Chapter 2

The Epidemiology of Behçet's Disease

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Abstract

Behçet's disease (BD), a chronic vasculitis affecting any type of the blood vessels, was first described by a Turkish dermatologist Hulusi Behçet. Although it has a worldwide distribution, it is commonly seen in the Silk Road countries around the Mediterranean Sea. The country in which the disease is most commonly seen is Turkey with a prevalence of 20–602/100,000. The disease most appears between the second and fourth decades of the life. BD affects both genders equally. However, the gender distribution may differ among different regions.

Keywords: Behçet's disease, epidemiology, prevalence, age, pathergy, HLAB51

1. Introduction

Behçet's disease (BD) is a chronic multisystem vasculitis, which affects any type and shape of blood vessels, particularly veins [1, 2]. The disease was first described in 1937 by a Turkish dermatologist, Hulusi Behçet, as a triple symptom complex, aphthous stomatitis, genital ulcers and relapsing uveitis [3]. Most widely used classification criteria is suggested by The International Study Group (ISG) for BD in 1990 [4]. According to the ISG, the major criterion exactly required for the diagnosis is recurrent oral ulceration at least three times a year. Additionally, at least two of the minor criteria: genital ulceration, skin lesions (erythema nodosum, necrotic folliculitis, and papulopustular lesions), ocular lesions (posterior uveitis, total uveitis, and retinal vasculitis), and positive pathergy testing are required for the diagnosis [4].

2. Epidemiology

2.1. Prevalence

BD has a worldwide distribution. But it is commonly seen in the Silk Road countries around the Mediterranean Sea, including Spain, Portugal, Turkey, Iran, and Far East countries like China and Japan [5, 6]. The prevalence of the disease along the silk route is 14–20/100,000 [7]. BD is most common in Turkey with the prevalence of 20–602/100,000 [8, 9]. The other more prevalent countries are Iran, China, Tunisian, Korea, Israel, and Japan [8, 10, 11]. In North European, American, and African countries BD is less frequent [12, 13]. The prevalence of BD in some countries is shown in **Table 1** [8, 9, 12, 14–20].

Since 1982, the supported hypothesis about the etiopathogenesis of BD has been that the genetic material and the exogenous agents responsible for the disease were carried during the immigration of ancient nomadic tribes [15]. Many studies focus on immigrations so far have investigated how the genetic or environmental factors affect the development of BD. In 1997 in Germany, 218 patients with BD were investigated. Of these patients, 89 were German, 100 were Turkish, and 29 were from other nationalities. The prevalence of BD was found 0.16/100,000 in German population and 4.51/100,000 in Turkish population. The prevalence of BD in Turkish population was higher than German population. However, it was 5–18-fold lower than the prevalence found in Turkey. This study suggested that the genetic and environmental factors are both effective in the development of the disease [15]. Another similar study was performed in 2015 in the Rotterdam area of Netherland [5]. Eighty-four patients of Dutch, Turkish, or Moroccan origin with BD were identified. The prevalence of BD was found 1/100,000 in Dutch, 71/100,000 in Turkish and 39/100,000 in Moroccan population. The study mentioned that the prevalence of BD in different ethnic group was similar to that among the

Country	Prevalence (1/100,000)
Turkey [8, 9]	20–602
Israel [14, 15]	50–185
Iran [12, 16]	16.7–100
Iraq [17]	17
Japan [9]	7–13.5
China [18]	2.62
Kuwait [12]	2.1
Italy [19, 20]	4.1–15.9
Germany [21]	0.9
USA [12]	0.33

Table 1. Worldwide prevalence of Behçet's disease.

original countries of these patients. However, another study reported that no patient with BD was detected in Hawaii, where the Japan population is relatively high [11].

2.2. Age and gender

Behçet's disease can be seen at any age, but it mostly appears between the second and fourth decades of life [22]. In a study from Ankara, Turkey, the mean age of the patients with BD was found 37.2 [23]. In a study from Japan, the mean age of onset was found 36.8 [24]. The mean age of onset of BD in many countries was shown in **Table 2** [5, 13, 15, 23–34].

