sclerotherapy with single-dose OK-432 in a growing cervical lymphangioma. Cervicothoracic lymphangioma is a rare congenital anomaly that is mostly asymptomatic. We would like to share our experience of a rare cause of dyspnea by lymphangioma. In our case, the patient presented with dyspnea and paroxysmal cough caused by cervicothoracic lymphangioma and sclerotherapy alleviated tracheal compression and relieved the dyspneic symptoms.

Key Words: Dyspnea, lymphangioma, sclerotherapy

I read with great interest the article reported by Efe et al, which presented the excellent result obtained by the use of sclerotherapy with single-dose OK-432 in a growing cervical lymphangioma.[1] Cervicothoracic lymphangioma is a rare congenital anomaly that is mostly asymptomatic.[2,3] I would like to share our experience of a rare cause of dyspnea by lymphangioma.

A 19-year-old woman presented with dyspnea and paroxysmal cough lasting for a week. Her neck appeared swollen. A chest radiograph showed a large mass of soft tissue in the lower neck and right thorax around the paratracheal region, with an external indentation on the trachea (Fig. 1A). Chest computed tomography scans revealed a huge cystic mass in the lower neck abutting the thyroid gland. The mass extended into the mediastinum, encased the trachea, and compressed it, resulting in a narrowing of the lumen, which suggested a cervicothoracic cystic lymphangioma (Fig. 1B). The patient underwent transcutaneous injection of a sclerosing agent with ethanol (Fig. 1C). Hoarseness developed after the sclerotherapy and spontaneously resolved in 2 months. The patient had dyspnea that was relieved by the sclerotherapy, with no recurrence or vocal cord paralysis at the 6-month follow-up (Fig. 1D).

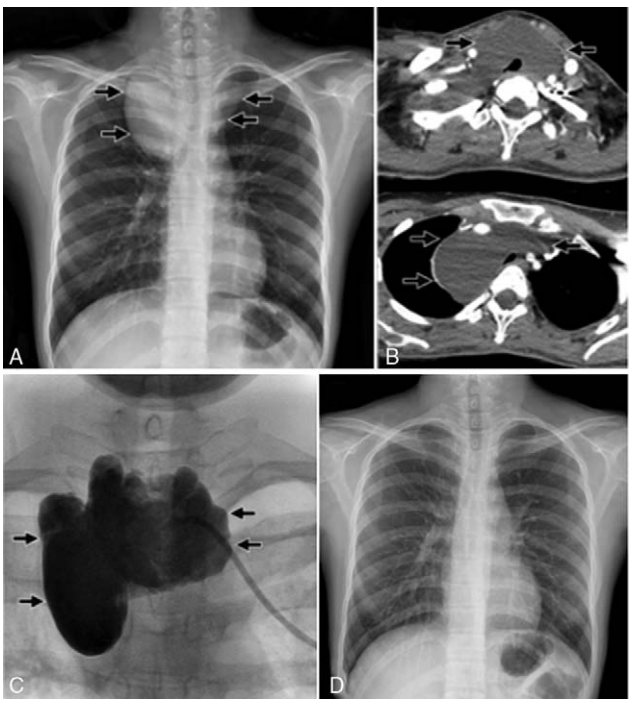

FIGURE 1. A large soft tissue mass (arrows) in the lower neck and right thorax around the paratracheal region (A) encases and compresses the trachea, resulting in a narrowing of the lumen (B). Fistulography shows a huge cervicothoracic cystic lymphangioma (arrows) without extravasation (C). No new cystic mass found 6 months after sclerotherapy (D).

In our case, the patient presented with dyspnea and paroxysmal cough caused by cervicothoracic lymphangioma. Sclerotherapy alleviated tracheal compression and relieved the dyspneic symptoms.

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Olfactory Dysfunction Associated With Neuro-Behçet Disease

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Introduction: Neurologic involvement associated with Behçet disease (BD) is defined as a different entity: Neuro-Behçet disease (NBD). Behçet disease presents with olfactory dysfunction. It is not known whether this is the consequence of mucosal involvement or neurologic involvement.

Objective: The aim of this study was to investigate whether olfactory dysfunction was further aggravated as the result of neurologic involvement.

