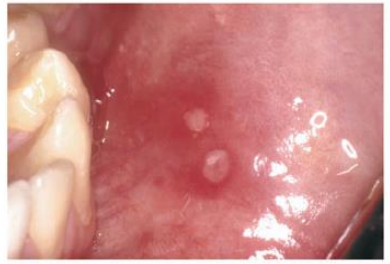
Tıp Fakültesi

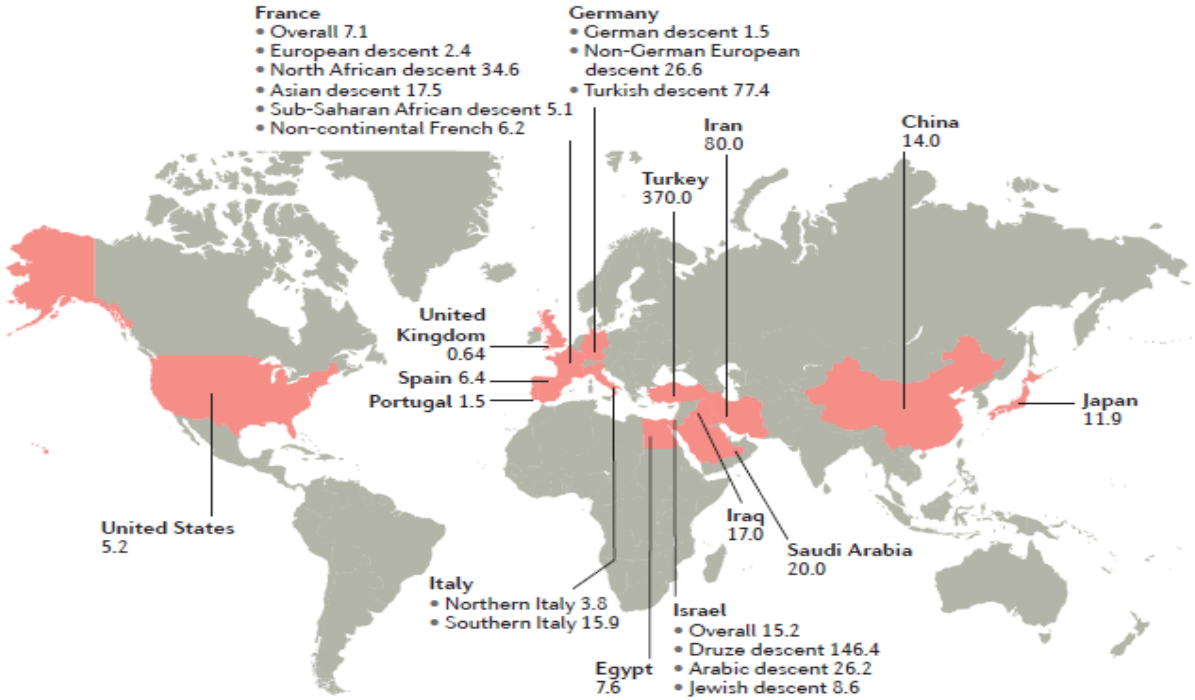
Behçet Hastalığı:
Sınıflandırmadaki Yeri ve Klinik Fenotipleri

Haner Direskeneli
Marmara Tıp Fakültesi
İç Hastalıkları ABD - Romatoloji BD



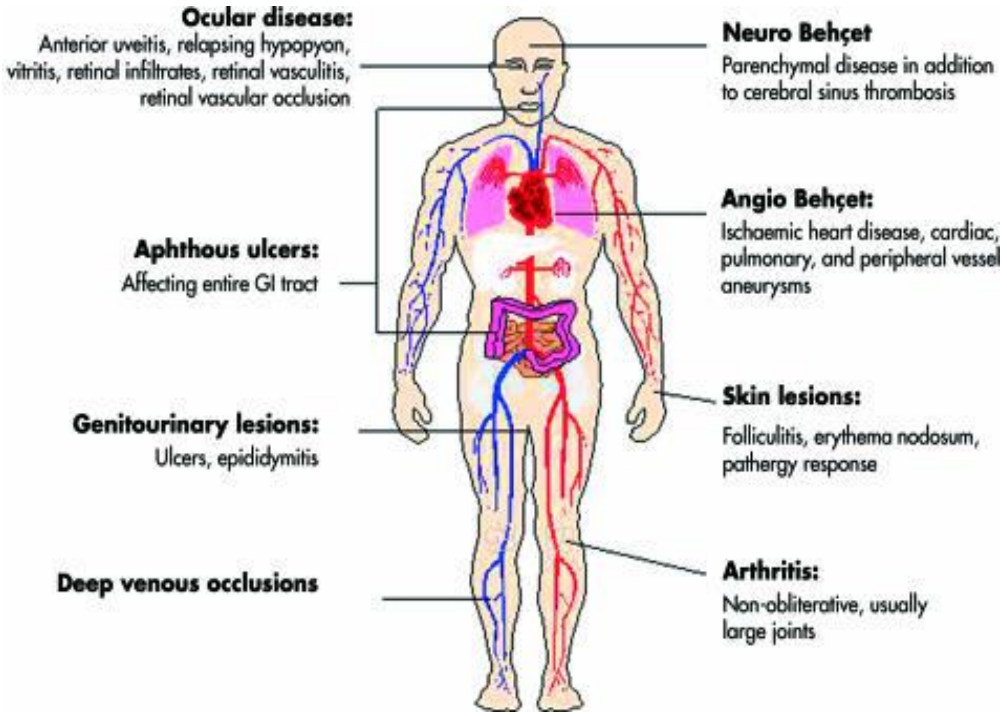
Epidemiyoloji

- **Remisyon relapslar ile klinik seyir**
- **Başlangıç yaşı: 20-35 yaş**
  - ***Çocuklarda nadir***
- **E/K: yaklaşık bir**
  - ***30 yaş altı erkeklerde daha ağır seyir***
- **Ailevi öykü**
- **Prevelans: 2-660/100.000**
  - **Çevresel faktörler:**
  - ***Türkler için: - Almanya'da: 77/100.000***
    - Türkiye'de: 370/100.000



