SLEEPJ, 2021, 1–13

doi: 10.1093/sleep/zsaa191
Advance Access Publication Date: 21 September 2020
Original Article

ORIGINAL ARTICLE

Stridor during sleep: description of 81 consecutive cases diagnosed in a tertiary sleep disorders center

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Abstract

Study Objectives: To describe the characteristics of stridor during sleep (SDS) in a series of adults identified by video-polysomnography (V-PSG).

Methods: Retrospective clinical, V-PSG, laryngoscopic, and therapeutic data of patients diagnosed with SDS in a tertiary referral sleep disorders center between 1997 and 2017.

Results: A total of 81 patients were identified (56.8% males, age 61.8 ± 11.2 years). Related etiologies were multiple system atrophy (MSA), amyotrophic lateral sclerosis, spinocerebellar ataxia type 1, anti-IgLON5 disease, fatal familial insomnia, brainstem structural lesions, vagus nerve stimulation, recurrent laryngeal nerve injury, the effect of radiotherapy on the vocal cords, cervical osteophytes, and others. Stridor during wakefulness coexisted in 13 (16%) patients and in MSA was only seen in the parkinsonian form. Laryngoscopy during wakefulness in 72 (88.9%) subjects documented vocal cord abductor impairment in 65 (90.3%) and extrinsic lesions narrowing the glottis in 2 (2.4%). The mean apnea–hypopnea index (AHI) was 21.4 ± 18.6 and CT90 was 11.5 ± 19.1. Obstructive AHI > 10 occurred in 52 (64.2%) patients and central apnea index >10 in 2 (2.4%). CPAP abolished SDS, obstructive apneic events and oxyhemoglobin desaturations in 58 of 60 (96.7%) titrated patients with optimal pressure of 9.0 ± 2.3 cm H20. Tracheostomy in 19 (23.4%) and cordotomy in 3 (3.7%) subjects also eliminated SDS.

Conclusions: SDS in adults is linked to conditions that damage the brainstem, recurrent laryngeal nerve, and vocal cords. V-PSG frequently detects obstructive sleep apnea and laryngoscopy usually shows vocal cord abductor dysfunction. CPAP, tracheostomy, and laryngeal surgery abolish SDS.

Statement of Significance

The majority of adults with stridor during sleep (SDS) are unaware of displaying this abnormality that requires the report of a reliable informat of the patient's sleep. Clinicians should be aware that SDS indicates laryngeal narrowing which is often caused by incomplete separation of the vocal cords during inspiration. This laryngeal abnormality may be disclosed in most of the cases by laryngoscopy during wakefulness despite stridor occurs when the individual is asleep. In a few cases, laryngoscopy detects mechanical reduction of the glottis by an extrinsic mass. Video-polysomnography is essential to identify SDS and related obstructive sleep apneic events and oxyhemoglobin desaturations. Treatment of SDS should be individualized according to the underlying condition, patient's prognosis, and laryngoscopic and video-polysomnographic findings. Therapy includes CPAP, tracheostomy, and laryngeal surgery.

Key words: stridor; sleep; vocal cord abductor impairment; laryngoscopy; video-polysomnography; continuous positive airway pressure; tracheostomy; laryngeal surgery

Submitted: 13 June, 2020; **Revised:** 2 September, 2020

Introduction

Stridor is a high-pitched respiratory sound produced by turbulent airflow through a partially obstructed upper airway [1]. Abnormalities that obstruct the upper airway and cause stridor are usually located in the glottis and can be extrinsic to the larynx (e.g. neurodegenerative diseases damaging the nucleus ambiguus in the medulla oblongata, iatrogenic injury of the recurrent laryngeal nerve) or intrinsic to the larynx (e.g. edema of the vocal cords, laryngomalacia, and glottic web) [2–4]. In adults, stridor commonly appears first during sleep (SDS) and later may be present during wakefulness (SDW) when the narrowing of the glottis becomes almost complete [5]. In severe cases with bilateral vocal cord abductor immobility (Gerhardt syndrome), the vocal cords are fixed in the midline position and this situation may lead to respiratory insufficiency and death [6, 7]. Because SDS in adults is associated with sleep-disordered breathing and is considered a potential life-threating situation [7, 8], it is usually managed with therapeutic strategies such as continuous positive airway pressure (CPAP), tracheostomy, and laryngeal surgery (e.g. cordotomy and vocal cord lateralization) [6–8]. Previous studies on SDS focused in a single condition (e.g. multiple system atrophy [MSA]) or consisted in case reports. There are no previous publications describing SDS in consecutive adults diagnosed in sleep centers showing different etiologies. We describe SDS in a series of consecutive adults diagnosed by video-polysomnography (V-PSG) in our tertiary sleep disorders center over a 20-year period.