Methods: Sixteen patients diagnosed with NBD and 16 healthy control patients with similar demographic characteristics were recruited as the healthy control group. Expanded Disability Status Scale (EDSS) scoring was used for quantification of neurological disability. All diagnoses were confirmed and categorized with magnetic resonance imaging studies in all patients individually: parenchymal or nonparenchymal. A well-established test of orthonasal olfaction developed at the CCCRC was used. Correlation analysis was carried out.

Results: The mean CCCRC score of NBD patients was 4.60 out of 7, and this group was diagnosed to be moderately hyposmic, whereas the average score of the control group was 6.5; the difference was

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significant ($P < 0.0001$). CCCRC scores of NBD patients were significantly lower compared both healthy control patients and those of BD patients reported in the literature. Mean EDSS score of NBD patients was 1.75 ± 1.0 out of 10 (0—no neurologic disability and 10—worst neurologic disability). Magnetic resonance imaging of NBD patients revealed 4 nonparenchymal and 12 parenchymal patients. Neuro-Behçet disease patients with parenchymal involvement presented with (worse) EDSS scores. Mean olfactory CCCRC score of this group was 4.38 whereas the average olfactory score of the vascular group was 5.25 out 7. Average EDSS score of vascular group was 0.75, much better compared to higher average neurologic disability score of 2.08 for the parenchymal group. Significant correlation existed between the duration of NBD and both olfactory and neurologic dysfunction scores.

Conclusion: Neuro-Behçet disease present with aggravated olfactory dysfunction compared to BD. Neurologic involvement—especially parenchymal involvement—seems to deteriorate the olfactory dysfunction. Duration of disease is correlated with this severity of dysfunction.

Key Words: Behçet, CCCRC, EDSS, Neuro-Behçet, olfaction, olfactory dysfunction, olfactory function

In 1937, Behçet disease (BD) was first defined by a Turkish dermatologist named Hulusi Behçet: a triple symptom complex of recurrent aphthous ulcers, genital ulcers, and uveitis.[1] Other most commonly seen symptoms are arthritis, positive pathergy test, thrombophlebitis, central nervous system involvement, and gastrointestinal ulcers. Behçet disease is a multisystem inflammatory disease most commonly seen in the Mediterranean, middle and far east.[2] Behçet disease diagnosis is based on the criteria defined by International Study Group for BD[3]: presence of oral ulceration plus any 2 of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive Pathergy test was accepted as BD in the absence of other clinical explanations. Neurologic involvement associated with BD was first defined in 1941.[4] Prevalence of Neuro-Behçet disease (NBD) ranges according to diagnostic criteria and changes between 1.3% and 59%.[5,6]

Olfactory dysfunction has been associated with a variety of neurodegenerative and psychiatric disorders.[7,8] In a previously published study, we found that olfactory dysfunction associated with BD but was not able to differentiate whether olfactory mucosa impairment or neurologic involvement was responsible for the olfactory dysfunction.[9] In this follow-up study, we investigated a group of Neuro-Behçet patients to see whether olfactory function was deteriorated as the result of neurologic involvement.

MATERIALS AND METHODS

All participants were tested for olfactory function with the approval of the local ethics committee and in accordance with the National Health and Medical Research guidelines. All volunteers were provided with information about the procedures, and written informed consent was obtained prior to the study. Study was conducted in accordance with Helsinki Guidelines for Clinical Research.

Sixteen patients diagnosed with NBD were recruited from vent of neurology. Sixteen healthy control patients with similar demographic characteristics were recruited as the healthy control group. Behçet disease was diagnosed based on the criteria defined by International Study Group for BD[6]: presence of oral ulceration plus any 2 of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive Pathergy test was accepted as BD in the absence of other clinical explanations. Healthy subjects were negative for all of these criteria.

All individuals in both groups were subjected to a detailed otolaryngological examination. All participants in both groups were examined in detail for any condition with the potential to cause olfactory dysfunction: septum deviation, nasal polyposis, congenital olfactory dysfunctions, history of a septum operation or head trauma, chronic rhinosinusitis, allergic rhinitis, and psychiatric and neurological disorders such as Parkinson or Alzheimer disease. Patients with any of these were excluded from the study.

