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*Original Article*

# Comparison of Clinical Features with Behçet's Disease Between Paediatrics and Adults Patients

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**Abstract**

***Background:*** Behçet's disease (BD) is a multifactorial auto-inflammatory disorder that affects various organ systems. This study aims to provide a comprehensive analysis of the clinical features, diagnostic approaches, and treatment strategies employed in BD. ***Methods:*** We conducted a thorough review of the literature to gather pertinent information on the clinical manifestations, diagnostic criteria, and therapeutic modalities for BD. We meticulously examined the findings from relevant studies and guidelines, synthesising key insights. ***Results:*** BD is characterised by recurring oral aphthae, genital ulcers, ocular involvement, and cutaneous manifestations. Despite primarily affecting individuals in the 20-40 year age range, a notable percentage of cases exhibit paediatric onset. Because there are no definitive laboratory tests, the diagnosis of BD relies primarily on clinical criteria. Proposals for multiple diagnostic frameworks exist, and the disease phenotype shows significant heterogeneity across ethnicities, geographical regions, and age cohorts. Genetic factors, particularly HLA-B51 positivity, confer increased susceptibility to BD. Different types of treatments are available depending on how many organs are affected. These may include colchicine, corticosteroids, traditional and biologic disease-modifying anti-rheumatic drugs, and targeted therapies like TNF-α inhibitors, anti-interleukin-1, and anti-interleukin-6 agents. However, determining the optimal therapeutic approach remains an area of active investigation and necessitates personalised patient management. ***Conclusion:*** Patients with BD diagnosed at different ages or genders may exhibit different clinical findings. Especially, more severe organ involvement and a higher disease activity-related BD may exist in adults than in children with BD. Adult patients needed more intense immunosuppressive treatment.

**Key words** *Behçet's disease; Clinical manifestations; Diagnosis; Treatment*

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## Introduction

Behçet's disease (BD) is a multi-systemic and multi-factorial auto-inflammatory disease that can affect all types and sizes of vessels. It is characterised by recurrent oral aphthae, genital ulcers, eye involvement, and skin findings.[1] Hulusi Behçet, a dermatology professor, first described BD in 1937 as a trilogy of aphthous stomatitis, genital ulcers, and uveitis.[2] BD's geographic distribution extends along the former Silk Road, from the Far East to the Mediterranean basin.[1] Although BD predominantly affects young adults between the ages of 20 and 40, 4-26% of patients present during childhood.[1,3] Typical clinical findings associated with BD may manifest over several years in the paediatric age group, resulting in a longer lag

time in diagnosis compared to adult patients.[4] There is no definitive laboratory test for diagnosing BD, and various sets of diagnostic criteria have been proposed. The phenotype of the disease varies among different ethnic groups, countries, and age groups.[3] Genetic factors play a role in disease predisposition, such as the association of BD with HLA-B51.[1] HLA-B51 positivity increases the risk of BD by 1.3 to 16 times.[5] Treatment generally depends on the involved organs. Colchicine is commonly used to control recurrent oral aphthae and genital ulceration. In cases of severe ulcers, short-term steroids can be effective. Corticosteroids, as well as conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs), are additional treatment options for chronic lesions. For severe vascular, neurological, or ocular involvement, a mix of steroids, immunosuppressive drugs, and tumour necrosis factor alpha (TNF-α) inhibitors may be needed. Recent studies have shown that anti-interleukin-1 and anti-interleukin-6 treatments are beneficial in BD patients who do not respond to traditional therapies.[4] Clinical findings, treatment response, disease severity, and outcomes may exhibit some differences between paediatric and adult BD patients. However, there are only a few studies in the current literature that have compared paediatric-onset and adult-onset BD patients.[6-8] In this study, our aim was to compare the demographic and clinical features of paediatric and adult patients with BD in order to better understand the overall course of the disease and facilitate the transition of paediatric patients to adult clinics.

