Increased frequency of obstructive sleep apnea syndrome in Behçet's syndrome patients with superior vena cava syndrome

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ABSTRACT

Objective. *Superior vena cava syndrome (SVCS) is a medical emergency which can also be seen in Behçet's syndrome (BS). Having noted that BS patients with SVCS frequently complained of sleep disturbances, snoring and sleep apnea, suggesting obstructive sleep apnea (OSA), we formally surveyed the risk for OSA among BS patients with SVCS and suitable controls using the Berlin questionnaire.*

Methods. *We studied 28 patients, all male, with SVCS (Group 1), 129 with vascular involvement without a SVCS (Group 2) and 151 with no vascular involvement (Group 3). In addition, 100 apparently healthy individuals (Group 4) were studied. The Berlin questionnaire (BQ), a validated screening tool with a high sensitivity and modest specificity that identifies individuals with high-risk for OSA, was administered to all study participants.*

Results. *The study groups were similar with regard to age (Group 1, mean age: 44.3±9.7; Group 2, mean age: 41.5±8.7, Group 3, mean age: 40.4±9.4 and Group 4, mean age: 42.1±9.4) mean body mass index and the frequency of hypertension and other comorbidities. The frequency of those patients at high-risk for OSA according to the BQ was 57%, 17%, 17% and 11% in Groups 1, 2, 3 and 4, respectively ($p<0.05$). Age-adjusted ORs of OSA compared to healthy controls (Group 4) was 11.00 (95%CI: 4.01–30.07) for Group 1, 1.78 (95%CI: 0.81–3.94) for Group 2, 1.92 (95%CI: 0.90–4.14) for Group 3.*

Conclusion. *BS patients with SVCS are at high risk for OSA. This is probably due to the external pressure of the significant presence of venous collaterals that surround the upper airways. Our results should be further confirmed by polysomnography, and future research should be carried out to clarify the causes of this association.*

Introduction

Behçet's syndrome (BS) is a multi-systemic complex disorder with a distinct geographic distribution which includes Mediterranean basin, the Middle East and Far East (1, 2). The pathogenesis is still unclear, however genetic, immunologic and environmental factors are thought to activate innate and adaptive immune system. Several cytokines and pathways were found to play a role in the pathogenesis BS. Recently, Th1 and Th17 pathways are thought to play role in the innate response abnormality that is observed in BS (3, 4). The mean age of onset is in the third decade (5). The disease course is characterised by exacerbations and spontaneous remissions while abating as the years pass (5). Recurrent skin mucosa lesions and sight threatening panuveitis are the hallmark of the disease, however, it may also involve joints, cardiovascular, gastrointestinal and central nervous system. BS can cause substantial morbidity, such as blindness, post thrombotic syndrome, severe neurological disability and is also associated with increased mortality rate (5). Vascular involvement in BS can be seen in up to 40% of the patients with a definite male preponderance and usually occurs early during the disease course (6, 7). Both veins and arteries of all sizes are affected while venous involvement is more common than arterial disease. Venous disease is characterised by significant in situ thrombosis, thickening of vessel walls, insufficiency and profound collateral formations whereas aneurysms and rarely thrombotic occlusions characterise arterial disease (6-8). Lower extremity deep and superficial veins are most frequently affected veins followed by vena cavae, iliac and hepatic veins. Affected arteries on the other hand include pulmonary, iliac and femoral arteries and carotids.

Superior vena cava syndrome (SVCS) usually presents as a rare complication

of lung cancer or lymphoma (9, 10). It is often found at initial presentation and manifests as a medical emergency (11). It can also be seen in BS (6). Contrary to the severe outcome seen in malignant conditions, SVCS in BS usually has a benign course, rarely complicated by haemoptysis, pleural effusions or a chylothorax (12, 13). We had noted that BS patients with SVCS frequently complained of sleep disturbances, snoring and sleep apnea, suggesting an obstructive sleep apnea syndrome (OSA) an observation, to the best of our knowledge has not been reported before.

