Editorial

Behçet's syndrome in the 2000s: "Where is the wisdom we have lost in knowledge?"

H. Yazici

Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical School, Istanbul University, Turkey.

Hasan Yazici, MD, Professor

Please address correspondence to:
Prof. Hasan Yazici,
Division of Rheumatology,
Department of Internal Medicine,
Cerrahpasa Medical School,
Istanbul University,
34098 Istanbul, Turkey.
E-mail: hasan@yazici.net

Received on August 17, 2016 and accepted on September 1, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 102): S23-S25.

Key words: Behçet's syndrome

Everybody knows we still do not know the cause(s) of Behçet's syndrome (BS). My intention is to discuss how, these days, we go about trying to improve this with particular emphasis on whether the in vogue lumping of BS with disease groups we know more about is fruitful. Humankind has the tendency to ascribe the unknown to the known. Hence, centuries ago, our ancestors named the new islands they discovered by sailing west from Europe, the West Indies. What is more, the French, Spanish and British had their own West Indies. Likewise BS, over the years, has been tried to be assigned to three main disease categories: the *seronegative spondyloarthritides* (SpA), the *autoimmune diseases* (AUID) and the more recent *autoinflammatory diseases* (AID).

I had almost started my academic career trying to reject the notion that BS was among the SpA (1). Apart from the obvious incongruent HLA associations the clinical pictures simply did not bear enough similarities. However, a low profile debate continued for many years. My default counter argument has been that some degree of increased sacroiliitis was also present in patients with rheumatoid arthritis (RA) and nobody would really include RA among the SpA. Later on, about a decade ago we noted that enthesitis, surely a pathology much in the realm of SpA, was also associated with a subgroup of our BS patients who predominantly had arthritis and acne (2). After this report we were immediately advised what we were saying was rather contrary to what we had been preaching all along. Our reply was simple. This subgroup of BS patients were still HLA B27 negative (3). Also we emphasised, as we still try to do, had all of us, students of BS, been busier finding out how BS differed from rather than looked like a disease group, perhaps our observations about enthesitis and BS would have come much earlier. I have to point out here that in later studies we also saw this rather unique subgroup of acne/arthritis/enthesitis also segregated separately in the families (4).

More recently the debate whether BS belongs to the SpA was rekindled and this time the elements of debate came not from simple radiography or now historical HLA typing by serology. There is evidence from the genetic association studies that mutations in the ERAP1 gene, ERAP1 being an important enzyme in the functionality of the Class I MHC loci like HLA B51, are associated with HLA B51 positive patients with BS (5, 6), HLA B27 positive patients with AS (7) as well as HLA-Cw6 positive patients with psoriatic arthritis (PsA) (8). On the other hand this association among the BS patients is in the opposite direction to what had been noted among the AS and PsA patients. Homozygosity in the ERAP1 mutations in HLB51 positive patients confers increased disease risk in BS while they confer decreased risk in AS and PsA. Moreover, the ERAP1 association in BS has been noted in only a fraction of the BS patients (5, 6). What is what with the ERAP1 allele negative BS patients, however, is not discussed. Meanwhile we are told that this association does not hold true for the Japanese patients who, apparently carry this allele in very low frequencies (5). This is curious because we all know that the HLA B51 association was originally described among the Japanese BS patients (9). Do we then assume there is a molecule different from ERAP1 which alters the functionality of the Japanese patients who carry HLA B51? Finally, it is worth noting what we have at hand is somewhat different from the situation where one finds any one allele is

Competing interests: none declared.

significantly associated with any one disease. In that situation we are hopeful that with more significant associations we will solve the riddle for that one disease, presumably with the pathways involved etc. In the case at hand, however, it is as if, we are also banking on what will perhaps additionally be genetically deciphered in the other disease (AS in our example) while we know that mutations in one enzyme work in the opposite direction between the lumpee and the lumped.

A similar over-lumping, I am afraid, is apparent in the recently proposed concept "'MHC-1-opathy' unified concept for spondyloarthritis and Behçet disease" (10). We have already voiced our objections to this lumping (11) by mainly raising the issues: A. There are many patients with BS or AS who are HLA B51 or HLA B27 negative. How does this new concept explain the pathogenesis in these patients? and B. As we mentioned above, the acne/arthritis/enthesitis cluster of BS patients, phenotypically the closest group of BS patients to this new concept were HLA B27 negative (3).

Finally, the authors had suggested that IL-17-IL-23 pathway was very important in the pathogenesis of MHC-1-opathies. Why, then, anti-IL17 treatment has singulary been unsuccessful (12) in BS while it was surely shown to be successful in managing PsA and AS (13, 14)? In addition, Apremilast, another molecule - most probably working in a different pathway than the IL17-23 (15) - has been successful in managing PsA (16) and BS (17) while it has not been particularly successful in managing AS (18).

