

Contact allergy in patients with chronic venous leg ulcers – possible role of chronic venous insufficiency

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The purpose of this study was to evaluate frequency of contact allergy in patients with chronic venous leg ulcers (CVLU) and to estimate possible relationships between allergic contact reactions and characteristics of both chronic venous insufficiency (CVI) and CVLU. We performed patch tests with the European standard series, antibiotics, glucocorticosteroids and ointment vehicles in 50 patients with CVLU. Patients underwent detailed CVI diagnostics using colour flow duplex ultrasound examination, ankle brachial pressure index determination and leg ulcers area measurement. Positive patch tests results were found in 80% and polyvalent allergy in 56% of patients. Statistically significant correlations were recorded between CVI and CVLU duration, CVLU duration and CVLU area and between CVI duration and polyvalent allergy frequency. Statistically significant differences were observed between coexistence of superficial and deep system insufficiency and CVLU duration, characteristics of contact allergic reactions and CVI duration, frequency of allergic contact reaction and presence or absence of long saphenous vein insufficiency, incidences of vein thrombosis and characteristics of contact allergic reactions as well as between characteristics of contact allergic reactions and both CVLU duration and area. Complex pathophysiological processes, including inflammatory reactions, in course of CVI may influence development of allergic contact reaction in CVLU patients.

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Chronic venous leg ulcers (CVLU) developing in the course of chronic venous insufficiency (CVI) affect 1–2% of European population (1, 2). Complex pathophysiological processes, which take place in the course of CVI cause the development of characteristic clinical signs. Disturbances in the low extremity venous blood flow lead to venous hypertension (1–9). Allergic contact dermatitis coexisting with CVLU creates a difficult clinical problem from both diagnostic and therapeutic standpoint. It affects up to 60–85% of patients with CVLU (10–18). The most common contact allergens found in the CVLU patients are balsam of Peru, fragrances mix, neomycin, gentamycin, glucocorticosteroids and lanolin (10, 12–15, 17, 19, 20). Differences between data on frequency of contact hypersensitivity to several allergens published by various authors are probably due to local topical treatment standards. Allergic contact dermatitis in patients with CVLU is thought to be a wound-healing impairing factor (18, 20, 21). Moreover, delayed type of hypersensitivity in this

patient group can develop without typical clinical signs. On the other hand, it is considered that the degree of CVI may influence not only clinical picture of CVLU but also the coexisting contact dermatitis. The aim of our study was to analyse the frequency of contact allergy in patients with CVLU and to estimate possible correlations between allergic contact reactions and characteristics of both CVI and CVLU.

Materials and Methods

50 patients suffering from CVLU were enrolled in the study. 38 patients were female (76%) and 12 patients were male (24%). The mean age of patients was 66.2 years (range from 48 to 81 years). Duration of CVI ranged from 5 to 45 years (mean 22.2 years) and CVLU ranged from 6 month to 35 years (mean 7.2 years). All patients underwent detailed clinical examination concerning contact allergy, CVI and CVLU including duration of the disease, predisposing factors and

the incidence of vein thrombosis in the past. The data concerning characteristics of vein thrombosis were collected on the basis of patients medical history. For further analysis, the general term vein thrombosis with no differentiation of deep and superficial vein system is used. Patients with hypertension in arterial vessels of leg system were excluded from the study. Only patients with no current or previous dermatological problems of ulcer surrounding skin were enrolled in the study in order to avoid false positive patch tests results due to activation of additional inflammatory processes. Moreover, patients with diabetes mellitus were excluded from the study. Clinical diagnosis of CVLU and CVI was proved with the use of clinical part of CEAP (clinical, aetiological, anatomic and pathophysiologic) classification, colour duplex ultrasound examination and ABPI (ankle brachial pressure index) determination. Measurement of CVLU area was based on the planimetry method. In all patients, patch tests were performed.

