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Review Article

Ear, nose and throat manifestations of Behçet's disease: a review

C J Webb, R J Moots*, A C Swift†

Abstract

Objective: To review Behçet's disease and to describe its clinical features in the head, neck and upper respiratory tract.

Method: A literature review was undertaken, following a Medline search of publications over a 30-year period, and utilising the expert knowledge of one of the authors (RJM) with a specialist interest in Behçet's disease.

Results: Twenty-seven articles with ENT relevance were obtained. Otorhinolaryngological manifestations included symptoms and signs in the mouth, nose, sinus, larynx and ear.

Conclusion: Behçet's disease is usually considered to be a condition affecting the oral cavity, eyes and genitals. This article shows that most patients will also exhibit other ENT symptoms, hearing loss in particular. Indeed, Behçet's disease may present with features other than the classic triad of symptoms. Raised awareness of the clinical features within the head and neck region will hopefully enable early diagnosis and treatment of this potentially serious condition.

Key words: Behçet's Disease; Otorhinolaryngological Diseases; Otolaryngology

Introduction

In 1937, a Turkish dermatologist, Professor Hulusi Behçet, defined a triple symptom complex of recurrent aphthous ulcers, genital ulcers and uveitis. The triad is referred to as Behçet's disease, although a few authors prefer the term Behçet's syndrome.

However, six years prior to Behçet's description, Adamantiades, a Greek physician, is reported to have published an account of the disease in a French journal.[1] The disease complex became known as Adamantiades–Behçet's disease, although this term is rarely used today.

Interestingly, about 2500 years before either of these descriptions, Hippocrates is quoted as writing about a patient with aphthous ulceration, defluxions about the genital parts, watery ophthalmies of a chronic character, and large herpetic lesions.[2]

Although Behçet's disease is well known to involve the classical triad of disorders affecting the mouth, eyes and genitals, it is a multisystem autoimmune condition that has several other manifestations. These clinical features affect the head, neck and upper respiratory tract. Patients with Behçet's disease may therefore present primarily to an otorhinolaryngologist. However, because of the rarity of the condition, the true diagnosis may not be considered.

This article reviews the various manifestations of Behçet's disease and addresses the various clinical aspects appropriate to otorhinolaryngology. The epidemiology, aetiology and pathogenesis of the disorder are reviewed.

Method

A critical review of the literature with special reference to otorhinolaryngology was performed. A Medline search was conducted, using the following search terms (either singly or in combination): Behçet's disease, Behçet's syndrome, ear, nose, throat, aetiology, investigations and treatment. A total of 223 articles was retrieved using these criteria.

Some topics were covered repeatedly by several papers; we therefore limited references to such articles by choosing the most comprehensive or those reporting the latest evidence. Other papers were referenced repetitively and were obtained whether or not they appeared in the Medline search. We distilled the search down to 27 papers of significance or relevance for the purpose of this article. The specialist expertise of one of the authors (RJM), who has a specialist interest and provides a tertiary referral service for patients with

From the Department of Otorhinolaryngology, Royal Liverpool and Broadgreen University Hospital, and the Departments of *Rheumatology and †Otorhinolaryngology – Head and Neck Surgery, University Hospital Aintree, Liverpool, UK.
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Behçet's disease, was also utilised to formulate this review article.

Epidemiology

The incidence of Behçet's disease varies according to geographical location. The highest prevalence is seen in the Mediterranean region, Middle East and Far East (1 per 10 000 people). Interestingly, these countries are all part of the old silk trading route. The prevalence is lower in the Caucasian populations of Europe and North America (1 in 20 000).[3]

Behçet's disease affects primarily young people, although it may develop at any age. The usual age of onset ranges from 20 to 35 years. The male:female ratio also varies with geographical location, and ranges from 24:1 in Iran,[3] through approximately 1:1 in Western Europe, to 1:1.75 in Korea.[4]

Pathogenesis

The aetiology and pathogenesis of Behçet's disease is not fully understood.

The histology of the specific lesions shows vasculitis that differs from other forms of systemic vasculitis in that it involves both arteries and veins, and vessels of any size.

Behçet postulated an infectious viral cause, and still today this remains one plausible theory.

