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ORIGINAL ARTICLE

Vascular acrosyndromes in young adult population. Definition of clinical symptoms and connections to joint hypermobility

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Abstract

Objectives Clinical recognition of vascular acrosyndromes is often challenging. The term Raynaud's phenomenon (RP) is commonly overused to describe any form of cold-related disorder. This study aims to formally evaluate peripheral vascular symptoms affecting the population, aged ≤ 40 years, and identify any correlations to joint hypermobility (JH).

Patients and methods Fifty patients (31 males, 19 females) with vasomotor symptoms enrolled in this five-year prospective observational study. Clinical examination by a rheumatologist and a vascular surgeon was performed along with cardiology, echocardiographic and Doppler evaluation. Patients underwent blood cell count, biochemistry, thyroid and selectively immunologic testing. Twenty-four (48%) of them performed nailfold capillaroscopy. The SPSS for Windows, v.17.0, Chicago, USA, was used for the statistical analyses.

Results Twenty-eight patients (56%) presented with erythromelalgia (EM), 6 (12%) with acrocyanosis (AC) and 9 (18%) as a combination of the above disorder. RP diagnosed in five (10%) while two patients (4%) presented as a mix of EM-RP. There was no correlation with abnormal laboratory tests. Increased incidence of JH was found in EM and AC patients. Among those who were tested with nailfold capillaroscopy, 75% had abnormalities ranged from mild to autoimmune-like diseases.

Conclusions Erythromelalgia is the commonest functional vasculopathy in young population followed by acrocyanosis and a combination of these conditions. Joint hypermobility is markedly increased, indicating that dysautonomy may be considered the causative factor following a trigger event. Overall, RP was observed in 14% of patients. Clinical recognition of these disorders avoids unnecessary investigation.

Key Points
- *Vascular acrosyndromes in young adults are commonly functional disorders resembling vascular algodystrophy induced by thermic stress.*
- *Dysautonomy of joint hypermobility is the co-factor influencing the appearance of the vascular disorders.*
- *Raynaud's phenomenon accounts to approximately 14% of vascular acrosyndromes presented in the young adult population.*

Keywords Acrocyanosis · Capillaroscopy · Dysautonomy · Erythromelalgia · Raynaud's phenomenon

Introduction

Peripheral vascular disorders have multiple etiologies, they affect more often women, and cold exposure is the most constant triggering factor [1]. They commonly termed abusively as Raynaud's phenomenon and further classification depends primarily on underlying clinical or laboratory findings [2, 3]. Many medical specialities are involved in the diagnosis and treatment of vascular acrosyndromes, and this complicates further their terminology and classification. As a result, the terms vasospastic or vasoconstrictive, biphasic or triphasic, primary or secondary, and disease or syndrome are often

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attributed to Raynaud's phenomenon depending on its presentation and possible accompanying illnesses [2, 4]. Maurice Raynaud, in his thesis, described the reversible vasospasm characterised by pallor and the accompanying skin colour changes [5–7]. Despite this, many attempts have been performed to facilitate diagnosis, and although newest classification criteria have been proposed for Raynaud's phenomenon (RP), the determination of vascular acrosyndromes is primarily clinical, depending much on physician's expertise [8–12].

Erythromelalgia and acrocyanosis are often underestimated or misrecognised. Both terms are the Greek etymologic characterisation of the clinical signs. Erythromelalgia (Erythros=red, melos=limb, algos=pain, which stands for the painful red limbs) is paroxysmal vasodilatation of the palms and fingers and less commonly the feet, and the precise aetiology remains unknown [13, 14]. Acrocyanosis (acro=extremity, cyanosis=bluish discolouration) is characterised by painless blue mottling of hands and feet. Similarly to Raynaud's phenomenon in both erythromelalgia and acrocyanosis, primary and secondary forms are identified. The latter is attributed to myeloproliferative, neoplastic, metabolic or autoimmune diseases and medications identically to RP [14–16].

This study aims to clarify the type of vascular acrosyndromes presented as an initial complaint in young population, in an outpatient basis and to conjugate these findings to joint hypermobility, a condition that is well characterised by autonomic nervous system dysfunction [16–18].