(Yazıcı H, Nat Rheumatol, 2018)

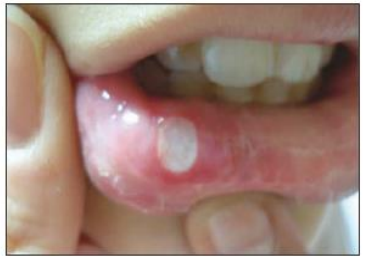
Behçet Hastalığı: Klinik



Semptom	*Prevelans (%)*
* Oral ülserler	97-98
* Genital ülserler	70-80
* Cilt (Folikülit, E. Nodozum)	50-80
* Cilt Prik testi (Paterji)	30-70
* Göz	40-50
Artrit/artralji	40-50
Vasküler	20-30
MSS	3-5
Gastro-intestinal	30 (Japonya) < 5 (Türkiye)

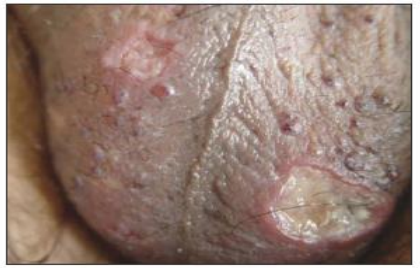
* : ISG Kriterleri

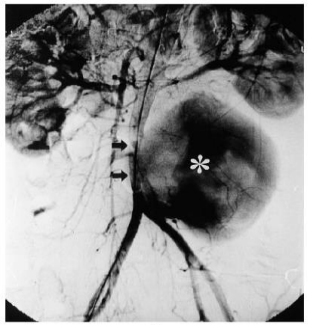
Behçet Hastalığı - Tanısal Süreç

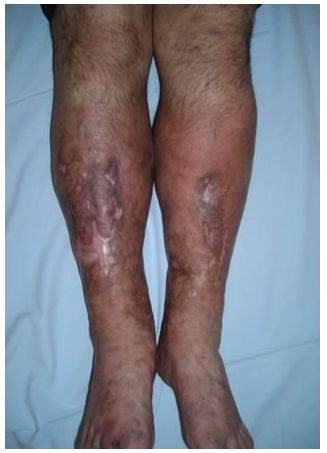


- **Özgün-olmayan (non-spesifik) bulgular**
  - ***Oral ülserler, mukokutan (eritema nodosum, folikülit)***
  - ***Ön üveit***
  - ***Eklem bulguları***
  - ***Gastro-intestinal***

- **Özgün bulgular**
  - ***Genital ülserler***
  - ***Arka üveit/retinit***
  - ***Vasküler tutulum***
  - ***MSS tutulumu***







Behçet Sendromu - Tanı kriterleri
(International Study Group, Lancet, 1990)

Tekrarlayan oral ülser varlığı

- **Başka nedene bağlı olmayan, aftöz ya da herpetiform, 12 ay içinde en az 3 kere tekrar eden**

Aşağıdakilerden en az ikisinin varlığı

1. ***Tekrarlayan genital ülserler***
2. ***Göz tutulumu*: ön, arka üveit, vitröz sıvıda biomikroskop ile hücre görülmesi ya da retinal vaskülit**
3. ***Cilt tutulumu*: eritema nodosum, pseudo-folikülit, papulo-püstüler lezyonlar, akneiform nodüller *(post-adelosan ve steroid almayan hasta)***
4. ***Paterji testi pozitifliği***

The International Criteria for Behçet's Disease (ICBD)

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test*	1*

scoring $\geq$ 4 indicates Behçet's diagnosis

	ISG (95% CI)	ICBD (95% CI)
Sensitivity	77.9% (71.3 to 83.6)	97.9% (94.7 to 99.4)
Specificity	69.1% (58.0 to 78.7)	19.1% (11.3 to 29.1)

Blake *et al. BMC Musculoskeletal Disorders* (2017)

