Original Investigation
Orijinal Araştırma

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Demographic findings of patients diagnosed with pernio and comparison of their vitamin B12, folate and ferritin levels with a control group

Pernio tanısı konulan hastaların demografik bulgularının incelenmesi ve B12 vitamin, folat ve ferritin düzeylerinin kontrol grubu ile karşılaştırılması

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Abstract

Background and Design: Pernio is an inflammatory disease that occurs in the acral regions of the body after exposure to cold. The study aimed to investigate the demographic findings of patients diagnosed with pernio and to determine the role of vitamin B12, folate and ferritin values in the pathogenesis of pernio.
Materials and Methods: This study was conducted in pernio patients diagnosed at the Ağrı State Hospital, Dermatology Outpatient Clinic (Ağrı, Turkey) between September 2015 and April 2016. The healthy control group participants were of similar age and gender. Vitamin B12, folate and ferritin levels were compared between the groups.
Results: The patient and control groups were similar in age and gender. Vitamin B12 and ferritin levels were significantly lower in the patient group ($p<0.05$). Folate levels did not differ significantly between the groups ($p>0.05$).
Conclusion: According to the data obtained from our study, when the demographic findings of the pernio patients were compared with those in the literature, the results were found to be similar. In the patients with pernio, it is likely that low Vitamin B12 was involved in the pernio etiology via the mechanism of vasoconstriction/vasodilatation.
Keywords: Pernio, folic acid, vitamin B12, ferritin, demographic

Öz

Amaç: Pernio, soğuğa maruz kalma sonrasında vücudun akral bölgelerinde oluşan enflamatuvar bir hastalıktır. Çalışmamızda pernio hastalarının demografik bulguları incelenerek B12 vitamin, folat, ferritin düzeylerinin pernio patogenezindeki yerini bulmayı amaçladık.
Gereç ve Yöntem: Bu çalışma, Eylül 2015-Nisan 2016 tarihleri arasında Ağrı Devlet Hastanesi Dermatololoji Polikliniği'ne başvuran pernio tanısı alan hastalar ile benzer yaş ve cinsiyet özelliklerine sahip kontrol grubunda gerçekleştirildi. Grupların B12 vitamin, folat, ferritin düzeyleri karşılaştırıldı.
Bulgular: Hasta ve kontrol grupları yaş ve cinsiyet açısından benzerdi. Hasta grubunda B12 vitamin ve ferritin düzeyi anlamlı olarak düşüktü ($p<0,05$). Folat düzeyi açısından olgu-kontrol grupları arasında fark bulunmadı ($p>0,05$).
Sonuç: Çalışmamızda elde ettiğimiz veriler ışığında pernio hastaların demografik bulguları literatürdeki çalışmalarla karşılaştırıldığında, benzer sonuçlar bulunmuştur. Çalışmamızda B12 vitamin düşüklüğünün homosistein mekanizması üzerinden vazospazma yol açmak suretiyle pernio patogenezinde rol alması muhtemel olabileceği düşünülmektedir.
Anahtar Kelimeler: Pernio, folik asit, vitamin B12, ferritin, demografi

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Introduction

Pernio is an inflammatory disease that is characterized by subjective complaints such as itching, burning and pain. Pernio appears as a bluish red or purple lesion occurring in the acral regions of the body after exposure to cold conditions[1,2]. This lesion, which usually develops after a long period of exposure to cold temperatures above the freezing point, begins within the first 12-24 hours and limits itself within three weeks[3]. Its etiology can be attributed to genetic factors, nutritional irregularities, low body mass index (BMI), anorexia, hormonal changes, systemic diseases, and myelodysplastic diseases[4]. Although the physiopathology of pernio is not completely understood, it is thought to develop due to the secondary inflammatory response provoked in the acral regions of the body by cold-induced vasoconstriction[5,6].

This study aimed to determine the role of vitamin B12, folate and ferritin levels in the pathogenesis by investigating the demographic findings of pernio patients.

Materials and Methods

This prospective study was conducted with 91 patients presenting at the Ağrı State Hospital Clinic of Dermatology Outpatient between September 2016 and April 2017 and in 91 healthy controls. It was approved by the Ethics Committee of the Van Training and Research Hospital (approval number: 2016/4). Informed consent was obtained from all patients included in the study.

The study was carried out at latitude 39 °C 43'N and longitude 43 °C 3' E at an altitude of 1632 m where the average temperature from November to April over the last 74 years has been between -10.8 °C and 6.2 °C[7].