OSA is a common condition in which there are intermittent partial and complete limitations in airflow, with associated hypoxia and sympathetic arousals during sleep (14, 15). It is associated with obesity, older age, male gender, hypertension and smoking (14, 15). The Berlin questionnaire (BQ), which includes questions about snoring, daytime somnolence, body mass index (BMI), and hypertension, is a relatively short and validated screening tool with a high sensitivity and modest specificity that identifies individuals with high risk for OSA (16).

We formally surveyed the degree of risk for OSA among BS patients with SVCS and suitable controls using the BQ.

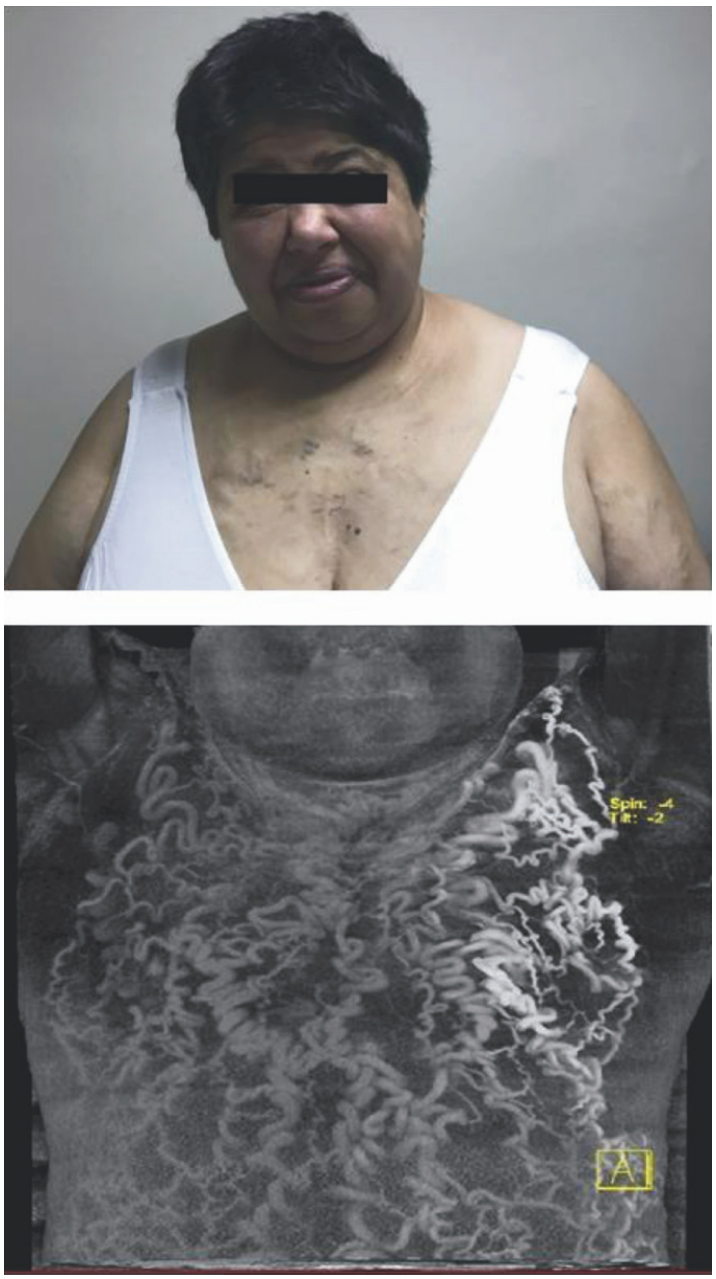

Fig. 1. Physical signs of superior vena cava syndrome in a patient with Behçet's syndrome who raised awareness of OSA in such patients.
A: Extensive venous collaterals can be visualised on the chest wall and the arms. The patient presented with SVCS and simultaneously skin-mucosa manifestations due to BS at the age of 25 in 1991. She received intravenous cyclophosphamide monthly for 2 years. In 2010, she started to have attacks of dyspnea and oedema which were responsive to intravenous diuretic therapy. In 2016, she was admitted to the intensive care unit due to acute hypercapnic respiratory failure and was initiated on bi-level positive airway pressure ventilation and treated with diuretic therapy. At this admission, further review of her history revealed daytime sleepiness, loud snoring and episodes of apnea during sleep. She started to receive continuous positive airway pressure therapy and since then she did not need to be hospitalised for dyspnea.
B: Angiographic reconstruction of computed tomography of chest demonstrates extensive collateral circulation around the neck.