Patch testing

Patch tests were performed with the European standard series (TROLAB, Hermal, Germany) supplemented with the glucocorticosteroids (tixocortol pivalate, budesonid and betamethasone-17-valerate) and gentamycin (Chemotechnique Diagnostics, Vellinge, Sweden) and ointment vehicles, lanolin and eucerin (Hospital Pharmacy, Poznan, Poland) (Table 1). For patch testing, Finn Chambers[®] on Scanpor (Epitest, Tuusula, Finland) were used. Results were recorded at 48-hr and 72-hr time points. For topical glucocorticosteroids, the verifying readings were performed at the day 7. According to ICDRG (International Contact Dermatitis Research Group), reactions evaluated as ++ and +++ pluses were considered as positive and reaction evaluated as + plus was considered as doubtful. For further analysis only ++ and +++ pluses reactions were regarded.

Ultrasound examination

All patients underwent ultrasound examination of the low extremities venous system. Duplex imaging was performed with the use of Aloka SSD-680EX ultrasound 7.5 MHz probe. Patients were examined (standing position) using manual calf compression and Valsalva manoeuvre. Venous reflux was defined as the presence of reverse flow lasting longer than 1 s (2, 22, 23).

Table 1. List of allergens tested in CVLU patients with the number and percentage of positive reactions

Allergen	Concentration (%)	Number and percentage of positive reactions
Potassium dichromate	0.5	3 (6%)
Neomycin sulphate	20	10 (20%)
Thiuram mix	1	0
Paraphenylenediamine	1	2 (4%)
Cobalt chloride	1	3 (6%)
Benzocaine	5	2 (4%)
Formaldehyde aq.	1	0
Colophony	20	3 (6%)
Clioquinol	5	5 (10%)
Balsam of Peru	25	19 (38%)
N-Isopropyl-N-phenyl-4-phenylenediamine	0.1	1 (2%)
Wool alcohols	30	15 (30%)
Merapto mix	2	4 (8%)
Epoxy resin	1	1 (2%)
Paraben mix	16	10 (20%)
4- <i>t</i> -Butylphenol	1	3 (6%)
formaldehyde resin		
Fragrance mix	8	10 (20%)
Quaternium-15	1	0
Nickel sulphate	5	4 (8%)
Kathon/Euxyl/Grotan	0.01	0
Mercaptobenzothiazole	2	1 (2%)
Sesquiterpenelactone mix	0.1	0
Primin	0.01	1 (2%)
Tixocortol pivalate	1	8 (16%)
Budesonide	0.01	10 (20%)
Betamethasone-17-valerate	1	2 (4%)
Gentamycin sulphate	20	2 (4%)
Lanolin	Pure	1 (2%)
Eucerin	Pure	1 (2%)

ABPI determination

ABPI is defined as quotient of systolic pressure measured on the height of ankle joint (dorsal foot artery, posterior tibial artery) and arm (brachial artery). Patients were examined in laying position. Patients with the evidence of arterial disease ($ABPI \leq 0.8$) were excluded from the study. ABPI was also used to demonstrate the hypertension in the venous system (22–24).

CVLU area measurement

CVLU area measurement was performed with the use of planimetry method. Gird-based technique as the initial method was used to determine ulcer area. Then the polar planimetry was used for the detailed area measurements. This classical planimetry method is widely used in cartography, and its measurement error does not exceed 0.2% of the analysed area (25). In case of multiple CVLU in 1 patient, the sum of measured areas was processed for further analysis.

Data analysis

Results were analysed by Mann–Whitney test, Spearman correlation, Fisher exact test and Fisher–Freeman–Halton test.

Results

Positive patch tests results were obtained in 40 patients (80%). In 28 patients (56%), polyvalent allergy and in 12 patients monovalent allergy were found. Frequency of multiply positive reactions (polyvalent allergy, that is positive reaction to 2 or more unrelated allergens) is detailed in Table 2. Positive patch test results in our group of patients are characterized in Table 1.

Ultrasound examination revealed in 32 patients (64%) isolated superficial vein system insufficiency. In 4 patients (8%), CVI symptoms were due to deep vein system insufficiency. 14 patients (28%) have shown coexisting insufficiency in both venous systems. ABPI results ranged from 1.1 to 1.5. CVLU area ranged from 1.3 cm² to 391 cm² (mean 51.2 cm²).

