Phenotype Clusters in Behçet's Syndrome, Myth or Reality: A Systematic Review

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Background

- The presence of distinct clinical phenotypes with clustering of certain organ manifestations were suggested in Behçet's syndrome.
- However, studies from different cohorts have shown variability in the phenotypes that were defined.
- This finding challenges the concept of phenotype clusters since organ manifestations that cluster together would be expected to be uniform across cohorts.

Methods

- An electronic search was carried out in PubMed, EMBASE, and Cochrane Library to find articles published until February 2022 using the key words of Behcet*.
- Two reviewers independently performed a screening of titles, abstracts, and the full-texts using Covidence.
- 7685 studies searched, 32 full texts were assessed,
- 11 studies were identified as relevant for data extraction.

Clinical phenotype clustering across cohorts

Author, year	n (♂/♀)	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Demir, 2022 Turkey	225, (31/33)	MC (OU, GU, EN, PPL)	PPL - Arthritis-entesopathy	U	V	GI	
Zou, 2021 China	69, (31/38)	MC (GU, EN, PPL)	U, V, NBS	GI			
Zou, 2021 China	860, (462/398)	MC (GU, EN, PPL)	U	GI	J	CVS, NBS	
Zou, 2021 China	152, (73/79)	MC (GU, EN, PPL)	U, V, NBS	GI	J		
Soejima, 2021 Japan	657, (285/372)	MC (OU, GU and Skin inv.) w/o J	U	Negative correlation of GI &U	MC (OU, GU and Skin inv.), J	NBS	
Soejima, 2021 Japan	6754, (2764/3990)	MC (OU, GU and Skin inv.) w/ o J	U, OU, GU and Skin inv.	Negative correlation of GI &U	MC (OU, GU and Skin inv.), J	NBS	U, OU, Skin inv.
Sota, 2020 Italy	396, (178/218)	MC (OU, GU, EN, PF)	U	Negative correlation of J and PPL			
Kurosawa, 2018 Japan	2218	♂,U, HLA-B51-positive, NBS	♀,GU, onset age: <30 years, U-negative, HLA-B51-negative, NBS negative involvement-negative"	Onset age: 30–39 years, skin lesions, arthritis			
Karaca, 2012 Turkey	186, (108/78)	MC (GU, EN)	U	STM, DVT	J, PPL, OU		
Karaca, 2012 Turkey	221, (148/73)	MC (OU, GU, EN)	U	STM, DVT	J, PPL		
Arida, 2009 Greece	142, (80/62)	No cluster was found					
Tunc, 2002 Turkey	272, (153/119)	MC (OU, GU, EN)	U	STM, DVT	J, PPL		
Krause, 1999 Israel	68, (30/38)	MC (GU, PPL)	Negative correlation of STM and EN	GI, PPL	J	DVT, NBS	

CVS: Cardiovascular system, DVT: deep vein thrombosis; EN: erythema nodosum; GU: genital ulcers; GI: gastrointestinal involvement J: joint involvement;
MC: mucocutaneous involvement; NBS: Neuro-Behçet syndrome, OU: oral ulcers; PF: pseudofolliculitis; PPL: papulopustular lesions; STM: superficial thrombophlebitis;
U: uveitis; V: vascular involvement

10/11 studies demonstrated clustering of organ manifestations (12 cohorts); whereas no clusters were identified in one study.

Possible Predictors of the Differences in Clusters Reported in These Studies

a. Study design
b. Statistical analysis (method and variables that are included in the analysis)
c. Patient population (pediatric vs adult),
d. Setting (dermatology vs rheumatology),
e. Diagnostic criteria (ISG vs ICBD),
f. Disease duration
g. Definition of organ involvement (such as papulopustular vs folliculitis, or parenchymal nervous system involvement vs dural sinus thrombosis,
h. Ascertainment of manifestations (confirmed gastrointestinal involvement vs any diarrhea),
i. Time interval (manifestations throughout the disease course vs manifestations that were active during the last 3 months, and
j. Change in natural history of BS over decades.