BH’da Sınıflandırma - SpA Grubu

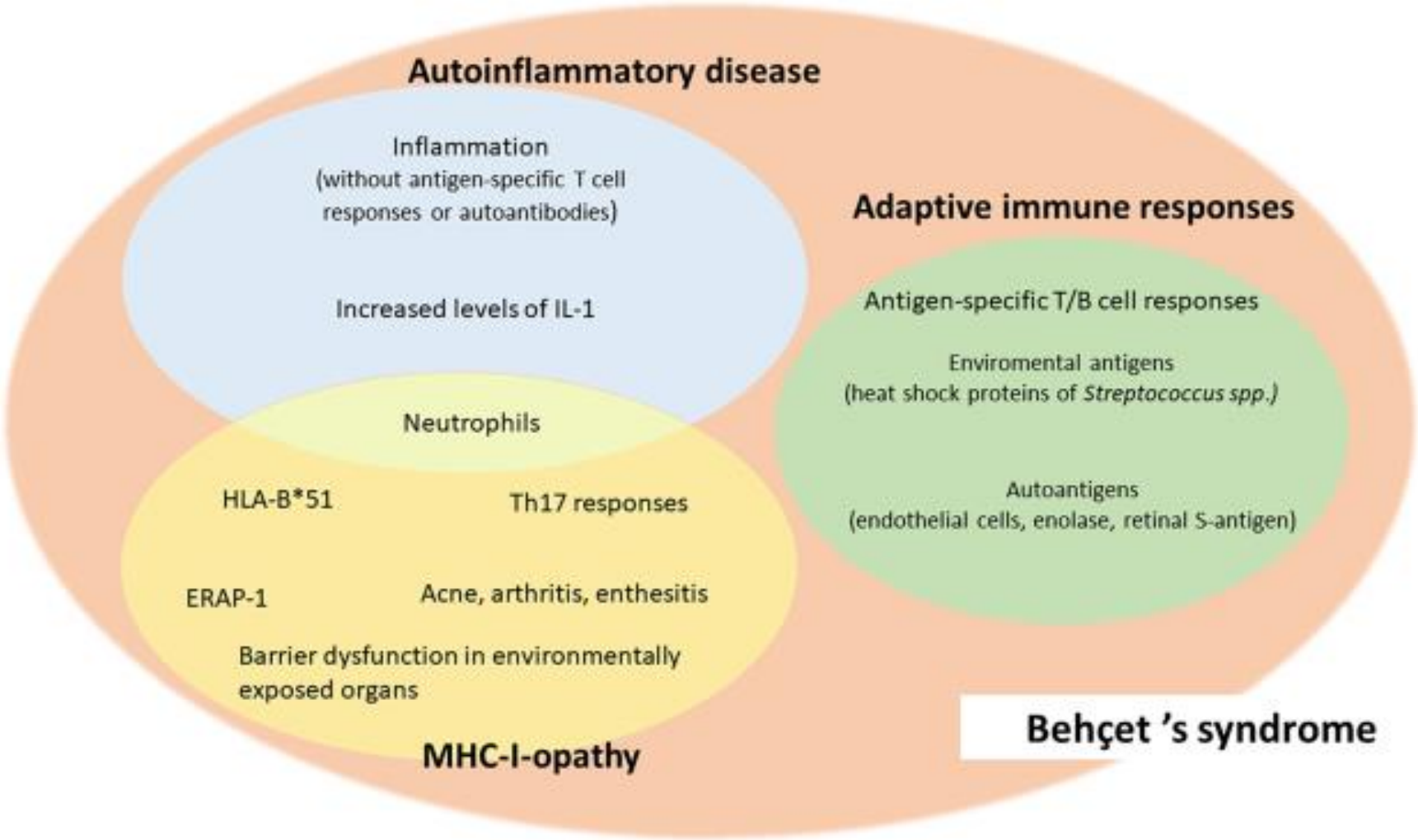
- **Moll JM, Haslock I, Macrae IF, Wright V (1974) Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. Medicine (Baltimore) 53:343–364**

- **Sakroileit, HLA-B*27 (-)**
- **Anterior vs posterior üveit**

	Behçet's (%)	Crohn's (%)
Oral ulcers	100	10
Nodular lesions	50	2–10
Pyoderma gangrenosum	<1	1–10
Rectal, anal disease	<1	10–15
Perforation	25–50	2
Fistula	5–10	20–30
Stricture	8	17
Granulomas	<1	10–15
ASCA	28–49	62–41

(Yazıcı H, Clin Rev All Immunol, 2012)

Behçet Patogenezinde farklı immün mekanizmalar olabilir mi ?



(Mattioli I,.. Direskeneli H, Emmi G. Front Med, 713052, 2021)

Behçet Hastalığı - Klinik Sınıflama

	Behcet H	Oto-inflamatuar	SpA	Oto-immün
Genetik (HLA)	Sınıf I	Inflamazom	Sınıf I	Sınıf II (DR)
Periodik seyir	+/-	++	-	-
Şiddet (Erkek)	++	+/-	+/-	-
Artrit	Mono/oligo	Mono/oligo	Mono/oligo	Poli
Otoantikorlar	-	-	-	++
Lenfadenopati	-	-	-	++
Ek Otoimmün (+)	-	-	-	++

(Yazıcı H, Intern Rev Immunol 1997, değiştirilerek)

Target Organ Associations in Turkish Patients with Behçet's Disease: A Cross Sectional Study by Exploratory Factor Analysis

Table 2. Factors derived from the rotated varimax.

Factor Eigenvalues	1.983	1.467	1.096	1.008	
Percentage of explained variance	24.79	18.34	13.71	12.60	
Loadings	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Communalities**
Oral ulcers	**0.608**	–0.088	0.057	0.471	0.603
Genital ulcers	**0.790**	0.024	–0.236	–0.022	0.680
Erythema nodosum	**0.656**	0.317	0.160	0.269	0.629
Papulopustular skin lesions	0.311	–0.163	–0.361	**0.629**	0.649
Joint involvement	–0.028	0.014	0.153	**0.863**	0.769
Uveitis	–0.035	0.009	**–0.919**	–0.026	0.846
Superficial vein thrombosis	–0.025	**0.866**	0.008	0.045	0.752
Deep vein thrombosis	0.011	**0.853**	–0.010	–0.088	0.735

(Tunc R, J Rheumatol, 2002)