Material and methods

We studied 28 BS patients with SVCS (Group 1), 129 BS patients with vascular involvement other than SVCS (Group 2), and 151 BS patients with no vascular involvement (Group 3) who attended the dedicated BS outpatient clinic at Cerrahpasa Medical Faculty of University of Istanbul-Cerrahpasa, Turkey, between October 2016 and November 2018. All BS patients were male ≥18 years old and fulfilled the International Study Group diagnostic criteria (17). One hundred apparently healthy hospital staff who were age- and gender-matched to the patients were also studied (Group 4).

BQ (see appendix) was used to evaluate OSA. Information on clinical characteristics, disease duration and current medications were obtained from the medical records. Comorbidities and smoking habits were prospectively recorded.

Berlin questionnaire

The BQ (appendix) includes questions about snoring (category 1), daytime somnolence (category 2), and the presence of hypertension and/or increases in BMI (category 3) (16). The overall BQ score was calculated from the responses to the three categories.

Scores from the first and second categories were positive if the responses indicated frequent symptoms (>3-4 times/week), whereas the score from

the third category was positive if there was a history of hypertension or a BMI >30 kg/m^2 (16). Patients were scored as being at high-risk for OSA if they had a positive score on two or more categories, while those who did not were scored as being at low-risk (16).

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all study participants and the patient presented in Figure 1A. The ethics committee of Cerrahpasa Medical Faculty approved the study (393887/2016).

Statistics

Comparisons of continuous variables between groups were made by one-way analysis of variance using the Bonferroni correction. The categorical variables were compared by the chi-square test or the Fisher exact test. Logistic regression analysis was applied to calculate the adjusted odds ratios (ORs) and 95% confidence intervals [CI] of OSA among study groups. Healthy controls were accepted as the reference group in logistic regression analyses. All tests were performed using SPSS for Windows, v. 18.0, software (SPSS Inc, Chicago, IL, USA).

Table I. Demographic and clinical characteristics.

	Group 1 (BS with SVCS) n=28	Group 2 (BS with vascular involvement other than SVCS) n=129	Group 3 (BS with no vascular involvement) n=151	Group 4 (Healthy controls) n=100	*p*
Age, mean ± SD, years	44.3 ± 9.7	41.5 ± 8.7	40.4 ± 9.4	42.1 ± 9.4	0.162
Disease dur., mean ± SD, years	18.7 ± 9.4	13.6 ± 7.5	11.7 ± 6.4	-	<0.001
Behçet manifestations, n (%)					
Skin lesions	28 (100)	126 (98)	150 (99)	-	0.385
Arthritis	7 (25)	30 (23)	43 (29)	-	0.606
Uveitis	7 (25)	57 (44)	80 (53)	-	0.018
Parenchymal NBS	1 (4)	1 (1)	2 (1)	-	0.495
LEVT	15 (54)	121 (94)	-	-	<0.001
PAA/PAT	4 (14)	14 (11)	-	-	0.531
BCS	4 (14)	1 (1)	-	-	0.04
VCI thrombosis	5 (18)	10 (8)	-	-	0.147
CVST	5 (18)	8 (6)	-	-	0.057
Peripheral artery involvement	1 (4)	5 (4)	-	-	NS (1)
Comorbidites*, n (%)					
Diabetes mellitus	1 (4)	5 (4)	3 (2)	0	0.631
Hyperlipidaemia	0	0	0	0	-
Hypo/hyperthyroidism	0	1 (1)	0	0	
Current drugs, n (%)					
Off treatment	9 (32)	27 (21)	25 (17)	-	0.150
Non-bio. Immunosupp.$^{\alpha}$	11 (39)	71 (55)	47 (31)	-	<0.001
Colchicine	7 (25)	33 (26)	89 (59)	-	<0.001
Steroids	4 (14)	15 (12)	13 (9)	-	0.553
Interferon	1 (4)	6 (5)	5 (3)	-	0.843
Anti-TNFs	3 (11)	15 (11.6)	10 (6.6)	-	0.332
Anticoagulants	3 (11)	1 (1)	-	-	0.018