On the basis of clinical medical history, following data concerning vein thrombosis were obtained: in 26 patients (52%), there was at least 1 episode of vein thrombosis in the past. In 24 patients (48%), there was no proof of such CVI complication. In the group of patients with positive medical history, 11 patients (22%) had 1 episode and 15 patients (30%) had multiple episodes (from 2 to 10) of vein thrombosis.

CVI and CVLU characteristics

Considering CVI and CVLU characteristics, correlations between CVI and CVLU duration (Spearman rank correlation coefficient $r = 0.5238$, $P < 0.001$) and between CVLU duration and CVLU area were evaluated (Spearman rank correlation coefficient $r = 0.4691$, $P < 0.001$). Comparing coexistence of superficial and deep system insufficiency and CVLU duration, non-parametric Mann–Whitney test was used. The obtained difference was statistically significant ($P < 0.05$). The CVLU

Table 2. Frequency of polyvalent allergy (sensitization to 2 or more unrelated allergens) in the examined group of patients

Number of positive reactions in 1 patient	Frequency (%)
2	32.1
3	17.9
4	21.4
5	10.7
6	7.1
7	3.6
9	7.1

duration in the case of coexistence of both superficial and deep system insufficiency was longer (median was 9.0, and lower and upper quartiles were 5.0 and 15.0) than in the case when insufficiency affecting only 1 venous system was recorded (median was 4.5, and lower and upper quartiles were 2.0 and 10.0). Moreover, statistically significant difference was found between patient group with coexistence of superficial and deep system insufficiency and medical history of multiple incidences of vein thrombosis (60% of cases, $P < 0.01$) in comparison with the group of patients with single incidence (27.27%) and with no vein thrombosis incidences in the past (8.33%) (Fisher–Freeman–Halton test).

CVI and characteristics of contact allergic reactions

Comparison between allergic contact reactions characteristics and CVI duration was performed with non-parametric Mann–Whitney test (Table 3). The obtained differences were statistically significant and as follows: contact allergic reaction ($P < 0.05$), polyvalent contact allergic reaction ($P < 0.01$), balsam of Peru ($P < 0.05$), wool alcohols ($P < 0.01$) and fragrance mix ($P < 0.05$). Relationship between CVI duration and polyvalent allergic contact reaction in terms of correlation is presented in Fig. 1 (Spearman rank correlation coefficient $r = 0.3730$, $P < 0.01$). The association between presence of long saphenous vein insufficiency and allergic contact reaction frequency was recorded (Fisher exact test). In the group of patients with the presence of long saphenous vein insufficiency,

Table 3. Comparison between allergic contact reaction characteristics and CVI duration

	CVI duration (years) – median and lower and upper quartiles
Allergic contact reaction	
Positive patch test results	25.0 (15.0–30.0)
Negative patch test results	12.5 (10.0–20.0)
Polyvalent allergic contact reaction	
Multiply positive reactions (present)	25.0 (20.0–31.0)
Multiply positive reactions (absent)	15.0 (10.0–20.0)
Balsam of Peru	
Positive patch test results	25.0 (20.0–32.0)
Negative patch test results	20.0 (10.0–30.0)
Wool alcohols	
Positive patch test results	30.0 (20.0–35.0)
Negative patch tests results	20.0 (10.0–25.0)
Fragrance mix	
Positive patch test results	31.00 (25.0–37.0)
Negative patch test results	20.0 (12.5–27.5)

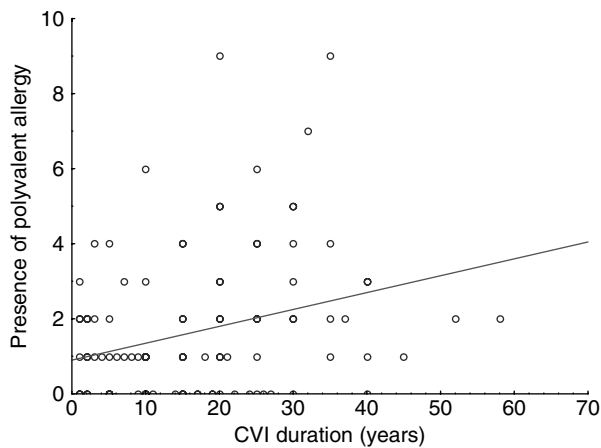


Fig. 1. Correlation between CVI duration and polyvalent allergy.

