Exacerbation of Behçet's syndrome and familial Mediterranean fever with menstruation

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ABSTRACT

Objective. *Menstruation triggers several conditions such as migraine, recurrent aphthous stomatitis and acne vulgaris in healthy individuals. There is evidence that Behçet's syndrome (BS) and familial Mediterranean fever (FMF) may exacerbate during menstruation. The aim is to assess whether BS and FMF patients experience menstrual flares.*

Methods. *Females of reproductive age with BS and FMF seen consecutively at the outpatient clinic of Cerrahpasa Medical Faculty at Istanbul, as well as apparently healthy hospital workers were studied using a standardised questionnaire. BS patients were asked whether they experienced increased skin-mucosa lesions during the menstrual period. A similar questionnaire assessing this time the frequency of abdominal pain, chest pain and fever attacks was given to the patients with FMF. The healthy controls received both questionnaires.*

Results. *A total of 200 BS patients, 240 FMF patients and 250 healthy controls were studied. The most commonly reported symptom among both BS patients (51%) and healthy controls (62%) was the acneiform lesion. At least 79% patients with FMF reported attacks with menstruation, notably abdominal pain which, majority thought, could be differentiated from dysmenorrhea. Additionally, 76% of healthy controls reported having abdominal pain consistent most probably with dysmenorrhea.*

Conclusion. *This survey showed that, in 68% of the patients with BS at least one skin mucosa lesion was exacerbated with menstruation, this was most commonly acneiform lesion. Menstruation had a slightly stronger effect on FMF, triggering at least one symptom in 79%. The main limitation of the study was the self-reported assessment methodology.*

Introduction

Menstruation triggers or exacerbates various conditions such as acne, erythema nodosum, recurrent aphthous stomatitis, migraine, epilepsy and several autoimmune diseases including rheumatoid arthritis, multiple sclerosis and myasthenia gravis (1-5). Menstrual flares may be due to reduction in progesterone or estrogen levels. Both hormones play substantial role in the immune modulation with substantial anti-inflammatory effects and possibly contribute to the pathogenesis of autoimmune diseases (6).

The pathogenesis of Behçet's syndrome (BS) is unknown. There is evidence that hormones might play a role in disease mechanisms (7-9). We had for some time observed skin-mucosa lesions of BS to exacerbate around menses and we could not find formal data on this issue.

Furthermore, there are several surveys showing that menstruation acts as one of the triggering factor in patients with familial Mediterranean fever (FMF), suggesting an effect of hormonal changes in disease expression (10-12). None of these observations had been controlled.

In this study, we wanted to formally assess whether there is a relationship between menstruation and cardinal symptoms of these two diseases compared with apparently healthy controls.

Methods

We studied 200 patients with BS and 240 patients with FMF consecutively seen at the rheumatology outpatient clinic of Cerrahpaşa Medical Faculty, between June 2015 and July 2016. All BS patients fulfilled the ISG diagnostic criteria while the FMF patients fulfilled the Tel-Hashomer criteria. Additionally, age matched 250 apparently healthy hospital staff with no previous

history of BS or FMF were studied as healthy controls. Post-menopausal women were excluded. A standardised questionnaire was used to evaluate whether BS or FMF patients experienced flares around the menstrual period. Formal education level of the study participants was also sought. The questionnaire distributed to BS patients assessed flares of skin-mucosa lesions such as oral ulcers (OU), genital ulcers (GU), acneiform lesions (if yes where: face, back/chest or extremities) and nodular lesions (EN) around menstruation. The questionnaire for FMF patients assessed whether the patient experienced fever episodes, abdominal or chest pain similar to that experienced during periodic attacks (of at least one day duration), and whether the patient could differentiate FMF attacks from dysmenorrhea. Information about flares of skin-mucosa lesions were not assessed among the FMF patients and similarly flares of serositis were not queried among the BS patients. The questionnaire for the healthy controls, on the other hand, was formed merging both questionnaires, with obviously deleting the inquiry about whether the patient could differentiate FMF attacks from 'dysmenorrhea'. Additionally, as a control question to test a possible recall bias, the participants were asked if they experienced headaches during the same period. The questionnaire was distributed to all patients to be completed while waiting to be seen. Following this, the same physician (GG) went over the filled form with each patient.

Clinical characteristics related to each disease and drugs used were taken from patient's charts. Thirteen patients with FMF and 9 patients with BS were re-interviewed approximately 6 months apart. Answers to each item were compared, and the overall reliability was found to be acceptable (kappa: 0.613).