Materials and methods

Inclusion criteria

We used clinical approaches to classify vascular acrosyndromes; in particular, the presence of pallor in Raynaud's phenomenon, as pallor is the hallmark of digital ischemia. We consider that any other deviation from that specific clinical sign should be interpreted as a different entity. We used the descriptive terms erythromelalgia (EM) and acrocyanosis (AC) for those disorders with prominent red or blue extremity discolouration respectively and in accordance with their etymology.

We also observed a combination of the above maladies, specifically EM with RP (mix ErR) and EM with AC (mix ErA). Combined vasculopathy has also been reported in medical literature and sometimes associated with joint hypermobility [19].

Vascular acrosyndromes and specifically pallor were verified upon examination, either by a photograph of the patient's extremities during an attack or performing a provocative test.

The above clinical approach is useful and relevant to rheumatology clinical practice as it is sometimes related to autoimmune diseases, more commonly systemic lupus erythematosus or scleroderma.

Study population

We recruited patients with vascular disorders of the extremities who examined consecutively during two years, from January 2010 until April 2012, at the rheumatology outpatient clinic of 424 General Military Hospital. Our hospital is a tertiary unit, based in Macedonia, North Greece, and offers medical support to army personnel, veterans, their families and civilians. Patients were asked to participate in this prospective observational study and written informed consent was obtained, according to the Declaration of Helsinki. The study was approved by the Hospital's Ethical Committee.

Sixty-seven subjects were identified with vascular acrosyndromes. They enrolled in the study if they were under 40 years of age in order to facilitate the diagnosis of joint hypermobility, as it is well known that joint motion is typically restricted upon ageing. Data of patients older than this limit were also recorded. Seven patients refused to participate mainly due to distance limitations and their professional activities, while fifty subjects fulfilled the primary criterion and enrolled in the study.

Clinical and laboratory investigation

Patients' medical history and habits were recorded as they underwent a clinical examination by a rheumatologist and vascular surgeon. Medication history, smoking and manual work were among the recorded parameters. The presence of other related skin abnormalities such as livedo reticularis or ulcers was thoroughly examined. Joint laxity was evaluated according to the nine-point Beighton hypermobility score and the Hakim and Grahame five-point questionnaire [20, 21]. The condition was present if a subject had 4 or more joints affected in a total of nine examined sites. Alternatively, if there was a Beighton scoring 3/9 plus positive Hakim and Grahame questionnaire. The latter performed to identify manual workers who, marginally, do not fulfil Beighton's criteria due to the nature of their occupation. A referral to cardiology consultation followed by an echocardiographic study performed to subjects with clinically overt or suspected murmurs. Patients had a full blood cell count, renal and liver blood biochemistry, measurement of thyroid stimulating hormone (TSH), erythrocyte sedimentation rate (ESR) and C-reactive protein as well as antinuclear (ANA) and anti-DNA antibodies. Selectively, when ANA testing was positive, or there was clinical suspicion for an autoimmune disease, further laboratory examination was performed including, anti-Ro, anti-La, anticentromere and anti-Scl-70 antibodies as well as

anticardiolipin IgG and IgM antibodies, lupus anticoagulant test and VDRL. All subjects had a chest x-ray to exclude any lung abnormality or the presence of anatomy defaults such as cervical ribs. Finally, twenty-four patients (48%) underwent nailfold capillaroscopy.

Statistics

The SPSS standard version 17.0 for Windows (SPSS Inc., USA) was used for the statistical analyses. The median values, along with the 5th and 95th percentile position, were estimated for variables in each group. Non-parametric tests were used for comparisons. The Mann-Whitney non-parametric test and Fisher's exact test were used for comparisons between groups, for continuous and categorical data, respectively. For comparison of categorical data in more than two groups, the Kruskal-Wallis analysis of variance (ANOVA) was applied. The level of statistical significance was set to 0.05.

Patient follow-up

Patients were followed up monthly for the first three months and quarterly for the following year. Patients were re-evaluated five years after their initial visit or upon their request earlier of this time limitation. Those who were unable to attend the clinic at the end of the study were conducted by phone, answering to simplified questions related to the initial condition and their general health. A five-point outcome scale for the vascular acropathy was responded to, ranging from no change from baseline, moderate improvement, significant improvement, to resolved or worsened symptoms. The medical history, medications and habits were re-evaluated along with the type of occupation.