Regional and ethnic factors may affect the time of the diagnosis of the illness. The diagnosis of the disease is delayed in areas where the prevalence of the disease is lower [12]. In a study from Germany, it was reported that the time of diagnosis of BD in Turkish patients was earlier than in German patients. The diagnosis was later and more difficult in German patients than in Turkish patients, so that we should keep in mind that some German patients might be followed with wrong diagnosis for long times before the diagnosis of BD [15, 35].

Patients with earlier onset have more severe disease [36]. In a study from Tunisia, BD patients with onset before age of 20 and after age of 40 were compared each other. Cutaneous involvement, pseudo folliculitis, and vena cava thrombosis were more frequent in patients with earlier onset. In contrast, joint involvement was more frequent in patients with later onset [28]. Mortality in the group with earlier onset was 2.46% but no patients had died due to BD in the group with later onset [28]. Some authors reported that BD patient with earlier onset had more ophthalmic manifestations and active course of the disease [37, 38].

Country	Age of onset	Male/female
Turkey [23, 25]	37.2–38.02	0.69–1.03
Japanese [24]	36.8	0.74
Iran [26]	26.2	1.4
Israel [27]	34.9	1.22
Netherlands [5]	43	0.64
Senegal [13]	32	1.6
Tunisian [28]	29.12	2.1
Germany [15, 29]	24.5–27.4	1.51–1.38
Saudi Arabia [30]	29.3	3.4
China [31]	35.8	1.4
Italy [32]	33	1
England [33]	32	0.96
USA [34]	29.25	0.3

Table 2. Age and gender ratio distribution among countries.

BD is uncommon in children. Patients with initial symptoms at age 16 years or lower are classified as juvenile-onset BD [39]. The prevalence of juvenile BD is unknown. However, in few series, it was reported that 3.3 and 26% of the patients with BD were juvenile-onset BD [2]. The clinical symptoms are not different from adults but the diagnosis may be delayed in pediatric patients because of mild symptoms [2]. Juvenile onset patients had more familial cases compared with adult-onset patients [39]. There are some different series presenting juvenile BD. In the study of Allali et al., one-third of the patient had family history [40]. In the series of Kone-Paut et al., family history was reported as 9 and 24.4%. But in adults, family history was found as 2.2% [41–43]. The clinical features of juvenile BD in different series are seen in **Table 3** [40–42, 44–48].

BD disease affects both the gender equally [12]. But the gender distribution may differ between different regions. A few studies showed that male predominance was seen in Middle Eastern countries, while female predominance was seen in Asian countries [1]. The male/female ratios from the studies are shown in **Table 2**.

Gender affects the clinical findings and the severity of the disease as well [12]. In a long-term study performed by Kural-Seyahi et al., it was implicated that the disease is more severe in male patients, and vascular disease might be the major risk factor of death in male patients [49]. Saadoun et al. supported that male sex, arterial involvement and a high number of BD flares were independently associated with the risk of mortality [50]. In 2015, Bonitsis et al. presented a meta-analysis of the gender-specific differences in BD. They investigated both the German registry of BD and systematic literature review meta-analysis (52 other publications from Turkey, Asia, Southern Europe, Northern Europe, South America, the USA, and North Africa/Middle East) [29]. They found that vascular disease (superficial and deep venous thrombosis and heart involvement), folliculitis, papulopustular skin lesions, positive pathergy test and ocular disease are more common in males, while erythema nodosum, genital ulcers and joint involvement are more common in females [29].