BH'da Organ Tutulumu İlişkileri

Study, year	*n*	Method	Clusters or significant associations
Tunc et al. 2002	272	Factor analysis	1: Genital ulcers, and erythema nodosum 2: Superficial and deep vein thrombosis 3: Uveitis 4: Papulopustular skin lesions and joint involvement
Karaca et al. 2012	407	Factor analysis	1: Genital ulcers, and erythema nodosum with or without oral ulcers 2: Superficial and deep vein thrombosis 3: Uveitis 4: Papulopustular skin lesions and joint involvement with or without oral ulcers
Tascilar et al. 2014	882	Correspondence analysis	Cerebral venous sinus thrombosis and pulmonary artery involvement Budd–Chiari syndrome and vena cava involvement
Seyahi et al. 2014	343	Chi-square test	Budd–Chiari and peripheral major vessel disease
Bitik et al. 2016	295	Chi-square test	Posterior uveitis and parenchymal neurological involvement
Hussein et al. 2018	249	Logistic regression analysis	Severe eye involvement negatively associated with genital ulceration and vascular involvement

(Seyahi E, Int Emer Med, 2019)

BH'da Fenotipler (1)

- **Cilt-Mukoza Sınırlı (% 30)**
  - **E=K, rekürren oro-genital ülserler, foliküler ve nodüler lezyonlar**
  - **Spontan düzelme sık, major morbidite/mortalite yok**

- **Eklem Fenotipi (% 10)**
  - **E=K, Rekürren asimetrik, alt-ekstremite ağırlıklı artrit**
  - **Deformite, sakroileit, HLA-B*27 (-), mukokutan ?**
  - **Spontan düzelme sık, major morbidite/mortalite yok**

(Seyahi E, Int Emer Med, 2019)

BH'da Fenotipler (2)

- **Oküler Fenotip (% 50)**
  - **E>K, non-granülomatöz pan ya da arka-üveit**
  - **Tedavisiz sık görme kaybı**

- **Vasküler Fenotip (% 10-20)**
  - **E>K, venöz/arteriyel tutulum**
  - **En önemli mortalite nedeni**
    - **Pulmoner anevrizma, Budd-Chiari sendromu**

(Seyahi E, Int Emer Med, 2019)

BH'da Seyrek Fenotipler (3)

- **Parankimal MSS tutulumu (% 5)**
  - **E>K, ağırlıkla beyin sapını tutan meningoensefalit**
    - **Serebellar korteks korunmuş**
  - **Oküler tutulum ile sık beraber**
  - **Morbidite yüksek, mortalite hafif artmış**

- **Gastro-intestinal tutulum (< % 5)**
  - **E=K, inflamatuar-barsak hastalığı benzeri tutulum**
  - **Cerrahi girişim: % 50'ye varan oranda (10 yıl)**
  - **Mortalite artışı sınırlı**

(Seyahi E, Int Emer Med, 2019)

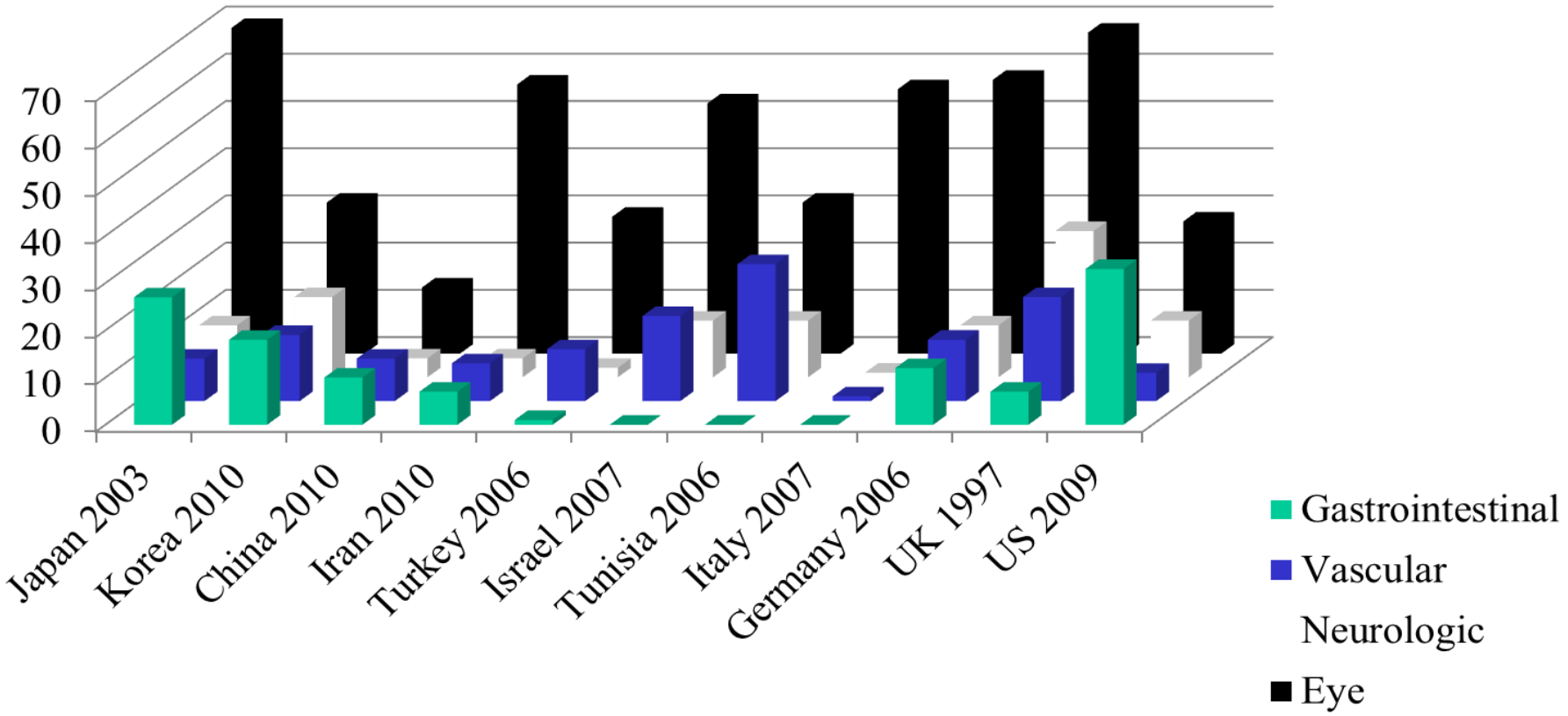
BH'da Fenotipler - Farklı Türkiye Serisi

