ORIGINAL ARTICLE

Otorhinolaryngological Manifestations in Patients With Behçet Disease☆

Carmelo Morales-Angulo, a,∗ Sandra Vergara Pastrana, a Sergio Obeso-Agüera, a Leticia Acle, a Miguel Ángel González-Gay b

a Servicio de Otorrinolaringología, Hospital Universitario Marqués de Valdecilla, Santander, Spain
b Servicio de Reumatología, Hospital Universitario Marqués de Valdecilla, Santander, Spain

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KEYWORDS
Behcet syndrome; Otolaryngology; Hearing loss; Vertigo; Oral ulcer

Abstract
Introduction and objectives: Behçet’s disease (BD) is a systemic immune-mediated vasculitis of unknown origin characterised by recurrent orogenital ulceration, ocular inflammation and skin lesions.

The aim of our study was to identify ear, nose and throat (ENT) manifestations associated with BD.

Patients and methods: Retrospective review of the medical records of all patients diagnosed with BD who attended a tertiary public hospital in Cantabria (Spain) over a period of 22 years. Clinical manifestations, in particular those concerning ENT, were retrieved from medical records. A medical literature review of ENT manifestations was conducted.

Results: Thirty-three patients (age range: 17–64 years) were included in the study. Most of them presented oral ulcers (97%). Eight patients (24%) presented oropharyngeal ulcers and 5 patients (15%) experienced audiovestibular symptoms (high frequency sensorineural hearing loss, vertigo and bilateral vestibular hypofunction). One patient had symptoms compatible with vestibular neuronitis as the presentation manifestation of Neuro-Behçet. In 4 patients (12%) the presence of odynophagia secondary to the presence of oropharyngeal lesions, initially interpreted as acute or recurrent tonsillitis, was the first manifestation of the disease, alone or associated with cutaneous or ocular lesions.

Conclusions: In addition to the characteristic oral ulcers present in most patients with BD, ulcers in the oropharynx, occasionally interpreted as acute pharyngitis, are also common in these patients. Audiovestibular manifestations frequently appear during the course of the disease and may be the first symptom of central nervous system involvement.

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∗ Corresponding author.
E-mail addresses: cmorales@humv.es, carmelo.morales@unican.es (C. Morales-Angulo).
Introduction

Behçet’s disease (BD) is a systemic immune-mediated vasculitis characterised by the presence of recurrent oral and genital ulcers, ocular inflammation and skin lesions. The aetiology and pathogenesis of BD are unknown, although it has been demonstrated that the presence of HLA-51 represents a significant predisposing genetic factor, particularly among patients from the Middle and Far East. The interaction between genetic and environmental factors appears to modulate the prevalence and expression of BD.

BD can affect any age group, but its onset before puberty and after the sixth decade of life is relatively rare. The most common age of presentation is around the third decade of life, with a balanced male/female ratio.

BD has an endemic distribution along the ancient Silk Road, but is unusual in Europe and the USA. The highest prevalence has been found in Turkey, with 370 patients/100 000 inhabitants. In North-western Spain, González-Gay et al. found a mean annual incidence of 0.66 cases/100 000 inhabitants. It is noteworthy that in recent years, countries like Germany have observed a doubling of the incidence since 1989, reaching 1:100 000 inhabitants, whilst others like Japan have registered a reduction. No differences have been found regarding socioeconomic aspects.

Being a multisystemic vasculitis, almost any part of the organism may be affected. Recurrent and painful oral ulcers are present in 90%-100% of patients with BD. Other common clinical manifestations include genital ulcers (60%-80%), ocular lesions (67%-95%), skin lesions (41%-94%), arthritis (47%-69%) and neurological involvement (8%-31%).