Clinical features (%)	Kone-paut [42]	Kone-paut [41]	Krause [44]	Karıncaoğlu [45]	Atmaca [46]	Eldem [47]	Uziel [48]	Allali [40]
***N* (patients)**	65	55	19	33	110	20	15	12
Oral aphthosis	96	100	100	100	100	100	100	100
Genital aphthosis	70	79	31.9	82	83	65	33	75
Cutaneous findings	92	78	89.5	52	76	35	93	16.7
Pathergy test +	–	–	41.2	37	45.5	–	40	58
Ocular signs	60	87	47.4	35	31	80	53	53
Articular findings	56	17	47.4	40	22	40	73	25
Gastrointestinal findings	14	–		36.8	–	5	46	8.3
Neurological findings	15	10	26.3	7.2	3.6	15	4	40
Vascular findings	15	21	10.5	9.6	3.6	5	0	33.3

Table 3. Clinical features of pediatric BD.

2.3. Epidemiology of clinical findings

Regional and environmental factors may affect clinical findings of BD. Prevalence of different clinical findings may differ among the patients from different regions [12]. Frequency of presence of oral aphthosis is almost same in patients from all regions with the rate of 96–100% [1, 12]. In Japan, 4.6–15% of endogen causes of uveitis are BD [13, 51]. In a study from Japan, 69% of the patients had ocular findings [52]. But uveitis is quite rare in Australia [1]. Neurological features are more common in Caucasians (23%) than Middle Eastern series (3–10%) and frequency of seizures was found to be higher than Turkish series (27 and 5%, respectively) [53]. Another study detected that Sub-Saharan African BD patients had a higher frequency of CNS involvement compared to North African and European BD patients [54]. Intestinal BD is rare in Mediterranean countries but it is more common in Japanese BD patients [12]. Clinical findings of patients from different regions are shown in **Table 4** [13, 23, 24, 28–30, 55].

2.4. Pathergy reaction

Pathergy reaction is a nonspecific skin hyper reactivity to minor trauma. Positivity is defined as occurring of a papule or pustule, 24–48 h after intradermal injection of skin with 20 gauge needle [1]. Positive pathergy test is one of the diagnosis criteria of BD [4]. The pathergy reaction is highly sensitive and specific for BD in patients from Silk Road countries like Turkey, from some Mediterranean, the Middle Eastern countries and Japan. However, it is rarely observed in patients from Northern Europe, USA and Australia [1, 56]. Although the pathergy test lost its sensitivity during the past 35 years, it is still a valuable diagnostic test [57]. Some studies from Japan and Turkey have reported a decrease in the positive pathergy reaction in BD [56]. In 1979, the skin pathergy positivity rate was found 84% in patients with BD in a study from Turkey [58]. In another study from Turkey in 1991, the rate was found 65% [59]. In a more recent study from Turkey, the rate of pathergy test positivity was

Country	Oral ulcer	Genital ulcer	Skin findings	Ocular findings	Articular findings	Vascular findings	Gastrointestinal findings	Neurological findings	Pulmonary findings	Pathergy test +
Turkey [23]	100	73	52	40	22	9.6	1	3.5	2.6	39
Germany [29]	99.7	72.8	79.9	50.4	54.1	22.4	11.5	12.1	1.3	28.5
Senegal [13]	100	96	30	44	40	18	2	24	–	32
Japan [24]	99	72.3	88.8	61.6	52.1	8.0	12.3	10.2	–	–
Iran [55]	97.5	65.7	64.6	58.1	39.4	9.1	7	10.6	1	52.3
Saudi Arabia [30]	100	87	57	65	37	25	4	44	–	17.5
Tunisia [28]	100	85	74.4	46.5	45.7	34.9	7	32.6	–	57.7

Table 4. Clinical findings of BD among some countries.

