Behçet's disease: Does lack of knowledge result in under-diagnosis ?

Sirs,

The prevalence of Behçet's disease (BD) has been estimated at 80 – 380/100,000 in Turkey (1) and 0.12 – 0.33/100,000 in the US (2). Pathergy test positivity is one of the major criterion for making the diagnosis of this condition. The differential diagnosis includes many conditions, and it is usually difficult to recognize the disease in non-endemic parts of the world. Incomplete forms may even be harder to diagnose with any certainty. We set out to determine if a lack of knowledge about the basics of Behçet's disease may play a role in the relative rarity of the diagnosis in the USA. We tried to assess the knowledge among internal medicine residents from two different regions in the US and two different Mediterranean regions regarding Behçet's disease, and the pathergy test. The same physicians were asked questions about the PPD test for tuberculosis, as a control arm.

A 16-item questionnaire was developed including both closed and open-ended items, testing knowledge of Behçet's disease, the pathergy test, and the PPD test (Fig. 1). We chose two centers in the USAfrom different geographic areas to get a more composite picture of residents. It was given to internal medicine residents from four university centers: St. Louis University Health Sciences Center (A) and Weill Medical College of Cornell University (B) in the USA, Shaare-Zedak Medical Center (C) in Israel, and Cerrahpasa Medical Faculty (D) in Turkey. In a single session, residents were asked 10 questions about Behçet's disease and 3 questions each about pathergy test and PPD. Rates of correct responses between internal medicine residents from the US and internal medicine residents from Israel and Turkey were compared using Fischer's exact test.

Sixty-nine internal medicine residents participated in this study (A: 26, B: 13, C: 10, D: 20). Table I shows the percentage of correct answers given for each category of questions. There was a statistically significant difference between the rate of correct responses among internal medicine residents in the US compared to those in Israel and Turkey with respect to Behçet's disease and the pathergy test, while differences in the proportions of correct answers to PPD testing were of borderline significance.

Knowledge of Behçet's disease, and in particular the pathergy test among the internal medicine residents tested was significantly lower in the US than among those in Israel and Turkey. The difference in the preva-

PPD questions

1. What is the strength of PPD inoculated ?
2. When do you read the PPD results ?
3. Describe the cut-off limits for a positive PPD in an immune-competent host.

Pathergy questions

1. Pathergy test is used for the diagnosis of _____
2. When would you read it ?
3. What would you consider a positive pathergy test ?

Behçet's disease questionnaire

1. In the absence of other clinical explanations, which of the following criteria is a MUSTfor Behçet's disease ?
a) Oral ulcer
b) Recurrent genital ulcer
c) Eye lesions
d) Skin lesions
e) Pathergy test

2. The usual absence of conjunctivitis and urethritis usually differentiates Behçet's disease (BD) from Reiter's syndrome.
True or False

3. The HLAtype most frequently associated with BD is

4. In BD, the young female patient has the worst prognosis.
True or False

5. Colitis in BD frequently involves the rectum.
True or False

6. Which of the following statements is true about BD-related oral and/or genital ulcerations.
a) Both oral and genital ulcers leave scars after healing
b) Genital ulcers are usually deeper than oral ulcers and usually leave scars after healing
c) Penis and perianal area are the most commonly involved in genital ulceration
d) Vaginal wall is not affected by ulceration in BD
e) Tonsils and pharynx are commonly involved in BD

7. What is the most common eye manifestation of BD ?
a) Anterior/posterior uveitis
b) Conjunctivitis
c) Corneal ulceration
d) Papillitis
e) Arteritis

8. BD is a leading cause of acquired blindness in Japan.
True or False

9. Which of the following statement best describes arthritis associated with BD ?
a) Most frequently small joints of the hands and feet are involved
b) Synovial fluid is commonly non-inflammatory
c) Synovial histology is diagnostic
d) Less than 1/3rd of the patients develop signs or symptoms of joint involvement
e) The arthritis is usually a non-deforming, non-erosive peripheral oligoarthritis

10. Which of the following statement is true about BD?
a) BD can involve large and small veins
b) BD only affects large size arteries
c) BD only affects medium to large size arteries
d) BD only affects small to medium size arteries
e) Veins are not affected in BD

Fig. 1. Questionnaire given to medical students in the USA, Israel and Turkey, to test their knowledge of Behçet's disease and the pathergy test.

Table I. Percentages of correct answers.

	PPD	BD	PT
United States	61%	35%	21%
Israel & Turkey	70%	65%	66%
p value	0.05	< 0.0001	< 0.0001

BD: Behçet's disease; PT: pathergy test.

lence of Behçet's disease in these two regions of the world may partly explain this disparity in the response to Behçet's disease-specific questions, given that the exposure to Behçet's disease patients would be different. Although we need to keep in mind that this was a study among a small number of internal medicine residents, our results were strongly significant.