Results

The peak time for the manifestation of vascular acrosyndromes in subjects aged ≤ 40 was between late autumn and early spring, when cold and humidity in Greece are at the highest level. The male/female ratio in this cohort was 31/19, and their median age was 22 years [range 18–38] and 29 years [range 18–39] respectively. Independent samples 2-tailed *t* test revealed a statistical difference between male and female age groups ($p = 0.002$), but the mean symptom duration was similar in both sexes ($p = 0.543$). In contrast, in subjects aged over 40 years, the vascular acrosyndromes were most common in women and usually secondary to, or accompanied autoimmune diseases. Demographic and clinical data of patients are presented in Table 1. Two parameters that affect the appearance of vascular acrosyndromes are smoking and manual occupation. In our cohort, the smoker/non-smoker's ratio was 1.38 (29/21). Smoking rates were higher in males (Fisher's exact test, $p = 0.07$). All subjects were minimally social or occasional alcohol consumers; thus, we consider that alcohol consumption did not affect the emergence of vascular acrosyndromes. Erythromelalgia was the most prevalent disorder that affected more than half (56%) of the young adult population.

Acrocyanosis was not favourable to women as it was present exclusively in six (12%) male patients who were all smokers with a substantial impact on the manual occupation.

Combined biphasic skin colour changes observed in several patients. Nine subjects (18%) had both erythromelalgia and acrocyanosis symptoms (mix ErA). The male/female proportion was 7:2.

Additionally, two female patients (4%) presented with a combination of erythromelalgia and RP (mixErR). In this specific group, we observed that the intensity and the duration of cold exposure define the form that prevails, which may change over time, even on the same day. In our cohort, pure Raynaud's phenomenon accounts for 10% of the participants. The percentage rises to 14% of the study population if we include the subjects with the combination form (mixErR).

The median age of patients with Raynaud's and mixErR was greater than the rest of vascular acrosyndromes, with some statistical differences presented in Graph 1. The shortest median age was observed in acrocyanosis patients (median 21; range 19–23), followed by erythromelalgia (median 23.5; range 18–39). The highest median age was observed in Raynaud's patients (median 37; range 29–39), followed by mixErR (median 28; range 25–31). We conclude that an escalated type of vascular acrosyndromes prevails upon ageing, with Raynaud's phenomenon being a latter manifestation.

Disease duration varied substantially in subjects with erythromelalgia and acrocyanosis while a shorter period was noted in patients with Raynaud's symptoms. We assume that digital ischemia was a more worrying condition that prompted patients for an earlier medical consultation.

Joint hypermobility was an exceptional finding in patients with vascular acrosyndromes. Interestingly, 85.7% of those with erythromelalgia had this particular feature, while it was observed in the two patients with mixErR and on 66.7%, 33.3% and 25% of subjects with mixErA, acrocyanosis and Raynaud's phenomenon respectively. Overall, similar rates of joint hypermobility were found between genders (Fisher's exact test, $p = 0.351$). Performing a one-way ANOVA post hoc analysis with Bonferroni adjustment, there was a statistical difference in HMS prevalence between erythromelalgia and Raynaud's patients ($p = 0.019$).

We noted that erythromelalgia is characterised by vascular dilatation, and this contributes to the characteristic red colour of the extremities. Light pressure on the extremity causes pallor interrupting the blood flow at that site, which is followed by delayed refilling of vessels upon

Table 1 Demographic and clinical data of patients

	Young adults ≤ 40 years of age			Adults > 40 years of age		
	Male ($n = 31$)	Female ($n = 19$)	Total ($n = 50$)	Male ($n = 2$)	Female ($n = 8$)	Total ($n = 10$)
Age						
Median [range]*	22 [18–38]	29 [18–39]	24 [18–39]	43.5 [42–45]	49 [41–57]	46.5 [41–57]
Smoking (%)**	23 (74)	6 (31.5)	29 (58)	1 (50)	2 (25)	3 (30)
Manual occupation (%)	13 (41.9)	3 (15.8)	16 (32)	0	2 (25)	2 (20)
Disease duration						
Months [range]	5 [1–120]	6 [2–108]	5 [1–120]	94 [8–180]	120 [8–264]	121 [8–264]
Vascular acrosyndromes (%)§						
Erythromelalgia	16 (51.6)	12 (63.2)	28 (56)	–	2	2
Acrocyanosis	6 (19.4)	0	6 (12)	–	–	–
MixErA	7 (22.6)	2 (10.5)	9 (18)	1	1	2
Raynaud's	2 (6.4)	3 (15.8)	5 (10)	1	5	6
Mix ErR	0	2 (10.5)	2 (4)	–	–	–
Comorbidities						
RA	–	–	–	0	1	1
SpA	3	1	4	–	–	–
SLE	–	2	2	–	–	–
SSc	–	–	–	1	3	4
uCTD	–	1	1	0	2	2
IBD	–	1	1	0	1	1
Vasculitis	1	0	1	–	–	–
STR	10	4	14	0	1	1