467 hasta - ISG (+): % 92, ICBD (+): % 96

Disease Manifestations	Vascular C1, n = 132 (31.2%)	Eye C2, n = 66 (15.6%)	MSK C3, n = 60 (14.2%)	Mucocutaneous C4, n = 165 (39%)
Mucocutaneous	Yes	Yes	Yes	Yes
MSK	Yes	No	Yes	No
Gastrointestinal	No	No	No	No
Uveitis	No	Yes	No	No
Superficial thrombophlebitis	Yes	No	No	No
Vascular	Yes	No	No	No
CNS parenchymal	No	No	No	No

Oğuz E, J Clin Rheumatol, 2023)

Behçet Hastalığında Ülkesel Klinik Farklılıklar



Behçet's syndrome in Italy: a detailed retrospective analysis of 396 cases seen in 3 tertiary referral clinics

Internal and Emergency Medicine (2020) 15:1031–1039

Clinical features throughout the course of Behçet's syndrome	*N* (%)
Recurrent oral ulcers	389 (98.2)
Genital ulcers	265 (66.9)
Pseudofollicular lesions	144 (36.4)
Papulopustular lesions	111 (28.0)
Erythema nodosum	109 (27.5)
Ocular involvement	170 (42.9)
CNS involvement	21 (5.3)
Gastrointestinal involvement	135 (34.1)
Vascular involvement	96 (24.2)

Factor's eigenvalues	1.86	1.58	1.21
Percentage of variance explained	26.5	22.5	17.3
Loadings	Factor 1	Factor 2	Factor 3
Oral aphthosis	0.313	−0.892	–
Genital aphthosis	0.899	–	–
Erythema nodosum	0.504	–	–
Pseudofolliculitis	0.641	–	–
Papulopustular lesions			−0.828
Uveitis	–	0.865	–
Arthritis	–	–	0.744

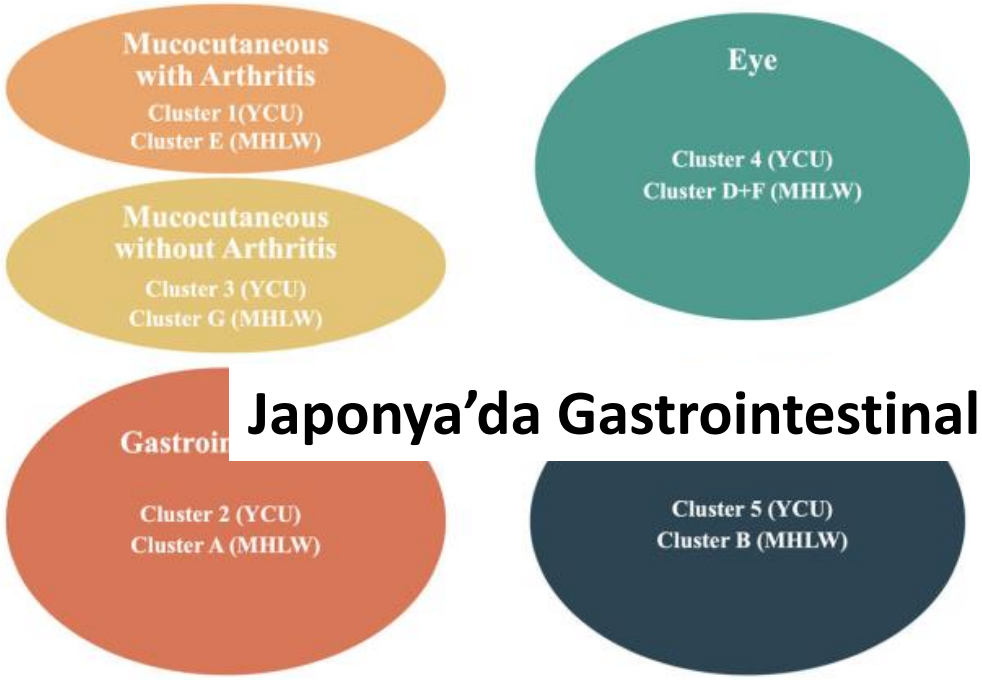
BH'da Organ Tutulumu İlişkileri - Japonya

