

Epididymo-Orchitis in Behcet's Disease: A Review of the Wide Spectrum of the Disease

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Received: 04 Aug. 2016; Accepted: 13 Apr. 2017

Abstract- Behçet's disease is a chronic, recurrent, inflammatory disorder characterized by orogenital ulcers and skin lesions; serious manifestations also include ocular, large vessel, gastrointestinal and neurological involvement. Genetic and unknown environmental factors modify the wide clinical spectrum of the disease. During the long clinical course of the disease, testicular and epididymal involvement has been reported, with scrotal pain and swelling being the most common symptoms. In this review, we discuss the various aspects of epididymo-orchitis in Behçet's disease patients, and we evaluate the diagnostic approaches as well as the empirical therapeutic modalities of this entity.

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Acta Med Iran 2017;55(8):482-485.

Keywords: Behçet's; Orchitis; Epididymitis; Diagnosis; Therapy

Introduction

Behçet's disease (BD) is a chronic, relapsing, multisystemic, inflammatory disorder characterized by variable clinical course. The etiopathogenesis of this disease remains to be clarified.

Persons of both gender and any age can be affected, although with differences in various populations (1,2). BD is mainly seen along the Silk Road (3), the Middle East and the countries of the Mediterranean basin (1,2).

Any system and organ can be involved, although with differences in frequency in various regions.

Among the organs, epididymitis and testicular involvement are seen in different prevalence in BD patients.

Epididymo-orchitis in BD has not received much attention, and even in recent reviews of the disease, there is no mention (4-6). In the EULAR recommendations, there is no mention of the treatment of epididymo-orchitis (7). Additionally, a few studies have been published concerning the clinical features and treatment of this disorder (8-12).

This review presents data on epididymo-orchitis including epidemiology, clinical manifestations, diagnosis, differential diagnosis and management of this interesting entity.

Epidemiology

The prevalence of orcheo-epididymitis in BD varies in different regions and even in the same area, according to the number of patients studied and the date of the studies. Therefore, the prevalence of each region is analyzed separately.

Far east

The prevalence of epididymo-orchitis in BD patients in Korea is 0.6% (13), while in a more recent study in the same country is 4.6% (11), in Japan 6% (14) and in China 1.9% (15).

Middle east

The prevalence of this manifestation in Jordan is 27% (16), in Iraq 31% (8), in Saudi Arabia 4% (17), in Israel 6% (18) and in Iran 4.7% (9).

Mediterranean and European countries

In this area, the prevalence is in Turkey 19.2% (20), while in a more recent study the estimate ranges between 5% to 10% (21). In Italy is 10.5% (22), in Egypt 16% (23), in Greece 12.5% (24), in France 2% (25) and in Germany 10.8% (26). The prevalence in *the USA* is 2% (27).

The prevalence of epididymo-orchitis in BD in a

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more recent meta-analysis there was estimated to be 14.2% (28).

HLA B51/5 and epididymitis in patients with BD

It was found that in these patients with epididymitis the prevalence was 15.8%, while in those without epididymo-orchitis was only 5.2% (28). In one study, all patients with epididymo-orchitis in BD had HLA B51/5 (10).

The prevalence of epididymo-orchitis in patients with BD has a geographic distribution and differs also between juvenile and adults. The prevalence in juvenile was 25%, while in adults was 8.9% (10). Other investigators reported lower prevalence 5% and 6% respectively (29,30). However, most of the investigators consider that childhood cases are rare (12). Patients with epididymo-orchitis have high prevalence of cutaneous involvement, genital ulcers, arthritis, central nervous system manifestations and pathergy test compared to those without this complication (11).

Etiopathogenesis of epididymo-orchitis in BD

The etiology of this entity is unknown at present, although a vasculitis like mechanism has been postulated (9,10). Histological studies of these organs are not available (31). Presumably, the inflammation results from the vasculitis which is thought to underlie disease manifestation in other organs (31). Another possibility could be an infection.

However, repeated urinary cultures and seminal fluid were negative (8), and even the inflammation subsides with the administration of anti-inflammatory drugs (10) or with corticosteroid and colchicine (12). Therefore, there is no definitive evidence for the participation of infectious agents in these cases (31).

Recently, investigators considered that BD belongs to the wide spectrum of auto-inflammatory diseases. However, for a number of reasons it is not the case (32,33). In addition, it has been documented that testis is involved in other, non BD, vasculitic syndromes (34), including polyarteritis nodosa (35), giant cell arteritis, Goodpasture syndrome, cryoglobulinemic vasculitis syndromes (35). Wegener granulomatosis (35) and Henoch-Schoenlein purpura. In this group of vasculitis includes the isolated testicular vasculitis (34). These data permit to conclude that epididymo-orchitis in BD is part of vascular disease (31).