Abbreviations: *MixErA*, combined erythromelalgia and acrocyanosis symptoms; *MixErR*, combined erythromelalgia and Raynaud's symptoms; *RA*, rheumatoid arthritis; *SpA*, seronegative spondylarthropathies; *SLE*, systemic lupus erythematosus; *SSc*, systemic sclerosis; *uCTD*, undifferentiated connective tissue disease; *IBD*, inflammatory bowel disease; *STR*, soft tissue rheumatism

Comparisons for young adult group:

*Independent samples 2-tailed *t* test, $p < 0.05$

**Fisher's exact test, $p < 0.05$

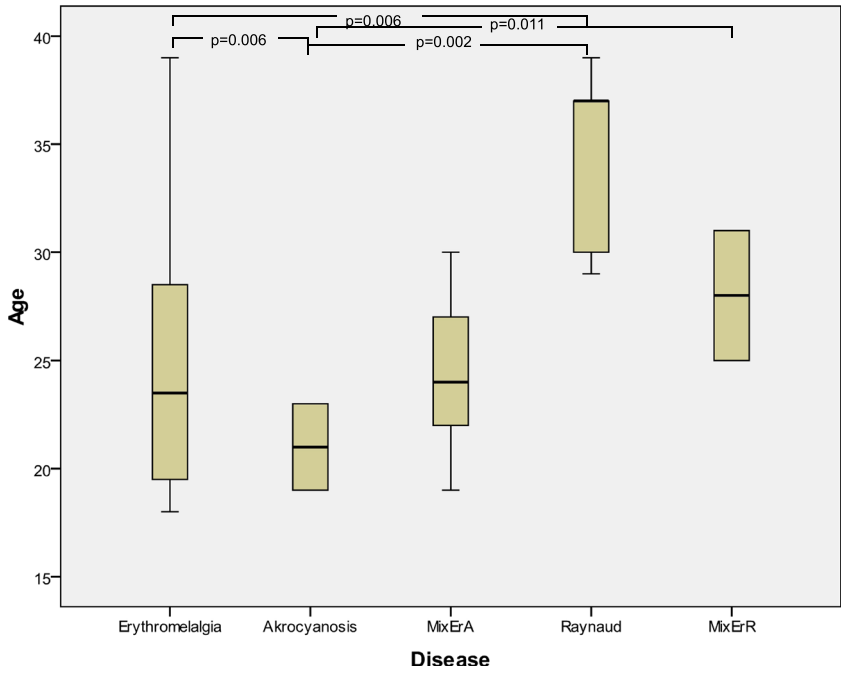
§ Kruskal-Wallis chi-square test, $p < 0.05$

the withdrawal of force (Fig. 1). We named this sign as the *late blood restoration test* (LBRT), which is a simple manoeuvre that indicates the congestion of vessels with blood. This test confirms a vasoparalysis and not a constrictive disorder in subjects with erythromelalgia, suggesting an autonomous nerve dysfunction. An additional sign for erythromelalgia that we often observed is the lifting of the arm above the level of the body for approximately half a minute. This simple procedure resolves the signs of erythromelalgia instantly and is also positive in acrocyanosis patients. Chilblains, presenting as ulcerations were observed in a small number of subjects in all groups except those with Raynaud's phenomenon (Table 2). Particular consideration should be given to avoid misinterpretation of these lesions as digital ulcers attributable to RP.

Mild cardiac valve disturbances, mainly cardiac murmurs, without any clinical significance, were noted in 18 (36%) of subjects, while mitral valve prolapse in 4 (8%) subjects.