allergic contact reaction frequency was higher (92.5% of cases, $n = 37$, $P < 0.05$) in comparison with the group of patients with no long saphenous vein insufficiency (60% of cases, $n = 6$). Interesting observations were made considering relationships between incidences of vein thrombosis and allergic contact reaction characteristics (Fisher–Freeman–Halton test). Statistically significant differences were found between groups of multiple incidences of vein thrombosis and cases of presence (37.5% of cases) or absence (0%) of allergic contact reaction ($P < 0.01$) as well as cases of presence (43%) or absence (14%) of polyvalent allergic contact reaction ($P < 0.05$). Moreover, statistically significant difference was observed between groups of no incidences (20% of cases) and multiple incidences (53%) of vein thrombosis and wool alcohols positive reactions ($P < 0.05$).

CVLU and characteristics of contact allergic reactions

Comparison of CVLU duration and allergic contact reaction frequency revealed no statistically significant differences (non-parametric Mann–Whitney test) (Table 4). Other results showed that in the group of patients with polyvalent allergy, the mean CVLU duration was significantly longer ($P < 0.05$). Moreover, the duration of CVLU was significantly longer in patients with wool alcohols positive reactions ($P < 0.05$). The CVLU areas were significantly smaller in patients with neomycin sulphate-positive reactions ($P < 0.01$) and tixocortol pivalate positive reactions ($P < 0.05$).

Discussion

Allergic contact dermatitis which complicates the course of CVLU may present itself as a difficult

Table 4. Comparison between allergic contact reaction characteristics and CVLU duration and area

	Mean CVLU duration (years) $\pm$ SD
Allergic contact reaction	
Positive patch test results	7.6 $\pm$ 6.9
Negative patch test results	5.5 $\pm$ 6.4
Polyvalent allergic contact reaction	
Multiply positive reactions (present)	8.7 $\pm$ 7.3
Multiply positive reactions (absent)	5.2 $\pm$ 5.7
Wool alcohols	
Positive patch test results	10.7 $\pm$ 8.5
Negative patch test results	5.7 $\pm$ 5.5
Neomycin sulfate	
Positive patch test results	5.36 $\pm$ 4.6
Negative patch tests results	62.7 $\pm$ 96.3
Tixocortol pivalate	
Positive patch test results	17.4 $\pm$ 36.9
Negative patch test results	57.6 $\pm$ 94.7

to diagnose disease which in many cases is due to non-characteristic clinical picture. Moreover, the chronicity of this problem, wide spectrum of possible responsible therapeutic products and occlusive dressings create promoting factors for both development of delayed type of hypersensitivity and continuous changes in the allergens pattern. Another very important problem presented in our study is the prevalence of polyvalent allergic reactions in patients with CVLU.

Our results confirm the results obtained by other authors showing the high prevalence of allergic contact dermatitis and the most common contact allergens, mainly concerning balsam of Peru, fragrances mix and parabens (11, 12, 15, 16, 18–20). Allergic contact reaction caused by antibiotics in most of the cases was due to neomycin, and we found less cross-reactions between neomycin and gentamycin (4% of patients), which is 1 of the lowest results comparing with the literature data (2–20%) (19, 26). Our study also demonstrates important prevalence of contact allergy to glucocorticosteroids in CVLU patients. Very interesting observation concerned ointment vehicle patch tests results. Lanolin contact allergy is still a widely discussed problem in the literature (16, 18–20, 27–29). In our study, we have not observed high incidence of contact allergy due to sensitization to lanolin or eucerin. Moreover, only in 1 case, we obtained the coincidence of pure lanolin and wool alcohols positive patch tests results. In fact, the problem of lanolin allergy still remains unclear. Wolf described 4 lanolin paradoxes (29). The first one characterizes lanolin as a component of topical medications responsible for contact sensitization of patients as a generally safe agent for majority of the world population. The 2nd one refers to