Circulating levels of tumour necrosis factor (TNF), interleukin 1β, interleukin 8, and myeloperoxidase are raised in patients with Behçet's disease. Peripheral blood monocytes exhibit an exaggerated response to certain streptococcal antigens in this group of patients.[5,6]

A genetic predisposition is likely, given the geographical locations of Behçet's disease along the historical silk trading route in the Mediterranean and Orient.[2] The risk of developing Behçet's disease is also higher among siblings of affected patients,[7] and the disease presents at an earlier age in the children of affected parents.[8]

The only genetic factor so far identified as being part of the disorder is the presence of the major histocompatibility complex allele HLA-B51. Although more common in patients with Behçet's disease, this allele is not present in all patients. In addition to HLA-B51, TNF β2 allele is also more common in patients with Behçet's disease. The TNF β2 allele leads to a higher production of TNF, which might induce a more severe and prolonged inflammatory response to antigens in contact with mucosal surfaces.[2]

Much research has been done to determine how human leukocyte antigen B51 leads to the development of Behçet's disease. A recently discovered addition to the T-cell receptor family has been located on the surface of natural killer cells and γδ T cells. This receptor has been termed the killing inhibitory receptor. It has been postulated that human leukocyte antigen B51 may regulate the expression of killing inhibitory receptor on the cell surface. In patients with Behçet's disease, the expression of killing inhibitory receptor has been shown to be defective. It has further been postulated that defective expression of killing inhibitory receptor causes a defect in the regulation of T cell response, which may lead to an abnormal response to infection at the mucosal surface.[9]

Clinical features

Behçet's disease is generally quoted as presenting with recurrent oral ulceration, genital ulcers and ocular disorders such as uveitis. However, many other clinical features have been described.

Our review of the literature discovered three systematic reviews reporting audio-vestibular dysfunction[10–12] and one case report of destructive sinusopathy.[13]

One patient from our unit also had pharyngolaryngeal stenosis secondary to Behçet's disease.

Oral features

Recurrent oral ulceration (i.e. more than three attacks a year) is the most frequent presenting symptom of Behçet's disease.[14] Typically, the ulcers are multiple, of variable size (2–20 mm), and occur extensively on the buccal membrane, tongue, palate and in the oropharynx (Figure 1). The ulcers are classically painful, unlike those of some other rheumatic diseases, such as systemic lupus erythematosis. They are surrounded by erythema and the larger ones heal with scarring. During relapses of Behçet's disease, the oral ulcers become more persistent, lasting up to six weeks. As recurrent aphthous ulceration is frequently the initial feature of Behçet's disease, the differential diagnosis at this stage is challenging. However, six or more painful ulcers of variable size with surrounding erythema occurring on the soft palate or in the oropharynx should heighten suspicion of Behçet's disease, especially if associated with scars.[15]

Laryngeal and oropharyngeal features

Behçet's disease affecting the larynx has been reported in a 44-year-old man with dyspnoea and

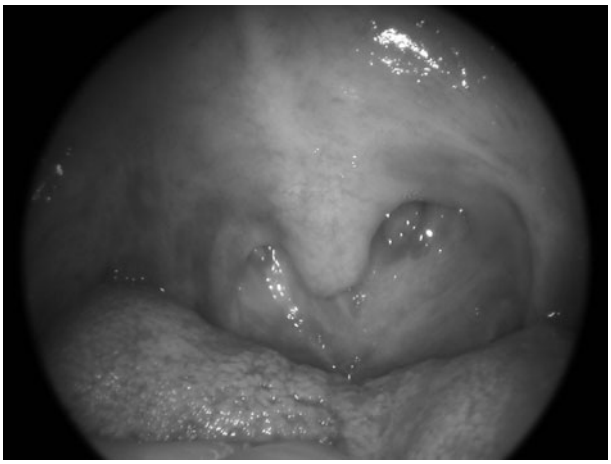

FIG. 1

Oropharyngeal ulceration in a 57-year-old woman with Behçet's disease.

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dysphagia, oedema of the lateral laryngopharyngeal walls and a swollen, omega-shaped epiglottis that occluded the airway.[16] The patient subsequently underwent epiglottectomy and thyrohyoidopexy, but symptoms recurred two years later due to scar formation.

We found three case reports describing two patients with pharyngeal stenosis. Stenosis of the pharynx at the junction of the oropharynx and hypopharynx was described in a 33-year-old Jamaican man, six years after being diagnosed with Behçet's disease.[17] Stenosis of the oropharynx, lateral hypopharyngeal walls and involvement of the epiglottis was described in a 13-year-old boy with a four-year history of Behçet's disease, who subsequently had three years of systemic steroid treatment.[18,19]

The authors have recently treated a 57-year-old woman with laryngopharyngeal scarring from Behçet's disease (Figure 2). The supraglottis was stenotic and the epiglottis omega-shaped, eroded and distorted. The patient subsequently required a tracheostomy and medical treatment with systemic steroids and infliximab.

