Editorial

What Behçet syndrome is not

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For the last decade, and surely starting with the author, I note a sense of frustration among the students of Behçet syndrome (BS). It is as if the more we learn about this overly complex construct, the less we really understand what BS is about. In another editorial, not in the very distant past, I had attempted to express my frustration in the words of TS Eliot, searching "wisdom in knowledge" (1).

More recently, I am beginning to consider that the main cause of our frustration probably lies in the way we conduct and interpret basic and clinical research in BS. Genomics, with its ever-improving technology, has indeed confirmed the older genetic associations and described new ones. There is, however, one major scientific drawback of gene searching. It is not hypothesis-driven and is inductive, that is generalisations come after observations. It surprises me why we have not tried to deductively, where observations follow and are tailored to generalisations to evaluate, and commonly attempt to falsify their veracity, test what we learned from the genomic data in family studies. These should surely include twins and if national twin registries are considered unrealistic because of paucity of numbers, why not aim for an international twin registry?

Another critical issue with genetic studies is that their findings are commonly turned into clinical lumps. I had already criticised one such lumping, the concept of MHC-I-opathy (2) in a previous editorial (1). Recently, two further lumps appeared. The first was the concept of Behçet-like phenotypes (3) while the concept of Behçet spectrum of diseases (4) is more recent. The former represents a sizeable group of mainly paediatric conditions with monogenic autoinflammatory gene mutations (3). A popular example is the heterozygotic presence of a mutation in the gene of A20, a regulatory protein of the NFκB inflammatory pathway as described in five families with children with a phenotype resembling BS (5). These children have episodes of inflammatory activity, including aphthosis and uveitis, the more specific features of which, on closer inspection, are very distinct from BS. To some of us, an increased presence of pyrin mutations among patients with BS (6) provide convincing evidence that the two conditions are somewhat related. The well-established observation that while amyloidosis is the most feared complication of FMF, it is rarely observed in BS (7), does not seem to be noteworthy to these colleagues. In this line, it is worth remembering that CRP levels are usually modestly elevated in BS (8), while they are a hallmark of FMF attacks, signalling, at least quantitatively, diverse types of inflammation in these two conditions. As for the phenotype, the potentially blinding uveitis, the major organ disease in BS, is almost never seen in FMF.

The concept of Behçet spectrum of diseases (4) proposes that these individuals with ordinary canker sores, if they carry the necessary HLA genes, go on to present as PFAPA while, should they carry necessary HLA class I genes, they develop full blown BS. In this scheme, patients with ordinary canker sores represent the mildest, while those with BS the severest clinical phenotype. I suggest that the Achilles heel of the initial work that proposed this spectrum lies in the very starting point of this study. The authors notably said (4) that the reason that they embarked on this study had been the observation that "Many adults with Behçet disease have reported symptoms earlier in childhood that fulfil the diagnostic criteria for PFAPA (3, 20)". We had recently

pointed out (8) that such evidence was most unconvincing in those two quoted articles. In one of the articles (the original reference 3) only 1/60 of PFAPA patients went on to develop BS after years of follow-up (10) and in the other (original reference 20), adult patients with BS reported about the oral ulcers that they had around a mean age of 3 years (11).

It must be underlined that the clinical lumps I have been criticising are mainly based on genetic data. Thus, the lump proposals criticised are not hypothesis-driven and thus rather inductive. In this line, as students of BS, it is to our discredit that almost no family and twin studies with state-of-the-art genetic tools are at hand in BS, which would bring us nearer to hypothesis-driven and deductive, falsifiable study results. I strongly suggest that only with such data will we have a clearer view of what BS is about.

