Thoughts on the proposed links between Behçet's disease and familial Mediterranean fever

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Behçet’s syndrome (BS) is an inflammatory disorder characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis and skin lesions (1, 2). Involvement of the central nervous system, gastrointestinal tract and large vessels is less frequent but may be life threatening. The disease is prevalent among Turks, Japanese, Koreans, Iranians, Saudi and non-Ashkenazi Jews and Moslems in Israel.

Familial Mediterranean fever (FMF) is mainly inherited as an autosomal recessive condition. It is characterized by recurrent attacks of fever, and peritonitis, pleuritis, arthritis, or erysipelas-like skin lesion (3, 4). The disease is common among Turks, Armenians, Middle-Eastern Moslems and non-Ashkenazi Jews.

FMF and BS have some common clinical and genetic features. On the other hand there are also some features that are uncommon. Table I summarizes these findings. It is seen that the dissimilarities outnumber the similarities. On the other hand there are enough clinical features that might cause a wrong diagnosis in either direction especially in a patient of a Mediterranean background.

In 1997, Schwartz et al. reported that they found 39 patients with concurrent FMF and BD (5). While some of the patients had incomplete BS, 16 had the complete syndrome according to the International Study Group for Behçet’s Disease criteria (6). Since these patients were recruited from a survey of 4000 FMF patients, the researchers concluded that the concomitant occurrence of FMF and BD (1:250) was much higher than expected in the general Israeli population (7). Furthermore, they suggested that BS should be included among other vasculitides - common in FMF. Later, Birlik et al. described a case involving coexistence of FMF and BD and suggested that both disorders may have a common etiopathogenetic mechanism (8).

Based upon the above observation, Fresco et al. tried to investigate the reverse association – i.e.: the prevalence of FMF among BS patients – reasoning that if the previous findings had been biological, then the reverse would also be true (9). In this study two control groups were used; one consisted of 82 Rheumatoid Arthritis (RA) patients and the second was comprised of 270 healthy individuals. The authors did not find a higher than expected number of FMF patients among 344 BS patients. The prevalence of FMF was similar among the RA patients cohort as well as among the healthy persons group. The same group also formally looked at this association in another study designed to reassess the validity of the International Study Group Criteria for BS (6). They found out that none of the 108 patients with FMF studied fulfilled the diagnostic criteria for BS (10).

Recently, in a study by Ben-Chetrit et al. the frequency of BS among FMF patients and the reverse association were investigated. They found 2 BS patients among 355 FMF patients and 2 (same patients) FMF patients among 53 BS patients (11). Statistical analysis supported the findings that the association

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<th>Table I. Features of Behçet’s syndrome and familial Mediterranean fever.</th>
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<td>BS</td>
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<td>Skin-mucosa lesions including oral ulceration</td>
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<td>Eye lesions</td>
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<td>Arthritis</td>
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between FMF and BS was higher than expected in both directions (FMF in BS and BS in FMF). Nevertheless, the small number of patients (only 2) with concomitant disease was of concern. Thus the issue of the prevalence of concomitant BS and FMF has not been settled. The main drawback of the Schwartz and Ben-Chetrit studies is the lack of appropriate controls. In cases where we look for the prevalence of a disease among a population of sick patients, one has to take as a control a similar cohort of healthy individuals from the same ethnic origin. For example, Schwartz et al. should test the prevalence of BS among 4000 healthy individuals of North African and Arabic origin. Another appropriate control would be a similar number of patients from the same origin who have rheumatoid arthritis or another chronic inflammatory disease. Without such controls it is still possible that the findings of Schwartz et al. and Ben-Chetrit et al. are related to the ethnic origin of the group rather than to their FMF disease. In favor of the latter possibility is a recent study by Jaber et al. which described a relatively high prevalence of BS among a healthy Moslem community from a small town in Israel (12: 10000) (12).

Another point in studies looking at disease concurrence is the co-morbidity issue. Having more than one disease clearly increases the chances of being detected by a health-provider. The inclusion of disease controls in concurrence studies lessens the impact of this important bias at least to some degree. During the second FMF conference in the year 2000, Livneh et al. reported that FMF may be expressed in individuals harboring a single coding mutation in MEFV (13). This observation was based upon a thorough study of 8 FMF-BS patients who were heterozygous for the M694V mutation and in whom no additional mutation was found on the non-carrier chromosome. Further widening their conclusion they claimed that these findings “may mirror a more generalized rule that FMF may be precipitated in carriers of a single mutated gene by environmental factors or genetic factors not directly associated with MEFV”. Support for the reverse pre-disposition can be found in the study of Toutou et al. who discovered a higher than expected frequency of MEFV mutations in BS compared with a controlled cohort of healthy individuals from the same ethnic origin (14). They suggested that MEFV mutation can act as an additional susceptibility factor in BS. In a recent “Letter to the Editor”, Akpolat et al. further extended the role of MEFV gene in BS (15). They looked for MEFV mutations in 3 patients with BS two of whom had amyloidosis. They found that one of them was homozygous for M680I. Since the patient had no symptoms of FMF, they concluded that in this patient a double dose of an MEFV mutation serves as a risk factor for the development of amyloidosis as a complication of BS rather than FMF.

On the other hand, in the study by Ben-Chetrit et al. there was no difference in any of the clinical manifestations of BS patients heterozygous for MEFV mutations, as compared with those who had no mutations at all (11). Furthermore, none of the 16 BD patients with a single MEFV mutation expressed FMF clinically. This study did not support a mutual enhancing effect of FMF in cases of BS and vice versa.

The main critique about the studies claiming a mutual enhancing effect is again a more appropriate control of other groups with inflammatory diseases. The fact that MEFV mutations are found in BS patients from populations with a high carrier rate is not surprising. Had they looked for these mutations in the RA group of patients from the same ethnic origin, similar results would probably have been found. In the case of Akpolat et al. it is not clear why the patient could not simply have BS and FMF (asymptomatic, type II?). Amyloidosis can develop in clinically asymptomatic FMF patients, since the sub-clinical inflammatory process continues despite the lack of complete attacks. Another possible explanation would be that the patient’s renal disease suppressed the clinical expression of FMF (16). In summary, the possible association between FMF and BS is exciting and thought provoking. What we seem to need at this point are more clinical and laboratory studies more carefully designed especially with respect to the inclusion of the all important healthy and diseased controls. Until such studies are available, a patient caution is in order.

References