The second big disease lump to which BS had been ascribed to is the AUID group. Although there are many dissimilarities between BS and the bone fide AUIDs like RA or systemic lupus (19) there is little doubt some pathways involved in autoimmunity are also operative in BS (20). One important consideration is that HLA Class II, rather than Class I molecules assume a more important role in the classical AUID like RA and SLE. Another consideration is that disturbances in acquired rather than innate immunity have been considered the hallmark of AIDs while problems in innate immunity are widely acknowledged as being much more important in AIUDs, we are about to discuss in relation to BS. I also briefly point out here that there have been proponents of super- lumping, the main lump of SpA in the AID (21) since problems with innate immunity in SpA are considered more important than those of acquired immunity, just as considered in AID.

The inclusion of BS in the third and the most recent lump, that of AID, is also somewhat problematic. As we had already pointed out years ago (22), BS starting with its usual onset in early adult life and its complex genetic association actually has little resemblence to classic onset AUIDs with their usual onset in the paediatric age and monogenic, Mandelian inheritence pattern. Of course, yet another small lump comes to the rescue. There are monogenic and complex AIDs. Hard to take issue against, really.

More recently, yet another important asymmetry has been highlighted between BS and AIDs. Vasculitis, a hallmark of BS, is uncommon in AIDs apart from the occasional association with FMF (23). Discussing clinical similarities a good example of the zealousness to include BS among the AIDs had been the proposal that uveitis, almost the hallmark of BS is also shared, for example, by Blau syndrome among AID (24). In this analogy the totally different nature of the uveitis in Blau syndrome (sarcoid eye disease) from what one sees in BS is singularly neglected.

MEFV mutations in familial Mediterranean fever (FMF) and their association with BS is also worth discussing here. On one hand, after the bright-line announcement of MEFV mutations as the cause of FMF almost 2 decades ago (25, 26), it is now apparent that this is debatable (27). I had all along suspected it would come to this since no population specificiy was available with the initial findings, since by the nature of the methodology used (positional cloning) no patients with other diseases had been studied to give us more information about disease specifity. In time an association of the MEFV mutations with BS (28, 29) were observed and this has also been used as another reason to include BS among the AIDS. To me this is quite similar to the proposed ERAP-AS-PsA -BS association I discuss above where an important molecule common and perhaps important in the pathogenesis of separate morbid entities is again being used to announce likeness. Perhaps an example outside medicine will help what I am trying to say. I am sure Istanbul, New York and Paris have many problems, like air pollution, traffic, sewage disposal, etc. in common. On the other hand can we really say they are the same, or even rather alike?

It is apparent that I am enthusiastic in proposing a splitter's, rather than a lumper's approach to decipher BS. It is, as if, whenever a molecular/genetic perturbance in one biologic pathway in a certain medical condition (like AS) is observed and this is followed by the recognition of more or less similar perturbance in another condition (like BS) the two conditons are lumped. Why do we shy away from starting first to consider both AS and BS as construct-diseases. That is as we do not know their exact aetiology(s), pathogenesis and in many instances their disease expression, course, response to therapy and outcomes differ. In brief, they differ considerably from "real-diseases" like septic arhritis or gout and thus, should better perhaps be labelled as "construct-diseases". Granted some of the elements of these constructs are stronger like the HLA B27 and sacroiliitis in AS and uveitis and scrotal ulcers in BS. However, I strongly suggest that a biologic perturbance we observe in one important immunologic/inflammatory pathway which might not even be in the same direction as I indicate above (5, 6) – should not prompt us to immediately lump the two constructs together. Would it not be more fruitful to use our more precise knowledge and base our research efforts on teasing out the differences in our construct-diseases first? On the other hand, we should meanwhile not ever forget we must also seek precision in our non-molecular observations as well. Is it

not unfortunate that all the fine GWAS data at hand contain rather limited or no information about the phenotypes of the patients studied? Another important issue is the relative paucity of self-criticism in basic science work (30). I argue that less bright line and more self critical basic science reporting will lead to more rapid progress.

Finally, I find it amusingly surprising that many of the reasons for the current lumping are derived from precise knowledge thanks to the molecular advances. These, I am told, also herald precision medicine which, in turn, evangelises personalised medicine, whatever that means. It is actually daunting, as a clinician and perhaps a clinical researcher, how I will recognise my individual patient among all this lumping, let alone appreciate and hopefully conduct meaningful research. Or should I better remind us all what T.S. Eliot wrote in "The Rock" many years ago?

"Where is the wisdom we have lost in knowledge?"

"Where is the knowledge we have lost in information?"

Acknowledgement

I am grateful to Eldad Ben-Chetrit and Yusuf Yazici for sharing their thoughts/criticisms in the preparation of this manuscript.

