

Behçet's disease and other autoinflammatory conditions: What's in a name?

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With the fifth supplement our name has changed. One obvious reason for this can be found in the accompanying editorial by Eldad Ben-Chetrit. FMF research over the last few years, in a new turn, has been increasingly addressing "autoinflammation". This happened in the context of the recently discovered pyrin mutations, rather than the clinical and therapeutic findings related to the phenotypic prototype. As editors, we are interested in providing a forum for this exciting work in our supplement.

However, implicit in the new name is the notion that Behçet's disease (BD) is also an autoinflammatory condition. Is this justified?

Although perhaps not very openly said, the designation of "autoinflammatory" to BD has been a recent acknowledgment that this condition has many features that do not fit into the traditional concept of autoimmunity. Apart from dissimilarities in demography, geographical distribution and the clinical findings regarding the immunologic component, most importantly the specificity of the pathologic response has not yet been demonstrated to anybody's satisfaction (1).

A recent and usefully provocative editorial (2) gives further reasons why BD might be considered autoinflammatory. In this editorial the fully appreciated ethnic/genetic component in BS is proposed as an important link between the traditional autoinflammatory diseases and BD.

There are issues related to this proposal that need to be further discussed:

a. Autoinflammatory syndromes like TRAPS (tumor necrosis factor receptor-associated periodic syndrome), MWS (Muckle-Wells syndrome), HIDS (hyperimmunoglobulinemia D with periodic fever syndrome), FMF and to some extent Crohn's disease are strongly associated with well defined mutations in the TNF receptor, pyrin, or the CARD/NOD genes. Apart from some loose associations with MEV mutations (3,4) no mutations that involve the CARD/NOD genes have been shown in BD and the data on the TNF polymorphisms have not been conclusive (5-7).

b. The association proposed between FMF and BD has not been very con-

vincing (8,9).

c. Apart from Crohn's disease and FMF, the other autoinflammatory conditions are all very rare and thus far, perhaps due to differences in awareness and medical facilities, have almost solely been reported in the West. This is not the case for BD. In fact, in an endemic area such as Turkey, the prevalence of BD is quite similar to RA (10,11).

Although true population studies are wanting, for an endemic area it would be fair to say that among the diseases we are discussing, BD and Crohn's disease – depending on the geography – have the highest population frequencies followed – with a considerable gap – by FMF and the remainder of the rare diseases in the autoinflammatory group with strong and well defined monogenic genetic components. In fact, one can readily make the generalization that, for at least the autoinflammatory conditions and perhaps for many other diseases, the more polygenic a condition is, the more frequently it will be seen in the population. Thus, as we already strongly suspect (12), the genetic component in BD may also turn out to be polygenic – if we ever sort this out to everybody's satisfaction – rather than monogenic as in the more true-to-form autoinflammatory conditions.

d. A close look at the clinical manifestations also reveals important differences. Most of these entities begin in infancy, whereas pediatric BS is rather infrequent. Paroxysmal attacks that last from a couple of hours to a couple of weeks with frequent serosal involvement and fever characterize the former whereas they are not typical of BS (13, 14). The panuveitis, acneiform lesions and granulomatous lesions that are attributed to the Blau and PAPA syndromes are shadowed by the rarity of the former (15) and the nosologic discussions on the independent validity of the latter (16). Arthritis and skin involvement are non-specific findings that are also observed in SLE; as prototype autoimmune disease. Moreover, the extensive vasculitis, the hypercoagulability, the more severe disease among males and the less severe course of the disease after age 40 are findings that

are peculiar to BS.

Among the autoinflammatory syndromes Crohn's is probably closest to BD in frequency and in clinical manifestations. Even here a close scrutiny reveals important differences between Crohn's and BS. The "autoinflammation gene", CARD15/NOD2 of Crohn's disease, has not been found in BD (5). Furthermore the type of uveitis or the genital ulceration that is present in BD – scrotum being perhaps the most androgen-sensitive tissue, in a condition that is definitely more severe among males – are quite dissimilar.

e. Perhaps the most important difference between BD and the other conditions is the disease course. All other autoinflammatory conditions run an undulating but a relentless course whereas BD, as a rule, abates with the passage of time in the vast majority (17). This feature of BD seems to differ it not only from other automimmune conditions like RA and SLE but also from the so-called autoinflammatory diseases. These considerations makes one strongly think that the genetic abnormality (ies?) in BD are probably not the main disease cause(s) unless we postulate a very unusual interaction with the environment.

In short although we really like our new name the skeptic in us takes us back to the times when lumpers put BD along with the spondarthritides (18). No harm, in fact much stimulating thought, came from this contention followed by the more popular autoimmune theory. Now we go to the autoinflammatory.

It was near where your Supplement is published, in fair Verona, where the poet had Juliet tell Romeo: "What is in a name? That which we call a rose by any other name would smell as sweet." Let the dedicated students of BD, this still a true enigma, not consider it vile nor, more importantly, be content about a name.

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