These results remind us that lack of Behçet's disease knowledge may contribute to decreased recognition and thus the underdiagnosis of Behçet's disease, resulting in the reported low prevalence in the US. It may also contribute to missing the disease among individuals from the Middle East and Far East communities, where the prevalence of Behçet's disease would be expected to be higher, in the US. Only by improving the education of internists with respect to Behçet's disease will the true prevalence of this condition be realized.

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References

1. YAZICI H, FRESKO I, TUNC R, MELIKOGLU M: Behçet's syndrome: Pathogenesis, clinical manifestations and treatment. *In* Ball GV and Bridges SL (Eds.): *Vasculitis*, New York, Oxford University Press, 2002; 406-32.
2. KAKLAMANI VG, VARIOPOULOS G, KAKLAMANIS PG: Behçet's disease. *Semin Arthritis Rheum* 1998; 27: 197-217.

Familial Mediterranean fever and Celiac sprue – Are they related?

Sirs,

Familial Mediterranean fever (FMF) is a genetic inflammatory disease, presenting with recurrent febrile bouts of peritonitis, arthritis and pleuritis. In most cases, there is a favorable response to colchicine prophylaxis (1). FMF is related to several other inflammatory diseases and vasculitides including inflammatory bowel disease, polyarteritis nodosa, Henoch-Schönlein purpura, protracted febrile myalgia, and Behcet's disease (2). About 20% of colchicine treated FMF patients display colchicine intolerance, manifested by 1-10 soft or watery stools/day. This condition is at times unresponsive to dose adjustments in colchicine and/or anti-diarrhea medications (3). Failure to respond to colchicine, which is marked by ≥ 1 febrile attack per month despite a maximal colchicine dosage (≥ 2 mg/day), occurs in 5-10% of patients. The reasons for colchicine treatment failure are unknown.

Celiac sprue (CS) is a genetic autoimmune disorder resulting from sensitivity to gluten. In some populations its prevalence is estimated to be between 1–1.5% (4). CS shares some of the clinical features (abdominal pain, diarrhea, arthralgia, arthritis) of FMF, and tends to be commonly associated with other inflammatory and autoimmune diseases (5). Anti-endomysial antibodies (AEA) of the IgA type are highly specific and sensitive markers of the disease (6).

We speculated, based on the above analogies, on a possible association between FMF and CS. This association could explain the colchicine intolerance of some FMF patients in whom borderline CS intestinal changes become evident only from additional noxios stimulus inflicted by colchicine. In addition, we believed that clinically silent CS might nevertheless cause colchicine absorption failure, leading to colchicine "unresponsiveness". Finally, we hypothesized that diarrhea during resolution of abdominal FMF attacks may also be partially related to the possible FMF-CS association occurring in some patients.

We therefore collected and studied serum samples for the presence of AEAin the following groups: 20 patients with FMF and colchicine-related diarrhea; 10 patients unresponsive to colchicine; and 20 FMF patients with no history of diarrhea during attacks or resulting from colchicine therapy. Serum collected from 20 healthy individuals and 20 CS patients was used to determine the normal and pathological levels. All patients were of Jewish ancestry. AEA was studied using a kit (ImmuGlo™ Anti-Endomysial Antibody (EMA) Test System, IMMCO Diagnostic, Inc. Buffalo, NY, USA) according to the manufacturer's instructions (an indirect immunofluorescence antibody test for both IgAand IgG).

None of the patients from the different subgroups studied had elevated titers of AEA (< 1/2.5), compared to a mean positive titer (1/100) in the CS patients. These results do not support an association between FMF and CS, and do not support CS as the culprit of diarrhea in FMF attacks or FMF colchicine intolerance. Furthermore, there was no indication that CS is the underlying mechanism of FMF colchicine treatment failure. A larger study is desirable to confirm these findings.

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References

1. LANGEVITZ P, LIVNEH A, PADEH S *et al.*: Familial Mediterranean fever: New aspects and prospects at the end of the millennium. *Isr Med Ass J* 1999; 1: 31-6.
2. LIVNEH A, LANGEVITZ P, ZEMER D *et al.*: The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996; 26: 612-27.
3. BEN-CHETRIT E, LEVY M: Colchicine: 1998 Update. *Semin Arthritis Rheum* 1998; 28: 48-59.
4. MAKI M, MUSTALAHTI K, KOKKONEN J *et al.*: Prevalence of Celiac disease among children in Finland. *N Engl J Med* 2003; 348: 2517-23.
5. FARRELL RJ, KELLY CP: Current concepts: Celiac sprue. *N Engl J Med* 2002; 346: 180-8.
6. FARRELLRJ, KELLY CP: Diagnosis of Celiac sprue. *Am J Gastroenterol* 2001; 96: 3237-45.