Study, year	*n*	Method	Clusters or significant associations
Kurosawa et al. 2018	2218	Correspondence analysis	1: Male, eye disease, HLA-B51 (+), neurologic involvement 2: Female, genital ulcers, onset age: < 30 years, no eye disease, HLA-B51 (-), no neurologic involvement 3: Onset age: 30–39 years, skin lesions, arthritis
Suwa et al. 2018	3213	Logistic regression analysis	Eye involvement negatively associated with genital ulceration and gastrointestinal involvement
Suzuki et al. 2018	7950	Chi-square test	Gastrointestinal involvement negatively associated with eye involvement, vascular involvement negatively associated with genital ulceration and positively associated with HLA-B51

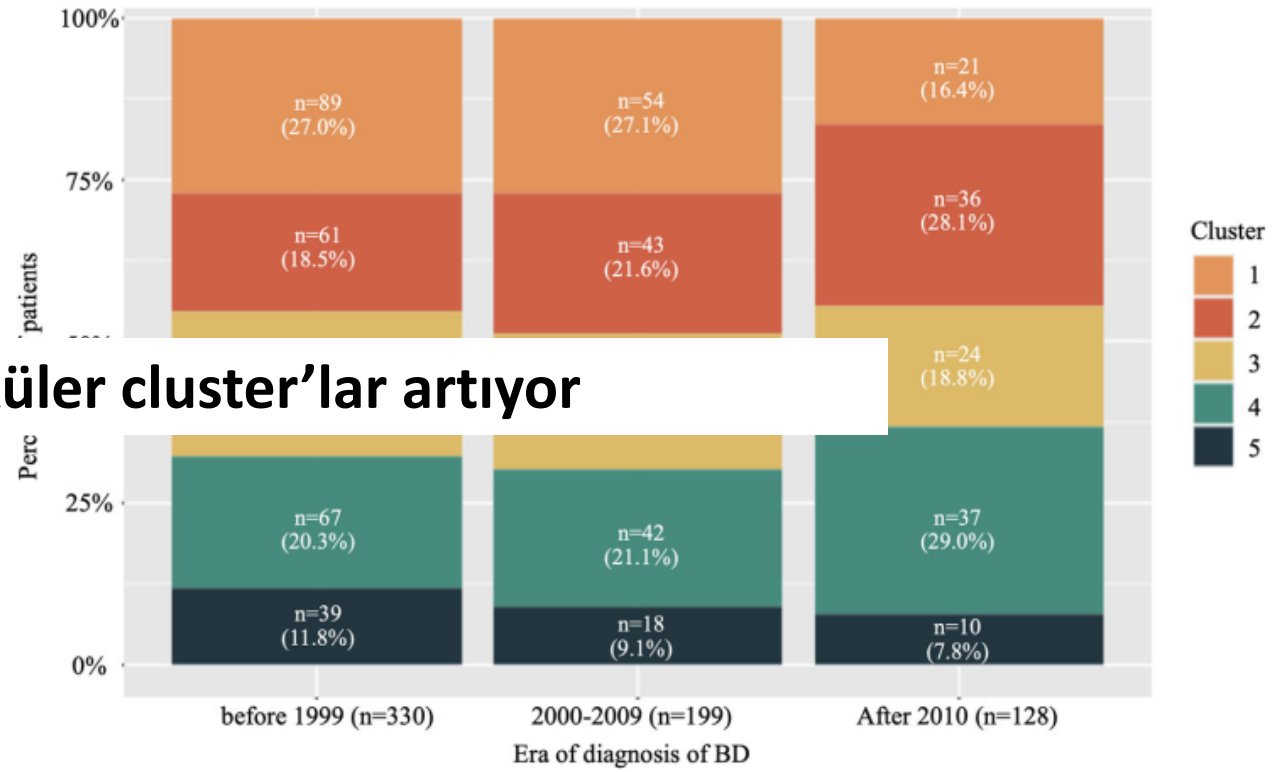
(Seyahi E, Int Emer Med, 2019)

Changes in the proportion of clinical clusters contribute to the phenotypic evolution of Behçet's disease in Japan

