Internal and Emergency Medicine (2019) 14:639–643
https://doi.org/10.1007/s11739-019-02154-9

EDITOR'S PAGE

Behçet's syndrome: focus on pathogenetic background, clinical phenotypes and specific treatments

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Received: 2 July 2019 / Accepted: 10 July 2019 / Published online: 17 July 2019

Keywords Behçet's syndrome · Genetic · Environment · Microbiome · Phenotypes · Anti-TNF-alfa

Introduction

Since its first description in 1937 [1], Behçet's syndrome (BS) represents a dilemma both for clinicians and researchers. However, many steps forward the comprehension of the main pathogenetic pathways involved in the development of BS have been done [2]. In addition, the management of this complex neutrophilic vasculitis has been improved, and now an increasing number of different drugs are available for its treatment [3]. Given the broad spectrum of manifestations, the interest for BS involves many different specialists (dermatologist, ophthalmologist, neurologist, and rheumatologist). In addition, internists must be aware of this condition, and take BS into account for the differential diagnosis of specific clinical settings (e.g. apparently cryptogenic vascular events, gastrointestinal manifestations resembling Crohn's disease, recurrent oral aphthosis or erythema nodosum mimicking infectious diseases, etc.) [4].

In this special issue, a focus on some of the pathogenetic mechanisms, the main clinical phenotypes and specific treatments have been dedicated to BS.

Etiopathogenesis

BS has a complex etiopathogenesis, and a specific genetic background drives the immune response to environmental factors (mainly infectious) [2].

Since the first report by Ohno and colleagues [5], the Human Leukocyte Antigen-B51 (HLA-B*51) has been confirmed in different populations as the most strongly genetic risk factor for BS developing [6]. However, depending on the genetic ancestry, the frequency of HLA-B*51 varies, ranging from 15 to 60% of BS patients, thus not fully explaining the genetic susceptibility of this syndrome [7-9].

Recently, several different genetic studies have also identified non-HLA variants with biological meaning (e.g., *IL10*, *IL23RIL12RB2*) [10, 11]. A GWAS has recently shown that the Endoplasmic Reticulum Aminopeptidase Protein 1 (*ERAP1*) gene is associated with BS, and that *ERAP1* is epistatic with HLA-B*51 allele [11]. Interestingly, *ERAP1* encodes for a molecule in the endoplasmic reticulum that cuts the N-terminal amino acids from epitope precursors for HLA class I presentation [10, 12, 13]. These mechanisms have profound biological consequences. Indeed, the activation of immune response could depend on the antigen presentation to T cells in the context of the HLA-B*51. The latter is able also to activate innate immune response interacting with natural killer and γδT cells. Moreover, polymorphisms of *ERAP1* could lead to unfolded protein response, thus favouring autoinflammatory processes [14].

In their case–control genetic study, Padula and colleagues focused their attention on the analysis of the two most consistently BS-associated *ERAP1* polymorphisms, namely rs17482078 and rs27044 in a small group of Italian BS patients matched with a control group with similar ethnic features [15].

Interestingly, they found a significantly higher frequency of rs17482078 A allele and AA genotype in BS patients than in controls and a strong association between AA genotype and BS. In addition, the risk hypothetically attributable to the genetic component of the disease was estimated, showing that AA genotype has a large effect on the disease risk. In comparison to other populations [8, 10, 16–18], in the Italian cohort, the association between rs17482078 and BS susceptibility was weaker. No genotypic correlations, neither

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functional effects were found for the rs27044 G polymorphism in the Italian population.

ERAP1 variants preferentially conferred disease risk in HLA-B*51-positive BS patients [9, 10]. Different from other studies [10, 18], Padula and co-workers did not found any correlation between HLAB*51 and both rs17482078 and rs27044.

Although limited by the small sample size, this paper has shown for the first time that also in the Italian population, a *ERAP1* polymorphism confers risk of BS developing.

Mumcu and Direskeneli reviewed for this topical collection on BS, the main environmental factors able to trigger the disease. A comprehensive revision of the literature on the role of microbiome in BS was also performed [19].

Two main studies have investigated the role of both dietary and non-dietary triggering factors in BS [20, 21]. Stress and fatigue have been independently reported by a French and a Turkish study as a common self-triggering factor for most BS patients [20, 21]. Different foods have been correlated with the occurrence of oral ulcers (OU), possibly through an histamine-related irritative mechanism [20, 21], together with oral and skin trauma [20, 22–24]. On the other hand, smoking habit seems to be protective for OU development [25, 26].

Hormonal factors could partly explain the severity of ocular and vascular BS manifestations in men (due to activation of neutrophils by androgens) and the recurrence of mucocutaneous manifestations in women (due to menstruation) [27–29].

Among the infectious agents, bacteria (and *Streptococci* in particular) have been suggested as triggering factors in the pathogenesis of BS, mainly for mucocutaneous manifestations [22, 24, 30, 31].

More recently, as for many other immune-mediated conditions, a role for microbiome was suggested in BS. To date, three main studies on faecal microbiome in BS exist. Consolandi et al. reported a significant reduction in bacterial biodiversity in BS patients, together with a reduction in butyrate production, a short chain fatty acid able to regulate the immune responses [32]. Differently, no changes in bacterial diversity were reported in a study from Japan [33]. Recently, a metagenomic study confirmed both a distinct microbiome signature in BS in respect to healthy controls, and a reduction in butyrate-producing bacteria [34]. Some alterations have been also described in salivary microbiome [35].

