Contemporary possibilities of the diagnosis and treatment in Behçet's disease

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SUMMARY

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Behçet's disease (BD – Behçet's disease/BS – Behçet's syndrome) is a chronic, systemic inflammatory vasculitis of unknown etiology, characterized by recurrent episodes of variable vessel vasculitis with heterogenous clinical features. Although the pathogenesis is unclear, some studies have shown that immunological aberrations and infection-related triggers (cytokines, interleukins, inflammatory cells, oxidative stress), including autoantigens are believed to mediate the development in patients with a genetic predisposition to the disease. The diagnosis of Behçet's disease is sometimes difficult because of general and wide-ranging symptoms. An early management of Behçet's syndrome enables a better treatment strategy. Corticosteroids are the mainstay of the therapy. Other options used as induction or maintenance therapy are colchicyne, AZA, ciclosporin-A, cyclophosphamide. Recently, novel biotherapy approaches, including interferon-alpha, TNF-alpha antagonists and other therapies targeting interleukins, have shown promising results in the treatment. In the review, we provide current concepts of immunopathogenesis, disease symptoms and standards of diagnostic and therapeutic management.

Key words: *Behçet's disease, vasculitis, uveitis, autoimmune disease, COVID-19*

STRESZCZENIE

Współczesne możliwości rozpoznawania i leczenia w chorobie Behçet'a

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Zespół Behçeta (BD – Behçet's disease/BS – Behçet's syndrome) jest przewlekłym, układowym zapaleniem naczyń o nieznanej etiologii, charakteryzującym się nawracającymi epizodami zapalenia naczyń o zmiennym przebiegu i heterogennym obrazie klinicznym. Chociaż patogeneza choroby jest niejasna, niektóre badania wykazały, że u pacjentów z predyspozycją genetyczną do rozwoju choroby, pośredniczące aberracje immunologiczne i czynniki wyzwalające związane z infekcjami (cytokiny, interleukiny, komórki zapalne, stres oksydacyjny), w tym autoantygeny mogą przyczyniać się do rozwoju objawów. Rozpoznanie choroby Behçeta jest niekiedy trudne, z uwagi na ogólne i szerokie spektrum objawów oraz incydentalny charakter tego zespołu. Wczesne rozpoznanie zespołu Behçeta umożliwia lepszą strategię leczenia. Podstawą terapii są kortykosteroidy. Inne opcje stosowane jako terapia indukcyjna lub podtrzymująca to kolchicyna, AZA, cyklosporyna-A, cyklofosfamid. Ostatnio, nowe metody bioterapii, w tym interferon alfa, antagoniści TNF-alfa i inne terapie ukierunkowane, wykazały obiecujące wyniki w leczeniu. W pracy poglądowej przedstawiamy aktualne koncepcje dotyczące immunopatogenzy, objawów choroby i standardów postępowania diagnostycznego oraz terapeutycznego.

Słowa kluczowe: *zespół Behçet'a, zapalenie naczyń, zapalenie błony naczyniowej, choroba autoimmunologiczna, COVID-19*

In 1930, during the annual meeting of the Medical Society of Athens, a Greek ophthalmologist, *Benediktos Adamantiades*, presented to the gathering a case report of his 30-year-old male patient. In the course of some as yet undescribed ailments, the patient presented a unique set of symptoms involving genital ulcerations, arthritis, and signs of uveitis. In 1937, *Hulusi Behçet* described similar cases of three patients presenting with similar clinical symptoms and classified their disease as systemic vasculitis. *Behçet's* syndrome (BS) is a chronic, multisystemic disease characterized by a heterogeneous clinical picture in the course of vasculitis. Phenotypes of different forms of the disease vary mainly in terms of symptoms and course, depending on the geographic region of its occurrence.

EPIDEMIOLOGY

BS occurs almost exclusively in the Middle East, among populations living along the historic Silk Road, a trade route known since antiquity that extended from eastern Asia to the Mediterranean basin. The highest risk of the disease is in Turkey (370 cases per 100,000 population) and in Asia (Japan, China, Korea), the Middle East, and North Africa. It also occurs in the United States of America (0.12-0.33 cases per 100,000 population), South America, and southern Europe (0.64 cases per 100,000 population) [27]. Interestingly, these ethnic differences persist among migrants (or descendants of migrants) who live in areas where the disease is naturally rare, affecting people of North African or Turkish descent [14].

