varicose veins after crossectomy

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Abstract: Objective: to analyze the features of clinical course of lower limb varicose vein disease and acute thrombophlebitis of varicose veins for the patients with undifferentiated connective tissue dysplasia (UCTD) after crossectomy.
Materials and Methods. The prospective clinical cohort study involved 132 female patients with varicose disease who underwent crossectomy, of which 67 patients with dysplasia were included into the main group, whereas patients without dysplasia were included into the control group. Examination of patients and ultrasound scanning of leg veins were conducted in 3, 6, 12, and 36 months. The Cox regression analysis was used to assess the effect of dysplasia on the risk of developing thrombophlebitis of varicose veins.
Results. The progress of varicose disease clinical manifestations of after crossectomy was detected in 57 (85.1%) female patients with dysplasia and in 14 (21.5%) without it (p=0.002), which resulted in phlebectomy. The recurrent thrombophlebitis of varicose veins was found in 22 (32.8%) female patients with dysplasia vs. 5 (7.7%) without it (p=0.002). Cox regression model Exp (B), which characterizes the predicted change of risks for dysplasia, was 4.216 (95% CI 1.595-11.147).
Conclusion. The clinical course of varicose disease in patients with UCTD is characterized by the progression of clinical manifestations of chronic venous insufficiency of a lower limb. UCTD results in over 4.2-fold risk of developing the recurrent thrombophlebitis of varicose veins after crossectomy.

Keywords: undifferentiated connective tissue dysplasia, varicose disease, recurrence of acute thrombophlebitis of varicose veins.

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Introduction

Lower limb varicose vein disease (LLVVD) is detected in 20-25% of the working-age population in economically developed countries [1]. Acute thrombophlebitis of varicose veins (ATVV) develops in 4-62% of patients with LLVVD [2, 3]. In 7.3-44.0% of patients with ATVV, deep vein thrombosis is detected [4, 5]. Clinical manifestations of pulmonary embolism are distinguished in 4.7-13.3% of patients with ATVV [6-9]. The ascending forms of ATVV of the great saphenous vein (GSV) present the greatest danger [10–12]. If there is a high risk of spreading thrombotic masses from the GSV into the deep veins of the limb, it is necessary to perform a crossectomy (Troyanov-Trendelenburg operation) [2]. Currently, there are no recommendations regarding the timing of the second stage of surgical treatment – phlebectomy [2, 13], and recurrence of ATVV develops in 13.4% of patients [14].

Undifferentiated connective tissue dysplasia (UCTD), caused by a mutation in the genes responsible for the synthesis and spatial orientation of collagen, leads to disruption in the development of connective tissue, and may affect the clinical course of LLVVD and ATVV [15-18]. UCTD has phenotypic markers that are detected in over 97.0% of patients with venous thrombosis [19]. At present, the effect of UCTD on the features of the clinical course of LLVVD and ATVV after crossectomy has not yet been studied.

Objective – to analyze the features of the clinical course of varicose disease of the lower limbs and acute thrombophlebitis of varicose veins in patients with UCTD after crossectomy.

Materials and Methods

Our prospective clinical cohort study included 132 patients with LLVVD who underwent crossectomy between 2012 to 2017 due to the development of ATVV of GSV trunk and a high risk of thrombus transfer to the femoral vein. Age ranged 35-49 years (mean age of 42.5±4.4 years). The duration of LLVVD was 4-9 years (mean: 7.4±2.1 years). The duration of ATVV before admission to the hospital was 1-5 days (mean: 4.1±1.2 days).

We used the international classification of chronic diseases of the leg veins – CEAP (C - clinic, E - etiology, A - anatomy, P - pathophysiology).

Criteria for inclusion in the study: female gender; age from 35 to 49 years; class of chronic venous insufficiency

sensu CEAP: C2, C3; the proximal boundary of the thrombus located at the level of the saphenofemoral fistula; signed informed consent.

Two cohorts were identified: the main group of 67 female patients with UCTD and the control group of 65 women without it. The studied groups of patients were comparable in terms of gender, age, comorbidities, duration of LLVVD and ATVV, and class of chronic venous insufficiency.