detected as 39% [23]. The decrease of pathergy test positivity rate can be also seen in some Japanese studies. In a study from Japan in 1972 the rate of positive pathergy test was found 75%, while in an other study performed in 2011 this rate was found %50 [56]. These differences may be occurred due to different applying techniques. One of the important methods is using non-disposable/blunt needles. In 2000, it was reported that clinical evaluation of the pathergy test conducted intradermally with non-disposable/blunt needles is sufficient for both the diagnosis and determination of the activation of Behçet's disease [60]. Also it is shown that surgical cleaning of the test area before needle prick reduced the prevalence of pathergy test positivity rate [61]. This information suggests that the positive reaction might be a cutaneous response to some bacteria living on the surface of the skin. In a recent study, performed by Togashi et al. suggested that a new diagnostic pathergy test may solve the methodological problems [62]. They performed a skin prick test with filter-sterilized saliva on forearm skin. Of the patients with BD, 90% showed indurative erythema at the skin site pricked with self-saliva, and 60% of recurrent aphthous stomatitis patients showed weak reaction. They suggested that skin prick test using self-saliva can be a diagnostic test for differentiating BD from other mucocutaneous diseases [62].

The reactivity of the pathergy test is suggested to be correlated with HLA-B51 in Mediterranean countries [63]. Rates of pathergy positivity from different studies are shown in **Table 4** [13, 23, 24, 28–30, 55].

2.5. Genetic factors and epidemiology

Although familial cases were reported, a Mendelian inheritance model specific to BD is not present [12]. In the western series, familial case rates were as follows: 0.7–2.7% in Italy, 3.6% in England and 4.5% in Portugal. The familial case rates were 11.9–13.4% in the studies from Tunisia, Israel, and Korea studies [12, 15, 64]. In a study from Turkey, family history was reported as 31.2% [65]. Multiple studies have demonstrated that BD is strongly associated with the presence of HLA-B5 and its split antigen HLA-B51 [12, 66]. The association with HLA-B5 was first described by Ohno et al. in 1973 [56]. The genetic material of the BD might be carried in parallel with population movement between the Mediterranean and Asia. Supporting this content is that the distribution areas of this antigen among healthy control populations are the ancient trade route and the region in which BD is commonly seen [67]. HLA-B51 frequency is high in the Mediterranean countries but it is low in western countries like USA and England [12]. In recent studies, many new genes other than HLA-B51 (IL-10 signaling pathways, IL6–174 G/C, MMP-9, CLEC16A, NKFB1, IL-23 receptor gene, IL-18, IL-6, IL10, Vitamin D receptor, etc.) associated with BD were also identified [36]. Shigemura et al. studied on six patients over four generations with BD in 2016, and they found a common heterozygous missense mutation in A20/TNFAIP3; a gene known to regulate NF-κB signaling. Mutation in A20/TNFAIP3 was likely responsible for increased production of human inflammatory cytokines by reduced suppression of NF-κB activation. They suggested that this mutation may lead to the autosomal-dominant Mendelian mode of BD transmission in this family [68].

3. Conclusion

BD has a worldwide distribution. But it is commonly observed along the Silk Road countries between the Mediterranean Sea. It is most common in Turkey. The prevalence of the disease, the frequency of the clinical findings, and genetics may differ between different regions. The disease is more severe among males than females. Diagnosis of BD is difficult, and the disease must be recognized, because early diagnosis is important for the early treatment.

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References

[1] Leonardo NM, McNeil J. Behcet's disease: is there geographical variation? A review far from the silk road. Int J Rheumatol. 2015;2015:945262. doi:10.1155/2015/945262

[2] Koné-Paut I. Behçet's disease in children, an overview. Pediatr Rheumatol Online J. 2016 Feb 18;14:10. doi:10.1186/s12969-016-0070-z

[3] Behçet h. ÜberrezidivierendeaphtÖsedurchein Virus verursachteGeschwüre am Mund, am auge und den Genitalien [Caused about recurrent aphtous by a virüs Ulcers of the mouth, the eyes and genitals]. DermatolMonatsschrWochenschr 1937;105:1152–7.

[4] International Study Group for Behcet's disease. Lancet. 1990;335:1078–80.

[5] Kappen JH, van Dijk EH, Baak-Dijkstra M, van Daele PL, Lam-Tse WK, van Hagen PM, van Laar JA. Behçet's disease, hospital-based prevalence and manifestations in the Rotterdam area. Neth J Med. 2015;73:471–7.

