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Behçet's disease in children: single-center experience

Çocuklarda Behçet hastalığı: tek merkez deneyimi

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Abstract

Aim: In this study, it was aimed to summarize the demographics, and clinical and laboratory findings of children who were diagnosed as having Behçet's disease, and also to determine the efficacy, duration, and adverse effects of the treatments.

Material and Methods: The records of 34 patients who were diagnosed according to the International Behçet Study Group criteria between 1980 and 2013 in the Department of Pediatric Nephrology and Rheumatology, Hacettepe University Faculty of Medicine, were retrospectively reviewed and all demographic and clinical features were recorded. In the light of these data, the sex and age distribution, clinical and laboratory findings, most commonly preferred treatment approaches, efficacy of treatments, and adverse effects during treatment were analyzed.

Results: Of the 34 children with Behçet's disease, 18 (53%) were male and 16 (47%) were female, and the mean age was 11.18±3.34 years. There was no significant difference in age distribution of the male and female patients ($p<0.05$). In 97% (n=33) of the patients, the first symptom was recurrent oral aphthae. In order of frequency, the other mucocutaneous findings were pseudofoliculitis and pustular lesions (82%), genital ulcers (62%), and pathergy positivity (50%). System involvements in order of frequency were as follows: joint findings (38%), ocular findings (35%), vascular involvement (32%), neurologic involvement (18%), gastrointestinal involvement (5.8%), and pulmonary involvement (5.8%). Colchicine was the most commonly preferred drug (88%). Steroids were added to treatment in patients with skin involvement. Azathioprine was added in patients with uveitis. Anticoagulant therapy, cyclophosphamide, and anti-tumor necrosis factor-alpha were added in patients with vascular involvement. In patients with gastrointestinal system involvement, sulfasalazine was added to treatment. Diarrhea was the most common adverse effect in patients who used colchicine. In the patients who used steroid treatment, gastrointestinal symptoms such as unintentional weight gain, acne, and agitation were observed (17%). One patient who received interferon treatment had symptoms of depression and agitation.

Conclusion: The aim of this study was to review the general characteristics of pediatric patients with Behçet's disease and to emphasize the importance of early diagnosis and correct treatment in terms of mortality and morbidity.

Keywords: Behcet's syndrome, HLA-B51, pediatrics

Öz

Amaç: Bu çalışmada Behçet hastalığı tanısı almış çocuk hastaların demografik, klinik ve laboratuvar bulgularının özetlenmesi, uygulanan tedavilerin etkinliği, etki süreleri ve karşılaşılan yan etkilerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Hacettepe Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Nefroloji ve Romatoloji Bilim Dalları'nda 1980–2013 yılları arasında Uluslararası Behçet Çalışma Grubu ölçütlerine göre tanı almış 34 hastanın arşiv dosyaları ve elektronik kayıtları geriye dönük olarak incelenerek tüm demografik ve klinik özellikleri kaydedildi. Bu veriler ışığında çocukluk çağı Behçet olgularının cinsiyet ve yaş dağılımı, klinik ve laboratuvar bulguları, en çok tercih edilen tedavi yaklaşımları, tedavilerin etkinliği ve tedavi sırasında karşılaşılan yan etkiler incelendi.

Bulgular: Otuz dört çocuk Behçet hastasının 18'i (%53) erkek ve 16'sı (%47) kızdı ve yaş ortalaması 11,18±3,34'tü. Kız ve erkek hastaların yaşlarının dağılımında anlamlı fark yoktu ($p<0,05$). Hastaların %97'sinde (n=33) ilk başvuru yakınması tekrarlayan oral aft idi. Sıklık sırasına göre diğer mukokutanöz bulgular; psödofolikülit ve püstüler lezyonlar (%82) genital ülser (%62), paterji pozitifliği (%50) idi. Sistem tutulumları ise sıklık sırasına göre; eklem bulguları (%38), göz bulguları (%35), vasküler tutulum (%32), nörolojik tutulum (%18), gastrointestinal tutulum (%5,8) ve akciğer tutulumu (%5,8) oranında saptandı. Kolşisin en çok tercih edilen ilaçtı (%88). Cilt tutulumu olan olgularda tedaviye steroid, üveit olgularında azatiopürin, vasküler tutulumda antikoagülan tedaviyle birlikte siklofosfamid ve anti-tümör nekrozis faktör (TNF)-alfa, gastrointestinal sistem tutulumu olgularında sülfalazin tedaviye eklenmişti. Kolşisin kullanan hastalarda en sık rastlanan yan etki ishaldi. Steroid kullanan hastalarda gastrointestinal sistem yakınmaları, istemsiz kilo alımı, akne ve ajitasyon yakınmaları (%17) gözlemlenmişti. İnterferon tedavisi alan bir hastada depresyon ve ajitasyon yakınmaları ortaya çıkmıştı.