The occurrence of variation in the course of the disease, depending on the region of occurrence is a well-documented phenomenon; the frequency of gastrointestinal lesions is higher in patients in Japan, but they are rare in Mediterranean and European populations. Similarly, pulmonary lesions are less common in Japan but more frequent in Europe. The sex ratio in the incidence rate also varies according to the region of occurrence; males are more commonly affected than females in Turkey and Arab countries, and the ratio is usually 2-3 males to 1 female, whereas in Japan and some European countries, females are more affected [12]. Familial cases have been described, but they are rare. *Behçet's* disease (BD) can affect men and women of all ages, but most commonly develops between 10 and 45 years of age. The occurrence of familial or childhood cases of BD affects patients with congenital syndromes. BS is very rare in Poland, with approximately 20 well-defined cases described to date.

CRITERIA FOR DIAGNOSING THE DISEASE

Innovative criteria for the diagnosis of *Behçet's* disease – ICBD, or International Criteria for *Behçet's* Disease, were introduced in 2013, and are currently (2021) valid guidelines. The previous guideline recommended for use was the ISG – International Study Group in 1990. The most recent data clearly differs from these previous guidelines. The criterion of recurrent oral sores is no longer a mandatory condition for diagnosis. The criterion of pathergy has been updated as optional. In addition to the previously used five main hypotheses, two new ones have been used in ICBD, namely nervous system involvement and the criterion of cardiovascular involvement [13].

The onset of the disease is often scarcely symptomatic or the first symptoms are not specific such as fever, weight loss, weakness. Organ symptoms and

Table 1. Diagnostic criteria for BS- ISG and ICBD position [4]
Tabela 1. Kryteria diagnostyczne dla pozycji BS- ISG i ICBD [4]

The criteria of ISG 1990	Definition	Updated criteria ICBD 2013	Points
Recurrent oral aphthous	Minor/major aphthosis or herpetic ulcers (at least 3 times per year)	Aphthous changes in the oral cavity	2
Recurrent genital aphthae	Aphthous-type ulcers or scars	Aphthous lesions in the genital area	2
Ocular involvement	Anterior/posterior uveitis or cells in the vitreous body or retinal vasculitis	Ocular involvement	2
Skin manifestations	Pseudofolliculitis or erythema nodosum-like or acneiform nodules in post-adolescent patients who have not been treated with steroids	Skin lesions	1
Positive pathergy test	Physician-assessed outcome within 24-48 hours (i.e., formation of inflammatory skin lesions after minor skin trauma)	Vascular involvement	1
		CNS involvement	1
		Positive pathergy test	1
ISG position: • Recurrent ulcer-like lesions in the oral cavity are mandatory for diagnosis of the disease • Less common but serious symptoms are absent		ICBD position: • Higher test sensitivity (from 81% to 94%), lower specificity (from 96% to 92%) • Pathergy test is problematic to evaluate in areas of low prevalence (sensitivity in European and US patients is lower)	

Discussion: The diagnosis of *Behçet's* disease is based on the presence of recurrent painful ulcers (aphthae) of the mouth (occurring at least 3 times a year) and 2 additional criteria: recurrent genital ulcers, eye lesions, skin lesions, pathergy. A score >3 indicates the diagnosis of the disease. The pathergy test score is not included in the primary scoring system. Nevertheless, given its specificity for *Behçet's* syndrome, an additional score can be given if the pathergy test is performed [4]. As evaluated, scoring six or more points means the diagnosis of the disease with the probability of 99%.

tissue manifestations appear only as a result of ischemia and complex reactions at the cellular level.

MUCOCUTANEOUS LESIONS

Oral aphthae in BD are recurrent (often more than three episodes per year). They are often the first noticeable symptom and may occur long before other disturbing lesions. They affect almost all patients with BS. As shown in ongoing studies, mucosal lesions do not always precede other serious forms of this disease (ocular, neural, vascular), but patients should remain under constant observation of the attending physician so that they are promptly diagnosed and treated when disturbing symptoms appear.