The diagnosis of BD is based on clinical criteria. The most frequently used are those published by the International Study Group for Behçet’s Disease in 1990 (Table 1), although

<table>
<thead>
<tr>
<th>Table 1 Diagnostic Criteria of Behçet’s Disease According to the International Study Group for Behçet’s Disease From 1990</th>
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<tbody>
<tr>
<td>Presence of recurrent oral aphthosis</td>
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<tr>
<td>Small or large ulcers or herpetiform ulcers which recur at least 3 times within a period of 12 months</td>
</tr>
<tr>
<td>Along with 2 of the following</td>
</tr>
<tr>
<td>Genital ulcers</td>
</tr>
<tr>
<td>Aphthosis or scar ulcers</td>
</tr>
<tr>
<td>Ocular lesions</td>
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<tr>
<td>Anterior uveitis, posterior uveitis or vitreous cellularity or retinal vasculitis</td>
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<tr>
<td>Skin lesions</td>
</tr>
<tr>
<td>Erythema nodosum, pseudofolliculitis or papulopustulous lesions or acneiform papulae in post-adolescent patients without any steroid treatment</td>
</tr>
<tr>
<td>Positive pathergy test</td>
</tr>
<tr>
<td>Following intracutaneous injection with 21G needle</td>
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</tbody>
</table>

Source: International Study Group for Behçet’s Disease.
other sets of clinical criteria are also used. The diagnosis in the early stages of the disease is often difficult.

New biological treatments developed in recent years have significantly improved the prognosis of visual impairment and neurological disorders, which represent the most disabling clinical manifestations in these patients. The aim of our study was to describe the ENT manifestations in patients with BD in a region of Northern Spain, as well as to conduct a review of the medical literature regarding such manifestations.

Material and Methods

We conducted a retrospective descriptive study at a tertiary hospital in Cantabria (Spain) between January 1991 and April 2013. We included in the study patients who were diagnosed with BD based on the criteria of the International Study Group for Behçet’s Disease from 1990 (Table 1), who had presented ENT symptoms during their evolution, and who were examined by the Otolaryngology Service. We gathered the main clinical data related to the ENT disease from the medical records of patients.

We conducted a review of the literature regarding the ENT manifestations described in association with BD, based on data from Medline and using the following keywords: otorhinolaryngology, ear, larynx, pharynx, trachea, nose, hearing loss, vertigo, facial palsy and oral ulcers, combined with Behçet’s syndrome and Behçet’s disease.

Results

We reviewed the medical records of 42 patients who were allegedly diagnosed with BD. We excluded from the study 8 patients because they did not meet the criteria for BD described previously or else suffered a different disease. Of the 33 patients who met the criteria for BD, 22 were male (63.6%) and 12 were female (36.4%). The mean age at diagnosis was 35 years, with a range between 17 and 64 years.

Oral ulcers were present in 32 patients (97%), representing the most frequent presentation symptom, alone or associated with ocular or cutaneous manifestations. The most frequent locations of these symptoms were the tongue (30%), oropharynx (26%), lips (24%), gums (10%), oral mucosa (9%) and larynx (3%). The number of ulcers ranged between 1 and 15 per outbreak, with a mean number of 5. Their size was between 1 and 5 mm, with the most common size being approximately 2 mm and with a highly variable persistence time (from 2 weeks duration to chronic ulcers). The background was usually white with erythematous borders. A total of 8 patients presented symptoms of odynophagia which were initially considered as acute tonsillitis with poor response to treatment. Of these, 4 cases were even diagnosed initially with recurrent tonsillitis, prior to the diagnosis of BD. Another patient was initially diagnosed with a fungal infection and recurrent oral aphthosis, and another with recurrent oral aphthosis. Various treatments were used, both local (usually corticosteroids and anaesthetic) and systemic, with varying results. One patient presented a complete remission of the ulcers after treatment with infliximab.

Six patients suffered audiovestibular symptoms throughout their evolution. One of them presented symptoms which were clinically compatible with vestibular neuronitis, which was the first manifestation of central nervous system (CNS) involvement in the context of BD (Neuro-Behçet). Another 2 presented nonspecific vertigo symptoms and 3 patients developed sensorineural hearing loss at high frequencies.

Table 2 summarises the ENT manifestations found in our series of patients. Table 3 summarises the ENT manifestations found in the medical literature.