Criteria for exclusion from the study: post-thrombotic syndrome, history of venous surgery, deep and perforator vein thrombosis, cardiovascular insufficiency, oncological diseases, hormonal drugs, diuretics, anticoagulants, nonsteroidal anti-inflammatory drugs, dyslipidemia, thrombophilia, impaired renal function, decompensation of metabolic processes in diabetes mellitus, hormonal status disorders as a result of thyroid diseases, pregnancy, breastfeeding, allergies.

Phenotypic markers were studied to identify UCTD. Eighty-two phenotypic signs of UCTD were assessed: asthenic, craniocephalic, ocular, vertebrogenic, cosmetic, and cardiovascular signs. We studied dolichostenomelia, joint hypermobility, arachnodactyly, deformity of the legs, feet, chest, anomalies in the development of nails, hair, teeth, and auricles. The detection of five or more markers was considered confirmation of UCTD presence [20].

Patients were observed prospectively, the examination was carried out according to the standard protocol. The criteria for evaluating the study were clinical and ultrasound signs of LLVVD and recurrence of ATVV. Identification of the progression of LLVVD, as well as the development of ATVV relapse, was carried out by collecting an anamnesis, complaints, and taking into account the data of the limb examination. Clinical signs of LLVVD progression and relapse of ATVV were confirmed by the venous duplex scan. Examination, as well as ultrasound scanning of the veins, were performed after 3, 6, 12, and 36 months. In patients with recurrent ATVV, the examination was conducted at the onset of the event.

For 10 days after surgery, all patients received low molecular weight heparin. Vitamin K antagonists were added on the postoperative day 5 for six weeks at a dosage until the therapeutic values of the international normalized ratio (2.0-3.0) were reached. Elastic compression in the hospital was prescribed around the clock; after discharge, it was recommended to use compression products during the daytime hours. The protocol was approved by the Ethics Committee at V.I. Razumovsky State Medical University of Saratov.

The distribution of data in all groups was close to normal. Descriptive statistics methods were used with the determination of mean values and standard deviation. Means were compared using Student's t-test. Relative values were compared by the Fisher method, $\chi 2$, random variables were compared by the Pearson conjugacy method. The effect of independent variable factors on the development of ATVV recurrence was analyzed via constructing a Cox regression model taking into account the Wald criterion (IBM SPSS Statistica 26.0). Differences were considered significant at $p<0.05$.

Results

During 36 months of follow-up, 57 (85.1%) patients with UCTD exhibited progression of clinical manifestations of LLVVD, which required phlebectomy. Venous duplex scan revealed a significant increase in the number of incompetent perforator veins from 4.7±0.6 to 6.6±0.5 (p=0.014), an increase in the average diameter of incompetent perforator veins from 3.3±0.4 to 4.6±0.2 (p=0.012), and also an increase in the GSV diameter from 8.7±0.6 to 10.5±0.5 (p=0.021).

In 51 (78.5%) patients without UCTD, within 36 months of follow-up after crossectomy, regression of the clinical manifestations of varicose veins was noted. Elimination of vertical venous reflux as a result of crossectomy contributed to a significant reduction in the diameter of the GSV from 9.0±0.8 mm to 6.4±0.3 mm (p=0.001), which led to the restoration of its valvular apparatus functional viability. Indications for phlebectomy after crossectomy were identified only in 14 (21.5%) patients without UCTD (p=0.003). Crossectomy in 51 (78.5%) patients without UCTD became the final procedure of surgical treatment, and the second stage was not required.

ATVV recurrence during 36 months of follow-up was detected in 27 (20.5%) patients involved in the study, including 22 (32.8%) with UCTD and 5 (7.7%) without it (p=0.002). Pearson's correlation coefficient (r) was 1.0, indicating a strong association of UCTD with recurrent ATVV.

In eight patients with UCTD and one without it, recurrent ATVV was complicated by femoral vein thrombosis, which caused pulmonary embolism in two patients with UCTD (p=0.001). It should be emphasized that out of 22 patients with UCTD, 11 (50.0%) patients developed a relapse of the disease already 1.5–2 months after crossectomy.