Another unfortunate aspect of how we do not understand BS is our wrong approach to formulating and understanding disease criteria. As Jim Fries had famously said: "Presence of disease 'criteria' affirms our ignorance of the essence of disease." (12). Thus, we surely need them. However, to classify them into diagnostic criteria for patient care and classification criteria for research purposes is simply ill-advised (13). Moreover, there are two additional and especially important methodological issues in preparing these criteria. Unfortunately, these methodological problems were also present in the currently widely used ISBD criteria for recognising/classifying BS (14), the methodology of which was mostly formulated in the author's apartment: 1. Since every probability is dependent on a prior probability, a truly useful set of criteria recognising a disease can never be formulated without, at least an estimation of, the prior probability of the disease sought in the setting in which these criteria are formulated and will be used. There are around twenty different sets of disease criteria for recognising BS and none gives the necessary importance to disease prevalence. 2. The usual method of developing disease criteria includes forming a large group of patients with a particular disease. This large group (Cohort I) is made up of patients diagnosed with a particular disease, together with a predetermined check list of clinical/laboratory/imaging/tissue pathology specifics of these patients. The same group of experts, usually and rightfully from different geographies, also send in another set of patients, surely along with their salient disease features (Cohort II). The next obvious step is to make a statistical comparison of the features of the patients in Cohort I to those in Cohort II. However, a historical mistake is made before this comparison. The mistake is to randomise the Cohort I into a training, or a criteria development, and a validation set. This exercise in futility, this most inappropriate randomisation, almost ensures that usually a good validation will be achieved in the end, since the very purpose of a randomisation, given an adequate sample size, is to form a subgroup that represents the characteristics of the original group. We made this mistake in preparing the ISBD Criteria for BS 32 years ago (14). It is rather sad to see that our otherwise learned colleagues, representing both the ACR and EULAR, have just made the same mistake in preparing the ANCA-associated vasculitis criteria (15).

In brief, I venture to say that we are perhaps skidding in BS research recently and not gaining much ground in deciphering what BS is. I strongly suggest we need more hypotheses-driven and deductive clinical and basic research with surely more emphasis on splitting rather than the popular and populist lumping. An acronym, if you will, would be HDFS (Hypothesis driven, Deductive, Falsifying, Splitting) for this effort. Finally, if we plan to formulate yet other criteria set for recognising BS, let us not forget the all-important prior probabilities and the due respect to the required absolute independence of the development and the validation groups in our criteria making effort.

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References

1. YAZICI H: Behçet's syndrome in the 2000s: "Where is the wisdom we have lost in knowledge?" *Clin Exp Rheumatol* 2016; 34 (Suppl. 102): S23-5.
2. MC GONAGLE D, AYDIN SZ, GÜL A, MAHR A, DIRESKENELI H: 'MHC-I-opathy'-unified concept for spondyloarthritis and Behçet disease. *Nat Rev Rheumatol* 2015; 12: 731-40.
3. PERAZZIO SF, ALLENSPACH EJ, EKLUND KK *et al*.: Behçet disease (BD) and BD-like clinical phenotypes: NF-κB pathway in mucosal ulcerating diseases. *Scand J Immunol* 2020; 92(5): e12973.
4. MANTHIRAM K, PREITE S, DEDEOGLU F et al.: Common genetic susceptibility loci link PFAPA syndrome, Behçet's disease, and recurrent aphthous stomatitis. *Proc Natl Acad Sci USA* 2020; 117: 14405-11.
5. ZHOU Q, WANG H, SCHWARTZ DM *et al*.: Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. *Nat Gene* 2016; 48: 67-73.
6. LIVNEH A, AKSENTIJEVICH I, LANGEVITZ P *et al*.: A single mutated MEFV allele in Israeli patients suffering from familial Mediterranean fever and Behçet's disease (FMF-BD). *Eur J Hum Genet* 2001; 9: 191-6.
7. YURDAKUL S, TUZUNER N, YURDAKUL I, HAMURYUDAN V, YAZICI H: Amyloidosis in Behçet's syndrome. *Arthritis Rheum* 1990; 33: 1586-9.
8. MUFTUOGLU 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.
9. BEN-CHETRIT E, YAZICI H: How to classify PFAPA? No hard evidence for associated CAPS or CARD variants and not any for links with Behçet's syndrome. *Clin Exp Rheumatol* 2021; 39 (Suppl. 132): S14-7.
10. WURSTER VM, CARLUCCI G, FEDER HM JR, EDWARDS KM: Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *J Pediatr* 2011; 59: 958-64.
11. CANTARINI L, VITALE A, BERSANI G *et al*.: PFAPA syndrome and Behçet's disease: a comparison of two medical entities based on the clinical interviews performed by three different specialists. *Clin Rheumatol* 2016; 35: 501-5.
12. FRIES JF: Disease criteria for systemic lupus erythematosus. *Arch Intern Med* 1984; 144; 252.
13. YAZICI H, YAZICI Y: Criteria for Behçet's disease with reflections on all disease criteria. *J Autoimmun* 2014; 48-49: 104-7.
14. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335:1078-80.
15. YAZICI H, YAZICI Y: A methodologic problem and a conceptual issue related to the new 2022 antineutrophil cytoplasmic antibody-related vasculitis criteria sets. *Arthritis Rheumatol* 2022 Jun 17. https://doi.org/10.1002/art.42269.