Table 2 | ENT Manifestations Found in Our Series.
---|---
- Oral ulcers 32 (97%)
- Oropharyngeal ulcers 8 (24%)
- Laryngeal ulcers 2 (6%)
- Audiovestibular manifestations (15%)
  - Hypoacusis 3
  - Vertigo 3
- Epistaxis 1 (3%)
- Maxillary sinusitis 1 (3%)

Table 3 | Otorhinolaryngological Manifestations in Behçet’s Disease Described in the Literature.
---|---
**Ulcers**
- Oral 12,13
- Oropharyngeal 12,13
- Laryngeal 12,13
- Oesophageal 14

**Audiovestibular disease**15-18
- Sudden or progressive, unilateral or bilateral sensorineural hypoacusis
- Recurrent vertigo
- Instability secondary to bilateral vestibular hypofunction
- Bilateral Menière’s syndrome

**Sinonasal disease: dysosmia, nasal obstruction, ulcers, pain**19
- Sinonasal destructive lesions 20

**Pharyngolaryngeal stenosis**12,21-23

**Tracheoesophageal fistula**24,25

**Pharyngeal membranes**26
(1 case)a

**Vocal cord paralysis**27,28

**Facial paralysis**29,30

**Inflammation of auricular cartilages (MAGIC syndrome)**31,32
(1 case)a

**Necrosis of the skin of the external auditory canal**/facial paralysis /Horner/carotid tear 13

MAGIC syndrome: Mouth and Genital ulcers with Inflamed Cartilage.
a Infrequent/exceptional: in brackets those diseases of which only 1 case has been described in the literature.
b Frequent.
c Very frequent.
Discussion

Recurrent oral ulcers represent the most common clinical manifestation of BD, appearing in 78% of patients at the time of diagnosis, and virtually 100% during the evolution of the disease. Moreover, although oral ulcers are the main diagnostic criterion of BD in all the series of criteria used, their presence is not essential for the diagnosis of BD in the new criteria proposed by the International Team for the Revision of the International Criteria for Behçet’s Disease. In some aspects, such as frequency (from continuous ulcers, through monthly outbreaks to episodes every 3 months or more), duration (from a few days to over 15 days), age of onset (especially between the third and fifth decades of life) and frequency of family history of recurrent oral ulcers (approximately 30%), oral ulcers in BD are similar to those in recurrent aphthous. Nevertheless, it is much more frequent to find outbreaks with 6 or more concomitant ulcers, presence of ulcers in the oropharynx (especially the tonsillar pillars and uvula, 95% in BD versus 5% in recurrent aphthosis), great variability in the size of concomitantly appearing ulcers and diffusely erythematous ulcer contours in BD than in recurrent oral aphthosis.

It is important to note that, because the ulcers frequently appear in the oropharyngeal area, it is not uncommon to confuse an outbreak of BD ulcers with acute or recurrent pharyngitis, as was the case with 4 patients in our series. Ulcers may also appear in the larynx, pharynx and oesophagus. The histological findings of oral ulcers are nonspecific, with intraepidermal vesicles and leukocytoclastic vasculitis with perivascular infiltrate of neutrophils, lymphocytes, mast cells and macrophages being reported.