Neuro-Behçet Diagnosis

Neuro-Behçet disease diagnosis was based mainly on clinical evaluation of signs and symptoms. Expanded Disability Status Scale (EDSS) scoring was used for quantification of neurological disability: EDSS is a widely used method of quantifying disability and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of people with multiple sclerosis (EDSS). All diagnoses were confirmed with magnetic resonance imaging (MRI) studies in all patients individually: differentiation of parenchymal and nonparenchymal involvement was done by experienced radiologists.

Olfactory Assessment

A well-established test of orthonasal olfaction developed at the CCCRC was used. The CCCRC test includes a butanol threshold test and an odor identification test using common odors: these tests were conducted as described previously.[10,11]

Butanol Threshold Test

For each trial, 2 glass bottles were presented to the subject. One contained water and the other a dilute concentration of butanol. The bottles were of identical appearance and were presented simultaneously. Subjects were instructed to occlude one nostril and place the tip of the first bottle immediately beneath the other nostril. Then, the second bottle was sampled in a similar manner, and the subject had to choose which of the bottles contained something other than water. If the choice was incorrect, the next stronger concentration of butanol was presented along with a bottle containing only water. Once the subject correctly identified the same butanol concentration 5 times in a row, the score was recorded for that nostril. Then, the other nostril was tested separately, and the scores for both nostrils were averaged to arrive at the final score. The strongest butanol concentration (bottle 0) was 4% butanol in deionized water. Each subsequent dilution (bottles 1–9) was a 1:3 dilution with deionized water. Possible scores ranged from 0 to 9, but all scores 7 and higher were scored as 7 per the CCCRC test.

Odor Identification Test

Common household items with characteristic odors (peanut butter, soap, mothballs, Vicks vapor rub, chocolate, coffee, cinnamon, and baby powder) were placed in opaque jars. Subjects chose from a printed list containing the correct items as well as an equal number of distractor items. The forced choice items included the following: Vicks, burnt paper, wood shavings, coffee, baby powder, peanut butter, spearmint, cinnamon, soap, chocolate, mothballs, grape jam, ketchup, black pepper, and rubber. The ability to sense Vicks indicates intact trigeminal nerve function. This odor was easily identified by all subjects and was not included in the final score. Possible scores ranged from 0 to 7 correctly identified items. Scores for both nostrils were averaged to arrive at the final score. Scores for the butanol threshold test and identification tests were subsequently averaged to arrive at a composite score for orthonasal

olfactory ability. As in the CCCRC test, scores were grouped as follows: 0 to 1.75, anosmia; 2.00 to 3.75, severe hyposmia; 4.00 to 4.75, moderate hyposmia; 5.00 to 5.75, mild hyposmia; and 6.00 to 7.00, normal.[10,11]

Nasal Endoscopy

Meticulous nasal endoscopic evaluation was carried out individually on each patient. Patients received oxymetazoline decongestion 5 minutes prior to assessment. A Karl Storz rigid endoscope 0° (4 mm diameter) was used for this procedure. Pathological nasal lesions were recorded by the same otorhinolaryngologist. The inferior turbinate and Little's area were examined via nasal endoscopy. The septum was scrutinized for any presence of a septal crest or deviation. The middle meatus was observed: the middle turbinate, uncinate, and ethmoid bulla were observed when possible. The superior turbinate was observed along with the superior meatus when possible. The olfactory cleft was also observed, although this was not possible for some patients because of discomfort. Typical endoscopic lesions at typical sites were photographed and are included in Figure 1. All patients were individually questioned for nasal symptoms: nasal obstruction, epistaxis, crust formation, pain (nasal discomfort), and nasal itching. Nasal endoscopic findings, nasal symptom scores, and olfactory scores were evaluated to assess nasal manifestations of the disease.

Statistical Analysis

Statistical analysis was carried out using the Medcalc v 13.0. Mann–Whitney *U* test was used for analysis of quantitative variables, and correlation between parameters was analyzed with Pearson correlation test. *P* value < 0.05 was accepted as statistically significant.