NBS: neuro Behçet's syndrome; LEVT: lower extremity venous thrombosis; PAA/PAT: pulmonary artery aneurysm/pulmonary artery thrombosis; BCS: Budd-Chiari syndrome; VCI: vena cava inferior; CVST: cerebral venous sinus thrombosis; TNF: tumour necrosis factor alpha.
*Comorbidities other than hypertension; $^{\alpha}$Azathioprine and/or cyclosporine-A.

Results

Demographic and clinical characteristics of the patients are shown in Table I. Age, comorbidities other than hypertension and current treatments except non-biologic immunosuppressives and anticoagulants were well balanced across the groups. However, disease duration was significantly longer (p<0.001) and the frequency of uveitis was significantly lower in Group 1 than the others (p<0.001 and p=0.018, respectively).

Variables associated with OSA, categories of BQ and those with high risk are depicted in Table II. Study groups were similar with regard to mean age, mean BMI and the frequency of hypertension and other comorbidities. The BQ categorised 57% (16/28) of the BS patients with SVCS (Group 1) as having a high risk for OSA and this was significantly higher (p<0.001) compared to that found in the control groups. Positive responses to all 3 categories were significantly more common among patients with in Group 1. The frequency of those patients at high risk for OSA was 17%, 17% and 11% in Group 2, 3 and 4, respectively (p>0.05). Age adjusted ORs of OSA compared to healthy controls (Group 4) was calculated as 11.00 (95% CI: 4.01-30.07) for Group 1, 1.78 (95% CI: 0.81-3.94) for Group 2, 1.92 (95% CI: 0.90-4.14) for Group 3.

Although the mean BMI did not differ across the study groups, those patients with BMI ≥30 were more likely to be frequent in Group 1. Even after exclusion of 8 patients with BMI ≥30 in Group 1, the high risk for OSA in Group 1 persisted (Group 1: 40% (8/20), Group 2: 17% (22/129), Group 3: 17% (26/151) and Group 4: 11% (11/100), (p=0.017). Similarly OR's were unaffected when we adjusted for age, and for the presence or absence of BMI ≥30 and hypertension. Adjusted ORs of OSA was this time 9.7 (95% CI: 2.9-33.1) for Group 1; 2.0 (95% CI: 0.84-4.7) for Group 2; 2.6 (95% CI: 1.1-6.2) for Group 3.

Discussion

In this questionnaire survey, we observed that BS patients with SVCS had a 11-fold increased risk of developing OSA compared to the healthy controls. It has to be noted that this risk still persisted when we adjusted the subgroups according to BMI. On the other hand, developing OSA risk for BS patients without SVCS was relatively small.

The superior vena cava (SVC) is a thin-walled, low-pressure vein that drains most of the blood from the head, neck, upper extremities, and upper thorax (9, 10). It can be easily compressed by the surrounding structures found in the mediastinum, such as the trachea, right bronchus, aorta, pulmonary artery and lymph nodes (9, 10). SVCS may occur either when there is mechanical exter-

Table II. Variables associated with obstructive sleep apnea syndrome and categories of Berlin questionnaire.