Audiovestibular manifestations have also been described in patients with BD, as well as in other types of systemic vasculitis. In this context, Amor-Dorado et al. described a high frequency of audiovestibular manifestations in patients with giant cell arteritis confirmed by biopsy who improved with steroid treatment. These authors also reported a high frequency of benign paroxysmal vertigo in patients with giant cell arteritis, which they attributed to a possible cochlear ischaemia in the context of the vasculitic process. These manifestations may not be exclusive to patients with primary systemic vasculitis, like giant cell arteritis, or secondary systemic vasculitis, like BD, as they have been described in chronic inflammatory processes with an autoimmune basis, like sarcoidosis. Sensorineural hearing loss appears in between 23% and 32% of patients suffering BD. It is usually bilateral and predominantly affecting high frequencies. In this regard, sensorineural hearing loss has been described, predominantly affecting high frequencies, in 50% of cases of patients suffering ankylosing spondylitis, a chronic inflammatory rheumatic disease with predominant axial damage, but which, like BD, can cause uveitis. However, BD patients have also been reported to suffer bilateral hearing loss at low frequencies (usually associated to Ménière-type symptoms), flat audiometric curves, unilateral or bilateral sudden hearing loss (usually with a good response to high doses of corticosteroids), although some cases have required a bilateral cochlear implant due to profound hearing loss, chronic hearing loss associated to recurrent outbreaks of sudden unilateral hearing loss (with good response to treatment with cyclophosphamide) and severe bilateral hearing loss associated to meningitis. Studies using otoacoustic emissions have shown that the lesions are usually cochlear, which is consistent with data from other autoimmune diseases. It has been postulated that sensorineural hearing loss in BD is secondary to vasculitis of the vessels supplying the cochlea. In our series, the presence of sensorineural hearing loss was confirmed in 3 patients, all at high frequencies. Nevertheless, it should be noted that very few had undergone a previous auditory study.

As described in systemic vasculitis, vestibular lesions which are probably secondary to the vasculitic process are common in patients with BD. Bramal and Fainaru found that 37% of patients with BD presented vestibular alterations. In this study of 17 patients with BD, 14 reported a feeling of dizziness; spontaneous nystagmus was observed in 2 (11.8%) patients, abnormal saccades in 1 (5.9%), abnormal caloric tests in 5 (29.4%) and alterations in the rotational tests in 10 (58.9%) patients. Although rare, bilateral vestibular hypofunction may also appear in the context of BD, as was the case with 1 of our patients. There have also been several reports of patients with BD associated with endolymphatic hydrops, with a presentation similar to bilateral Ménière’s disease (with fluctuating hearing loss, severe bilateral hearing loss and vertigo). Moreover, Erbek et al. found that the vestibular evoked myogenic potentials of patients were delayed compared to those of control subjects. Mild forms of CNS (Neuro-Behçet) may appear with dizziness or vertigo as initial symptoms. One of our patients presented symptoms clinically compatible with vestibular neuritis, which represented the initial symptom of Neuro-Behçet, a finding which had been previously described in the medical literature.

Inflammation of the ear cartilage is not a manifestation of BD. Therefore, in those cases where it is observed, we must consider the association with recurrent polychondritis. Several cases of recurrent polychondritis and BD have been described, and the term ‘MAGIC’ syndrome has been proposed as an acronym for ‘Mouth and Genital ulcers with Inflamed Cartilage’. Kötter et al. suggested that since recurring polychondritis is associated with other rheumatic inflammatory diseases, such as systemic lupus erythematosus, spondyloarthropathy, rheumatoid arthritis and systemic vasculitis, in 30% of cases, MAGIC syndrome is not a single clinical entity, but rather a simple association of BD with recurrent polychondritis. None of our patients presented inflammation of the auricular cartilage.

Unlike granulomatous polyangiitis, formerly known as Wegener’s granulomatosis, sinonasal manifestations are rare in BD and are not highly characteristic of the disease. In a study of 400 patients with BD, Shahram et al. found sinonasal symptoms in 31 (8%) patients, of which the most frequent were dysosmia and nasal obstruction. Other findings included ulcers, pain, burning sensation and rhinorrhea. That series did not include any cases of nasal itching and epistaxis. Nasal examination only detected signs in 16 patients (5%): cartilaginous deformity (6 patients), unilateral nasal obstruction (4 patients), non-aphthous ulcers
(3 patients) and crusted ulcers (2 patients). No cases of aphthous ulcers, anterior rhinorrhea, nasal scarring or deformity, septal perforation or granulomatous or nodular cartilage lesions were found. One case has been described of a patient who presented pansinusitis with destructive lesions at the level of the nasal septum and turbinates, in whom Wegener’s granulomatosis had been ruled out. In our study, the sinonasal manifestations were uncommon and nonspecific.