Included in the study were 91 patients diagnosed with pernio who had erythematous, itchy, painful lesions located in the acral regions of the body which had lasted for more than three weeks. Patients who had a history of collagen vascular disease, peripheral vascular disease, Raynaud's disease or malignancy were excluded from the study. In order to minimize age and gender-related factors, a group of 91 controls with the same age and gender distribution were selected from among those who presented to the dermatology outpatient clinic with diagnoses of acne vulgaris, telogen effluvium and tinea infection, but had no history of collagen vascular disease, peripheral vascular disease, Raynaud's disease or malignancy.

Patients diagnosed with pernio were evaluated in terms of demographic characteristics such as age, gender, attack frequency, family history, areas of involvement, type of subjective complaints (e.g., pain, burning, itching and tingling), history of tobacco use, occupation and the month referred to the hospital. Age, gender, vitamin B12, folate and ferritin levels were compared between the patient and control groups.

Statistical Analysis

Data analysis was performed using the SPSS for Windows 17.0 software package. The distribution of continuous and intermittent numerical variables was investigated by the Kolmogorov-Smirnov test. Descriptive statistics were expressed as mean ± standard deviation for continuous and intermittent numerical variables. Categorical variables were given as number of cases and (%). The Student's t-test was used for analysis of parametric data. Unless otherwise indicated, $p<0.05$ was considered to be statistically significant.

Results

The mean age of the patients included in the study was 25.9±9.3 (2-55) years and 57.2% of the patients were female. There was no significant difference between the groups in terms of age and gender ($p>0.05$). It was determined that 52.7% were referred with a primary attack, the most common site of involvement was the heel (71.4%) and the most common complaints of the patients were burning and itching. In addition, all patients had typical blue/purple lesions and 7.7% had bullous lesions. The greatest number of patients were referred to the hospital in the months of February (24.2%) and March (24.2%). A family history of the complaint was seen in 25.3% and 57.1% had a history of smoking. The most common occupational types found in the patient group were construction workers (24.2%) and the self-employed (30.8%) (Table 1).

In the patient group, the vitamin B12 level was measured as 265.3±84.3 pg/mL, the folate level as 8.1±2.6 ng/mL and the ferritin level as 38.0±33.2 mg/L. In the control group, the vitamin B12 level was seen as 304.2±66.9 pg/mL, the folate level as 8.5±2.7 ng/mL and the ferritin level as 68.3±29.8 mg/L. No significant difference was found in the folate levels between the patient and control groups ($p>0.05$). However, vitamin B12 and ferritin levels were significantly higher in the control group ($p<0.05$) (Table 2).

Discussion

Although the pathogenesis of pernio is not completely understood, it is known as a neurovascular response due to exposure to cold temperatures above the freezing point in susceptible individuals[5]. It is thought that the secondary inflammatory response which develops after vasoconstriction as a result of exposure to cold is responsible for the pathogenesis of pernio[6,8]. Although its histopathology is non-specific, necrotic and spongiotic keratinocytes in the epidermis, T cell infiltration in the deep dermis showing perieccrine distribution[4].

The average age of patients diagnosed with pernio in our hospital was 28 years. Cases have been reported in all age groups, including children[5,9]. In our study, 57.2% of the patients were female. Spittell and Spittell[8], Akkurt et al.[10] and Külcü Çakmak et al.[11] reported a female dominance of 71%, 65.2% and 58.9% respectively. In the Midtun study, it was stated that increased vascular reactivity in acral regions exposed to cold was higher in female patients[12]. In addition, lesions are frequently associated with female patients and with low BMI[5,12].

In our study, 52.7% of the patients presented with a primary episode, while 47.3% presented with a recurrent episode. Pernio is observed more frequently between November and April[8]. In our study, February and March were the months when pernio was most frequently diagnosed.

Lesions can appear beginning symmetrically on the hands and feet along with lesions on the ears, nose, thighs and hips. Erosions, ulcerations or bullae-like lesions are also seen, but rarely. Clinically, lesions in the form of sensitive erythematous, purplish, edematous plaques are the most common foot involvement[5,9,10]. In our study, bullous lesions in the form of bluish-red, purple-colored lesions were detected in seven patients. The most common manifestation occurred in the feet. Arteriovenous anastomoses in the skin act as deep temperature regulators, triggering vasodilation due to cold. Different numbers of these anastamoses are

present in different parts of the body, the least number being on the plantar aspect of the feet, explaining feet being the most frequent area involved in pernio patients[13]. The most common complaints in our patients were burning/itching (35.2%) and pain (15.4%). However, 22% of the patients had combined complaints. Cappel and Wetter[14], in their study, reported the most common complaints as sensitivity (49%), itching (9%) and combined complaints (23%).