Soejima *et al. Arthritis Research & Therapy* (2021) 23:49

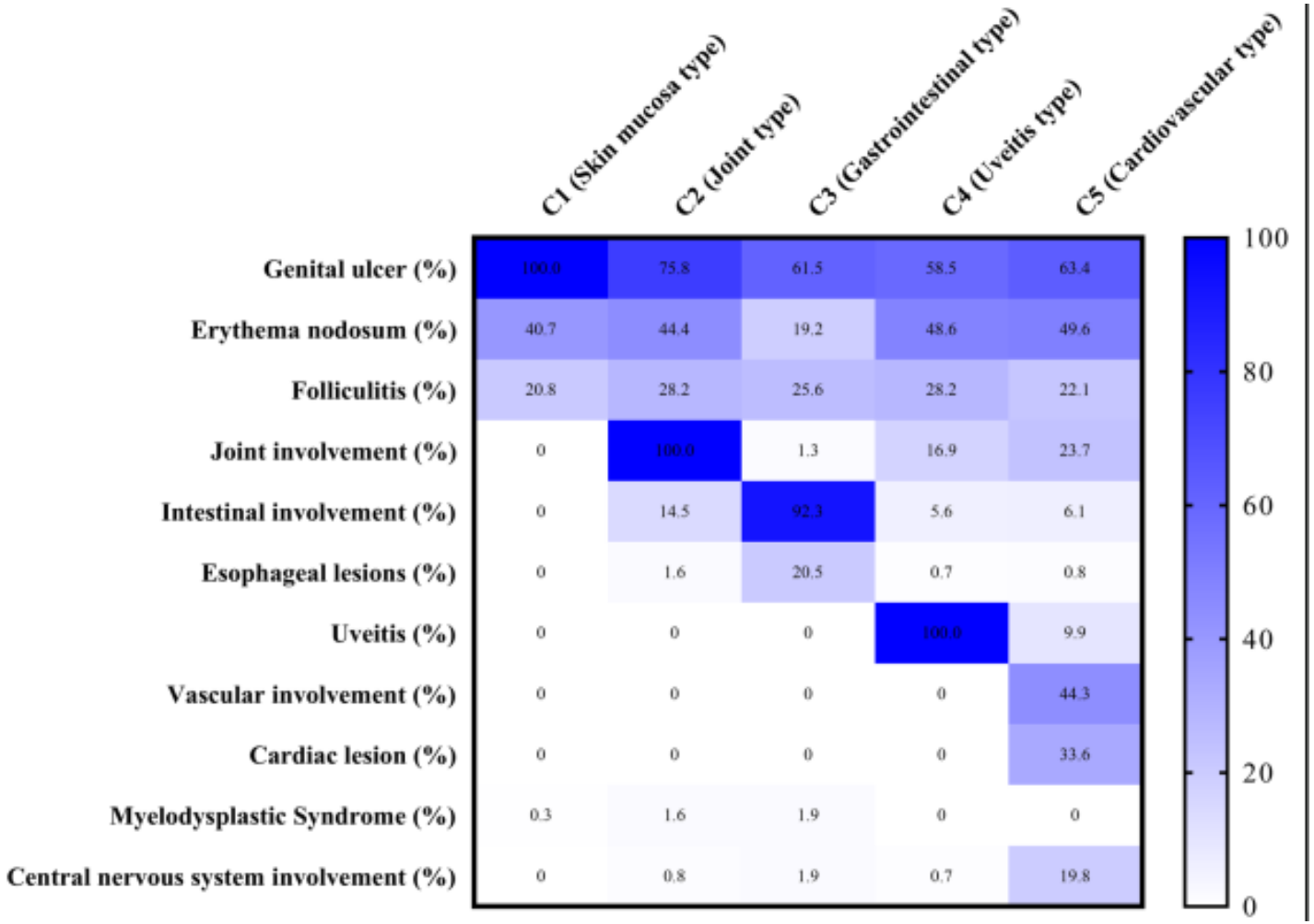


Japonya'da Gastrointestinal ve oküler cluster'lar artıyor



Cluster analysis of phenotypes of patients with Behçet's syndrome: a large cohort study from a referral center in China