Çıkarımlar: Bu çalışma ile çocukluk çağı Behçet hastalarının genel özellikleri gözden geçirilmiş, erken tanı ve tedavinin önemi vurgulanmak istenmiştir.

Anahtar sözcükler: Behçet hastalığı, çocuk, HLA-B51

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Introduction

Behçet's disease (BD) is an autoinflammatory disease that may involve many organ systems including the central nervous system, musculoskeletal system, and gastrointestinal system, and it is characterized by ocular and cutaneous findings, as well as recurring oral and genital ulcers. The Turkish dermatologist Hulusi Behçet first described the disease in 1937, as the triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis (1). Subsequently, superficial thrombophlebitis was added to these findings in 1946 (2).

In a recent multi-center study, 219 patients were examined prospectively, and it was emphasized that at least three of these criteria should be present for a diagnosis of pediatric BD: recurrent oral aphthous ulcers (at least three attacks per year), genital ulcers, skin involvement, eye involvement, neurologic involvement, and vascular involvement. Skin involvement is considered as necrotic folliculitis, acneiform lesions or erythema nodosum, whereas venous thrombosis, arterial thrombosis, and arterial aneurisms are regarded as vascular involvement (3). Behçet's disease is commonly observed in the region of the Silk Road, which also includes our country.

In our study, we aimed to evaluate the demographics, and clinical and laboratory characteristics of children who were followed up with a diagnosis of BD. We aimed to enlighten the approach to childhood BD by evaluating treatment efficacies and durations, as well as adverse effects and long-term follow-up data.

Material and Methods

Thirty-four patients who were followed up with a diagnosis of BD in Hacettepe University, Faculty of Medicine, Division of Pediatric Nephrology and Rheumatology between 1980 and 2013, were included in the study. The patient files and electronic records were examined retrospectively. According to the International Study group criteria, the presence of at least two of the following findings was considered as Behçet's disease: recurring oral aphthous ulcers (at least three times per year), genital ulcers, ophthalmologic findings, cutaneous findings, and a positive pathergy test (4, 5). The patients' demographic characteristics, ages at the time of diagnosis, findings at first presentation, pathergy tests, human leucocyte antigen (HLA)-5 and B51 positivity, family history, treatment after the diagnosis and treatment responses, complications related to medications and other complications were evaluated. In our study, the HLA-B51 concentrations were also examined because it was emphasized that this marker showed the strongest correlation with BD in a study in which studies related to childhood vasculitis were evaluated (6).

Changes in clinical findings can be evaluated using the Behçet Disease Current Activity Form (BDCAF). Common findings of BD are interrogated at clinical visits with this form (7). At each clinical visit, the patients were asked about the clinical findings that they thought they had, and the changes in these findings. In addition, physicians' observations were noted in their files according to the BDCAF criteria. Improvement in the laboratory findings was considered as treatment response. Currently, the tests used most commonly for the assessment of laboratory findings include the erythrocyte sedimentation rate (ESR) and C-reactive protein concentrations, and an approach of these values to normal values at the next visit is considered improvement in laboratory findings. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was obtained on August 1st, 2014, from Hacettepe University Non-interventional Clinical Research Ethics Committee (Project No.: LUT GO 14/12).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software was used for analysis of the data. The relationship between the variables and the normality of distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Median and minimum-maximum values were used for descriptive data. The Mann-Whitney U test was used for the comparison of continuous variables between the groups, and the Chi-square or Fisher's test were used for the comparison of percentages because the values observed in cells did not meet Chi-square test assumptions. A p value of <0.05 was considered significant.

Results

The patients' general characteristics

Sixteen (47%) of the 34 patients who were included in the study were female and 18 (53%) were male. The mean age was 16.55±4.11 years. The mean age at the time of first presentation was 11.18±3.34 years. No significant difference was found in the age distribution of the female and male patients ($p<0.05$). Third-degree consanguinity was present in the parents of one patient. There was no consanguinity between the parents of the other patients. Fifteen percent of the patients (n=5) had a family member with Behçet's disease. Six patients (18%) had relatives with rheumatic disease other than BD. The pathergy test was positive in half of the patients (n=17). HLA-B51 was positive in five of 10 patients in whom HLA-B51 concentrations were measured.