It is rare to find pharyngo-laryngeal manifestations other than ulcers in BD. However, several cases of pharyngeal stenosis have been described in BD patients at the level of the oropharynx, hypopharynx and larynx, typically years after the disease was diagnosed. These cases were attributed to myositis, but could be the result of scarring sequelae from the oropharyngeal ulcers. The literature describes a patient who presented dysphonia and dysphagia secondary to oedema of the laryngeal structures, who required epiglottectomy and thyrohyoid dissection with subsequent relapse due to scarring sequelae. In one of our patients we found laryngeal ulcers concomitant with oral ulcers. It is likely that the presence of ulcers at this level is more frequent than reported in the literature, since these patients were not routinely screened by pharyngolaryngeal endoscopy.

In addition to the presence of ulcers, 2 cases of tracheo-oesophageal fistulas at the oesophageal level have been described. Both required surgical treatment and presented a good subsequent evolution.

Unlike CNS involvement, which is frequent in BD, the manifestations of the peripheral nervous system, excluding the eighth cranial nerve, are rare. There have been isolated case reports of vocal cord paralysis and peripheral facial palsy, presumably secondary to vasculitis of the tenth and seventh cranial nerves, respectively.

There are no laboratory tests which help to confirm the diagnosis of BD and the diagnosis is based on clinical criteria. The most frequently used are those published by the International Study Group for Behcet’s Disease in 1990 (Table 1), although other different criteria are also used in some countries. A positive pathergy test (skin reaction developed 1–2 days after puncturing the skin with a sterile needle) can contribute to the diagnosis, but a negative result does not rule out BD, especially among the European population. In epidemiological studies of patients with BD in Spain, positive pathergy is also low.

Upon suspicion or confirmation of BD, otolaryngologists must perform a full exploration of the head and neck region, with special emphasis on the examination of the oral cavity and oropharynx, seeking the characteristic ulcers, which sometimes go unnoticed or are interpreted as acute tonsillitis when there is oropharyngeal predominance. The histopathological study of oral lesions is nonspecific, so their biopsy does not provide diagnostic information.

It is necessary to conduct a systematic nasofibroscopy seeking oropharyngeal, laryngeal and hypopharyngeal ulcers in patients with odynophagia or with symptoms suggestive of the onset of fibrosis or oedema of pharyngolaryngeal structures. Conducting a tonal and speech audiometry is also useful in the initial assessment of patients with BD since, as previously mentioned, the development of unilateral or bilateral sensorineural hearing loss during the course of the disease is not infrequent. Performing vestibular tests in patients suffering instability, dizziness or vertigo is important in order to contribute to the diagnosis of Neuro-Behcet or exclude the presence of peripheral vestibular disease.

Although sinonasal manifestations are uncommon, systematic exploration of the nostrils can help to rule out other inflammatory disorders which usually occur at this level, like Wegener’s granulomatosis.

Multiple treatments are used for BD, including glucocorticoids, colchicine, azathioprine, cyclosporine, tacrolimus, anti-TNF-alpha (infliximab and etanercept), thalidomide and rituximab. Oral lesions do not respond well to topical corticosteroid treatment, with variable responses to the previous treatments. Total remissions of recurrent oral ulcers have been described in patients treated with infliximab, as was the case with one of our patients. A comparative study of colchicine versus placebo confirmed that the use of colchicine is useful to treat oral ulcers, genital ulcers, pseudofolliculitis and erythema nodosum associated with BD. These results supported data from epidemiological studies which pointed to a decrease in the recurrence of outbreaks of oral ulcers in BD patients treated with this drug.

Conclusions

Apart from the presence of oral ulcers, which appear in almost 100% of BD patients, oropharyngeal ulcers, which are occasionally confused with outbreaks of recurrent tonsillitis, are also common in patients with this disease. As in other vasculitic processes, the presence of audiolymphear manifestations is also common, occasionally representing the presentation form of a more severe manifestation of the disease affecting the CNS.

References

Otorhinolaryngological Manifestations in Patients With Behçet