## Materials and Methods

The study included 72 paediatric BD patients younger than 16 years old who were followed up at the paediatric rheumatology outpatient clinic of Gazi University Faculty of Medicine between 2011 and 2021 and 99 adult BD patients who were followed up at the rheumatology outpatient clinic of Gazi University Faculty of Medicine between 2016 and 2021. We retrospectively reviewed the patients' medical records. All patients met the International Diagnostic Criteria for Behçet's Disease.[9] We recorded and compared the demographic characteristics of the patients, including gender, age, age at diagnosis, delay in diagnosis, oral aphthae, genital ulcers, erythema nodosum, pseudofolliculitis, vascular involvement, neurological involvement, musculoskeletal system involvement, gastrointestinal involvement, pathergy positivity, HLA-B51 status, family history, and treatments. Imaging techniques, gastrointestinal (GI) endoscopy, eye examinations, and tissue biopsies determined the organ involvement associated with BD. We evaluated disease activity using the Iranian Behçet's Disease Dynamic Activity Measure during the first and last visits.[10] Neuro-Behcet's, major vein thrombosis, retinitis, posterior/pan uveitis, and GI involvement were all considered serious diseases. On the other hand, anterior uveitis, mucocutaneous findings, musculoskeletal system involvement, deep vein thrombosis of the legs, skin lesions, and mild gastrointestinal symptoms were considered mild or moderate.[11] Our rheumatology clinics followed up with the patients at three-month intervals, and conducted ophthalmological examinations at six-month intervals. The IBM SPSS Statistics 21 program evaluated the statistical analysis. In the presentation of descriptive statistics, if the quantitative data showed a normal distribution, it was given as mean ± standard deviation, and if not, it was given as median with interquartile range. We expressed categorical data as numbers and percentages. We chose the appropriate one from the Chi-square or Fisher's exact test when comparing categorical data. A P value less than 0.05 was considered significant. The local ethics committee approved the study protocol (Gazi University, 2021-1178).

## Results

There were 72 paediatric and 99 adult patients with equal gender distributions. The mean age of the paediatric patients at the diagnosis of BD and at clinical data collection was 12 (2-14) and 16 (7-25) years, respectively. Respective analyses were 28 (11-56) and 38 (19-63) years in adult patients, respectively. The lag time in diagnosis was 9 months in paediatric patients and 7.5 months in adult patients. The comparisons of clinical and demographic findings between the two patient groups are shown in Table 1. It was more common in children to have HLA-B51 positivity ($p<0.001$), a family history of the disease ($p<0.001$), and findings in the musculoskeletal system ($p<0.001$). In adults, it was more common to have erythema nodosum ($p<0.001$), vascular involvement ($p=0.013$), and neurological involvement ($p=0.015$). Recurrent oral aphthae were present in all paediatric and adult patients. In the comparison of disease activity by IBDDAM activity scale at the first visit, the median activity score was 4 (2-14) in paediatric patients and 6 (2-16) in adult patients ($p=0.078$). Last visit, the median

activity score was 1 (0-4) in paediatric patients and 0 (0-6) in adult patients (p<0.001). The most common types of uveitis in paediatric patients were anterior (16.7%) and posterior uveitis (13.9%), followed by pan-uveitis, intermediate uveitis, and retinitis, while the most common types of uveitis in adult patients were pan-uveitis (30.3%), followed by posterior, anterior, intermediate uveitis, and retinitis. Vascular involvement was significantly higher in adult patients (p=0.019). Nine (12.5%) paediatric patients and 27 (27.3%) adult patients had vascular involvement. Vascular involvement patterns are given in Table 2. However, arterial involvement was more common in children, including pulmonary artery involvement in two patients, hepatic artery involvement in one, and thalamic artery involvement in one, while only 2 out of 99 adult patients had arterial involvement (6% vs. 2%) (p=0.215). Other vascular diseases were in the form of venous involvement. While there was only one paediatric patient with two different vascular site involvements, this condition was seen in three adults with BD. Neurological involvement-related BD was detected in 18 adult and 4 paediatric patients (18% vs. 6%, respectively, =0.015).