Genital ulcers affect 80% of all patients. In men, they most often appear on the scrotum and in women on the labia majora. These lesions should be evaluated by a dermatologist to differentiate their morphology from other venereal lesions in the area. Ulcers >1 cm in diameter leave scars. The occurrence of aphthous ulcers in the perianal area is rare and should be differentiated from changes seen in inflammatory bowel disease [14].

VENOUS THROMBOSIS AND NEURYSMS

Venous thrombosis in BS affects both superficial and deep veins, mainly in the lower extremities. Frequent recurrences of the disease lead to symptoms of the post-thrombotic syndrome: edema, hyperpigmentation and dermatitis, and venous ulcers (in 20% of cases). Adhesion of the inflammatory thrombus to the endothelium is characteristic. Thromboembolic disease is rare in BD [26].

Arterial involvement in BS affects only 3-5% of patients. It is therefore a unique presentation not only because of the rare diagnosis, but also because of life-threatening complications associated with peripheral, visceral, and pulmonary artery aneurysms. Inflammation is a promoter for the development of thrombotic events, where mechanism components such as fibrinogen, thrombin, factor Xa, and factor VIIa- lead to the development of the inflammatory cascade [3]. Understanding the contribution of these components and other factors (such as vessel wall damage) is crucial in determining the most effective therapeutic strategy. The median time of the detection of arterial complications takes approximately 7 years after diagnosis of the disease. Pulmonary artery thrombosis and pulmonary artery aneurysms are the most lethal forms of BD, which proceed with arterial involvement. The characteristic picture of the disease is created by hemoptysis and presence of thrombosis on x-ray or CT imaging.

OCULAR MANIFESTATIONS

Ocular involvement is predominant in BD. It occurs in approximately 50% of patients (in this group 70% are males, aged less than 25 years) and its course is severe, usually bilateral, and progressively impairs visual function [21]. The HLA-B51 allele responsible for BD susceptibility with ocular involvement has been described [28]. Uveitis is the most common ocular form of BD and one of the diagnostic criterion for the disease. Uveitis may involve the anterior segment of the membrane, the intermediate segment, or the posterior segment. The most severe form is nongranulomatous bilateral uveitis with retinal vasculitis [5]. Ocular involvement is the inaugural manifestation of BD in 20% of cases, but it can also develop 2-3 years after the onset of extraocular symptoms. The risk of blindness within 5 years is 15 to 25%, mainly due to macular involvement or retinal vasculitis [2].

MUSCULOSKELETAL SYMPTOMS

Musculoskeletal symptoms affect approximately 50% of patients with BD. Usually, arthritis does not lead to joint deformity or erosion and resolves within 1-3 weeks. Recurrences are troublesome and may simultaneously affect several or only one of the joints causing significant effusion [8]. Large joints such as the knee joint, elbow joint, and wrist joint are most commonly affected [34]. Spinal pain is rare [32]. The examination of synovial fluid in patients, usually shows its inflammatory nature. In BD, if sacroiliitis is absent, HLA-B27 is also

Table 2. Occurrence of HLA-B27 antigen in *Behçet's* disease and rheumatologic diseases [4]
Tabela 2. Występowanie antygenu HLA-B27 w chorobie *Behçeta* i chorobach reumatologicznych [4]

Differential diagnosis	Sacroiliac joint inflammation	Presence of the antigen HLA-B27
Behcet's syndrome patients		
- With acne and arthritis (n=30)	6 (20%)	2 out of 27 (7%)
- Without arthritis (n=27)	2 (7%)	0
- Patients with ankylosing spondylitis (n=16)	16 (100%)	NA
- Patients with reactive arthritis (n=12)	3 (25%)	NA

absent (which may be important in the differential diagnosis of other rheumatologic diseases such as ankylosing spondylitis or reactive arthritis) [7].