The study protocol was approved by the Local Ethics Committee of Cerrahpasa School of Medicine.

Statistics

Comparisons of continuous variables between groups were made by one-way analysis of variance using the Bonferroni correction. The categorical variables were compared by the chi-square test or the Fisher exact test. All tests were performed using SPSS for Windows, v. 18.0, software (SPSS Inc, Chicago, IL).

Table I. Skin-mucosa lesions associated with menstruation among patients with Behçet's syndrome and healthy controls.

	Behçet's syndrome, n=200	Healthy controls, n=250	*p*-value
Oral ulcer, n (%)			<0.001
Yes	63 (32)	11 (4)	
No	65 (33)	230 (92)	
Do not remember	72 (35)	9 (4)	
Genital ulcer, n (%)			<0.001
Yes	51 (25)	0	
No	130 (65)	249 (99)	
Do not remember	19 (10)	4 (1)	
Acneiform lesions, n (%)			0.002
Yes	101 (51)	156 (62)	
No	78 (39)	86 (34)	
Do not remember	21 (11)	8 (3)	
Nodular lesions, n (%)			<0.001
Yes	41 (21)	5 (2)	
No	130 (65)	237 (95)	
Do not remember	29 (15)	8 (3)	
At least one symptom, n (%)	135 (68)	164 (66)	NS
Headache, n (%)*			0.015
Yes	93 (51)	115 (46)	
No	72 (39)	124 (50)	
Do not remember	19 (10)	11 (4)	

*Only 184 BS patients answered the headache question. NS: non-significant.

Results

Demographic and clinical characteristics

While BS patients (36±8) and healthy controls (35±8) were of similar age, FMF patients (32±8) were significantly younger than both BS patients and healthy controls ($p<0.001$).

There were 200 patients with BS with a mean disease duration of 9±6 years. All patients had recurrent oral ulcers, in addition to papulopustular lesions (n=183; 92%), genital ulcers (n=171; 86%), erythema nodosum (n=142; 71%), and eye (n=57; 29%), joint (n=26; 13%), vascular (n=8; 4%) and gastrointestinal involvement (n=2). The majority of the patients (n=153; 77%) was using colchicine, followed by azathioprine (n=37; 19%), and glucocorticoids (n=13; 7%). A small portion was using interferon alpha (n=4), cyclosporine (n=4) and mycophenolate mofetil (n=1). A total of 23 (12%) patients were off treatment at the time of the survey.

There were 240 patients with FMF with a mean age of 32±8 years and mean disease duration of 13±9 years. A total of 14 patients (5%) had concomitant disease such as ankylosing spondylitis (n=8), secondary amyloidosis (n=2), Behçet's syndrome (n=1), uveitis (n=1), multiple sclerosis (n=1) and transverse myelitis (n=1). All FMF patients were using colchicine for a mean duration of 9±6 years. Apart from colchicine, 9 patients were using biological agents (anakinra: n=5, tocilizumab: n =2, canakinumab: n=1, interferon alpha: n=1) and 1 was using azathioprine.

Education

The frequency of patients with elementary school education or less among patients with BS and FMF and healthy controls were 53%, 34% and 21%, respectively, ($p<0.001$).

Signs and symptoms associated with menstruation – Behçet's syndrome vs. healthy controls

As shown in Table I, a total of 136 patients (68%) with BS reported exacer-

bation of skin-mucosa lesions during menstruation: led by acne (51%) followed by oral ulcers (32%), genital ulcers (25%) and erythema nodosum (21%). Except for acne, which was more common among the healthy controls (51% *vs*. 62%, respectively, p=0.002), all skin mucosa lesions were significantly more frequent among the BS patients (Table I).

Also the number of patients who reported headaches were slightly more (51% *vs*. 46%) among the BS patients.

We analysed whether medical treatment with colchicine, azathioprine and other immunosuppressives had any effect on menstrual flares, but we found that there was no difference between those who were receiving medical treatment and those who were not (data not shown).

Moreover, compared to the healthy controls, BS patients were less likely to have acne lesions on the face (92% *vs*. 74%) whereas more likely to have them on the extremities (3% *vs*. 23%) and on the back and chest (10% *vs*. 52%), (p<0.001). BS patients who reported having acne flares were significantly younger than those without (35±8 *vs*. 38±7, p=0.016). Therefore, we divided patients and controls in 3 age groups (17–30, 31–40, 41–50), to assess the age distribution of those with acne flares (Fig. 1). While the frequency of patients with acne flares decreased significantly with age in both BS and the healthy controls, the oldest age group of BS patients tended to have more acne flares during menstruation.