The patients' symptoms and findings at the first presentation

The most common symptom at the time of presenta-

tion was recurring oral aphthous ulcers (97%). The second most common cause of presentation at the time of first presentation was cutaneous lesions in the form of pseudofolliculitis and papulopustular lesions, especially in the extremities, back, and anterior part of the chest (82%). The third most common symptom at presentation was genital ulcers, which were observed in 62% of the patients (n=21). Although only five patients had uveitis at the first presentation (15%), uveitis developed in the advanced period in 12 (35%) patients. Eight of these cases were panuveitis, three were posterior uveitis, and one was anterior uveitis. At the time of diagnosis, seven (20%) patients had recurring headache, 13 (38%) had recurring myalgia and arthralgia, and four (11%) patients had recurring abdominal pain.

Distribution of patients with vascular involvement

Among 11 patients (32%) who were found to have vascular involvement in the follow-up, one had arterial involvement, nine had venous involvement, and one had both arterial and venous involvement. Among six patients who were found to have central nervous system (CNS) involvement, two had parenchymal involvement, and four had non-parenchymal involvement.

Pulmonary artery aneurism developed in two patients and gastrointestinal system (GIS) involvement developed in the other two patients (ulcerated lesions in the terminal ileum).

Treatment approaches

Colchicine was the most commonly preferred drug (88%), and the most commonly preferred treatment protocol in patients with mucocutaneous involvement (recurring oral ulcers, genital ulcers and cutaneous lesions) was a colchicine and steroid combination. Azathioprine was also added to this combination in 10 of 12 cases of uveitis. Anticoagulant treatment was given additionally to 10 of 11 patients who had vascular involvement. One patient who had sinus vein thrombosis and two patients who had pulmonary artery aneurism were treated with cyclophosphamide in addition to high-dose intravenous steroid treatment. In one patient who had pulmonary artery aneurism, anti-tumor necrosis factor (TNF)-alpha was added to treatment when thrombus in the inferior vena cava (IVC) and Budd–Chiari syndrome developed. The patients who had parenchymal CNS involvement were treated with steroid and azathioprine, but treatment was substituted with interferon-alpha 2a in the follow-up in one patient. The patients who were found to have GIS involvement (ulcerated lesions in the terminal ileum) were treated with sulphasalazine.

Adverse effects that are thought to be associated with treatment

The most common adverse effect was diarrhea in the patients who used colchicine. Gastrointestinal system symptoms, unintentional weight gain, acne, and agitation were observed in the patients who used steroid treatment (17%). Depression and agitation occurred in one patient who received interferon treatment.

The follow-up of all patients who were evaluated in the study is still continuing and no patients died. Regression in the frequency of episodes and symptoms was observed in the patients whose treatments were continuing. Anticoagulant treatment is being continued in one patient because vascular obstruction is ongoing.

Discussion

Early diagnosis and treatment is considerably important in BD to prevent the development of complications because it is a chronic and multi-system disease. In this study, the clinical findings and treatment approaches in 34 patients who were being followed up with a diagnosis of BD, were cited. In our study, the mean age at the first presentation was found to be 11.18±3.34 years. This was similar to the finding reported as 12.3 years in a multi-center study conducted by Karıncaoğlu et al. (8) in which 83 pediatric patients with BD were evaluated. The male/female ratio was reported as 33/32 in an international multi-center demographic study conducted by Kone-Paut et al. (9). This ratio was found as 18/16 in our study; no significant difference was found in terms of sex distribution (1,12/1).

In previous studies, oral aphthous ulcers were reported in 100% of the cases and genital ulcers were reported in 98.7% of cases (10). In our study, recurring oral aphthous ulcers were the most common cause for presentation in 97% of patients. In the study conducted by Kim et al. (11), cutaneous lesions other than oral and genital ulcers were reported with a rate of 27%. In contrast to the literature, the second most common cause for presentation in our patients was other cutaneous lesions (82%). Genital ulcers were found with a lower rate compared with other studies (62%). In a multi-center study conducted with 110 pediatric patients with BD in Italy, the second most common clinical finding was reported to be ophthalmologic involvement rather than genital ulcers (12). This suggests that the second most common findings show differences from country to country, though the most common clinical finding was oral aphthous ulcers.

Although it is accepted that a positive pathergy test has a high sensitivity and specificity in the diagnosis of BD, recent studies have reported that this tendency has de-

creased (13). Studies have reported positive pathergy tests with a rate of 40–50% (14). In our study group, this rate was found as 34% (n=17).