NEUROLOGICAL SYMPTOMS

CNS damage occurs in ~5% of patients and its causes include so-called parenchymal damage, when lesions result from the brain tissue inflammation (80%) and, less commonly, lesions in the cerebral vessels (20%) occurring with venous sinus thrombosis [5]. Neurological symptoms usually appear after 3-6 years of disease duration. The most typical and characteristic clinical manifestation of BD is tension-type headaches. They occur in more than 50% of cases. Associated symptoms are fatigue, irritability, and cognitive decline [17]. In almost two thirds of cases, neurological symptoms are acute and are interspersed with periods of remission. However, it should always be kept in mind that involvement of the nervous system is a poor prognostic sign and requires intensive, early immunosuppressive treatment [5]. In the case of fever with concomitant severe headache, thromboembolism should be ruled out by performing angio-MRI followed by cerebrospinal fluid examination to exclude encephalitis. CSF findings include elevated interleukin-6, protein and elevated cytosis (up to 400 cells/mm) [25]. If the course of the disease indicates parenchymal brain lesions (80%), cerebral vascular lesions are localized mainly in the brainstem and basal ganglia and at the level of the thalamus, and the prognosis is particularly unfavorable. It has been shown that central nervous system involvement was the cause of death for 11% of patients diagnosed with BD [5].

Visual involvement may also be associated with neurological manifestations: cranial nerve palsy, optic neuropathy or papilledema with mild intracranial hypertension [22].

GASTROINTESTINAL SYMPTOMS

The involvement of gastrointestinal lesions in BD affects approximately one-third of patients originating from Japan, while it is quite uncommon in the Turkish region [23]. Macroscopically, the gastrointestinal forms of BD resemble the lesions seen in *Crohn's* disease and those seen in hemorrhagic proctitis. Histologically, they are most often described as inflammatory and nonspecific. Volcano-shaped ulcers located in the ileocecal region are characteristic. Among subjective symptoms, abdominal pain, diarrhea, vomiting, and gastrointestinal bleeding are the most commonly reported. Perirectal and esophageal lesions are relatively uncommon. Gastrointestinal involvement resembles chronic inflammatory bowel disease in its course [14].

Table 3. Symptoms characteristic of *Behçet's* syndrome in patients with ulcerative colitis (UC) and *Crohn's* disease (CD) patients [10]
Tabela 3. Objawy charakterystyczne dla zespołu *Behçeta* u pacjentów z wrzodziejącym zapaleniem jelita grubego (UC) i chorobą *Crohna* (CD) pacjentów [10]

Symptoms	CD (n=93)	UC (n=130)
Oral ulceration	20 (21.5%)	32 (24.6%)
Genital ulceration	4 (4.3%)	0
Genital scaring	0	0
Papulopustular lesions	22 (23.6%)	23 (17.6%)
Nodular lesions	2 (2.4%)	3 (2.3%)
Arthritis	3 (3.2%)	2 (1.5%)
Vascular involvement	0	0
Eye involvement	0	2 (1,5%)
CNS involvement	0	0

PATHERGY TEST

The pathergy test, performed with a 20-gauge needle, is an adjunctive test in the diagnosis of BD A positive reaction is indicated by hyperreactivity of the skin at the site of the test. In a patient with BD, even mild irritation results in erythema, islets or forming pustules, up to 48 hours after the test. As shown in ongoing studies, a higher percentage of positive pathergy tests, was observed in patients living in the Middle East [11]. In recent years, however, a significant decrease in the frequency of positive reactions has been observed (in 1980, positive results were observed in 82% of the tested patients, whereas, in 2008, only in 23% of the patients). Studies evaluating the cause of these significant changes have shown that the results may be influenced by improvements in sterility during the procedure.

The use of disposable needles and surgical washing effectively reduce the number of positive results [6].

DIFFERENTIAL DIAGNOSIS

Table 4.

ETIOLOGY OF *BEHÇET'S* DISEASE

Although the etiopathogenesis of BD remains unclear, new data suggest that the inflammatory response in BS results from a disruption of homeostasis between specific and acquired immune response mechanisms in genetically predisposed individuals. Previous analyses have confirmed that the HLA-B51 leukocyte antigen allele is the strongest susceptibility factor for the development of BD, and recent studies have reinforced these data and allowed the identification of

Table 4. Differential diagnosis of *Behçet's* syndrome [31]
Tabela 4. Diagnostyka różnicowa zespołu *Behçeta* [31]