Table 1. Demographic findings of pernio patients

		Mean ± SD/ n (%)
Age, mean ± SD	-	25.9±9.3
Sex	Male, n (%)	39 (42.8)
	Female, n (%)	52 (57.2)
Episode frequency	Primary episode, n (%)	48 (52.7)
	Recurrent episode, n (%)	43 (47.3)
Lesion sites	Hands and feet, n (%)	42 (46.2)
	Hands only, n (%)	18 (19.8)
	Feet only, n (%)	31 (34.1)
	Heel, n (%)	65 (71.4)
	Ear, n (%)	9 (9.9)
Symptoms	Burning-itching sensation, n (%)	32 (35.2)
	Pain, n (%)	14 (15.4)
	Numbness-tingling sensation, n (%)	13 (14.3)
	Multiple symptoms, n (%)	20 (21.9)
	No symptoms, n (%)	12 (13.2)
Type of lesion	Typical blue/purple lesion, n (%)	91 (100)
	Bullous, n (%)	7 (7.7)
Month of hospital referral	January, n (%)	21 (23.0)
	February, n (%)	22 (24.2)
	March, n (%)	22 (24.2)
	April, n (%)	8 (8.8)
	November, n (%)	9 (9.9)
	December, n (%)	9 (9.9)
Family history n (%)		23 (25.3)
History of smoking n (%)		52 (57.1)
Occupation	Student, n (%)	17 (18.7)
	Construction worker, n (%)	22 (24.2)
	Housewife, n (%)	15 (16.4)
	Self-employed, n (%)	28 (30.8)
	Other (teacher, government employee, lawyer, etc.), n (%)	9 (9.9)

SD: Standard deviation

In our study, 25.3% of the patients were found to have a family history of pernio. Akkurt et al.[10] reported that the incidence in a first-degree relative was 19.6%. Singh et al.[15] in their study, found a family history of 9.3%. Although it is known that genetic factors have a role in the etiology of the disease, the frequency has not yet been clarified[4]. The studies of Külcü Çakmak et al.[11] and Raza et al.[16] concluded that for familial pernio, the familial risk factor relied on genetic factors rather than on similar conditions within the family.

When the demographic findings of our pernio patients were compared with those in the literature, similar results were found.

Studies have shown that vasospasm plays a role in pernio, while its pathogenesis was not completely clear[8,17]. In our study, the vitamin B12 levels of the pernio patients were statistically significantly lower than in the control group. A wide reference range (150-900 pg/mL) is suggested for normal levels of serum vitamin B12[18]. It is reported that particular caution should be taken when referring to these vitamin B12 levels since clinical findings of deficiency may occur in individuals with a lower baseline range (156-400 pg/mL)[19]. Hvas and Nexo[20] defined vitamin B12 levels below 169 pg/mL as vitamin B12 deficiency. They reported that vitamin B12 levels between 169-338 pg/mL defined a "grey zone", indicating that homocysteine-methionine cycle was dysfunctional (indicating insufficient DNA synthesis and methylation). They stated that vitamin B12 values only above 338 pg/mL could be considered adequate. Vitamin B12 levels were found to be in the grey zone in both the study group consisting of patients with pernio and in the control group, however, they were significantly lower in patients with pernio compared to the controls. In our study, the average level of vitamin B12 in patients diagnosed with pernio was 265.3±84.3. This value is in the range of levels that may affect the metabolism of homocysteine in which the vitamin B12 acts as a cofactor. Homocysteine is an essential amino acid containing a thiol group in its structure and it is metabolized from methionine. Homocysteine is remethylated back to methionine by vitamin B12-dependent methionine synthase in the presence of 5-methyltetrahydrofolate. Vitamin B12 is essential as a cofactor in the remethylation pathway in homocysteine metabolism (Figure 1). As homocysteine cannot be remethylated back to methionine in case of vitamin B12 deficiency, hyperhomocysteinemia will occur consequently[21]. Hyperhomocysteinemia causes lipid peroxidation and oxidative damage-associated endothelial damage[22,23].