[6] Keino H, Okada AA. Behçet's disease: global epidemiology of an Old Silk Road disease. Br J Ophthalmol. 2007;91:1573–4.

[7] Alpsoy E, Zobuboulis CC, Ehrlich CE. Mucocutaneous lesions of Behcet's disease. Yonsei Med J. 2007;48:573–585.

[8] Mahr A, Maldini C. Epidemiology of Behçet's disease. Rev Med Interne. 2014;35:81–9.

[9] Baş Y, Seçkin HY, Kalkan G, Takcı Z, Önder Y, Çıtıl R, Demir S, Şahin Ş. Investigation of Behçet's disease and recurrent aphthous stomatitis frequency: the highest prevalence in Turkey. Balkan Med J. 2016;33:390–5. doi:10.5152/balkanmedj.2016.15101

[10] Saylan T, Mat C, Fresko İ, Melikoglu M. Behcet's disease in the Middle East. Clin Dermatol. 199;17:209–23.

[11] Marshall SE, Behcet's disease. Best Prac Res Clin Rheumatol. 2004;18:291–311.

[12] Pamuk ÖN, Çakır N. [The epidemiology of Behcet's disease]. TürkiyeKlinikleri J Int Med Sci. 2005;1:39.

[13] Ndiaye M, Sow AS, Valiollah A, Diallo M, Diop A, Alaoui RA, Diatta BA, Ly F, Niang SO, Dieng MT, Kane A. Behçet's disease in black skin. A retrospective study of 50 cases in Dakar. J Dermatol Case Rep. 2015;9:98–102. doi:10.3315/jdcr.2015.1213

[14] Klein P, Weinberger A, Altmann VJ, Halabi S, Fachereldeen S, Krause I.Prevalence of Behcet's disease among adult patients consulting three major clinics in a Druze town in Israel. Clin Rheumatol. 2010;29:1163–6. doi:10.1007/s10067-010-1472-9

[15] Zouboulis CC, Kötter I, Djawari D, Kirch W, Kohl PK, Ochsendorf FR, Keitel W, Stadler R, Wollina U, Proksch E, Söhnchen R, Weber H, Gollnick HP, Hölzle E, Fritz K, Licht T, Orfanos CE. Epidemiological features of Adamantiades-Behçet's disease in Germany and in Europe. Yonsei Med J. 1997;38:411–22.

[16] Gharibdoost F, Davatchi F, Shahram F, Akbarian M, Chams C, Chams H, Mansoori P, Nadji A: Clinical manifestations of Behçet's disease in Iran. Analysis of 2176 cases. In Wechsler B, Godeau P eds. Behçet's disease. International Congress Series 1037. Amsterdam, ExcerptaMedicia, 1993,153–158.

[17] Al-Rawi ZS, Neda AH. Prevalence of Behçet's disease among Iraqis. Adv Exp Med Biol. 2003;528:37–41.

[18] Mok CC, Cheung TC, Ho CT, Lee KW, Lau CS, Wong RW. Behçet's disease in southern Chinese patients. J Rheumatol. 2002;29:1689–93.

[19] Cartella S, Filippini M, Tincani A, Airo P. Prevalence of Behçet's disease in the province of Brescia in northern Italy. Clin Exp Rheumatol. 2014;32:S176.

[20] Olivieri I, Leccese P, Padula A, Nigro A, Palazzi C, Gilio M, D'Angelo S.High prevalence of Behçet's disease in southern Italy. Clin Exp Rheumatol. 2013;31:28–31.

[21] Altenburg A, Mahr A, Maldini C, Kneifel CE, Krause L, Kötter I, Stache T, Bonitsis NG, Zouboulis CC. [Epidemiology and clinical aspects of Adamantiades-Behçet disease in Gemany. Current data]. Ophthalmologe. 2012;109:531–41. doi:10.1007/s00347-012-2601-4

[22] Onder M, Gürer MA. The multiple faces of Behçet's disease and its aetiological factors. J Eur Acad Dermatol Venereol. 2001;15:126–36.