Positive antinuclear antibodies were observed in a small proportion in all but acrocyanosis groups. The majority had titers less than 1/160, while one patient with erythromelalgia and history of systemic lupus erythematosus had ANA 1/1250 and positive anti-DNA antibodies. Furthermore, high titers of ANA were observed in one patient with RP without any other laboratory or clinical finding suggesting a latent autoimmune disorder.

In order to assess the morphology of capillaries, two experienced examiners (P.A. and. A.S.) blinded to patients' history performed nailfold capillaroscopy in thirty patients, twenty-four of them (48%) being in the studied group. We used an Optilia® videocapillaroscope with × 200 magnifying lenses, assessing the microcirculation in all except thumb fingers. Patients were advised to avoid vigorous activities and cold exposure at least 2 days before the examination, as well as taking caffeine and smoking 4 h before the inspection. They were also asked when was the last time they had removed their



Graph 1 Distribution of vascular acrosyndromes in relation to age. MixErA, combination of erythromelalgia and acrocyanosis; MixErR, combination of erythromelalgia and Raynaud's phenomenon. Mann-Whitney non-parametric test was used for comparisons between groups

fingernail cuticles, and if it was earlier than 20 days, they were excluded from the procedure to avoid interference with microtraumatic lesions. Findings were scored in a semi-quantitative manner on the following parameters: giant capillaries, microhaemorrhages and loss of capillaries. Interestingly, eighteen out of twenty-four examined patients (75%) presented abnormalities ranging from "early" to "active" sclerodermic pattern according to currently proposed classification (Fig. 2) [22].

Thirty-one patients (18 males, 13 females) were followed up to five years (mean 62.74 months, std. deviation 5.323). In half of the patients (51.6%), there was some level of improvement, with seasonal exacerbations while in nine subjects (29%), there was full resolution of symptoms. One female patient with mixErA developed RP at the end of the five years of follow-up time having a final diagnosis of mixed connective tissue disease. In five subjects (16%), there was no particular change from the baseline evaluation. Upon reviewing their medical history and habits, some level of improvement was noticed among those subjects that retired from army service, though without reaching statistically significant (Kruskal-Wallis chi-square test $p = 0.059$), anticipating that avoidance of cold exposure is the sound reason for the improvement in several subjects.

Discussion

In this study, we demonstrated that primary erythromelalgia is the most prevalent vasculopathy in young adults, five times more common than in patients older than 40 years of age. A combined syndrome of erythromelalgia-acrocyanosis is the second most prevalent vasomotor disorder followed by acrocyanosis symptoms alone. Deterioration of EM and AC was observed through the five years of study. Raynaud's phenomenon estimated to 10%, rising on the third place (14%)

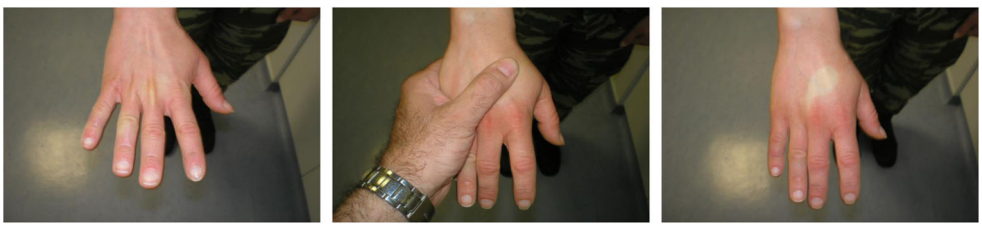


Fig. 1 Erythromelalgia is the commonest vascular acrosyndrome in young adults, which is verified by the *late blood restoration test*. Patients often report white colour changes of the extremities which are due to the interruption of blood flow of the dilated vessels at sites of light pressure. This is followed by delayed refilling of vessels upon the withdrawal of pressure

Table 2 Demographic and medical data of patients according to the spectrum of vascular acrosyndromes in young adult population

