Fever in Behçet's syndrome

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ABSTRACT

Objectives. *Fever is taken to be rare in Behçet's syndrome (BS) and when present it is usually considered to be associated with vascular disease. The aim of this study was to formally investigate the presence of fever as a clinical feature in BS patients and suitable controls.*

Methods. *The study consisted of 2 parts. In the first part, 500 patients with BS, 94 with familial Mediterranean fever (FMF), 100 with ankylosing spondylitis (AS), and 72 with systemic lupus erythematosus (SLE) along with 100 healthy controls (HC) were surveyed with the help of a questionnaire for the history of periodic fever episodes. In the second part, body temperature was measured in 98 newly diagnosed BS patients having at least one active BS lesion and 61 HC. Temperature was measured 3 times and the highest reading was used in the analyses.*

Results. *First part: history of fever episodes was present in 22% patients with BS, 87% with FMF, 33% with SLE and 8% with AS. None of the HC recalled a fever episode. Patients with BS who reported fever episodes were more likely to have major organ involvement such as vascular, neurological or joint involvement.*

Second part: The mean body temperature reading was similar (albeit statistically different) among patients with BS (36.72±0.42°C) compared to that of the HC (36.56± 0.27°C) (p=0.004).

Conclusion. *In this study, 22% of patients with BS reported a history of fever episodes. As previously reported, fever attacks seemed to be associated strongly with vascular, neurological or joint involvement. The increase in temperature accompanying active BS lesions was modest even when the highest values were considered.*

Introduction

Fever is taken to be rare in Behçet's syndrome (1-4). However, there are several case reports describing fever especially among patients with vascular or neurological involvement (5-10). Recently, we have reported fever among our patients with pulmonary vascular disease (11). Finally, there are even case reports identifying BS as a rare cause of fever of unknown origin (FUO) (12-15).

In the current work we aimed to reassess the frequency of fever in BS, as we believe for the first time, in a formal protocol, with suitable control groups. We also measured body temperature in newly diagnosed BS patients with active disease not using immunosuppressives or corticosteroids to assess whether active lesions of BS are accompanied by an increase in temperature.

Patients and methods

The study consisted of 2 parts: In the first part, a history of recurrent fever episodes was surveyed with the help of a questionnaire in consecutive BS, familial Mediterranean fever (FMF), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) patients along with healthy controls (HC). BS, FMF, SLE and AS patients were regular attendees of either the dedicated BS or the rheumatology outpatient clinic at Cerrahpasa Medical Faculty of University of Istanbul. The HC were apparently healthy volunteers chosen among the hospital staff. Answers to 'have you ever had recurrent fever episodes?' question were classified as 'yes', 'no' or 'do not know'. For the sake of simplicity, the responses of those who were unable to remember whether they had had fever were considered negative. Episodes of recurrent fever were identified as fever attacks a) recurring at least 3 times a year, b) present in any given time interval in the past and c) not associated with a specific infection. Additionally, symptoms present during fever episodes were recorded among BS patients. Clinical characteristics of BS patients were obtained from the charts.

By definition, all BS patients had skin-mucosa lesions as described in the ISG criteria (16). BS patients might have either solo skin-mucosa lesions or may have one or major organ involvement such as joint, eye, large vessel or CNS in addition to the skin mucosa lesions.

In the second part, body temperature was measured in recently referred patients or those we diagnosed as BS for the first time. Healthy controls were studied in parallel. BS patients were included in the study if they had at least one active BS lesion and were not using any immunossuppressives or corticosteroids except colchicine. A questionnaire – different from the one used in the first part – seeking demographic and clinical characteristics including BS signs, previous fever episodes and current signs of an infection was administered. A physical examination was also made at the same visit. Patients and controls who showed or reported any infectious signs or symptoms within a one month were excluded. Study subjects were seen 3 times about 4–5 days apart during a period of 2 weeks. Presence or absence of an active BS sign was recorded and body temperature was measured at each visit. Blood tests for ESR and CRP measurements were also done.