[23] Gündüz Ö, Gürler A, TuğrulAyanoğlu B, Erdoğan FG, Alhan A. Epidemiological properties of Behçet's disease who had been followed up at Behçet's disease center. TürkiyeKlinikleri J Dermatol. 2015;25:85–91.

[24] Kirino Y, Ideguchi H, Takeno M, Suda A, Higashitani K, Kunishita Y, Takase-Minegishi K, Tamura M, Watanabe T, Asami Y, Uehara T, Yoshimi R, Yamazaki T, Sekiguchi A, Ihata A, Ohno S, Ueda A, Igarashi T, Nagaoka S, Ishigatsubo Y, Nakajima H. Continuous evolution of clinical phenotype in 578 Japanese patients with Behçet's disease: a retrospective observational study. Arthritis Res Ther. 2016;18:217.

[25] Türsen Ü, Gürler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. Int J Dermatol. 2003;82:60–76.

[26] Davachi F, Shahram F, Akbarian M. Behcet's disease: analysis of 3443 cases. APLAR J Rheumatol 1997;1:2–5.

[27] Krause I, Uziel Y, Guedj D. Mode of presentation and multystem involvement in Behcet's disease:the influence of sex and age of disease onset. J Rheumatol. 1998;12:1566–9.

[28] Hamzaoui A, Jaziri F, Ben Salem T, Said Imed Ben Ghorbel F, Lamloum M, Smiti Khanfir M, Houman Mohamed H. Comparison of clinical features of Behcet disease according to age in a Tunisian cohort. Acta Med Iran. 2014;52:748–51.

[29] Bonitsis NG, Luong Nguyen LB, LaValley MP, Papoutsis N, Altenburg A, Kötter I, Micheli C, Maldini C, Mahr A, Zouboulis CC. Gender-specific differences in Adamantiades-Behçet's disease manifestations: an analysis of the German registry and meta-analysis of data from the literature. Rheumatology (Oxford). 2015;54:121–33. doi:10.1093/rheumatology/keu247

[30] alDalaan AN, al Balaa SR, el Ramani K. Behcet's Disease in Saudi Arabia. J Rheumatol. 1997;21:658–61.

[31] Zhang Z1, He F, Shi Y. Behcet's disease seen in China: analysis of 334 cases. Rheumatol Int. 2013;33:645–8. doi:10.1007/s00296-012-2384-6

[32] Salvarani C, Pipitone N, Catanoso MG, Cimino L, Tumiati B, Macchioni P, Bajocchi G, Olivieri I, Boiardi L. Epidemiology and clinical course of Behçet's disease in the Reggio Emilia area of Northern Italy: a seventeen-year population-based study. Arthritis Rheum. 2007;57:171–8.

[33] Chamberlain MA. Behcet's syndrome in 32 patients in Yorkshire. Ann Rheum Dis. 1977;36:491–9.

[34] Davari P, Rogers RS, Chan B, Nagler TH, Fazel N. Clinical features of Behçet's disease: A retrospective chart review of 26 patients. J Dermatol Treat. 2016;27:70–4. doi:10.3109/09546634.2015.1054781

[35] Kötter I, Vonthein R, Müller CA, Günaydın İ, Zierhut M, Stübiger N. Behçet's disease in patients of German and Turkish origin living in Germany: a comparative analysis. J Rheumatol. 2004;31:133–9.

[36] Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. Behçet's syndrome: a critical digest of the 2014–2015 literature. Clin Exp Rheumatol. 2015;33:3–14.

[37] Bang D. Treatment of Behçet's disease. Yonsei Med J. 1997;38:401–10.

[38] Huang ZJ, Liao KH, Xu LY. Study of 310 cases of Behçets's syndrome. Chin Med J.1983;96:483–90.