Cox regression analysis was performed to assess the effect of UCTD on the risk of recurrent ATVV. The presence of UCTD, the duration of LLVVD, and the class of chronic venous insufficiency were examined as predictors of recurrent ATVV risk.

Employed statistical software involved the construction of a model in two blocks using the direct inclusion method. *Table 1* presents the model results for the first block, confirming that some of the studied independent variables were significantly associated with the development of ATVV recurrence.

The coefficient (B) of the regression equation for UCTD amounted to 1.439 (Table 2). To assess the significance of the regression equation coefficients, the Wald criterion was used, which for the UCTD was 8.433 (p=0.004) (Table 2), which implied a significant contribution of UCTD to the predictive value of the developed model. The significance of Wald criterion for other studied predictors turned out to be more than 0.05 (*Table 2*), which indicated no statistically significant contribution of the studied predictors to the predictive value of created Cox model. The parameter Exp (B), characterizing the predicted change in risks for UCTD, was 4.216 (95% CI: 1.595-11.147) (*Table 2*).

Hence, as a result of Cox regression analysis, we discovered that patients with UCTD after crossectomy had a 4.2-fold greater increased risk of ATVV recurrence during 36 months of follow-up (*Table 2*).

Table 1. Cox regression model scores

–2 times the log of the likelihood	Overall score			Change from previous step			Change from previous block		
	χ^2	df	*P*	χ^2	df	*P*	χ^2	df	*P*
251.372	11.121	3	0.011	11.889	3	0.008	11.889	3	0.008

df – degrees of freedom.

Table 2. Cox regression model variables

Predictors of ATVV relapse	*B*	SE	Wald criterion	df	*P*	Exp (*B*)	95% CI for Exp (B)
UCTD	1.439	0.496	8.433	1	0.004	4.216	1.595-11.147
Duration of LLVVD (years)	–0.011	0.121	0.008	1	0.930	0.989	0.780-1.254
Class of chronic venous insufficiency of the limb	–0.451	0.425	1.123	1	0.289	0.637	0.277-1.465

B – regression coefficient, SE – standard error, df – degrees of freedom, Exp (*B*) – predicted risk change, CI – confidence interval.

Discussion

Currently, there are no unified approaches to the treatment and rehabilitation of patients with LLVVD with UCTD after crossectomy [18; 19], and there is no single tactic for the prevention of repeated episodes of ATVV [2].

As a result of a prospective clinical cohort study, we established that the clinical course of LLVVD against the background of UCTD was characterized by a tendency to progression of chronic venous insufficiency and a recurrent course of ATVV.

In women with UCTD, during 36 weeks after crossectomy, relapse of ATVV, along with thromboembolic complications, develop significantly more often than in patients without UCTD. Moreover, 50% of ATVV recurrences in patients with UCTD develop within the first two months after crossectomy.

Cox regression analysis demonstrated that during 36 weeks after crossectomy, the presence of UCTD increased the risk of recurrent ATVV by over 4.2 times. In this regard, in all patients with ATVV, it is advisable to examine their phenotypic status in order to reveal UCTD, if present. Patients with UCTD should undergo venous duplex scan of the lower limbs 1-2 months after crossectomy, immediately after the elimination of acute inflammation to decide whether the second stage of surgical treatment is appropriate.

In patients without UCTD, it is appropriate to make a decision regarding the indications for performing the second stage of surgical treatment (phlebectomy) no earlier than 6-8 months after crossectomy, since in 78.5% of cases, the elimination of vertical pathological venous reflux yields a significant reduction in the diameter of GSV and perforator veins, accompanied by the functional viability restoration of their valvular apparatus. Hence, phlebectomy is not required.

Conclusion

The clinical course of varicose veins in patients with UCTD is characterized by the progression of clinical manifestations of chronic venous insufficiency of the limb. UCTD yields more than 4.2-fold recurrence risk of varicose vein thrombophlebitis after crossectomy.

Conflict of interest: None declared.

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