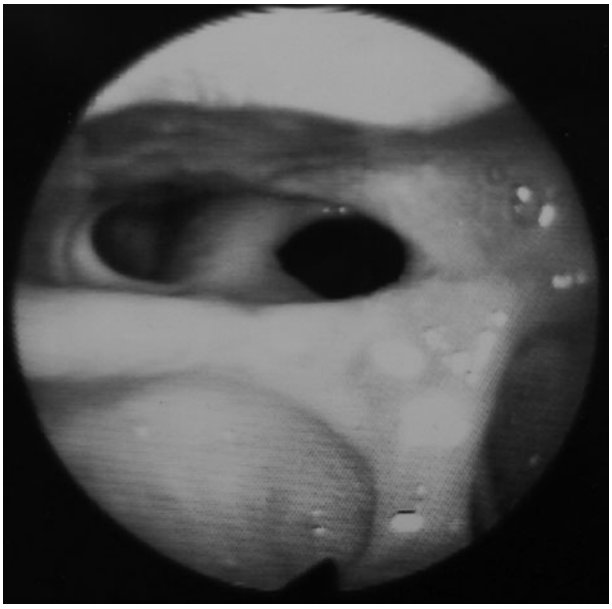

FIG. 2
Supraglottic and pharyngeal scarring and stenosis in a 57-year-old woman with Behçet's disease.

Otological features

The otological features of Behçet's disease can be divided into hearing loss and disequilibrium. One prospective study described sensorineural hearing loss in 27 per cent of 72 patients with Behçet's disease, compared with 6 per cent of 72 age- and sex-matched controls ($p < 0.05$).[10] The sensorineural hearing loss was variable, with descriptions ranging from unilateral to bilateral, mild to profound, and low frequency dominant to high frequency dominant.

Hearing and vestibular function was assessed in 20 patients with Behçet's disease and 20 controls.[11] Sudden sensorineural hearing loss was reported in two patients with Behçet's disease. Audiovestibular dysfunction occurred in 15 patients but in only three controls. Human leukocyte antigen B51 phenotypes were more common in the subjects than the controls. Cochlear dysfunction was more common than vestibular dysfunction, and cochlea and vestibular dysfunction could occur either singly or in combination.

Vestibular involvement has been postulated after 16 of 25 patients with Behçet's disease reported disequilibrium, compared with no such problems in a control group. However, vestibulopathy was not confirmed by objective tests, and although Frenzel glasses were used to detect nystagmus the results were not published within the paper.[12]

There has been one case report of a patient with documented chronic otitis media and Behçet's disease, but the significance of this is unclear.[13]

Paranasal sinus features

There is one case report in the English literature of sinus disease in a patient with Behçet's disease.[13] A 47-year-old man with rhinitis was found, on computed tomography (CT) scanning, to have destruction of the turbinates, a septal perforation and pansinusitis. The authors attributed this destructive sinusopathy to Behçet's disease, after excluding Wegener's granulomatosis. There was no mention of other disease processes being excluded.

Other non-ENT features

The non-ENT manifestations of Behçet's disease are legion, with the potential to affect almost any organ. The most common features are: oral ulceration; genital ulceration; skin lesions (such as erythema nodosum-like lesions); thrombophlebitis; eye lesions (particularly anterior and posterior uveitis); arthritis affecting multiple joints; non-specific gastrointestinal lesions (often characterised by ileocaecal ulceration); epididymitis; vascular lesions (including a thrombotic tendency, aneurysm formation and small vessel obliteration); neurological involvement (such as severe headaches, acute myelitis and saggital vein thrombosis); stroke and cerebral vasculitis.[3,20]

Patients with Behçet's disease may often give a history of pathergy (hypersensitivity of the skin to needle puncture), with skin reactions at venepuncture or body piercing sites. This feature is more commonly observed in patients from the Mediterranean than the UK.[21–23]

Diagnosis

There is no laboratory test for Behçet's disease. The diagnosis is therefore made entirely on clinical grounds, with an appropriate history, examination and exclusion of other autoimmune conditions.