**Table 1** The comparison of demographic and clinical characteristics of the patients

| | Children | | | Adult | | | p | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n=72 (%) | | | n=99 (%) | | | | |
| | Total | Famle | Male | Total | Famle | Male | * | † | ** |
| Family history | 24 (33.3) | 7 (20.6) | 17 (44.7) | 8 (8.1) | 4 (8.7) | 4 (7.5) | **<0.001** | **0.03** | 0.834 |
| HLA-B51 | 40 (55.6) | 16 (47.1) | 24 (63.2) | 27 (27.3) | 14 (30.4) | 13 (24.5) | **<0.001** | 0.170 | 0.510 |
| Oral aphthae | 72 (100) | 34 (100) | 38 (100) | 96 (97) | 46 (100) | 50 (94.3) | 0.136 | | 0.101 |
| Genital ulcer | 43 (59.7) | 19 (55.9) | 24 (63.2) | 56 (56.6) | 31 (67.4) | 25 (47.2) | 0.68 | 0.530 | 0.069 |
| Pathergy positivity | 15 (20.8) | 7 (20.6) | 8 (21.1) | 21 (21.2) | 10 (21.7) | 11 (20.8) | 0.952 | 0.961 | 0.905 |
| Erythema nodosum | 8 (11.1) | 5 (14.7) | 3 (7.9) | 38 (38.4) | 25 (54.3) | 13 (24.5) | **<0.001** | 0.359 | **0.002** |
| Folliculitis | 25 (34.7) | 12 (35.3) | 13 (34.2) | 32 (32.3) | 12 (26.1) | 20 (37.8) | 0.742 | 0.923 | 0.255 |
| Neurological involvement | 4 (5.6) | 2 (5.9) | 1 (2.6) | 18 (18.2) | 4 (8.7) | 14 (26.4) | **0.015** | 0.491 | **0.023** |
| Uveitis | 33 (45.8) | 18 (52.9) | 15 (39.5) | 53 (53.5) | 17 (37) | 36 (67.9) | 0.320 | 0.252 | **0.002** |
| Vascular involvement | 9 (12.5) | 4 (11.8) | 5 (13.2) | 28 (28.3) | 6 (13) | 22 (41.5) | **0.019** | 0.858 | **0.002** |
| Gastrointestinal system involvement | 6 (8.3) | 1 (2.9) | 5 (13.2) | 3 (3) | 3 (6.5) | 0 (0) | 0.125 | 0.117 | 0.059 |
| Musculoskeletal system involvement | 46 (63.9) | 21 (61.8) | 25 (65.8) | 26 (26.3) | 16 (34.8) | 10 (18.9) | **<0.001** | 0.723 | 0.189 |

*children-adult patients, †paediatric patients by gender, **adult patients by gender.

**Table 2** Vascular involvement by age groups

| Children | n (%) | Adult | n (%) |
|---|---|---|---|
| | 9 (12.5) | | 27 (27.3) |
| Vein thrombosis in CNS | 3 (4.2) | Vein thrombosis in CNS | 4 (4) |
| DVT | 3 (4.2) | DVT | 14 (14) |
| Pulmonary artery aneurysm + DVT | 1 (1.4) | DVT + PTE | 1 (1) |
| Hepatic artery aneurysm | 1 (1.4) | Hepatic vein thrombosis | 1 (1) |
| Pulmonary artery aneurysm | 1 (1.4) | IVC thrombosis | 1 (1) |
| | | IVC thrombosis + DVT | 1 (1) |
| | | PTE | 2 (2) |
| | | Retinal vein thrombosis. | 1 (1) |
| | | Coronary artery aneurysm | 1 (1) |
| | | Splenic and pulmonary artery aneurysm | 1 (1) |

DVT; deep vein thrombosis, PTE; pulmonary thromboembolism, IVC; inferior vena cava, CNS; central nervous system.