References

1. YAZICI H: Behçet's disease. *BMJ* 1978; 6142: 952.
2. HATEMI G, FRESKO I, TASCILAR K, YAZICI H: Increased enthesopathy among Behçet's syndrome patients with acne and arthritis: an ultrasonography study. *Arthritis Rheum* 2008; 58, 1539-45.
3. HATEMI G, FRESKO I, YAURDAKUL S *et al*.: Reply to letter by Priori *et al*. commenting on whether Behçet's syndrome patients with acne and arthritis comprise a true subset. *Arthritis Rheum* 2010; 62: 305-6.
4. KARACA M, HATEMI G, SUT N, YAZICI H: The papulopustular lesion/arthritis cluster of Behçet's syndrome also clusters in families. *Rheumatology* 2012; 51: 1053-60.
5. KIRINO Y, BERTSIAS G, ISHIGATSUBO Y *et al*.: Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1. *Nat Genet* 2013; 45: 202-7.
6. TAKEUCHI M, OMBRELLO MJ, KIRINO Y *et al*.: A single endoplasmic reticulum aminopeptidase-1 protein allotype is a strong risk factor for Behçet's disease in HLA-B*51 carriers. *Ann Rheum Dis* 2016; 10.1136/annrheumdis-2015-2090591136/2015-209059.
7. EVANS DM, SPENCER CC, POINTON JJ *et al*.: Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet* 2011; 43: 761-7.
8. STRANGE A, CAPON F, SPENCER CC *et al*.: A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 2010; 42: 985-90.
9. OHNO S, AOKI K, SUGIURA S *et al*.: HL-A5 and Behçet's disease. *Lancet* 1973; 2: 1383-4.
10. MCGONAGLE D, AYDIN SZ, GUL A, MAHR A, DIRESKENELI H: 'MHC-I-opathy'-unified concept for spondyloarthritis and Behçet's disease. *Nat Rev Rheumatol* 2015; 11: 731-40.
11. HATEMI G, KARATEMIZ G, YAZICI H: Behçet's disease: An MHC-I-opathy? *Clin Exp Rheumatol*, in press.
12. DICK AD, TUGAL-TUTKUN I, FOSTER S *et al*.: Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. *Ophthalmology* 2013; 120: 777-87.
13. MCINNES IB, SIEPER J, BRAUN J *et al*.: Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 2014; 73: 349-56.
14. BLAIR HA, DHILLON S: Secukinumab: A Review in Ankylosing Spondylitis. *Drugs* 2016; 76: 1023-30.
15. SCHAFER P: Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol* 2012; 83: 1583-90.
16. KAVANAUGH A, MEASE PJ, GOMEZ-REINO JJ *et al*.: Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014; 73: 1020-6.
17. HATEMI G, MELIKOGLU M, TUNC R *et al*.: Apremilast for Behçet's syndrome - a phase 2, placebo-controlled study. *N Engl J Med* 2015; 372: 1510-18.
18. PATHAN E, ABRAHAM S, VAN ROSSEN E *et al*.: Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. *Ann Rheum Dis* 2013; 72: 1475-80.
19. YAZICI H: The place of Behçet's syndrome among the autoimmune diseases. *Int Rev Immunol* 1997; 14: 1-10.
20. DIRESKENELI H: Autoimmunity vs autoinflammation in Behçet's disease: do we oversimplify a complex disorder? *Rheumatology* 2006; 45: 1461-5.
21. AMBARUS C, YEREMENKO N, TAK PP, BAETEN D: Pathogenesis of spondyloarthritis: autoimmune or autoinflammatory? *Curr Opin Rheumatol* 2012; 24: 351-8.
22. YAZICI H, FRESKO I: Behçet's disease and other autoinflammatory conditions: what's in a name? *Clin Exp Rheumatol* 2005; 23 (Suppl. 38): S1-2.
23. PELEG H, BEN-CHETRIT E: Vasculitis in the autoinflammatory diseases. *Curr Opin Rheumatol* 2017; in press.
24. GUL A: Behçet's disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy* 2005; 4: 81-3.
25. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. *Cell* 1997; 90: 797-807.
26. FRENCH FMF CONSORTIUM: A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; 17: 25-31.
27. OZEN S: The myths we believed in familial Mediterranean fever: what have we learned in the past years? *Semin Immunopathol* 2015; 37: 363-9.
28. RABINOVITCH E, SHINAR Y, LEIBA M *et al*.: Common FMF alleles may predispose to development of Behçet's disease with increased risk for venous thrombosis. *Scand J Rheumatol* 2007; 36: 48-52.
29. TASLIYURT T, YIGIT S, RUSTEMOGLU A, GUL U, ATES O: Common MEFV gene mutations in Turkish patients with Behçet's disease. *Gene* 2013; 5301: 100-3.
30. YAZICI H, GOGUS F, ESEN F, YAZICI Y: There was less self-critique among basic than in clinical science articles in three rheumatology journals. *J Clin Epidemiol* 2014; 67: 654-7.