Currently, HLA-B51 is considered as the strongest genetic risk factor for BD (15). Although HLA-B51 positivity is found with a rate of 20% in healthy individuals, this rate may increase up to 50–80% in patients with BD (16). In our study, HLA-B51 was found to be positive in five (50%) of 10 patients in whom HLA-B51 was tested.

In BD, the most common ophthalmologic complication is uveitis, which is bilateral in 75% of the cases. In addition, panuveitis was reported with a rate of 54%, posterior uveitis was reported with a rate of 29%, and anterior uveitis was reported with a rate of 17% when uveitis related to BD was classified (9). Similar to the literature, panuveitis was also found most commonly (67%) in our study; posterior uveitis was found with a rate of 25% and anterior uveitis was found with a rate of 8%. Posterior uveitis is a serious condition and is frequently treated with immunosuppressive agents including azathioprine and cyclosporine, and with corticosteroids (17, 18). In addition, interferon is very effective in severe cases of uveitis and preferred in many centers (19). In our patients with uveitis, steroid and azathioprine were preferred frequently. Among the patients who did not respond to treatment, treatment was substituted with cyclosporine A in four patients, with anti-TNF in two patients and with interferon in five patients. All cases of uveitis were successfully treated.

In other studies, the frequencies of neurologic and vascular involvement have been reported to be 15% (9). In our study, vascular involvement was found in 32% of patients, and neurologic involvement was found in 18% of the patients.

Yazıcı et al. (20) emphasized that BD had a more severe prognosis in young men in a study they conducted in 2001. The finding that pulmonary aneurism, which was considered to have the highest morbidity and mortality rate, was found in two boys in our study resembled this study. There are insufficient reports related to the correlation of age with disease prognosis in children.

There are no definite recommendations for the treatment of pediatric patients; basically, adult treatment guidelines are used. The drugs to be preferred primarily should be topical sucralfate or corticosteroids in the treatment of oral and genital ulcers (21). Colchicine was found to decrease the frequency of ulcers (22). In our study, colchicine and topical steroids were the most commonly used drugs in the treatment of patients who had oral and genital ulcers, and treatment was occasionally supported with short-term oral steroids. The frequency of oral and genital ulcers was reduced approximately three months after colchicine treatment was initiated. In patients who were resistant to treatment, a marked response was obtained approximately one month after oral steroid treatment was added to treatment. The most commonly preferred drug was colchicine, being recommended in 94% of the patients. However, two patients refused colchicine treatment considering the adverse effects. When describing the drug-related adverse effects that could develop, the family's concerns should be considered and it should definitely be emphasized that use of the drug could lead to some adverse effects, but the gain and loss balance should be adjusted adequately. The most common symptom related to colchicine is abdominal pain and diarrhea. Seventeen percent of patients (n=5) reported that they had drug-related diarrhea at least once during the time when they used colchicine. Oral steroids were used for approximately three months. The most common steroid-related adverse effect was GIS symptoms and weight gain, and symptoms including acne and agitation also occurred in some patients. Gastro-protective antacid and anti-reflux treatments should be recommended to avoid steroid-related adverse effects.

Vascular involvement developed in 32% of the patients. In the BD Treatment Recommendations Guideline published by Hatemi et al. (22), there is no definite consensus about the use of anticoagulants in vascular involvement. In our series, the patients who had vascular involvement, but did not have pulmonary involvement, were treated with heparin infusion or subcutaneous enoxaparin and warfarin.

Pulmonary artery aneurism was found in two of our patients and they were treated with cyclophosphamide in addition to high-dose IV and oral steroid treatment. In one of these patients, thrombus developed in the IVC and Budd–Chiari syndrome was found in the advanced period; TNF was added to treatment.

In this study, in which the general characteristics of childhood BD were examined, no patient died and the morbidity was found to be at an acceptable level. We think that this finding was caused by the early approach to the disease and careful treatment planning. Multi-center studies are needed both at the time of diagnosis and in the follow-up and treatment.

Some limitations of these studies should be considered. The fact that some tests for HLA-B51 concentrations could not be performed in all patients, and there was a limited number of patients may be considered as limitations. In addition, the fact that the patients were verbally asked about clinical findings and present findings

were noted in patient files rather than using a prepared form for the BDCAF should be considered as a limitation. Also, the study included a pediatric patient group from between 1980 and 2013 and innovations in treatment approaches occurred during this period; therefore, old and new approaches were compared, which should also be considered as a limitation.

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