Temperatures were taken between 13:00 and 16:00 pm in all subjects. A Genius™ 2 tympanic thermometer was inserted into the right ear. The highest of the 3 measurements was considered in the analyses.

All participants gave informed consent and the local ethics committee of Cerrahpasa Medical School approved the study.

Statistical analysis

Continuous data were given as the mean and standard deviation (SD). Data with non-normal distribution were expressed as median and interquartile range (IQR). Comparisons between groups were made by Student's *t*-test or one-way ANOVA followed by post hoc Tukey correction for continuous variables. The categorical variables were compared by the chi-square test or Fisher's exact test. Continuous variables with non-normal distributions were compared using Mann-Whitney U-test. The odds ratios and 95% confidence intervals (CIs) for fever frequency were calculated by binary logistic regression models among the BS patients. BS patients with solo skin mucosa lesions were accepted as the reference group.

A temperature ≥37ºC was set as the 75th percentile among the BS patients. All tests were performed using SPSS for Windows, version 13.0, software (SPSS Inc, Chicago, IL).

Results

In the first part we studied 500 (254 M, 246 F) BS, 94 (25 M, 69 F) FMF, 100 (59 M, 41 F) AS and 72 (4 M, 68 F) SLE patients and 100 (48 M, 52 F) HC. Demographic features and the frequency of giving a history of recurrent fever attacks are shown in Table I. The male/female ratio and age differed significantly among the study groups. FMF and SLE patients were more likely to be female, compared to patients with BS and AS and HC. In addition, FMF patients were more likely to be younger, whereas SLE patients were more likely to be older compared to the other study groups.

History of recurrent fever episodes was most frequent in FMF (87%) followed by SLE (33%) and BS (22%). It was rather low in AS (8%) and absent in HC (Table I).

Clinical characteristics of BS patients and variables associated with episodes of fever

Among the BS patients, 163 (51 M, 112 F) (33%) had only skin-mucosa lesions, whereas the remaining had one or more types of organ involvement in addition to the skin mucosa lesions as shown in Table II. Solo skin mucosa involvement was significantly more common among females compared to males (51/254 vs 112/246, $p<0.001$), whereas major organ involvement was significantly more common among males (eye involvement: 123/254 *vs*. 88/246, $p=0.004$; joint involvement: 75/254 *vs*. 53/246, $p=0.041$, vascular disease: 73/254 *vs*. 26/246, $p<0.001$, and neurological involvement (either parenchymal or vascular): 20/254 *vs*. 7/246, $p=0.013$).

Among 110 patients who had a history of recurrent fever episodes, all described at least one symptom concomitantly present at the time of the fever episodes. These were in decreasing order of frequency: arthralgia or arthritis (78%), oral ulcers (74%), deep vein thrombosis (22%), abdominal pain (21%), erythema nodosum (18%), eye attacks (15%), genital ulcers (15%), chest pain (11%) and headache (4%).

Among the BS patients, the frequency of fever episodes was similar between males and females (23% *vs*. 21%, respectively, $p=0.335$). Similarly, the mean age (35.6±10.4 *vs*. 36.4±10.4,

Table I. Demographic characteristics, disease duration and history of recurrent fever in patients and controls.

	Behçet's syndrome n=500	Familial Mediterranean fever n=94	Ankylosing spondylitis n=100	Systemic lupus erythmatosus n=72	Healthy controls n=100	*p*-value
Males, n (%)	254 (51)	25 (27)	59 (58)	4 (6)	48 (48)	<0.001
Age, mean ± SD, years	36.3 ± 10.4	27.4 ± 10.1	35.3 ± 9.2	40.9 ± 12.9	35.9 ± 9.3	<0.001
Disease duration, median (IQR), years	6 (2-12)	5 (3-12)	6 (2-15)	7 (3.5-12)	–	0.732
History of recurrent fever, n (%)						
Present	110 (22)	82 (87)	8 (8)	24 (33)	0	<0.001
Absent	375 (75)	11 (12)	90 (90)	46 (64)	100 (100)	
Do not remember	15 (3)	1 (1)	2 (2)	2 (3)	0	

p=0.493) and median disease duration (6.0; IQR: 2–11 years *vs*. 6.0; IQR: 3–12, *p*=0.487) did not differ between those with and without fever episodes.