Zou *et al. Arthritis Research & Therapy* (2021) 23:45

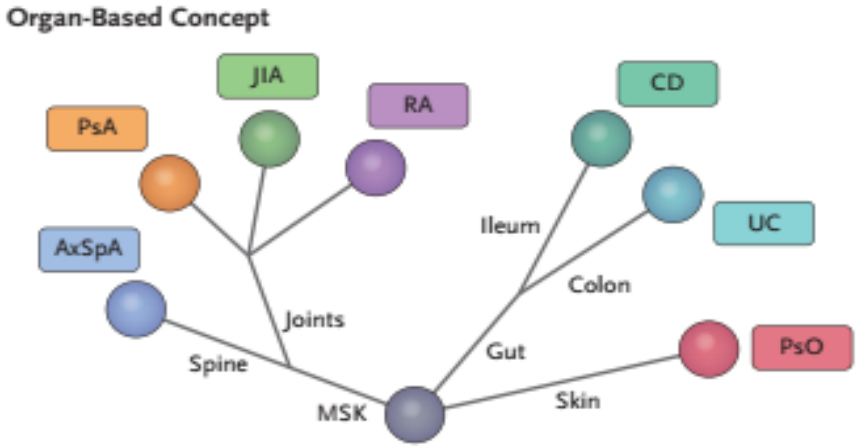


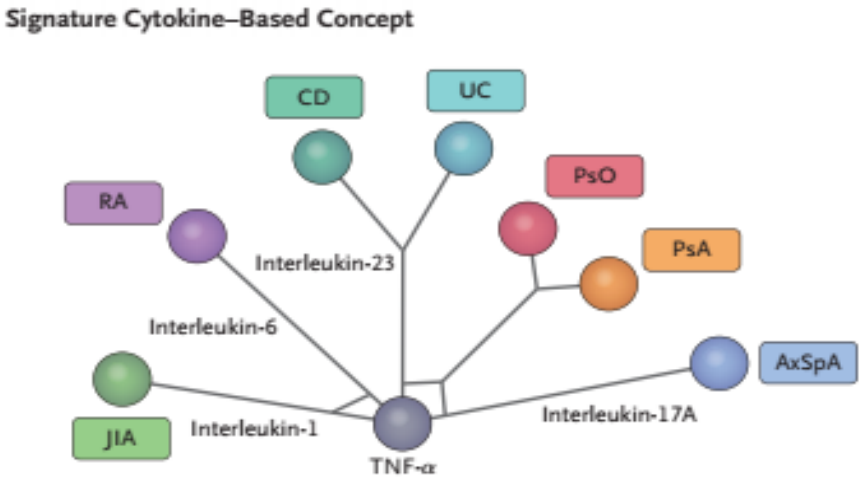
The NEW ENGLAND JOURNAL of MEDICINE

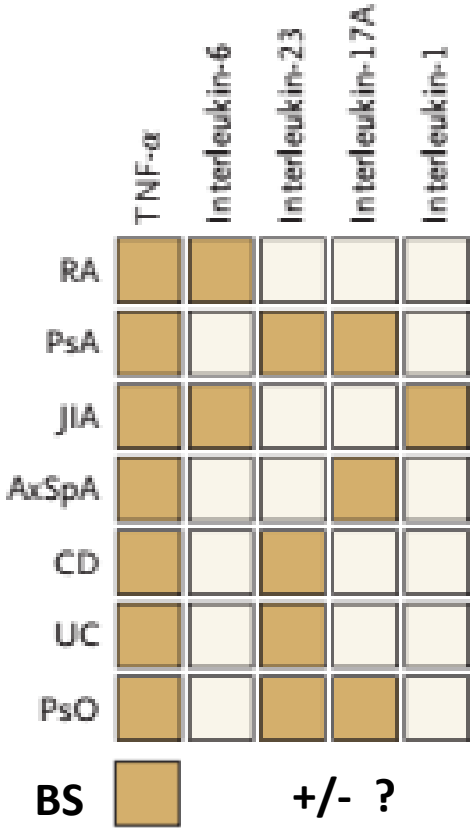
Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs

İmmün-kökenli İnflamatuar Hastalıkların Sınıflandırılması

Organ tutulumu vs sitokin ağı ?





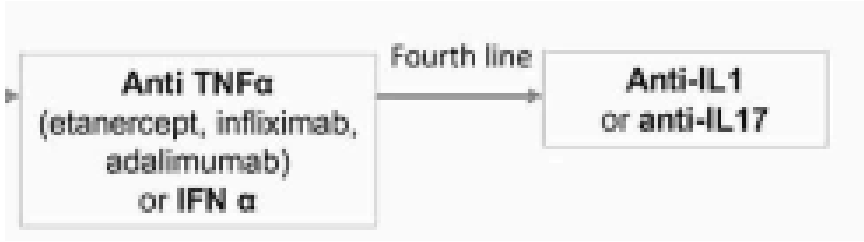


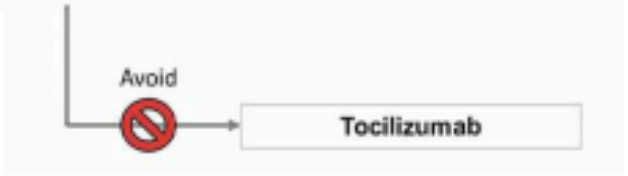
Georg Schett, M.D., Iain B. McInnes, M.D., Ph.D., and Markus F. Neurath, M.D.

Behçet'de farklı fenotipler (tutulumlar ?) farklı sitokin blokajına cevap verir

(Bettiol A, Front Immunol, 2019)

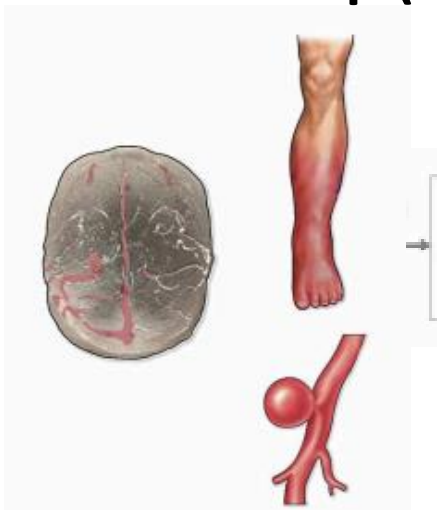
Mukokutan/artiküler tip

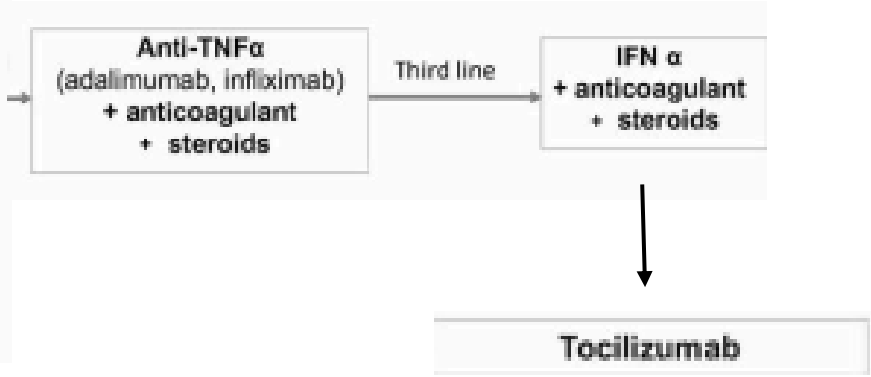




Oküler/ Parenkimal Nörolojik Tip

Vasküler Tip (DST ve periferik)





BH’da Fenotipler - Sonuç

- **Behçet Hastalığı farklı fenotipik seyirler gösterebilir.**

- **Muko-kutan ve eklem tutulumu ağırlıklı fenotipler SpA benzeri klinik özellikler ile seyrederler.**
  - ***Th17 yanıtı***
  - ***Akne/entezit/artrit***
  - ***İyi klinik prognoz***

BH’da Fenotipler - Sonuç (2)

- **Major organ tutulumları içinde 2 fenotip öne çıkmaktadır.**
- **Vasküler fenotip**
  - ***Periferik vasküler + MSS’de venöz tutulum***
- **Oküler + parenkimal MSS tutulumu**

- **Ancak prognozun değerlendirilmesi ve tedavi kararlarında hala en önemli ölçüt major organ (oküler, vasküler, MSS, GIS) hasarı/mortalite riskidir.**