Symptoms	**Commonly confused with**	***Behçet's* syndrome**
Oral ulceration	Purulent stomatitis	- More painful, more frequent, numerous
Papulopustular lesions	Acne vulgaris	- Localization in upper trunk and skin of extremities - Lesions usually in older age (>40 years)
Genital ulceration	Reactive arthritis, *Herpes simplex* infection, other sexually transmitted diseases	- Causes scar formation - More commonly on the scrotum and labia majora
Lower limb venous thrombosis	Idiopathic thrombosis, venous insufficiency, thrombophilia	- More common in males and younger (20-40 years) than in other diseases - Superficial and deep vein involvement - Bilateral limb involvement with recurrence and incomplete recanalization
CNS involvement	Multiple sclerosis, lymphoma, sarcoidosis, tuberculosis	- Affects brainstem and basal ganglia -The lesions are large and confluent - Brainstem atrophy is pathognomonic
Pulmonary artery involvement (PAI), abdominal aortic aneurysms	*Takayasu's* disease or large cell arteritis	- Males of younger age (PAI) - More often numerous, uniform thrombi (PAI) - Occlusions are thrombotic in nature - Proceeds with fever and elevated inflammatory parameters - Pulmonary artery aneurysms are almost pathognomonic for Behçet's disease

new genes that are also responsible for a predisposition to the disease (IL-10, IL-23R, IL-12RB2). Expression studies have shown that disease-associated IL-10 variants are associated with reduced expression of this anti-inflammatory cytokine, which may lead to generalized inflammation, thereby increasing susceptibility to BD [27].

Despite the fact that HLA-B51 is a known genetic factor, which is the most strongly associated with BD, the presence of HLA-B51 does not confirm or exclude the diagnosis [18]. An infectious (bacterial) agent may be a triggering factor of the disease, through an abnormal T-cell response to bacterial heat shock proteins (HSPs), causing secondarily, through