History of recurrent fever episodes was significantly less common among those with solo skin mucosa lesions (17%) compared to those with one or more major organ involvement (25%) (Table II). When patients with only skin mucosa involvement were taken as the reference group, the odds ratio of having fever episodes was significantly increased among patients with solo vascular disease (OR: 3.0), vascular disease combined with another major organ involvement (OR=4.0) and among those with both eye and joint involvement (OR=3.4) (Table II).

In the second part, we measured the body temperature of 98 (55 M, 43 F) different patients with BS and 61 (31 M, 30 F) HC. Table III shows the demographic characteristics, the frequency of clinical symptoms and levels of acute phase reactants at the time of temperature reading and mean temperature levels in BS patients and HC. BS patients were significantly younger than the HC. Forty-three of the patients (44%) were using colchicine regularly, whereas the rest were not using any drugs. Patients who were using colchicine had longer median disease duration (24 months, IQR: 8.4-60.0 *vs*. 4.8 months, IQR: 3.6–36, *p*=0.001) and also had less frequently genital ulcers (8/43 *vs*. 31/55, *p*=0.001) compared to those who were drug free. Apart from these, the demographic and clinical characteristics were similar between the two groups.

The mean body temperature was 36.72±0.42ºC among the BS patients and 36.56±0.27ºC among the HC (Table III). The frequency of patients with body temperatures ≥37ºC (26%) was significantly more common than the HC (8%), (*p*=0.007). Body temperature was recorded above 38ºC (38.7ºC) only in a 19 year-old female who came to the clinic with an uveitis attack. The temperature decreased to 36.4ºC 2 days later after she had been given corticosteroids. Among BS patients, body temperature was very slightly but significantly higher among those with active arthralgias (36.8±0.5ºC) compared to those without (36.6±0.3ºC), (*p*=0.013). Readings of fever among patients with signs of acute deep vein thrombosis were not significantly higher than those without (data not shown). During the second part of the study those patients who reported fever episodes had also higher temperature levels (37.0±0.6ºC) than those who did not (36.6±0.3ºC), (*p*=0.001). There was no difference in the mean body temperature levels with regard to gender and the presence or absence of skin-mucosa lesions, eye disease, pathergy positivity and colchicine use. ESR and CRP levels were also higher among those with upper percentile fever levels than the remaining [ESR: 33.3±22.3 mm/h *vs*. 21.2±16.5 mm/h, respectively (*p*=0.005), CRP: 7, IQR: 3–27 mg/L *vs*. 3, IQR: 3–10 mg/L, respectively, (*p*=0.013)].

Table II. History of recurrent fever episodes within the subgroups of Behçet's syndrome (n=500 in total).

Types of organ involvement	Prevalence of history of fever n (%)	OR (95% CI)	*p*-value
Eye (solo), n=126	15 (12)	0.7 (0.3-1.3)	0.267
Large vessel (solo), n=29	11 (38)	3.0 (1.3- 7.2)	0.010
Joint (solo), n=66	10 (15)	0.9 (0.4- 1.9)	0.793
Eye and joint disease, n=30	12 (40)	3.4 (1.4- 7.8)	0.005
Large vessel with joint or eye or neurological disease, n=70	31 (44)	4.0 (2.1- 7.5)	0.000
Neurologic with or without eye or joint, n=16	4 (25)	1.7 (0.5- 5.6)	0.399
Any type of major organ involvement overall, n=337	83 (25)	1.6 (1.0- 2.7)	0.043
Skin mucosa involvement (solo)*, n=163	27 (17)	–	–

* The 'solo skin mucosa involvement' group was taken as the reference group while calculating ORs.