Clinical manifestations

The onset symptom of epididymo-orchitis is scrotal pain in one or both testis and epididymis. The painful

swelling follows the initial symptomatology with or without fever (8,9). The presence of fever underlines a severe inflammation of these organs (9,11). On clinical examination, painful swelling and tenderness of epididymis or testis are seen, particularly on one side (8). In one study simultaneous findings were found such as oral ulcers, arthritis, uveitis, fever and senile ulcer (10). Other investigators found also the low prevalence of uveitis (11).

Epididymo-orchitis is seen several years from the onset of the disease and various clinical manifestations are proceeded (10). It has been documented that as first manifestation of the disease is very rare (8,9). The duration of inflammation lasts from 1 to 2 weeks and subsides with or without treatment. However, recurrence of epididymo-orchitis is not unusual and may be seen 2-3 episodes yearly (11). They have been reported from 1 to 8 times (9,10) or 1 to 10 such episodes (8). The recurrence can be observed after 1 to 15 years from the initial episode (10). In these patients thickness and nodularity of the affected organ is found (36).

Diagnosis of epididymo-orchitis in BD patients

The diagnosis of this manifestation is based on clinical grounds since laboratory tests are negative or normal (10,11). Repeated urinary cultures did not grow any pathogenic organism. Epididymo-orchitis usually follows other clinical manifestations of BD and very rarely is the presenting manifestation of the disease. Therefore, this helps to the diagnosis and even to differentially diagnose this entity from other causes of orchitis. In addition, imaging methods could confirm only the inflammation of the organs. Between these methods are the testicular ultrasound and scrotal magnetic resonance imaging which may assist in accurate localization of the pathologic involvement and differentiate other causes of the involvement of testis e.g. tumors *etc.* (31). However, are not specific for epididymo-orchitis in BD. In addition to certain causes is not very easy clinically to differentiate whether the epididymis or the testis proper is mainly involved in the disease process (8), although usually both organs are involved.

The accurate diagnosis could avoid surgical interventions considering infection with abscess (36). The early diagnosis and the early treatment can avoid severe consequences. To our knowledge, there are not available data to relate epididymo-orchitis with mortality in BD patients.

Investigators suggest that the occurrence epididymo-orchitis support the diagnosis of BD in young persons

when they come from countries with high prevalence of BD (10) and when fever is a dominant manifestation (12).

Differential diagnosis

In the case of suggestion of epididymo-orchitis can be screened to exclude other causes of epididymitis applying laboratory tests, including complete blood count, urinary cultures, ANA, VDRL, viral antibodies and circulating immune complexes (11).

Epididymo-orchitis could be the result of infection including tuberculosis (36), virus and other bacterial diseases. Pyogenic orchitis can be confused with the orchitis of BD (8) as additionally a wide spectrum of vasculitides e.g. polyarteritis nodosa, including the isolated testicular vasculitis (35). Other causes of testis swelling are also neoplastic diseases.

Treatment

The treatment of epididymitis-orchitis in BD patients is empirical and differs from other causes of this entity. In this particular manifestation of BD, to our knowledge, there is no controlled study for the management of the disease. Therefore, the treatment depends on the experience of the clinician (8-11). The mainstay of treatment includes the administration of colchicine and/or non-steroidal anti-inflammatory drugs. In resistant patients, corticosteroids should be administered (10). However, in most of the patient's colchicine and corticosteroids are successful and the inflammation subsides in a few days (10). It is only possible this testicular vasculitis to resolve spontaneously only with analgesics (11). In cases of recurrences combination of treatment is usually successful.

In scrotal ulcer with testis swelling conservative treatment necessitates bed rest, scrotal support, cooling, topical steroids and antibiotic treatment combined with analgesics (11).

Management of this vasculitis with anti-inflammatory drugs is usually inadequate to prevent recurrences, and therefore in this refractory cases azathioprine, cyclophosphamide, cyclosporine and other cytotoxic drugs could be administered (10,11,37).

In a reported case, dapsone was proved successful (8). However, in refractory cases to cytotoxic drugs, anti-TNF- α agents could be given. When infection is suspected antibiotics should be added (11). Severe manifestations, such as fever, myositis, and thrombophlebitis in patients with epididymo-orchitis in BD treatment includes also the administration of anticoagulants (22).

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