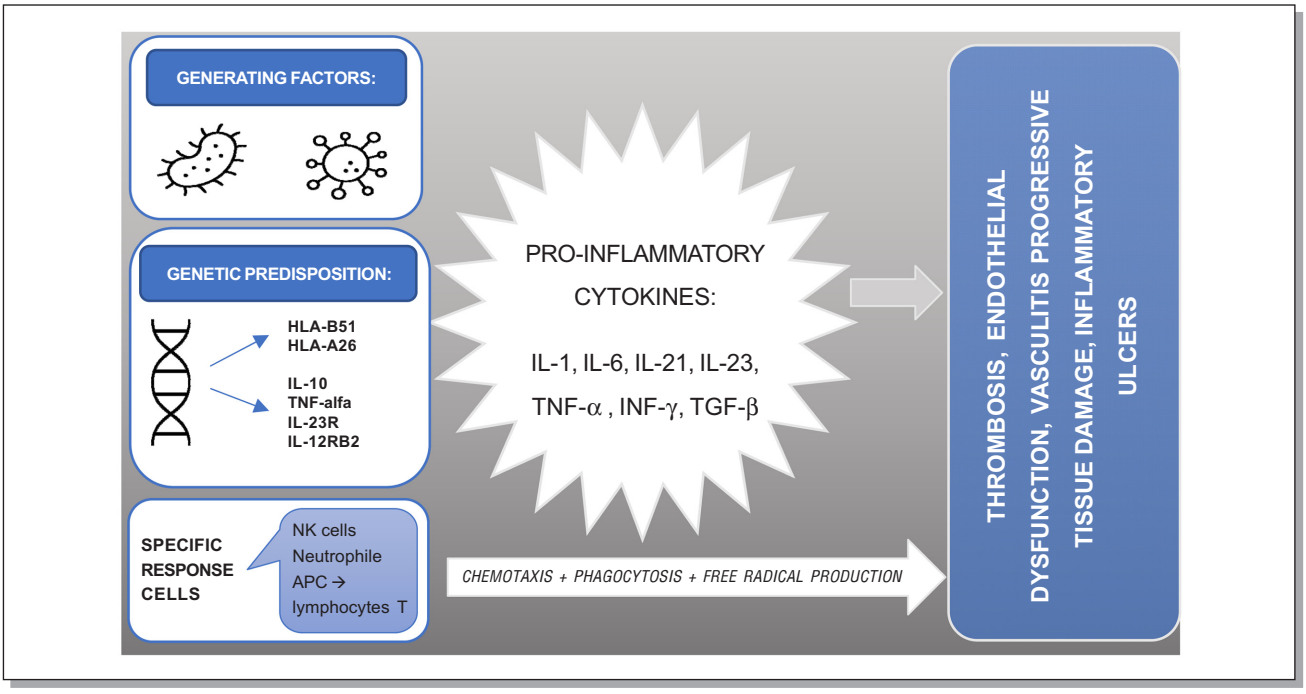

Figure 1. The role of innate immune cells in the pathogenesis of *Behçet's* disease [27]
Rycina 1. Rola komórek odporności wrodzonej w patogenezie choroby *Behçeta* [27]

cross-reactivity, the proliferation of autoreactive T cells against human HSPs.

A reduction in T1 and T17 lymphocytes, as well as regulatory T cells, has also been shown to occur in most patients. The most important cells involved in the inflammatory process in the course of BD are multinucleated neutrophils, NK cells, CD4+T lymphocytes and cytotoxic CD8+T lymphocytes; and cytokines IL-17, IL-23, IL-21 play a decisive role.

The studies also indicate the role of endothelial cell dysfunction in the pathogenesis of the disease. Chronic inflammation is associated with increased oxidative stress, and this in turn induces activation of platelets, leukocytes and endothelial cells through the release of proinflammatory cytokines. Neutrophils in patients with BS are hyperreactive, exhibit increased phagocytosis, superoxide production and NET, which potentially contributes to thrombus formation [14]. At least two syndromes of the disease have been described. The first includes superficial vein thrombosis, deep vein thrombosis, and cavernous sinus thrombi. The second includes acne, arthritis, and bursitis. The presence of these clusters suggests that there may be more than one disease mechanism operating in this complex disorder [33].

TREATMENT OF PATIENTS WITH *BEHÇET'S* SYNDROME

Pharmacological treatment is highly dependent on the clinical picture of the disease and its course. However, it is always directed individually towards the patient to achieve the best possible remission. Colchicine is the first-line treatment for oral and genital mucosal lesions, pustulopapular lesions, nodular lesions and arthritis. When the treatment does not work, azathioprine and colchicine as well as interferon-alpha and anti-TNF-alpha are currently recommended. Additionally, corticosteroids are recommended at each stage of treatment [9].

Ocular and neurological as well as vascular forms require specialized immunomodulatory therapy with cyclophosphamide and azathioprine, accompanied by systemic corticosteroid therapy. Surgery is also among the first-line therapies in these forms of the disease. Anti-TNF-alpha and interferon-alpha are used as indicated [29].

The use of anticoagulants in the treatment of the vascular form of BD remains controversial. Still, anticoagulation treatment is recommended because of vessel wall inflammation, which is the main cause of thrombosis associated with BD. However, according to recent recommendations and studies, anticoagulant treatment does not seem to reduce the risk of recurrent thrombosis [19]. The use of aspirin at an anti-aggregation dose is only considered after arterial damage consisting of a reduction in the lumen of the arteries has been established [14]. An exception to the use of anticoagulants in BS may be cerebral venous thrombosis [20]. Control of thrombotic events in BD is mainly achieved with immunosuppressive drugs rather than commonly used anticoagulants [24]. In particular, the use of azathioprine together with low doses of cyclosporine and in combination with corticosteroids should be considered for the prevention of thrombotic events [3].

Reduced doses of immunosuppressants and immunomodulatory treatment may be considered, excluding some cases when at least 2 years have passed since the remission without ocular, neurological, vascular symptoms [14].

Biologic drugs are beginning to play an increasingly important role in the treatment of BS. Observational studies using IFN-α and anti-TNF monoclonal antibodies have shown favorable results in refractory uveitis. A meta-analysis of case-control studies showed that immunosuppressive drugs significantly reduced the rate of recurrent deep vein thrombosis, whereas anticoagulants did not. Cyclophosphamide and high-dose glucocorticoids reduce mortality in pulmonary artery aneurysms and postoperative complications in peripheral artery aneurysms. Favorable results in gastrointestinal involvement have been obtained using 5-ASA derivatives and AZA as first-line treatment and thalidomide and/or anti-TNF monoclonal antibodies in refractory cases. Observational studies on nervous system involvement have shown improved outcomes after immunosuppressive drugs and glucocorticoids. A meta-analysis of case-control studies showed an increased risk of developing nervous system involvement with cyclosporine-A [19].