A positive pathergy test (with skin reaction developing one to two days after puncture of the skin with a sterile needle) can be helpful in making a diagnosis.[21] However, a negative pathergy test is not helpful in excluding the diagnosis, as many patients with Behçet's disease, particularly in Northern and Western Europe, are negative.[22,23]

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In 1990, the International Study Group for Behçet's Disease published simplified criteria for diagnosing Behçet's disease (Table I).[24] Their criteria were based on five previously suggested diagnostic criteria, but also included statistically significant features present in 914 patients with Behçet's disease. Apart from recurrent oral ulceration, no other ENT manifestations were included in the analysis. Although it was acknowledged that other ENT manifestations do occur in Behçet's disease, they cannot be used reliably to aid confirmation of the diagnosis. The major limitation of these diagnostic criteria is that patients without oral ulceration are excluded; whilst oral ulceration is a common feature, it is not present in every patient with Behçet's disease, particularly in the latter stage of advanced disease.

In 1987, the Behçet Syndrome Research Committee of Japan published their revised criteria,[25] which some authors prefer. These criteria do not exclude patients without oral ulceration, but are generally more complicated to use. In these criteria there are four major criteria, namely oral aphthous ulceration, skin lesions, eye lesions and genital ulcers, all of which are required to be present to diagnose complete Behçet's disease. However, there are also minor criteria, which include arthritis, vascular lesions, central nervous system lesions and others. These minor criteria can be used to aid a diagnosis of incomplete Behçet's disease or possible Behçet's disease, if all four major criteria are not fulfilled.

Management

If Behçet's disease is suspected, a full medical assessment is required, and blood tests should include serology for other autoimmune disorders. Flexible endoscopy of the upper respiratory tract is helpful in order to record the appearance, even if normal, since it can change with time. Biopsy of oral ulceration is not diagnostic and is non-specific; mucosal ulcers in Behçet's disease cannot be distinguished from aphthous ulceration.[26]

Pure tone audiometry is appropriate, and vestibular function tests may be helpful in those patients with vertigo.

TABLE I

DIAGNOSTIC CRITERIA FOR BEHÇET'S DISEASE: INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE[24]

Recurrent oral ulceration
Minor or major aphthous or herpetiform ulcers recurring ≥3 times in 12 mths
Plus 2 of the following:
Recurrent genital ulceration
– Aphthous ulceration or scarring
Eye lesions
– Anterior or posterior uveitis or cells in vitreous or retinal vasculitis
Skin lesions
– Erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules in postadolescent patients
Positive pathergy test

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The treatment of Behçet's disease remains challenging. However, in recent years there have been some major advances. Due to the complex nature of both the disease and the optimum treatment regimes, patients are best managed in centres with specialist expertise.

Oral ulceration often responds well to topical treatment with a tetracycline-triamcinalone mouthwash. Topical anaesthetic preparations are also helpful. A localised high-dose application of topical steroid, delivered via a standard asthma inhaler directly onto the ulcer, is another useful, effective method of treatment.[3]

Systemic corticosteroids (oral, intravenous or intramuscular) are effective in treating serious acute episodes, but long-term courses have significant side effects and are best avoided.[3] Low dose colchicine (200 μg two or three times per day) is effective for mucocutaneous disease.[20] Anticoagulants are essential for patients with thromboses.

Recently, success in controlling systemic disease has been achieved with immunosuppressants such as azathioprine, cyclosporine, tacrolimus and mycophenalate mofetil. Cyclophosphamide plays an important role where there is critical organ involvement.

Thalidomide is an effective agent for treating both mucocutaneous and systemic disease; it is known to reduce production of the proinflammatory cytokine tumour necrosis factor (TNF) α, which has been implicated in the aetiology of Behçet's disease. However, its side effects of peripheral neuropathy and catastrophic effects during pregnancy preclude its usage in more than a limited number of patients.

The development of highly selective biological anti-TNFα agents to treat rheumatoid arthritis, such as infliximab, has had highly effective applications for Behçet's disease. These drugs have been used successfully to treat serious organ involvement in Behçet's disease when other agents have failed.[27] Currently, their prohibitively high cost limits their use to the most seriously ill patients.

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Address for correspondence:
Mr A C Swift,
Department of Otorhinolaryngology – Head and Neck Surgery,
University Hospital Aintree,
Lower Lane,
Fazakerley,
Liverpool L9 7AL, UK.

Fax: +44 (0)151 529 5263
E-mail: Andrew_swift@yahoo.com

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