Hanratty et al.[21] reported that moderate increases in plasma homocysteine levels were associated with cerebral, coronary and

Table 2. Comparisons of demographic and laboratory parameters between groups

	Total	Patient (n=91)	Control (n=91)	p
Age, mean ± SD	25.9±9.0	25.9±9.3	25.8±8.8	0.777
Female, n (%)	104 (57.2)	52 (57.2)	52 (57.2)	<0.999
Vitamin B12, Mean ± SD	284.7±78.4	265.3±84.3	304.2±66.9	0.001
Folate, mean ± SD	8.3±2.6	8.1±2.6	8.5±2.7	0.286
Ferritin, mean ± SD	53.1±34.9	38.0±33.2	68.3±29.8	<0.001

SD: Standard deviation

peripheral vascular diseases. High levels of homocysteine can lead to impaired endothelial nitric oxide (NO) production and stimulate the proliferation of vascular smooth muscle cells[23]. In addition, endothelial injury leads to decreased release of NO and endothelium derived hyperpolarizing factor and an increase in the production of vasoconstrictor effective endothelin-1[24]. Several studies have demonstrated that hyperhomocysteinemia significantly affects most of the abovementioned regulatory mechanisms, which lower the levels of vasodilators and enhance the vasoconstrictive factors especially. Therefore, the pathogenic involvement of homocysteine in vasospastic phenomena leading to Raynaud phenomenon have been determined[25]. Increased homocysteine levels have been found to cause vascular damage via several mechanisms including endothelial damage and modifications in the circulating vascular tone mediators[26]. Although homocysteine levels could not be quantified in this study, low vitamin B12 levels in the pernio patient group have suggested that homocysteine metabolism might have been affected. We have considered that the levels of homocysteine of vitamin B12 were affected in the pernio patients as their vitamin B12 levels were in the grey zone, leading to the development of vasoconstriction. Therefore, we are of the opinion that vasoconstriction developing under these conditions is involved in the physiopathology of pernio. Despite the fact that our study is a case-control study, we could still have better explained the effects of vitamin B12 on the pathogenesis if we quantified the homocysteine levels concurrently. Further studies may establish the relationship of vitamin B12 and homocysteine levels with the development of pernio symptoms. Then, plasma levels of homocysteine are quantified in pernio patients and vitamin B12 supplementation may be a treatment option for these patients, considering that hyperhomocysteinemia can be resolved effectively with vitamin supplements. We expect that our study will pave the way for further similar studies.

In our study, the ferritin levels of pernio patients were found to be statistically lower than the control group when evaluated within the normal reference range. There was no significant difference in folate levels between the patient and control groups. Our study did not evaluate anemia due to the fact that we were not able to perform a complete blood count simultaneously. However, Külcü Çakmak et al.[11] reported that the complete blood count values of pernio diagnosed patients were not abnormal.

Study Limitation

Neither simultaneous homocysteine and ferritin level nor simultaneous complete blood count and vitamin B12 level measurements were performed and these were limitations of our study.

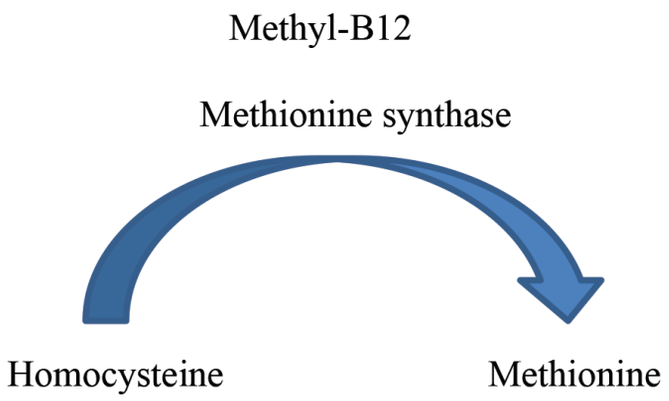

Figure 1. Homocysteine metabolism

Conclusion

In light of the the data obtained from our study, when the demographic findings of the pernio patients were compared with those in the literature, the results were found to be similar. In our study, it is thought that the induction of vasospasm through the homocysteine mechanism of low vitamin B12 may play a role in the pathogenesis of pernio. Although the ferritin levels were lower in the pernio patients than in the control group, they were within the normal reference range.