Table III. Demographic and clinical characteristics (at the time of temperature reading), acute phase reactants and temperature levels in Behçet's syndrome and healthy controls.

	Behçet's syndrome, n=98	Healthy controls, n=61	*p*-value
Males, n (%)	55 (56)	31 (51)	0.518
Age, mean ± SD, years	31.9 ± 9.4	35.1 ± 9.5	0.038
Disease duration, median (IQR), months	9.6 (4.8- 39.6)	–	
Clinical characteristics*, n (%)		–	
Oral ulcers,	76 (78)		
Genital ulcers,	39 (40)		
Papulopustular lesions,	68 (69)		
Erythema nodosum,	21 (21)		
Active uveitis,	43 (44)		
Arthralgia**	50 (51)		
Deep vein thrombosis	8 (8)		
Pathergy test positivity	39 (40)		
ESR, mean ± SD, mm/hour	24.3 ± 18.8	9.4 ± 6.4	<0.001
CRP, median [IQR], mg/L	3.5 (3-12)	3.0 (2-3.5)	<0.001
Temperature, mean ± SD, ºC (range)	36.72±0.42, (36.1-38.7)	36.56±0.27, (36.1-37.2)	0.004
Temperature ≥37 ºC, n (%)	25 (26)	5 (8)	0.007

* Clinical signs that are observed only during the study period were considered.
** Out of 50 patients, 7 had arthritis.

Discussion

In the current study, a history of recurrent fever episodes was present in 22% of BS patients. This was significantly less frequent than reported by FMF (87%) and SLE (33%) patients while more frequent than that reported by patients with AS (8%) and healthy controls (0%). Among the BS patients, a history of fever was significantly less frequent among those with only skin-mucosa lesions (17%) compared to those with major organ involvement

(25%). A history of fever tended to be associated mostly with vascular involvement and also with eye and joint involvement, only when these two were combined. The body temperature when measured among patients with active BS lesions was only mildly elevated –albeit statistically different – among BS patients compared to that among HC. Patients with arthralgia or arthritis were more likely to have a significantly higher, albeit with a very small difference, temperature levels compared to those with no such involvement.

Fever is not among the common manifestations of BS, however as we indicated in the introduction, there are a number of case reports or series in the literature reporting fever especially with vascular and neurological involvement (5-15). In a recent study by our group, fever was present in 47% (22/47) BS patients with pulmonary artery involvement and in 36% (17/47) was an initial symptom preceding other symptoms (11). Although we did not give the precise temperature recordings in that report (11), it was usually higher than 38ºC. Similarly, a high acute phase response is usually associated with vascular disease in BS (17).

The rise in temperature accompanied by an active BS lesion was very modest, as we observed in the second part. Fever attack was observed in only one patient (1/98): the patient had a body temperature of 38.7ºC during an eye attack. While the observation period to catch this kind of fever attack might have been rather short in the second part (up to 15 days), we preferred to include patients who had active disease and who had not received immunosuppressive treatment.

There is a recent trend to classify BS with the autoinflammatory disorders (18-19). Unprovoked episodes of inflammation, the absence of autoantibodies or antigen-specific T cells, the abnormalities in the innate immunity and some clinical similarities suggest that BS might be an autoinflammatory disease (2). On the other hand, in BS contrary to that seen in autoinflammatory diseases, there is no periodic serositis, no increased frequency in the paediatric age group and no association with a specific gene mutation (2). As again indicated in the current study, true fever attacks unless there is major organ involvement is most probably rare in BS.

Our study had several limitations. Although a history of recurrent fever episodes was sought in patients and controls using the same methodology, the first part of the study is subject to recall bias. While the use of control groups lessens this bias we also tried to further assess the reliability of our results in a completely different cohort that included 128 (69 M, 59 F) patients with BS about 1 year after the original study had been completed. We again used the same questionnaire. The frequency of fever episodes was found as 21% (27/128) this time, quite similar to the original result (22%). Also, the temperature readings among BS patients with a history of episodic fever were significantly higher than those without such a history. This could be another back-up for reliability.