– FMF vs. healthy controls (Table II)

A total of 190 (79%) patients with FMF reported having attacks which coincided with menstruation. As shown in Table II, 168 (70%) patients with FMF experienced abdominal pain, 21 (9%) had pleuritic chest pain or fever attacks during menstruation. Of the 168 patients who reported having menstrual abdominal attacks, 153 (91%) indicated that they could differentiate abdominal pain due to FMF from dysmenorrhea. As seen in Table II, the frequency of abdominal pain during menstruation was similarly high among the healthy controls (76%), whereas chest pain (27%) and fever (15%) were significantly less compared to that observed among the FMF patients.

The frequency of those with headache, was similar among both patients with FMF and healthy controls. Additionally, in the FMF group, the mean age of those with and without menstrual flare was not different.

Finally, it was noted that the number of patients who responded as 'do not remember' to each question seemed to be more common among the BS patients compared to that among the healthy controls (Table I). This was not true among the FMF patients compared to the healthy controls (Table II).

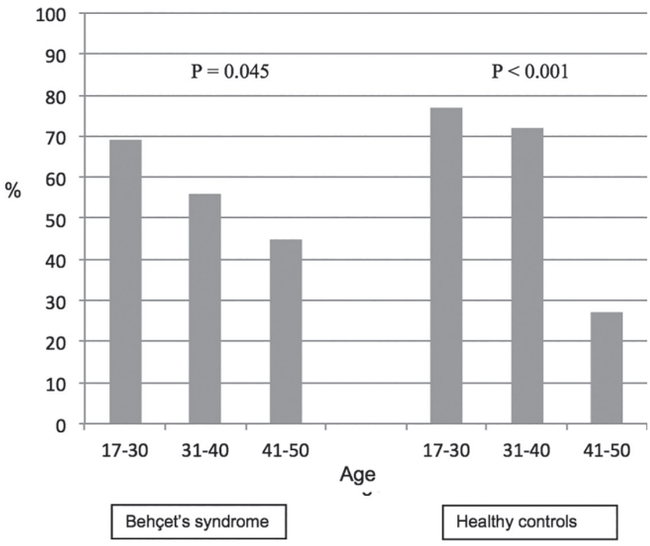

Fig. 1. The frequency of papulopustular lesions reported during the menstruation period according to age groups.

Table II. Signs and symptoms associated with menstruation among patients with Familial Mediterranean Fever and healthy controls.

	Familial Mediterranean Fever, n=240	Healthy controls, n=250.	*p*-value
Abdominal pain, n (%)			NS
Yes	168 (70)	189 (76)	
No	62 (26)	58 (23)	
Do not remember	10 (4)	3 (1)	
Chest pain, n (%)			<0.001
Yes	130 (54)	67 (27)	
No	102 (42)	179 (72)	
Do not remember	8 (4)	4 (1)	
Fever, n (%)			<0.001
Yes	93 (39)	38 (15)	
No	131 (55)	204 (82)	
Do not remember	16 (6)	8 (3)	
Headache, n (%)**			Not calculated
Yes	105 (47)	115 (46)	
No	107 (48)	125 (50)	
Do not remember	10 (5)	11 (4)	

**: Only 222 patients with FMF answered headache question. NS: non-significant.

Discussion

In our survey, we observed that at least 68% of BS patients reported having flares of skin-mucosa lesions during menstruation. This was most apparent for acne (51%) as compared with oral ulcers (32%), genital ulcers (25%) and nodular lesions (21%). On the other hand, at least 79% of FMF patients reported menstrual flares, most frequently manifested as attacks of abdominal pain (70%).

There is some evidence that hormones might affect disease mechanisms in BS, given that a. it is relatively rare before puberty (7-8), b. the disease gets into remission as patient ages (7-8),

c. most severe disease presentation is among the young males (7-8), d. the most pathognomonic lesions are on the genitalia, especially the scrotal skin, a most sensitive tissue to male hormones, and e. the acneiform skin lesion of this disorder being not different from acne vulgaris, an androgen dependent lesion, in macroscopic and histologic examination as well as an increased sebum excretion (9). Moreover, remission of the skin-mucosa lesions after administration of oral contraceptives, improvement during pregnancy and exacerbations related to menstruation, especially during the premenstrual period have been described (13-14).