Methods

Study participants

The study is a retrospective review of demographic, clinical, V-PSG, laryngoscopic, and therapeutic baseline data of all the patients diagnosed with SDS at the sleep disorders center of the Neurology Service in the Hospital Clinic de Barcelona, Spain, between April 1997 and March 2017. The Hospital Clinic de Barcelona is a referral institution for sleep disorders, laryngeal surgery, thoracic surgery, neurosurgery, movement disorders, prion diseases, and autoimmune neurological disorders among other disciplines.

Patients included in this study were identified from our database of individuals who underwent V-PSG at our sleep disorders center. In this database, the diagnosis of SDS was systematically coded. We defined the baseline period as the period when the first identification of SDS was done by V-PSG and patients underwent laryngoscopy and initial therapeutic management for SDS. Data collected from V-PSG, laryngoscopy, and initial therapeutic approach were obtained reviewing V-PSG studies and medical records.

Video-polysomnography

V-PSG was performed with synchronized audiovisual recording (Coherence 7, Deltamed, Paris, France) and consisted in electroencephalography (C3, C4, O1, O2, plus F3 and F4 since 2007, referred to the combined ears), electrooculography, electrocardiography, and surface electromyography of the mentalis muscle and of the right and left anterior tibialis. Electromyography of the upper limbs (biceps braquii or flexor digitorum superficialis) was added when comorbid rapid eye movement (REM) sleep behavior or other parasomnias were suspected. Nasal and oral thermistors, thoracic and abdominal strain gauges, and finger pulse oximeter were used to measure the respiratory variables. Nasal pressure cannula was added in 2008. Sleep architecture and associated events were scored according to the American Academy of Sleep Medicine recommendations [9]. Apnea was defined as a complete cessation of the airflow for >10 s. Hypopnea was defined as ≥30% reduction in nasal pressure signal excursions from baseline lasting >10 s and associated with either ≥3% desaturation from pre-event baseline or an arousal. The apnea–hypopnea index (AHI) was the number of apneas plus hypopneas per hour of sleep. The obstructive AHI was the number of obstructive apneas plus hypopneas per hour of sleep. The central apnea index was the number of central apneas per hour of sleep. The percentage of cumulative sleep time percentage with oxyhemoglobin saturation below 90% (CT90) and the nadir of oxyhemoglobin saturation were calculated.

When we reviewed the audio and polysomnographic recordings from V-PSG, SDS was identified when a crowing, harsh, and high-pitched sound that occurred during breathing was noted while the patient was asleep [1]. SDS was classified as inspiratory or expiratory, and also as continuous (when SDS occurred in ≥50% of the total sleep time) or intermittent (when SDS appeared in <50% of the total sleep time).

Laryngoscopy

Flexible fiberoptic laryngoscopy under video recording was performed during wakefulness by an experienced otolaryngologist who examined the upper airway structures and mobility of the vocal cords. Mobility of the vocal cords was classified as normal (Supplementary Video 1) or abnormal (Supplementary Videos 2–4).

We did not detect paradoxical adduction of the vocal cords during inspiration in our series. Thus, abnormal vocal cord motility during inspiration was classified as “partial abduction restriction” (partial obstruction of the glottic space) and “complete abduction restriction” (immobile vocal cord fixed in the paramedian position). Flickering movements of the vocal cords were noted when the arytenoid cartilage showed tremulous rhythmic movements during forced inspiration (Supplementary Video 3). The presence of flickering movements was considered an abnormal finding indicative of mild partial vocal cord abductor restriction [10–12]. Thus, abnormal vocal cord abduction during inspiration was classified as unilateral partial abduction restriction (UPAR), bilateral partial abduction restriction (BPAR), unilateral complete abduction restriction (UCAR), and bilateral complete abduction restriction (BCAR) [13, 14].