We did not collect information on drugs in the first part, which could be important especially for AS patients who had a substantially low frequency of fever episodes possibly due to NSAIDs. We included patients who were using colchicine in the second part. Another important limitation was the absence of diseased controls in the second part.

Conclusions

In this study, we found that 22% of patients with BS, especially those with vascular disease reported a history of fever episodes. However, when measured, the rise in temperature accompanied by active BS lesions is very modest even when the highest values were considered.

References

1. YURDAKUL S, FRESKO I, YAZICI H: Behçet's Syndrome. In: *Oxford Textbook of Medicine*. WARRELL DA, COX TM, FIRTH JD (Eds.) Fifth Edition, Oxford, Oxford University Press, 2010; 3684-8.
2. YAZICI H, UGURLU S, SEYAHI E: Behçet syndrome: is it one condition? *Clin Rev Allergy Immunol* 2012; 43: 275-80.
3. YAZICI H, HATEMI G: Empiricism in managing Behçet's syndrome. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S7-S9.
4. HATEMI G, SEYAHI E, FRESKO I, HAMURYUDAN V: Behçet's syndrome: a critical digest of the recent literature. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S80-S9.
5. BENAMOUR S: Fever in Behçet's disease. 107 Cases. *Clin Exp Rheum* 2010; 28 (Suppl. 60): S132-S132.
6. RIERA-MESTRE A, MARTÍNEZ-YELAMOS S, MARTÍNEZ-YELAMOS A, FERRER I, PUJOL R, VIDALLER A: Clinicopathologic features and outcomes of neuro-Behçet disease in Spain: a study of 20 patients. *Eur J Intern Med* 2010; 21: 536-41.
7. TALARICO R, BOMBARDIERI S: Behçet's disease: features of neurological involvement in a dedicated centre in Italy. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S69-S72
8. HARMOUCHE H, MAAMAR M, SAHNOUNE I, TAZI-MEZALEK Z, AOUNI M, MAAOUNI A: Fever revealing Behçet's disease: Two new cases. *Eur J Intern Med* 2007; 18: 146-7.
9. GOTO M, KOYAMA H, TAKAHASHI O, FUKUI T: A retrospective review of 226 hospitalized patients with fever. *Intern Med* 2007; 46: 17-22.
10. CHIARI E, FRACASSI F, D'ALOIA A *et al*.: Right ventricular thrombus and pulmonary thromboembolism/thrombosis in Behçet's disease: a case report. *J Am Soc Echocardiogr* 2008; 21: 1079.
11. SEYAHI E, MELIKOGLU M, AKMAN C *et al*.: Pulmonary artery involvement and associated lung disease in Behçet disease: a series of 47 patients. *Medicine* (Baltimore). 2012; 91: 35-48.
12. FATIMA J, SHUKLA V, KAROLI R: Behçet's syndrome presenting as FUO. *J Assoc Physicians India* 2010; 58: 331-2.
13. ERKEK E, AYASLIOGLU E: Fever of unknown origin as the initial presenting sign of Behçet's disease. *Scand J Infect Dis* 2006; 38: 829-30.
14. NIAMANE R, KARIM MOUDDEN M, ZYANI M, HDA A: Protracted fever of unknown origin as the presenting symptom of Behçet's disease. Report of a case. *Joint Bone Spine* 2005; 72: 175-6.
15. GOTFRIED M, JUTRIN H, RAVID M: Behçet's disease preceded by fever of unknown origin. *Arch Intern Med* 1985; 145: 1329.
16. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
17. MÜFTÜOĞLU AU, YAZICI H, YURDAKUL S *et al*.: Behçet's disease. Relation of serum C-reactive protein and erythrocyte sedimentation rates to disease activity. *Int J Dermatol* 1986; 25: 235-9.
18. GÜL A: Behçet's disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy* 2005; 4: 81-3.
19. MASTERS SL, SIMON A, AKSENTIJEVICH I, KASTNER DL: Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*). *Annu Rev Immunol* 2009; 27: 621-68.