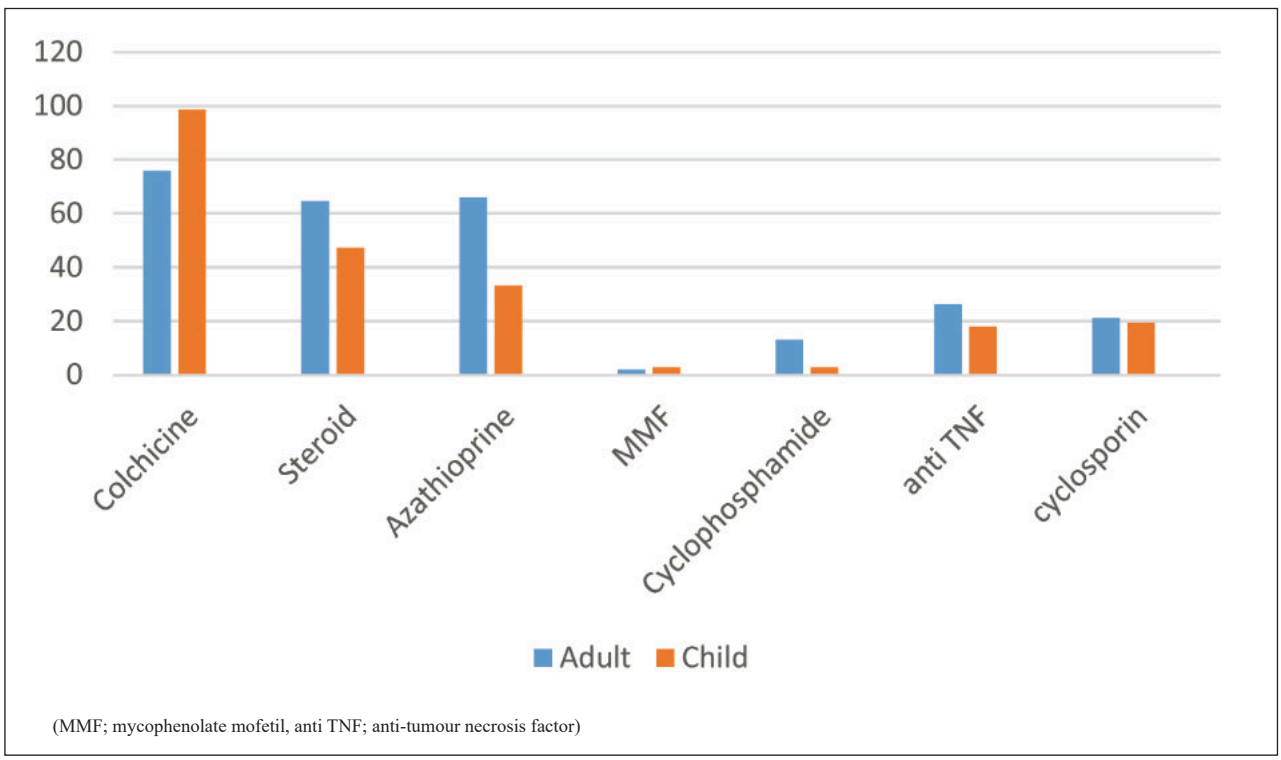
Among those, parenchymal neurological involvement was three times higher in adults relative to children with BD (n=13 out of 18 vs. 1 out of 4, 72.2% vs. 25.0%, p=0.006). Severe disease was more common in adult patients with a significant male predominancy. Vascular, neurological involvement, and uveitis were more common in adult male patients, while erythema nodosum was more common in adult females (p=0.002, p=0.023, p=0.002, and p=0.002, respectively). In addition, in children, severe disease was more common in males (Tables 1 and 3). The most commonly used treatment in paediatric and adult patients was colchicine (98.6-75.8%). Except for colchicine, the patients were receiving corticosteroid, azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, and anti-TNF-α treatments depending on organ involvement. While the use of colchicine was more common in paediatric patients (p<0.001), immunosuppressive agents were more common in adult patients (p=0.024) (Figure 1).