Clinical manifestations and phenotypes

In the manuscript titled "Does illness perception associate with disease symptoms in Behçet's disease?", Mumcu and colleagues investigated the patient's perspective in subjects affected by BS and psoriasis through a specific questionnaire [36]. According to previous findings, fatigue and pain were frequently reported by BS patients, impairing the quality of life [37]. In the study of this topical collection, musculoskeletal and eye involvements highlighted the negative beliefs about the illness, while the worst score on psychological attribution was reported by psoriatic patients [36].

The vascular involvement is one of the most important in BS patients in terms of morbidity and mortality, especially for the arterial manifestations [38, 39]. However, the venous involvement is certainly the most common, being the deep venous thrombosis (DVT) of the lower limbs the more typical vascular manifestation [40]. In the study by Seyahi, the diagnostic value of Doppler ultrasound (DUS) and the True Fast Imaging with Steady-state Precession (FISP) Magnetic Resonance (MRI) in the assessment of chronic DVT among male BS patients was compared [41]. The authors showed a comparable capacity of the two diagnostic method in detecting chronic thrombosis in BS, while showing a significant superiority of the True-FISP MRI venography in demonstrating the deep collateral vessels [41].

BS diagnosis is mainly based on the clinical features, since no specific biomarkers for this condition exist. In doubtful cases, the presence of a pathergy phenomenon (i.e. a non-specific tissue hyperreactivity reaction due to trauma) can help the physician to give the patient a definite diagnosis. No standard method to perform the pathergy test is available to date. In their prospective study on 100 BS patients, Kecici and colleagues [42] compared the evaluation of the skin pathergy test independently performed by two dermatologist by naked eye and dermatoscopy. No differences were found between the two methods, but the study revealed that the use of dermatoscopy reduces the interobserver variations of the test.

Besides vascular and mucocutaneous manifestations, BS is characterised by a plethora of different organ involvements. Indeed, it can involve joints, eyes, central nervous and gastrointestinal system, thus to be considered a syndrome rather than a unique distinct condition [43]. Although combinations of the different manifestations might occur, specific phenotypes (i.e. clusters of co-existing involvements) were described in different populations based on cluster analysis and association studies. In her review manuscript, Seyahi reported the main "disease phenotypes", namely the "mucocutaneous and articular", the "vascular" the "neurological and ocular" and the "gastrointestinal" ones [44].

Treatments

In the manuscript "Update on the treatment of Behçet's syndrome", Hatemi reviewed the main advances in the therapeutical management of BS [45] beyond the European

League Against Rheumatism (EULAR) recommendations very recently published [3].

Patients with mucocutaneous (i.e. OU, genital ulcers and erythema nodosum) and articular involvement should start colchicine as first-line drug. The use of disease-modifying antirheumatic drugs (DMARDs) (mainly azathioprine, AZA) should be considered in patients intolerant/resistant to colchicine [45]. The use of anti-TNF-α, interferon (IFN) α or thalidomide should be reserved to truly refractory or severe forms. A phase 3 randomised controlled trial (RCT) has shown efficacy and safety of the anti-phosphodiesterase 4 apremilast [46] for refractory OU. Recently, two studies have suggested the potential benefit of the anti-IL17 secukinumab and of the anti-IL12/23 ustekinumab for refractory mucocutaneous and articular manifestations [47, 48].

For the ocular involvement, AZA is the treatment of choice after an induction treatment with high-dose corticosteroids. In patients refractory to AZA, or with a severe presentation, and/or negative prognostic factor (male gender), anti-TNF-α (mainly infliximab and adalimumab) or IFN α should be used [49–58]. Recently, a potential role for the anti-IL agents (namely anakinra and canakinumab) has been suggested, despite with a lower effect size than anti-TNF-α [59–64].

To date few data suggesting the optimal drugs for the management of both gastrointestinal and neurological manifestations of BS are available. AZA and anti-TNF α can be useful, respectively, even for those doubt cases for multiple sclerosis and Crohn's disease [45]. Small case series have also suggested the use of tocilizumab in refractory central nervous system involvement [65].

The vascular involvement has been separately discussed in the review article by Emmi and colleagues [40], due to its peculiar pathogenesis and therapeutic management. Indeed, BS can be considered as the pathogenetic model of inflammation-induced thrombosis, mainly mediated by neutrophils [66–68]. In clinical practice, immunosuppressants (rather than anticoagulants) are able to reduce vascular recurrences. In patients with vascular manifestations, the use of immunosuppressants (mainly AZA) and additional anticoagulants should be recommended at least in selected patients. Cyclophosphamide should be used for severe refractory arterial involvement, while anti-TNF-α agents represent a valid second-line treatment for both venous and arterial manifestations [40, 69].

Recently biosimilars have entered the clinical practice in different fields of medicine (autoimmune diseases, oncology, and haematology). Questions about the different efficacy and safety with respect to originators have been raised; however, according to a study by Lopalco and colleagues on 13 BS patients switching from originator to biosimilar infliximab, biosimilar infliximab was characterised by a good safety and effectiveness profile [15].

We hope readers will enjoy this collection!

Acknowledgements The authors wish to thank the Associazione Italiana Sindrome e Malattia di Behçet (SIMBA) for the support to their clinical and research activity.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statements on human and animal rights This article does not contain any studies with human participants or animals.

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