RESULTS

Mean age of NBD group was 35.7 ± 10.8 whereas the healthy control group was 37.9 ± 14.5. Groups were similar in terms of mean age and demographic characteristics ($P > 0.05$). All patients were individually evaluated with the International Study Group Behçet Disease Criteria.[3] In NBD group, all of the patients (16/16) were positive for oral ulcerations, 11 (73.3%) patients were positive genital ulcers, 9 (60%) patients were positive for skin lesions and pathergy test, and 6 (33.3%) patients were positive for ocular lesions (Table 1). All of these findings were negative in the healthy volunteer control group. Endoscopical examination of both groups revealed insignificant difference (Table 2).

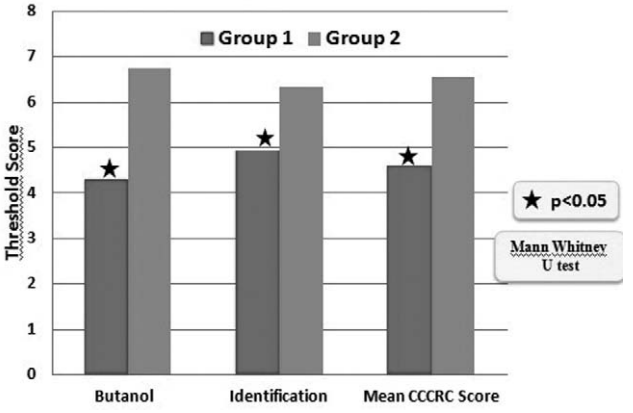

FIGURE 1. Comparison of mean olfactory scores.

TABLE 1. International Study Group Behçet Disease Criteria

	Number of Patients	Percentage
Oral ulcers	16	100
Genital ulcers	11	68.75
Positive skin lesions	9	56.25
Positive pathergy test	6	37.5

TABLE 2. Nasal Lesions and Nasal Symptoms

Groups	Itching	Obstruction	Epistaxis	Crusting	Pain	Lesion
NBD group	4 (25%)	2 (12.5%)	1 (6.2%)	2 (12.5%)	1 (6.2%)	2 (12.5%)
HC group	3 (18.7%)	1 (6.2%)	0 (0%)	1 (6.2%)	0 (0%)	0 (0%)
Statistic*	$P = 0.669$	$P = 0.544$	$P = 0.144$	$P = 0.544$	$P = 0.144$	$P = 0.097$

NBD, Neuro-Behçet disease; HC, healthy control.
* Pearson Chi-squared test was used for samples ($P < 0.05$).

The n-butanol odor threshold score of the NBD group was 4.28 ± 2.1; whereas the healthy control group's n-butanol threshold score was 6.73 ± 1.3, which was statistically lower in comparison ($P < 0.0001$). Similarly, odor identification scores were significantly lower in the NBD group (4.92 ± 2.1) compared with scores of the healthy volunteers (6.34 ± 1.1) ($P < 0.0001$). The mean CCCRC score of NBD patients was 4.60 out of 7, and this group was diagnosed to be moderately hyposmic, whereas the average score of the control group was 6.54 ± 0.8; the difference was significant ($P < 0.0001$), and the healthy group was evaluated as normosmic. CCCRC test scores are further detailed in Table 3. Neuro-Behçet disease group consisted of 4 severe hyposmic, 4 moderately hyposmic, 5 mildly hyposmic, and 3 normosmic patients. All patients except 1 mildly hyposmic were normosmic in the healthy control group. Detailed distribution is detailed in Table 3.

Mean EDSS score of NBD patients was 1.75 ± 1.0 out of 10 (0 no neurologic disability, 10 worst neurologic disability). Magnetic resonance imaging of NBD patients resulted with 4 vascular (2 males and 2 females) and 12 parenchymal patients. Neuro-Behçet disease patients with parenchymal involvement presented with higher (worse) EDSS scores compared with other 4 patients with nonparenchymal (vascular) involvements. Mean olfactory CCCRC score of this group was 4.38, whereas the average olfactory score of the vascular group was 5.25 out of 7. Average EDSS score of vascular group was 0.75, much better compared to higher average neurologic disability score of 2.08 for the parenchymal group. Expanded Disability Status Scale scores were found correlated to duration of disease (correlation analysis of EDSS scores and

TABLE 3. Comparison of CCCRC Orthonasal Test Results

Olfaction Degree	Mean CCCRC Score	NBD Group, N (%)	HC Group, N (%)
Normosmia	6.0–7.0	3 (18.75)	15 (93.75)
Mild hyposmia	5.0–5.75	5 (31.25)	1 (6.25)
Moderate hyposmia	4.0–4.75	4 (25)	0 (0)
Severe hyposmia	2.0–3.75	4 (25)	0 (0)
Anosmia	0.0–1.75	0 (0)	0 (0)

NBD, Neuro-Behçet disease; HC, Healthy control.