[39] Karincaoglu Y, Borlu M, Toker SC, Akman A, Onder M, Gunasti S, Usta A, Kandi B, Durusoy C, Seyhan M, Utas S, Saricaoglu H, Ozden MG, Uzun S, Tursen U, Cicek D, Donmez L, Alpsoy E. Demographic and clinical properties of juvenile-onset Behçet's disease: A controlled multicenter study. J Am AcadDermatol. 2008;58:579–84.

[40] Allali F, Benomar A, Karim A. Behçet's disease in Moroccan children: a report of 12 cases. Scand J Rheumatol. 2004;33:362–3.

[41] Koné-Paut I, Gorchakoff-Molinas A, Weschler B, Touitou I. Paediatric Behçet's disease in France. Ann Rheum Dis. 2002;61:655–6.

[42] Koné-Paut I, Yurdakul S, Bahabri SA, Shafae N, Ozen S, Ozdogan H, Bernard JL. Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. J Pediatr. 1998;132:721–5.

[43] Koné-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, Anton J, Hofer M, Chkirate B, Bouayed K, Tugal-Tutkun I, Kuemmerle-Deschner J, Agostini H, Federici S, Arnoux A, Piedvache C, Ozen S; PEDBD group. Consensus classification criteria for paediatricBehçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis. 2016;75:958–64. doi:10.1136/annrheumdis-2015-208491

[44] Krause I, Uziel Y, Guedj D, Mukamel M, Harel L, Molad Y, Weinberger A. Childhood Behçet's disease: clinical features and comparison with adult-onset disease. Rheumatology (Oxford). 1999;38:457–62.

[45] Karincaoglu Y, Borlu M, Toker SC, Akman A, Onder M, Gunasti S, Usta A, Kandi B, Durusoy C, Seyhan M, Utas S, Saricaoglu H, Ozden MG, Uzun S, Tursen U, Cicek D, Donmez L, Alpsoy E. Demographic and clinical properties of juvenile-onset Behçet's disease: a controlled multicenter study. J Am AcadDermatol. 2008;58:579–84.

[46] Atmaca L, Boyvat A, Yalçındağ FN, Atmaca-Sonmez P, Gurler A. Behçet disease in children. Ocul Immunol Inflamm. 2011;19:103–7. doi:10.3109/09273948.2011.555592

[47] Eldem B, Onur C, Ozen S. Clinical features of pediatric Behçet's disease. J Pediatr Ophthalmol Strabismus. 1998;35:159–61.

[48] Uziel Y, Brik R, Padeh S, Barash J, Mukamel M, Harel L, Press J, Tauber T, Rakover Y, Wolach B. Juvenile Behçet's disease in Israel. The Pediatric Rheumatology Study Group of Israel. Clin Exp Rheumatol. 1998;16:502–5.

[49] Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, Yurdakul S, Yazici H. The long-term mortality and morbidity of Behçet syndrome: a 2-decade

outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore). 2003;82:60–76.

[50] Saadoun D, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M, Cacoub P. Mortality in Behçet's disease. Arthritis Rheum. 2010;62:2806–12. doi:10.1002/art.27568

[51] Nakahara H, Kaburaki T, Tanaka R, Takamoto M, Ohtomo K, Karakawa A, Komae K, Okinaga K, Matsuda J, Fujino Y. Frequency of uveitis in the Central Tokyo Area (2010–2012). Ocul Immunol Inflamm. 2016;8:1–7

[52] Nakae K, Masaki F, Hashimoto T, Inaba G, Mochizuki M, Sakane T. Recent epidemiological features of Behçet's disease in Japan. In:Goeau P, Wechsler B, (eds). Behçet's disease. Amsterdam: Excerpta Medica, 1993. pp. 145–51.

[53] Joseph FG1, Scolding NJ. Neuro-Behçet's disease in Caucasians: a study of 22 patients. Eur J Neurol. 2007;14:174–80.