CVLU patients, indicating that lanolin cosmetic products can be applied on the normal skin even by patients with allergic contact dermatitis to lanolin in topical medications used for treatment purposes (27–29). Moreover, false-negative patch test reactions can be seen in lanolin-sensitive individuals (29). The explanation for this 3rd lanolin paradox can be that chemically lanolin is the complex mixture, and we do not exactly know the specific lanolin allergens (29, 30). It is even more complicated in the case of false-positive and false-negative results due to difficulties with reliability of lanolin patch test method (the fourth lanolin paradox) (29). There is no doubt about the need of careful and detailed allergological diagnostics in case of patients with chronic inflammatory skin diseases, which are the predisposing factors for developing allergic contact dermatitis (16, 18–20, 28). Results obtained in this study may confirm the presence of lanolin paradox in patients with CVLU. Therefore, the question concerning clinical relevance of lanolin and wool alcohols contact allergy and the role of wool alcohols as a screening markers for lanolin contact allergy seem to be still unclear and further investigations are necessary.

The most important results of our study concern the possible role of CVI and CVLU in the generation of conditions promoting the development of allergic contact dermatitis in patients suffering from CVLU. Relationships between allergic contact reactions and mainly CVI and less CVLU characteristics strongly indicate the presence of such CVI pathophysiological role.

Our findings can be classified a real novum in the way of approaching CVI and allergic contact dermatitis in patients with CVLU problems. In the search available literature we have not found similar analyses concerning relationship between CVI characteristics and contact allergy in patients with CVLU. Paramsothy et al. (31) found that the number of positive reactions increased almost linearly with ulcer duration. Our study does not confirm this observation; however, we found a linear relationship between CVI duration and polyvalent allergy frequency as well as statistically significant difference between the mean CVLU duration in patients groups with the presence or absence of polyvalent allergy.

However, there are some, not completely recognized mechanisms, suggesting possibility that CVI disturbances may influence the development or progression of allergic contact dermatitis. Gallenkemper et al. (10) found almost the same sensitization rate in the 2nd and 3rd degree of CVI according to Widmer classification, pointing out that sensitization starts early in CVI.

These data confirm those obtained by Bahmer (32), who in histopathological examination of stasis dermatitis biopsies observed accumulation of activated HLA-DR cells. Moreover, the number of inflammatory cells is also increased in comparison with the normal skin (33–35). Ya-Qi et al. (36) performed the histochemistry and immunohistochemistry examinations concerning dendritic cells in patients with CVLU. Signorelli et al. (37) in the venous hypertension conditions found the increased levels of TNF- α , IL-1 β and IL-6 in patient monocyte cultures. Authors conclude that functional activation of monocyte-macrophages is related to venous stasis as a consequence of venous hypertension. Both IL-1 and IL-6 are known as the 1 of the most powerful activators of immune system. They also stimulate the IL-2 T lymphocyte secretion, indirectly activating proliferation and differentiation of T lymphocytes. Moreover, IL-1 plays an important role in the Langerhans' cells antigen presentation.

As presented above, in the course of CVI, there is an accumulation of the complex pathophysiological processes, located both in the tissues and vessels, which in some cases seem to work as the contradicting factors, but also may promote the development of allergic contact dermatitis in CVLU patients. We plan to perform further and specific investigation of allergic contact dermatitis phenomenon, which should contribute to the better understanding of CVI role in the developing both CVLU and its common complication – allergic contact dermatitis.

In summary, on the basis of our clinical results, we would like to emphasize that the complex immunological mechanisms activated in the course of CVI, which are due to the venous hypertension, may be responsible not only for the development and character of CVLU but also for the promotion of allergic contact reaction mechanisms. Moreover, we suggest that all CVLU patients should undergo allergic diagnostic procedures which would contribute to the morbidity reduction.

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