TABLE 4. Comparison of Olfactory Scores: NBD Versus BD

	n-Butanol Threshold Test Score	Identification Test Score	Total CCCRC Test Score
NBD group	4.28 ± 2.1	4.92 ± 2.1	4.60 ± 1.1
BD group	5.57 ± 1.0	4.93 ± 1.3	5.25 ± 1.0
Control group	$6.47 \pm 0.7^*$	$6.15 \pm 0.8^*$	$6.31 \pm 0.6^*$

BD, Behçet disease; NBD, Neuro-Behçet disease.
$^*P < 0.0001$.

olfactory function results were not correlated ($P = 0.262$). Significant correlation existed between the duration of NBD and both olfactory and neurologic dysfunction scores (Table 4).

DISCUSSION

Neurologic involvement associated with BD is known to cause serious and long-lasting morbidities.[12] Neurologic involvement prevalence ranges from 5.3% to 14.3% in 3 different series.[12–14] Forty-three patients had NBD out of 439 (9.4%) patients in these 3 series. Neurologic involvement associated with BD manifests in 2 main categories: parenchymal form, which manifests as meningoencephalitis, and nonparenchymal form, which manifests as vascular complications that take part as the result of large venous thrombosis.[15–19]

Headache as a symptom of BD is not adequate for the diagnosis of NBD; other neurologic signs and symptoms accompanied by neuroradiological abnormalities and cerebrospinal fluid changes are needed for the diagnosis of NBD.[2] Parenchymal involvement is associated with brainstem, thalamus, basal ganglia, white matter and these can be confirmed with MRI.[2] Neuro-Behçet disease's onset ranges from third to fifth decade of life.[2] Systemic findings are followed by neurologic findings few years later: time period that lapses between onset BD and NBD ranges from 3 to 6 years.[16–18] Neuro-Behçet disease findings can manifest simultaneously with BD.[2] Wide range of symptoms, such as ophthalmoparesis, cranial neuropathies, and pyramidal dysfunctions, can manifest as a consequence of brainstem involvement.[2]

Healthy control group's mean olfactory score was 6.34 and categorized as normosmic. Mean CCCRC Olfactory score of NBD patients in this study was 4.6 out of 7 and these patients were categorized as moderately hyposmic. When compared to previously published study with similar age group, olfactory scores of NBD patients were significantly lower compared to BD.[9] Patients with parenchymal involvement had even lower scores (mean 4.38 out of 7; Table 5).

Although nasal lesions and nasal symptoms of the NBD group were not different from the healthy control group; olfactory results were poorer compared to both the healthy control and BD. This shows that neurologic involvement aggravates olfactory dysfunction independent from the mucosal involvement. Parenchymal involvement is associated with aggravated deterioration of both neurologic and olfactory functions.

TABLE 5. Correlation Analysis

	Significance (2-Tailed)	Pearson Correlation
EDSS score vs. duration of disease	$P = 0.026^*$	0.55
CCCRC score vs. duration of disease	$P = 0.047^*$	−0.50
CCCRC score vs. EDSS score	$P = 0.262$	−0.30

EDSS, Expanded Disability Status Scale.
*Significant correlation.

CONCLUSION

Although olfactory dysfunction has been shown in BD in previous publication, effect of NBD on olfactory dysfunction has been shown for the first time.[9] Neuro-Behçet disease present with aggravated olfactory dysfunction compared to BD. Aggravation of olfactory dysfunction with neurological involvement shows the sensorineural aspect of this impairment. Parenchymal involvement especially is associated with aggravated olfactory and neurologic dysfunction. Olfactory dysfunction can be de signal of neurological involvement.

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