[54] Savey L, Resche-Rigon M, Wechsler B, et al. Ethnicity and association with disease manifestations and mortality in Behçet's disease. Orphanet J Rare Dis. 2014;9:42. doi:10.1186/1750-1172-9-42

[55] Davatchi F, Chams-Davatchi C, Shams H, Nadji A, Faezi T, Akhlaghi M, Sadeghi Abdollahi B, Ashofteh F, Ghodsi Z, Mohtasham N, Shahram F. Adult Behcet's disease in Iran: analysis of 6075 patients. Int J Rheum Dis. 2016;19:95–103. doi:10.1111/1756-185X.12691

[56] Alpsoy E. Behçet's disease: a comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. J Dermatol. 2016;43:620–32. doi:10.1111/1346-8138.13381

[57] Davatchi F, Chams-Davatchi C, Ghodsi Z, Shahram F, Nadji A, Shams H, Akhlaghi M, Larimi R, Sadeghi-Abdolahi B. Diagnostic value of pathergy test in Behcet's disease according to the change of incidence over the time. Clin Rheumatol. 2011;30:1151–5. doi:10.1007/s10067-011-1694-5

[58] Tüzün Y, Yazici H, Pazarli H, Yalçin B, Yurdakul S, Müftüoğlu A. The usefulness of the nonspecific skin hyperreactivity (the pathergy test) in Behçet's disease in Turkey. Acta Derm Venereol. 1979;59:77–9.

[59] Ozarmagan G, Saylan T, Azizlerli G, Ovül C, Aksungur VL. Re-evaluation of the pathergy test in Behçet's disease. Acta Derm Venereol. 1991;71:75–6.

[60] Akmaz O, Erel A, Gürer MA. Comparison of histopathologic and clinical evaluations of pathergy test in Behçet's disease. Int J Dermatol. 2000;39:121–5.

[61] Fresko I, Yazici H, Bayramiçli M, Yurdakul S, Mat C. Effect of surgical cleaning of the skin on the pathergy phenomenon in Behçet's syndrome. Ann Rheum Dis. 1993;52:619–20.

[62] Togashi A, Saito S, Kaneko F, Nakamura K, Oyama N. Skin prick test with self-saliva in patients with oral aphthoses: a diagnostic pathergy for Behcet's disease and recurrent aphthosis. Inflamm Allergy Drug Targets. 2011;10:164–70.

[63] Kaneko F, Togashi A, Nomura E, Nakamura K. A New diagnostic way for Behcet's disease: skin prick with self-saliva. Genet Res Int. 2014;2014:581468. doi:10.1155/2014/581468

[64] Chang HK, Kim JW. The clinical features of Behcet's disease in Yongdong districts: analysis of a cohort followed from 1997 to 2001. J Korean Med Sci. 2002;17:784–9.

[65] Ozyurt K, Colgecen E, Baykan H. Does familial occurrence or family history of recurrent oral ulcers influence clinical characteristics of Behçet's disease? Acta Dermatovenerol Croat. 2013;21:168–73.

[66] Ahmed Z, Rossi ML, Yong S, Martin DK, Walayat S, Cashman M, Tsoraides S, Dhillon S. Behçet's disease departs the 'Silk Road': a case report and brief review of literature with geographical comparison. J Community Hosp Intern Med Perspect. 2016;6:30362. doi:10.3402/jchimp.v6.30362.eCollection2016

[67] Verity DH, Marr JE, Ohno S, Wallace GR, Stanford MR. Behçet's disease, the Silk Road and HLA-B51: historical and geographical perspectives. Tissue Antigens. 1999;54:213–20.

[68] Shigemura T, Kaneko N, Kobayashi N, Kobayashi K, Takeuchi Y, Nakano N, Masumoto J, Agematsu K. Novel heterozygous C243Y A20/TNFAIP3 gene mutation is responsible for chronic inflammation in autosomal-dominant Behçet's disease. RMD Open. 2016;2:e000223. doi:10.1136/rmdopen-2015-000223. eCollection 2016