	Group 1 (BS with SVCS) n=28	Group 2 (BS with vascular involvement other than SVCS) n=129	Group 3 (BS with no vascular involvement) n=151	Group 4 (Healthy controls) n=100	*p*
Hypertension, n (%)	5 (18)	12 (9)	8 (5)	6 (6)	0.103
BMI, mean ± SD	26.3 ± 4.7	26.0 ± 4.1	25.3 ± 3.7	26.5 ± 3.4	0.109
Snoring, n (%)	20 (71)	65 (50)	70 (46)	46 (46.0)	0.089
Snoring louder, n (%)	13 (46)	21 (16)	24 (16)	12 (12)	<0.001
Snoring ≥ 3-4 times a week, n (%)	17 (61)	24 (19)	29 (19)	12 (12)	<0.001
Snoring ever bothered other people, n (%)	17 (61)	29 (23)	37 (25)	15 (15)	<0.001
Stop breathing during sleep, n (%)	7 (25)	2 (2)	5 (3)	3 (3)	<0.001
Feeling tired/fatigued, n (%)	12 (43)	42 (33)	57 (38)	12 (12)	<0.001
Feeling tired/fatigued ≥ 3-4 times a week, n (%)	13 (46)	43 (33)	58 (38)	13 (13)	<0.001
Falling asleep while driving a vehicle, n (%)	3 (11)	9 (7)	17 (11)	6 (6)	0.411
Body mass index ≥ 30, n (%)	8 (36)	24 (19)	19 (13)	21 (21)	0.024
Category 1	18 (64)	34 (26)	41 (27)	18 (18)	<0.001
Category 2	12 (50)	32 (25)	44 (29)	9 (9)	<0.001
Category 3	12 (50)	33 (26)	24 (16)	24 (24)	0.011
High risk for OSA, n (%)	16 (57)	22 (17)	26 (17)	11 (11.0)	<0.001

OSA: obstructive sleep apnea; BMI: body mass index.

nal compression or internal obstruction. As reported in a review, nearly 90% of all cases of SVCS are caused by malignancies, with 75% of the malignant cases secondary to lung cancer and 15% secondary to non-Hodgkin lymphoma (9). Benign causes include intravascular devices causing thrombi, cardiac disease, mediastinal fibrosis, benign mediastinal tumours, vascular disease and infections (9, 10). SVCS is a rare but well recognised manifestation of BS (6). In a cohort of 882 patients with vascular involvement among 5970 BS patients, 79 (8.6%) were identified with SVCS (6).

Impairment of blood flow through the VCS leads to venous engorgement proximal to the site of the obstruction, resulting in the classic signs and symptoms (9, 10). There ensue dilated collaterals into azygous veins or the inferior vena cava. Patients present with dyspnea, cough, headache, facial, neck, and or arm swelling or oedema, hoarseness and distended neck and chest wall veins (9-11).

Contrary to the severe outcome seen in malignant conditions, SVCS in BS usually runs a benign course, most probably due to subacute or chronic onset that enables development and enlargement of the collateral venous systems. It is rarely complicated by hemoptysis, pleural effusion and a chylothorax (12, 13). We had noted that BS patients with SVCS frequently complained of symptoms suggesting OSA, an observation, to the best of our knowledge not previously made.

It is unclear why patients with SVCS are prone to develop OSA. BS patients with SVCS have considerable amount of collateral formations around the neck and upper torso which could be responsible of the external compression of the airways (Fig. 1A-B). Interstitial oedema of the airways due to the poor venous drainage could be another possibility. Sleep-related breathing problems were reported to be common in patients with idiopathic intracranial hypertension (18-20). Whether patients with SVCS also develop intracranial hypertension during sleep is unknown.

Interestingly there are reports of BS patients, with no reference to specific organ involvement, having poor sleep quality associated with fatigue or depression (21-27). Some of the studies quoted used sleep quality indices along with polysomnography, however, none noted an association between SVCS and OSA.

This study has several limitations. First, we could not use the polysomnography which is the gold standard for assessing OSA, because it requires an overnight evaluation in a laboratory setting. Instead we used BQ that has been validated and shown to have a good sensitivity but a modest specificity (28). Second, we included only male patients because there were only two female patients with SVCS in our cohort. Major vascular disease in BS is distinctly less common among females (5, 6) and there is a clear predominance of males with in OSA in the general population (29). Third, current treatment except anticoagulant and immunosuppressives were similar among the groups. However, we did not note that drugs such as benzodiazepine, opioid, myorelaxant and antidepressant may worsen OSA (30), which was one of the limitations of our study. Finally, we did not have a group of patients with SVCS due to non-BS related aetiologies.

BS patients with SVCS are at increased risk of having OSA as we now report. This may have important implications since OSA is associated with increased cardiovascular morbidity and mortality. Our results should further be confirmed by polysomnography.

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