	Erythromelalgia	Acrocyanosis	mixErA	mixErR	Raynaud	Total (%)
N (%)	28 (56)	6 (12)	9 (18)	2 (4)	5 (10)	50 (100)
Age						
Median [range]	23.5 [18–39]	21 [19–23]	24 [19–30]	28 [25–31]	37 [29–39]	
Male/female	16/12	6/0	7/2	0/2	2/3	31/19
Disease duration (months)						
Median [range]	5.5 [1–120]	5 [3–12]	7 [2–120]	14 [12–16]	3 [3–18]	
Manual work (%) *	7 (25)	5 (83.3)	2 (22.2)	0	2 (40)	16 (32)
Smoking (%) *	14 (50)	6 (100)	3 (33.3)	1 (50)	2 (40)	26 (52)
Joint hypermobility (%) **	24 (85.7)	2 (33.3)	6 (66.7)	2 (50)	1 (20)	
Beighton score						
Median [range]	5 [1–8]	2.5 [0–6]	5 [3–8]	5.5 [5–6]	2 [0–4]	
Hyperidrosia (%)*	12 (42.8)	0	5 (55.6)	0	1 (20)	
Digital ulcers (%)	3 (10.7)	2 (33.3)	1 (11.1)	2 (50)	0	
Antinuclear antibodies (%)	3 (10.7)	0	2 (22.2)	1 (50)	2 (40)	
Anti-DNA (%)	1 (3.6)	0	0	0	0	
Capillaroscopy						
Abnormal capillaries/*N* examined (%)*	7/11 (63.3)	3/4 (75)	3/3 (100)	2/2 (100)	3/4 (75)	
Improvement after 5 years *N* (%)	17	4	5	2	3	31 (62)
Moderate	2	0	2	0	0	4 (12.9)
Significant	7	3	1	1	0	12 (38.7)
Resolved	6	0	1	1	1	9 (29)
Worsened	0	0	0	0	1	1 (3.2)
No change from baseline	2	1	1	0	1	5 (16.1)

Abbreviations: *mixErA*, combined symptoms of erythromelalgia and acrocyanosis; *MixErR*, combined symptoms of erythromelalgia and Raynaud's phenomenon

*Kruskal-Wallis chi-square test: $p < 0.05$

**One-way ANOVA post hoc test: $p < 0.05$, between erythromelalgia and Raynaud's subjects

when we include subjects with mixed erythromelalgia and Raynaud's symptoms. This combination is attributable to biphasic Raynaud's phenomenon. Following observations published in medical literature, our patients with RP are older than those with other vasculopathies, and it is more likely to have an accompanying systemic immune disease [23]. In this context, we can assume an overuse of the term RP in clinical practice and the under-recognition of erythromelalgia and acrocyanosis.

We report an increased incidence of joint hypermobility in patients with erythromelalgia, which may explain the equal sex distribution in our study, in contrast to female predominance that is presented in the medical literature [24]. The co-existence of joint hypermobility elucidates much of these symptoms as it is well known that it is characterised by dysautonomia. Malfunction of autonomous nerve system of the affected by the cold limbs interprets the red colour of the skin, concomitant oedema and occasionally the over sweating of the extremities. This condition resembles more as a vascular algodystrophy, with the *late blood restoration test* (LBRT) being its hallmark. Our study offers additional knowledge to the observed neurogenic mechanisms in erythromelalgia patients [24, 25]. The simplified questions "do your fingers change colour when they are exposed to cold temperatures?" or "do they turn white, blue, or both?" classically proposed for approaching the diagnosis of RP should be carefully interpreted as they may interfere with dysautonomia and LBRT features in erythromelalgia subjects. We consider that *white fingers* upon triggering factors are the hallmark of Raynaud's phenomenon, and this question should be addressed to identify patients with RP. The elevation of arms above the level of the body resolves in short term the symptoms of erythromelalgia and acrocyanosis in some patients, facilitating their diagnosis [26].

Our findings may explain the "inheritance" and the female predominance of primary RP and other vascular reactions [16, 23, 27]. It is reported that about 25% of first-degree family members of a patient will also have RP [27, 28]. Based on our results, we assume that joint hypermobility (JH) is the primary inherited feature which affects the appearance of vascular