Management of stridor

Therapy for SDS was individualized in each subject according to clinical judgment based on several parameters including the nature of the underlying disorder, the patients’ prognosis and estimated life expectancy, vocal cord mobility on laryngoscopy, and the presence or absence of obstructive sleep apneic events. For example, in patients with MSA showing SDS, we used the following algorithm at baseline and at follow-up visits based

on our clinical experience and data reported from other centers (Figure 1):[7, 8, 13–16]

- Watchful waiting when there were (1) clinical absence of SDW, (2) absence of complete vocal cord abductoion restriction on laryngoscopy, and (3) AHI < 10 in V-PSG.
- Treatment with CPAP (given that is noninvasive and can be well tolerated) when there were (1) absence of SDW, (2) both vocal cords were not immobile in the midline position, and (3) AHI ≥ 10. Patients who accepted CPAP underwent a second V-PSG study where CPAP was manually titrated to the minimum pressure required to eliminate SDS, sleep apneic events, and oxyhemoglobin desaturations. Audiovisual monitoring during V-PSG allowed identifying the modification of SDS during CPAP titration in this second study. If CPAP was not tolerated or failed to control SDS, the possibility of therapy with tracheostomy was carefully evaluated according to the patient' clinical status, laryngoscopic findings, and the severity of the AHI.
- Tracheostomy was considered when either (1) stridor appeared during wakefulness, (2) respiratory distress occurred during wakefulness, or (3) both vocal cords were fixed in the midline position and the glottis was almost stenotic. If patients declined tracheostomy, CPAP therapy was offered.

Laryngeal surgery (e.g. posterior laser cordotomy) was considered based on the nature of the underlying disease (usually in non-neurodegenerative progressive diseases) and when the patient had no potential risk of aspiration. The study was approved by the ethics committee at our institution.

Statistical analysis

Descriptive demographical, clinical, V-PSG, and laryngoscopic data are given in mean, standard deviation number, and percentage. The date of the diagnosis of SDS was determined as the date when V-PSG was performed. The estimated stridor onset was determined by clinical history with the patient and a reliable informant (e.g. spouse and caregiver). Comparisons between MSA groups and central versus peripheral lesion groups were performed with χ^2 test and Mann–Whitney U-test, when appropriated.

Results

Demographic and clinical findings

We identified 81 patients with SDS, 46 (56.8%) men and 35 (43.2%) women with a mean age of 61.8 ± 11.2 (range, 34–86) years at the time of the diagnosis of SDS (Table 1).

None of the patients were self-aware of displaying peculiar respiratory sounds during their sleep. In 59 (72.8%) patients, SDS was clinically suspected by the referral physician based on the description that the bed partner or another informant gave about the type of respiratory sound they noticed during the patient's sleep. In the remaining 22 (27.2%) patients, SDS was documented incidentally when patients underwent V-PSG because other referral reasons such as nonrestorative sleep, suspected obstructive sleep apnea, and suspected REM sleep behavior disorder. Of note, 20 of the 22 cases with unexpected SDS had no bed partner or other reliable informant of the patient's sleep.

Conditions associated with SDS

The underlying cause of SDS was located in either the central or peripheral nervous system in 91.4% of the patients. Local lesions of the larynx causing SDS were found in the remaining 8.6% of the subjects. Table 2 lists the causes of SDS found in our series.