Cohort characteristics of the studies

Author, year	Country	Study population	Statistical method	Patient population	Timing of Cluster Analysis	Diagnostic criteria	Cluster Variables
Demir, 2022	Turkey	Multicenter cohort	Two-Step Cluster Analysis	Pediatric	Throughout the disease course	ISG and/or BDRC and/or PEDBD	Continuous variables: Current age, age at disease onset, duration of disease, IBDDAM, and PGA. Categorical variables: Gender, clinical manifestations, major organ involvements, and classification criteria.
Zou, 2021	China	Single center cohort	Hierarchical (Two-Step) Cluster Analysis	Pediatric	Throughout the disease course	ISG and/or BDRC and/or PEDBD and/or Cheng and Zhang criteria and/or ICBD	Continuous variables: Age, age at onset, duration of disease, and Krause score. Categorical variables: Sex, clinical manifestation (oral ulcer, genital ulcer, erythema nodosum, folliculitis, joint involvement), major organ involvement (uveitis, GIBS, cardiovascular involvement, CNS involvement and myelodysplastic syndrome.
Zou ,2021	China	Single center cohort	Hierarchical (Two-Step) Cluster Analysis	Adult	Throughout the disease course	ISG and/or BDRC and/or Cheng and Zhang criteria and/or ICBD	Continuous variables: Age, age at onset, duration of disease, and Krause score. Categorical variables: Sex, clinical manifestation (oral ulcer, genital ulcer, erythema nodosum, papulopustular lesions, joint involvement), and major organ involvement (uveitis, GIBS, cardiovascular involvement, parenchymal involvement, cerebral venous sinus thrombosis, cerebral arterial involvement, and myelodysplastic syndrome.
Zou ,2021	China	Single center cohort	Hierarchical (Two-Step) Cluster Analysis	Adult (late onset BS)	Throughout the disease course	ISG and/or BDRC and/or Cheng and Zhang criteria and/or ICBD	Continuous variables: Age, age at onset, duration of disease, and Krause score. Categorical variables: Sex, clinical manifestation (oral ulcer, genital ulcer, erythema nodosum, folliculitis, joint involvement), major organ involvement (uveitis, GIBS, cardiovascular involvement, central nerve involvement), and myelodysplastic syndrome. .
Soejima ,2021	Japan	Japan national BD registry	Ward's Hierarchical Cluster Analysis	Adult	Throughout the disease course	BDRC	Clinical variables: Oral ulcer, skin lesions, eye involvement, genital ulcer, arthritis, GIBS, vascular involvement, neurological involvement.
Soejima ,2021	Japan	Japan national BD registry	Ward's Hierarchical Cluster Analysis	Adult	Throughout the disease course	BDRC	Clinical variables: Oral ulcer, skin lesions, eye involvement, genital ulcer, arthritis, GIBS, vascular involvement, neurological involvement.
Sota, 2020	Italy	Multicenter cohort	Factor Analysis	Adult and Juvenile	At disease onset	ISG and/or ICBD	Clinical variables: Oral ulcer, genital ulcer, erythema nodosum, pseudofolliculitis, papulopustular lesions, joint involvement (only arthritis) and uveitis. *Symptoms presenting at onset with a frequency lower than 5% were excluded from the model to preserve robustness.
Kurosawa ,2018	Japan	Japan national BD registry	Hayashi's quantification third methods	NR	Throughout the disease course	BDRC	Clinical variables: Sex, age of onset, oral ulcer, skin lesions, ocular inflammation, genital ulcer, arthritis, GIBS, vascular lesions, neurologic involvement, pathergy test, HLA B51
Karaca ,2012	Turkey	Single center cohort	Factor Analysis and Hierarchical Cluster Analysis	Adult-Familial cases	Active manifestation/s during the previous 3 months	ISG	Clinical variables: Oral ulcer, genital ulcer, erythema nodosum, papulopustular skin lesions, uveitis, joint involvement (arthritis and/or arthralgia), superficial vein thrombosis, deep vein thrombosis *Clinical manifestations which had a frequency of <10% since diagnosis (GIBS, CNS and pure arterial involvement) were excluded from the analyses.
Karaca ,2012	Turkey	Single center cohort	Factor Analysis and Hierarchical Cluster Analysis	Adult Non-familial cases	Active manifestation/s during the previous 3 months	ISG	Clinical variables: Oral ulcer, genital ulcer, erythema nodosum, papulopustular skin lesions, uveitis, joint involvement (arthritis and/or arthralgia), superficial vein thrombosis, deep vein thrombosis *Clinical manifestations which had a frequency of <10% since diagnosis (GIBS, CNS and pure arterial involvement) were excluded from the analyses.
Arida ,2009	Greek	Single center cohort	X^2 test	Adult	Throughout the disease course	ISG	Clinical variables: Oral ulcer, genital ulcers, folliculitis, erythema nodosum, joint involvement, thrombophlebitis, GIBS, uveitis, CNS involvement.
Tunc ,2002	Turkey	Single center cohort	Factor Analysis	Adult	Last 3 months	ISG	Clinical variables: Oral ulcer, genital ulcer, erythema nodosum, papulopustular skin lesions, uveitis, joint involvement (arthritis and/or arthralgia), superficial vein thrombosis, deep vein thrombosis *Clinical manifestations which had a frequency of <10% since diagnosis (CNS, gastrointestinal system and pure arterial involvement) were excluded from the analyses.
Krause ,1999	Israel	Multicenter center cohort	Factor Analysis	Adult and Juvenile	Throughout the disease course	ISG	Clinical variables: Folliculitis, papulopustular skin lesions, erythema nodosum, genital ulcer, ocular (uveitis), GIBS, joint, superficial vein thrombosis, deep vein thrombosis, CNS involvement. *Oral ulcers (since all patients have ulcers), pathergy test and clinical manifestations with a very low rate of occurrence (less than 10%, including arterial involvement and pleuropulmonary manifestations) were not included.

BDRC: 1987 revised diagnostic criteria for BD by Behçet's Disease Research Committee of Japan
CNS: central nervous system CVST: cerebral venous sinus thrombosis; GIBS: Gastrointestinal Behçet's syndrome; IBDDAM: Iranian BD dynamic activity measure; ICBD; International Criteria for Behçet Syndrome; ISG: International Study Group criteria; NR: Not reported, PGA: physician global assessment

CONCLUSION

Differences between studies in clinical phenotype clusters may result from differences in study characteristics rather than real geographic or ethnic differences.