## Discussion

In this study, we presented a comparison of the demographic and clinical features of adult and paediatric patients with BD. Compared to adults, the more commonly noted family history and HLA-B51 positivity in our paediatric cohort highlighted the importance of host genetic factors for BD. Musculoskeletal findings were more common in children; on the other hand, neurological

**Table 3** Presence of serious disease by age groups and gender

| | | Severe Disease | | p |
|---|---|---|---|---|
| | | Yes | No | |
| | | n (%) | n (%) | |
| Children | | 22 (30.6) | 50 (69.4) | **0.002** |
| Adult | | 54 (54.5) | 45 (45.5) | |
| Adult | Female | 20 (43.5) | 26 (56.5) | **0.039** |
| | Male | 34 (64.2) | 19 (35.8) | |
| Children | Female | 6 (17.6) | 28 (82.4) | **0.025** |
| | Male | 16 (42.1) | 22 (57.9) | |




(MMF; mycophenolate mofetil, anti TNF; anti-tumour necrosis factor)

**Figure 1.** Medications in paediatric and adult patients (%)

and vascular BD were more common in adults. Therefore, the disease is milder in children than in adults. This finding suggested that Behçet's disease presents more frequently with milder symptoms at early ages and that the need for immunosuppressive treatment may be less. Paediatric patients take longer to develop a full-blown disease phenotype. Some of the children with BD may not meet the classification criteria.[12] Since the symptoms may occur at different times in childhood in BD, the time to diagnosis is approximately 3-5 years.[7] In this study, the time to diagnosis was nine months for children with BD. This is a significantly shorter time when compared to previous studies. This is mainly due to the increased awareness about BD in our clinic and partly due to the fact that our centre is a big referral centre with accumulated experience in BD.[13] We have a well-functioning transition process between paediatric and adult clinics for BD patients. Additionally, the adult rheumatology department makes patient referrals to us when there is suspicion of BD in the children of adult BD patients. In this context, collaboration between adult and paediatric rheumatology departments is important. Although phenotypic differences between paediatric and adult patients with BD were reported in a few previous studies, the available data is still limited.[6-8] Ishido et al compared the clinical features and gender of Behcet's patients and found that genital ulcers and oral aphthae were more common in female patients and eye problems in male patients.[14] Tursen et al found in another study that female patients were more likely to experience genital ulcers and erythema nodosum, while male patients were more likely to experience ocular, vascular, neurological, and pseudo-folliculitis.[15] According to Li et al,[16] genital ulcers were more common in female patients, while ocular findings, pseudo-folliculitis, pathergy test positivity, and vascular findings were more common in male patients. In our study, similar to these studies, erythema nodosum was more common in female patients, while vascular, ocular, and neurological findings were more common in male patients. Available data consisting of the comparison of BD patients between children and adults is summarised in Table 4. Karincaoglu et al reported that articular symptoms were the most commonly observed findings in both children and adults.[6] Makmur et al[7] and Hu et al[17] reported that arthritis was significantly higher in paediatric BD patients, and Hu et al. reported that all paediatric patients with BD, but only one-third of adult patients with BD, presented with recurrent oral aphthae. According to the latter studies, musculoskeletal symptoms were more common in children than adults in our study. HLA-B51 positivity was significantly more common in Italian adult patients.[8] In Turkey, paediatric patients reported more familial cases than adults.[6] Similarly, in our study, HLA-B51 positivity and familial history were more common in paediatric patients. We observed that oral aphthae was the most common initial manifestation in both groups, but there was no difference between the groups in terms of genital ulcers, whereas another study reported a higher incidence of genital ulcers in adults.[6] In our study, gastrointestinal system findings were more frequent in children, similar to the other studies.[6,7,17] Unlike the results of Karincaoglu et al, neurological involvement was more common in adult patients in our study.[6] Vasculitis accounts for a significant portion of the pathologic process in BD, and vasculitis can affect veins and arteries of all sizes. We currently do not know the specific cause of vascular thrombosis in BD cases.[18] While vascular involvement was higher in adult patients, four of the paediatric patients had arterial involvement compared to two adult patients, which was three times more prevalent in children (6% vs. 2%). Despite the low event number, this finding needs better clarification and deserves further study. In a recent paper in which 19 paediatric and 34 adult BD patients were included, there was no significant difference in clinical findings between paediatric and adult patients but a more favourable prognosis in children. Research demonstrated that early-onset disease, female gender, and the absence of initial serious organ involvement decreased the long-term risk of serious organ involvement.[8] According to these findings, severe organ involvement was more common in adult patients than paediatric patients in our study population. Considering the patients' IBDDAM activity scores during the first and last visits, the disease had a slightly more severe course in adult patients at the beginning compared to children, but there was no statistical difference. However, despite significant improvements in IBDDAM scores during the last visit in both groups, it was more prominent in adults. This may be due to their higher disease activity score at the time of admission, and we suggested that effective and timely treatment is critical to controlling disease activity. Nevertheless, adult patients needed more intense immunosuppressive treatment. The limitations of the study are the retrospective design and the small size of the adult patients with BD, but the relatively larger size of paediatric patients with BD renders our study stronger.