We observed that acne lesions were more likely to be found on the back/chest and extremities among the BS patients, whereas these were more commonly found in the face among the healthy controls. Similarly, several studies among healthy adolescent or adult population had shown that menstrual acne flares are usually observed in the face (15). Additionally, the acne flares among BS patients tended to be still continuing in older ages, when compared to the healthy controls. These findings are in line with our previous observations in BS (16) and suggest that the disease mechanisms of papulopustular lesions in BS somewhat differ from that of acne vulgaris.

We were surprised to see that acneiform lesions were less common in patients with BS. This could be due to the fact that some patients may have more severe acne therefore any exacerbation could be missed.

Erythema nodosum is another somewhat less specific lesion of BS which could be associated with sex hormones as it can appear in pregnancy in otherwise healthy subjects (17). In our study, 5 (2%) of our healthy controls had observed this lesion during menstruation.

It has long been known that FMF attacks are precipitated by menstruation (10-12). One telephone survey revealed that 53% (38/72) could have had attacks during their menstrual cycles (12). One prospective study showed that in 7% (10/141) attacks were restricted to the perimenstrual period (10). None of these studies included control groups. Furthermore, there have been case reports showing that oral contraceptives have successfully been used as an adjunct to colchicine (10-11).

Our study showed that 79% of female patients with FMF reported having attacks during their menses, the majority being attacks of abdominal pain. Although abdominal pain due to FMF resembles classical episodes of dysmenorrhea, 91% of FMF patients reported that they could easily differentiate abdominal attack due to FMF from dysmenorrhea. This rather high discrimination rate was also observed by others (12). Abdominal pain in the healthy controls must naturally be interpreted as due to dysmenorrhea, a condition that may be observed at high frequency rates (50–75%) particularly in young women (18). On the other hand, two groups from Turkey reported increased prevalence of *MEFV* variants in individuals with primary dysmenorrhea and suggested that this could be an incomplete form of FMF (19-20).

We noted that the frequency of headache flares were almost similar among BS (51%) and FMF patients (47%) and healthy controls (46%) and this somewhat reassured us against a possible recall bias. The frequency of headache was perhaps slightly higher in BS and even it would go higher had some of the indecisive patients responded affirmative. This could be understandable since headache is a well-known and quite frequent symptom in BS (being both present in ordinary attacks and also as a predictor of neurological involvement).

Our study shows that hormonal alterations during the menstrual cycle affect auto-inflammatory disease mechanisms. We know that at this stage of the hormonal cycle, there is sudden decrease of both estrogen and progesterone. Although the precise mechanisms are unknown, it is generally supposed that sex hormones have protective effects in many autoimmune diseases. For example, symptoms in many patients with rheumatoid arthritis have been shown to decrease in the postovulatory phase of the menstrual cycle (3). While we do not know exactly how this works in the setting of auto-inflammatory diseases, there have been some suggestions on this issue especially for FMF (10). Oestrogens have been shown to inhibit interleukin-1 beta induced interleukin 6 production, lower the expression of intercellular adhesion molecules and finally inhibit tubulin assembly, similar to the colchicine effect (10).

The main limitation of our study is that we used self-reported assessment methodology, rather than a prospective diary assessment. As we pointed earlier, menstrual attacks in both diseases should be verified with clinical examination and laboratory assesment. We are aware of that a multiple testing problem could have been present in our analyses of acne associations in BS (face *vs*. extremities and young *vs*. old). On the other hand, these analyses gave confirmatory results suggesting that a multiple testing bias was not probably operative. Also, comparing genital lesions with healthy controls could not be appropriate as control subjects by definition would not have such ulcers. Another important limitation is we could not get exact information whether flares took place pre- or during the menses and our results should be interpreted with this shortcoming. Finally, the healthy controls had better education than BS and FMF patients and this was somewhat expected as they were hospital employees. Due to the possible link between cognitive ability and education reported in several epidemiological surveys (21), this might have caused somewhat increased recall in the healthy control group. On the other hand the opposite also might be true, since it is well known that cognitive ability of BS patients in the absence of overt neurological disease could be impaired (22-23). Similarly, those who were indecisive in the current study were highly common only among BS patients. While this could be due to the less formal education level in BS patients, cognitive impairment could also have played a role.

To conclude, we found that skin-mucosa lesions in BS are triggered with menstruation in the majority of our patients. This is most apparent in acne, similar to that observed among the healthy controls. However, differ-

ent than seen in acne vulgaris and as expected, BS patients were more likely to have these exacerbations on the extremities and on the trunk and acne lesions tend to continue as the patient got older. Abdominal attacks of FMF patients are precipitated also with menstruation and this effect seems to be stronger than that observed in BS.

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