Ethics

Ethics Committee Approval: It was approved by the Ethics Committee of the Van Training and Research Hospital (approval number: 2016/4).
Informed Consent: Informed consent was obtained from all patients included in the study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: E.K., Design: E.K., Data Collection or Processing: E.K., Analysis or Interpretation: E.K., S.B., Literature Search: E.K., S.B., Writing: E.K., S.B.
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References

1. Long WB, Edlich RF, Winters LK, Britt LD: Cold injuries J Long Term Eff Med Implants 2005;15(1):67–78.
2. Chan Y, Tang W, Lam WY, Loo S, Li S, Au A, et al: A cluster of chilblains in Hong Kong. Hong Kong Med J 2008;14:185-91.
3. Vano-Galvan S, Martorell A. Chilblains. CMAJ 2012;184:67.
4. Cribier B, Djeridi N, Peltre B, and Grosshans E: A histologic and immunohistochemical study of chilblains. J Am Acad Dermatol 2001;45:924-9.
5. Prakash S, Weisman MH: Idiopathic Chilblains. Am J Med 2009;122:1152-5.
6. Simon TD, Soep JB, Hollister JR. Pernio in pediatrics. Pediatrics 2005;116:472-5.
7. T.C. Orman ve Su İşleri Bakanlığı Meteoroloji Genel Müdürlüğü Resmi İstatislikler Accessed: 10.02.2016.
8. Spittell JA Jr, Spittell PC: Chronic pernio: another cause of blue toes. Int Angiol 1992;11:46-50.
9. Gordon R, Arikian AM, Pakula AS: Chilblains in Southern California: Two case reports and a review of the literature. J Med Case Rep. 2014;8:381.
10. Akkurt ZM, Ucmak D, Yildiz K, Yürüker SK, Celik HÖ: Chilblains in Turkey: A case-control study. An Bras Dermatol 2014;89:44-50.
11. Külcü Çakmak S, Gönül M, Oğuz ID, Yayla D, Gül U, Köse K: Demographical, laboratory and associated findings in patients with perniosis. J Eur Acad DermatolVenereol 2014;28:891-4.
12. Midttun M: Blood flow rate in arteriovenous anastomoses: from the cradle to the grave. Clin Physiol 2000;20:360-5.
13. Takci Z, Vahaboglu G, Eksioglu H: Epidemiological patterns of perniosis, and its association with systemic disorder. Clin Exp Dermatol 2012;37:844-9.
14. Cappel JA, Wetter DA: Clinical characteristics, etiologic associations, laboratory findings, treatment, and proposal of diagnostic criteria of pernio (chilblains) in a series of 104 patients at Mayo Clinic, 2000 to 2011. Mayo Clin Proc 2014;89:207-15.
15. Singh GK, Datta A, Grewal RS, Suresh MS, Vaishampayan SS: Pattern of chilblains in a high altitude region of Ladakh, India. Med J Armed Forces India. 2015;71:265-9.

16. Raza N, Habib A, Razvi SK, Dar NR: Constitutional and behavioral risk factors for chilblains: A case-control study from Pakistan. Wilderness Environ Med 2010;21:17-21.
17. Shahi V, Wetter DA, Cappel JA, Davis MD, Spittell PC: Vasospasm is a consistent finding in pernio (Chilblains) and a possible clue to pathogenesis. Dermatology 2015;231:274-9.
18. Herrmann W, Schorr H, Obeid R, Geisel J: Vitamin B12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr 2003;78:131-6.
19. Lesho EP, Hyder A: Prevalence of subtle cobalamin deficiency. Arch Intern Med 1999;159:407.
20. Hvas AM, Nexo E: Diagnosis and treatment of vitamin B12 deficiency-an update. Haematologica 2006;91:1506-12.
21. Hanratty CG, McGrath LT, McAuley DF, Young IS, Johnston GD: The effects of oral methionine and homocysteine on endothelial function. Heart 2001;85:326-30.
22. McDowell IF, Lang D: Homocysteine and endothelial dysfunction: A link with cardiovascular disease. J Nutr 2000;130:369-72.
23. Tawakol A, Omland T, Gerhard M, Wu JT, Creager MA: Hyperhomocyst(e) inemia is associated with impaired endothelium-dependent vasodilation in humans. Circulation 1997;95:1119-21.
24. Cheng Z, Yang X, Wang H: Hyperhomocysteinemia and endothelial dysfunction. Curr Hypertens Rev 2009;5:158-65.
25. Lazzerini PE, Capecchi PL, Bisogno S, Cozzalupi M, Rossi PC, Pasini FL: Homocysteine and Raynaud's phenomenon: A review. Autoimmun Rev 2010;9:181-7.
26. Tousoulis D, Antoniades C, Marinou K, Vasiliadou C, Bouras G, Stefanadi E, et al: Methionine-loading rapidly impairs endothelial function, by mechanisms independent of endothelin-1: evidence for an association of fasting total homocysteine with plasma endothelin-1 levels. J Am Coll Nutr 2008;27:379-86.