In conclusion, patients diagnosed with BD at different ages or genders may exhibit different clinical findings, and the severity of the disease increases with age, potentially

**Table 4** The review of the current literature about children and adult patients with Behçet's disease

| Year | Author (Reference) | Number of patients | System involvement |
|---|---|---|---|
| 2003 | Tursen et al (15) | 1138 male, 1095 female adult | Genital ulcers and erythema nodosum are more common in females; ocular, vascular manifestations and folliculitis are more common in males |
| 2008 | Karincaoglu et al (6) | 83 children, 536 adult | Familial cases are more common in children Muco-cutaneous lesions and articular symptoms are the most commonly observed in both groups<br>Neurologic and gastrointestinal involvement are higher in children.<br>Oral ulcers are the most common initial manifestation of both groups.<br>Genital ulcers are more common in adult |
| 2017 | Ishido et al (14) | 2651 male, 3976 female adult | Genital ulcer and oral aphthous are common in female, ocular manifestations is more common in male |
| 2019 | Makmur et al (7) | 46 children, 560 adult | Ocular, vascular and skin manifestations more common in adult patients<br>Genital ulcer more common in female patients (both children and adult)<br>Ocular and vascular manifestations are more common in adult male patients |
| 2020 | Li et al (16) | 286 male adult, 203 female adult | Genital ulcers are more common in female, pathergy test positivity, skin and vascular findings are more common in males |
| 2021 | Sota et al (8) | 64 children, 332 adult | HLA-B51 positivity is more common in adults<br>Severe disease are more common in adult male patients |
| 2021 | Hu et al (17) | 572 articles | In children, all patients have recurrent oral aphthae, disease activity scores are lower, arthralgia; CNS and GIS involvement are more common<br>In adult, ⅓ of the patients recurrent oral aphthae, and also genital ulcer is more common |
| 2022 | Present study | 72 children, 99 adult | HLA-B51 positivity, family history and musculoskeletal system findings are more common in children<br>Erythema nodosum, vascular and neurological involvement are more common in adult<br>Vascular, neurological involvement and uveitis are more common in adult male patients<br>Erythema nodosum is common in females<br>Severe disease is more commonly encountered in adult and in males |

necessitating more intensive therapy. Especially, more severe organ involvement and a higher disease activity-related BD may exist in adults than in children with BD. A close collaboration and well-structured transition programme between paediatric and adult rheumatology clinics have particular importance in early diagnosis and to prevent organ damage with appropriate management of BD.

## Conflicts of Interest

The authors declare no conflict of interest.

## Author Contributions

S.A.B., M.A.Ö. and P.E.Ş. designed the study; P.E.Ş., D.G.Y. and R.K. collected and analysed data; P.E.Ş. and E.N.S.Y. wrote the manuscript; Ç.Y. and N.K. gave technical support and conceptual advice. All authors reviewed the results and approved the final version of the manuscript.

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