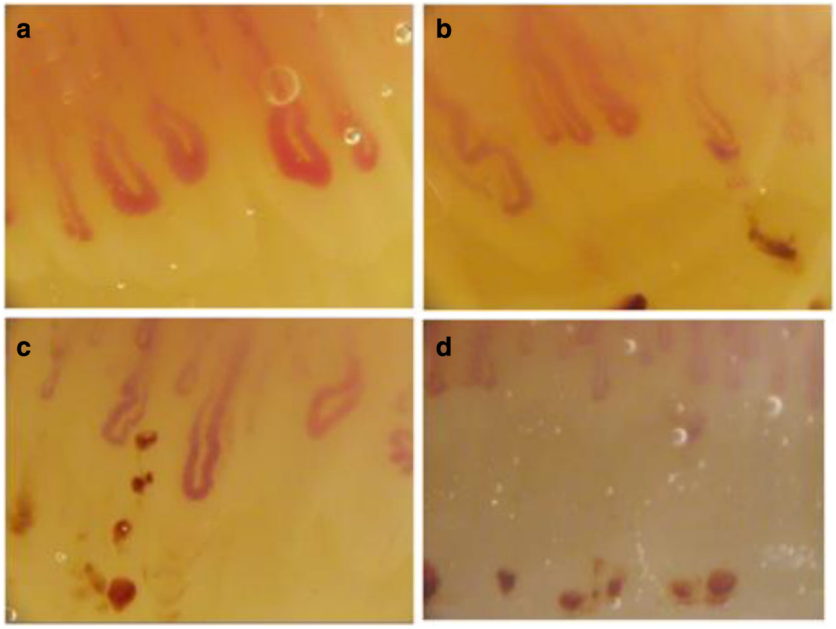


Fig. 2 Nailfold capillary abnormality patterns presented in patients with vascular acrosyndromes suggesting functional disorder. **a** Enlarged capillary loops. **b** and **c** Tortuous, enlarged capillaries, disarrangement and microhaemorrhages. **d** Microhaemorrhages

acrosyndromes upon triggering events. Lower Beighton scores due to manual occupation and male predominance, as well as smoking, were more prevalent in patients with acrocyanosis, anticipating that these attribute substantially to the specific vascular disorder [29].

The relatively small sample size, the military nature of our hospital, and the male/female ratios of the participants may be considered as major limitations of the study.

We observed digital ulcerations, attributable to chilblains, in all but pure Raynaud's subject groups. The lesions were healed in all patients within a few weeks after withdrawal from cold exposure and sudden reheating. Vitamin deficiencies were not among the recorded parameters as the role in vascular acrosyndromes is not clear. Even more, due to the latitude and the Mediterranean type of diet, vitamin D and C deficiencies were not expected, by the time this study was conducted. Just recently, studies confirm a circadian variation, which is reaching up to deficiency levels of 25(OH)D3 in the population of Southern Europe and Eastern Mediterranean countries [30, 31].

The assessment of the microcirculation by nailfold capillaroscopy frequently revealed giant capillaries and microhaemorrhages in both erythromelalgia and acrocyanosis patients, and they might be interpreted as non-specific functional disorders, as they are observed in other autoimmune conditions, such as rheumatoid arthritis [32]. In our opinion, the criteria that have been proposed for using the capillaroscopy in the diagnosis of RP should not rely on the above observations. It is rather more permanent abnormalities such as capillary loss, neovascularisation and avascular areas that correlate RP to an underlying secondary condition [33].

During a five-year follow-up period, we observed deterioration in the frequency and intensity of vasculopathies, as 67.7% of patients reported significant improvement or resolution of symptoms. Approximately in one-third of subjects, vascular acrosyndromes were resolved. In a similar study in Rochester, Minnesota, there was a 45.5% improvement or the resolution of symptoms after an eight-year follow-up time of patients with erythromelalgia [34]. We anticipate that better outcomes in our study were due to the termination of the one-year obligatory military service in Greece, resulted in the avoidance of extreme temperature changes, with this observation marginally not reaching statistically significant. We lost some of the followed up patients, mainly due to internal and external migration for professional reasons, and this may be considered as another limitation of the study. Only a 38-year-old female patient, with mixErA symptoms evolving eventually in RP, developed so far an undifferentiated connective tissue disease with high titers of ANA antibodies.

In conclusion, all types of vascular acropathies may be observed in subjects younger than 40 years of age, with erythromelalgia being the most prevalent. Dysautonomia of underlying joint hypermobility may be considered the causative factor. Vascular acrosyndromes are often deteriorating upon ageing and may be regarded as functional disorders in most cases. Raynaud's phenomenon is prevalent in older subjects who should be regularly followed up to detect early a possible latent connective tissue disease [35, 36].

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Compliance with ethical standards

Patients were asked to participate in this prospective observational study and written informed consent was obtained, according to the Declaration of Helsinki. The study was approved by the Hospital's Ethical Committee.

Disclosures None.

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