GENERAL PRINCIPLES AND RECOMMENDATIONS BASED OF EULAR 2018 RECOMMENDATIONS

In recent years, many new data on the management of BS have been published. This has influenced the creation of updated recommendations. Large studies involving many patients with BS included in the updated EULAR recommendations were mostly observational. The main new conclusions of this study compared with the results of the previous edition of the EULAR recommendations on BS were: an increase in the evidence for the satisfactory use of biologic drugs, especially TNF inhibitors, in patients with the involvement of all major organs refractory to conventional treatments, a review of surgical interventions for arterial aneurysms, and a meta-analysis showing that immunosuppressive drugs instead of anticoagulants

reduce the recurrence rate of deep vein thrombosis [19]. In addition to the above conclusions, the most important assumptions were:

– BD is a condition that typically follows a relapsing-remitting course, and the goal of treatment is to rapidly manage exacerbations and recurrent inflammation to prevent irreversible organ damage.
– A multidisciplinary approach is required to provide optimal care.
– Treatment should be individualized according to the age, gender, type and severity of organ involvement and patient preference.
– Ocular, vascular, neurological and gastrointestinal involvement may be associated with poor prognosis.
– In many patients, the symptoms of the disease may be relieved over time [9].

SARS-CoV-2 INFECTION AND *BEHÇET'S* DISEASE

A study has recently been published on the association between BD activity and treatment, and the risk of SARS-CoV-2 infection. The study group consisted of 335 patients, 14 of whom were infected with the virus during the first wave of the pandemic, showing a 4.2% prevalence of SARS-CoV-2 infection among patients with BD, being in line with the general population in Italy (4.4%). The comparison of the quantitative data of COVID-19 incidence in rheumatologic patients to those patients without SARS-CoV-2 infection has shown that the presence of symptoms of rheumatologic disease did not significantly affect the predisposition to disease between the two groups. Therefore, based on the results, the preliminary study suggests that patients with BD do not have a higher risk of SARS-CoV-2 infection and other serious complications, compared to the general population. Furthermore, unlike the general population, all cases of SARS-CoV-2 infection in BD patients were mild, no patients developed chronic pneumonia, no patients required hospitalization, and no patients died from severe respiratory failure during the course of COVID-19. Despite many publications on this highly topical topic, it is still under investigation whether or not patients with various autoimmune diseases receiving immunosuppressive therapy are more susceptible to SARS-CoV-2 infection [30]. Therefore, another publication aimed to analyze the prevalence of SARS-CoV-2 infections among patients with BS, evaluating a possible association between demographic and clinical characteristics and the risk of infection has shown that in the group where this relationship was studied the risk of SARS-CoV-2 infection or severe complications was not found to be higher in these patients compared to the general population [15]. The main results of the studies conducted to date (2021) show that there is no evidence that BD increases susceptibility to viral illness; there is no scientific evidence that viral illness leads to exacerbation of BS; and it has not yet been proven that any immunosuppressive drugs can increase the risk of SARS-CoV-2 infection.

PROGNOSIS

Men, especially those with an onset at a young age, are at a higher risk of serious organ complications. Uveitis can lead to blindness if not well controlled. Cardiovascular and central nervous system involvement are the main causes of mortality among BS patients [1,16]. Early and effective treatment is important to prevent irreversible changes and premature death.

SUMMARY

Specialized multidisciplinary care in an expert center is required for this rare disease with highly polymorphic expression, requiring prolonged treatment and a lifelong follow-up [14]. The publications available so far indicate that the effectiveness of new biological therapies is promising in controlling exacerbations and relapses. Education on treatment and disease management is essential to optimize care and maintain patient adherence to the principles of the planned therapeutic process, and it is the only chance for the physician to maintain satisfactory treatment outcomes.

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