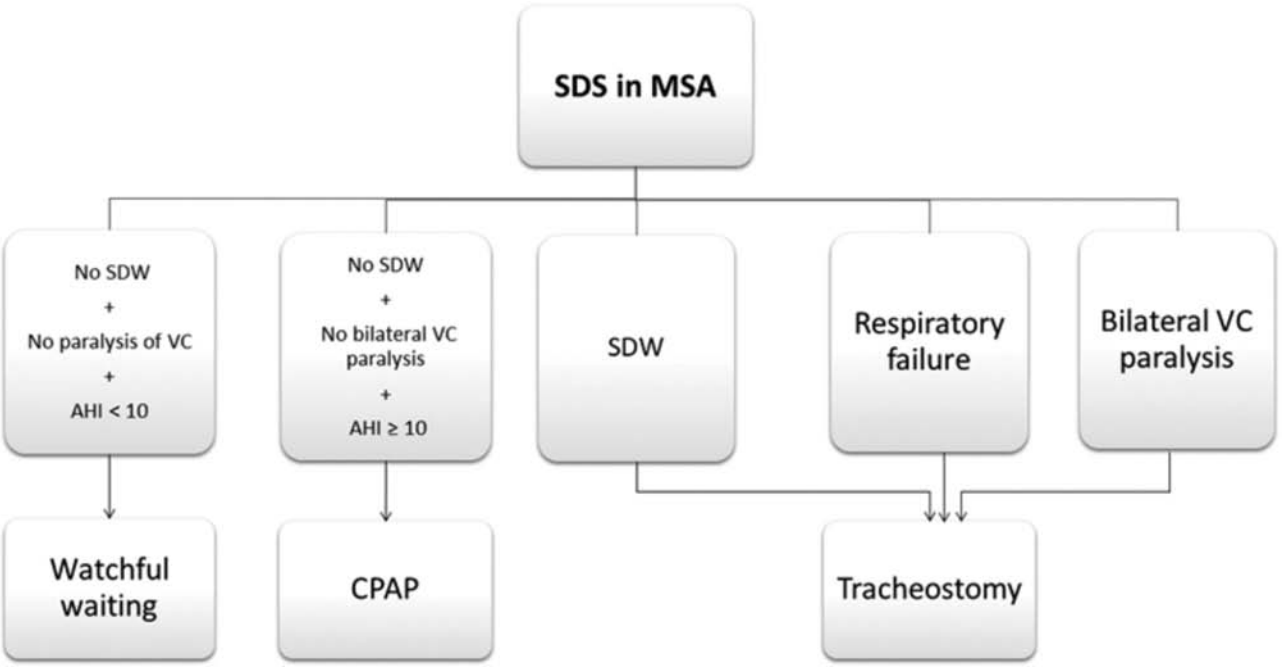

Figure 1. Therapeutical management of stridor during sleep in patients with MSA. SDS, stridor during sleep; MSA, multiple system atrophy; SDW, stridor during wakefulness; VC, vocal cords; AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure.

Table 1. Findings in patients with stridor during sleep

	Patients (*n* = 81)
Male sex, *n* (%)	46 (56.8)
Age at disease onset, y	58.7 ± 13.6
Age at stridor onset, y	60.6 ± 11.8
Stridor as the first disease manifestation, *n* (%)	4 (4.9)
Age at V-PSG, y	61.8 ± 11.2
Inspiratory stridor, *n* (%)	79 (97.5)
Expiratory stridor, *n* (%)	11 (13.6)
Inspiratory and expiratory stridor, *n*	9 (11.1)
AHI, *n*	21.4 ± 18.6
AHI > 5, *n* (%)	68 (83.9)
AHI > 10, *n* (%)	52 (64.2)
AHI > 30, *n* (%)	19 (23.5)
Obstructive apnea index, *n*	19.9 ± 18.1
Central apnea index, *n*	1.3 ± 6.8
CT90, *n*	11.5 ± 19.1
Nadir O_2Hb, *n*	84.2 ± 7.4
Stridor during wakefulness, *n* (%)	13 (16.0)
Laryngoscopy, *n* (%)	72 (88.9)
Abnormal vocal cord mobility in laryngoscopy, *n* (%)	65 (91.5)
Vocal cord bilateral impairment, *n* (%)	42 (64.6)
Vocal cord unilateral impairment, *n* (%)	23 (35.4)
Vocal cord flickering, *n* (%)	6 (9.2)
CPAP therapy, *n*	60 (74.1)
CPAP pressure, cm H_2O	9.0 ± 2.3
Tracheostomy, *n* (%)	19 (23.4)
Cordotomy, *n* (%)	3 (3.7)

Values are expressed as mean, standard deviation, number, and percentatges. V-PSG, video-polysomnography; AHI, apnea–hypopnea index; CT90, cummulative percentatge of sleep time with oxyhemoglobin saturation below 90; O_2Hb, oxyhemoglobin saturation; CPAP, continuous positive airway pressure.

Table 2. Conditions associated with stridor during sleep according to their anatomical location

	Patients *n* (%)
Lesion in the central nervous system	
Multiple system atrophy	49 (60.5)
Anti-IgLON5 disease	5 (6.2)
Fatal familial insomnia	2 (2.5)
Niemann–Pick disease type C	1 (1.2)
Parkinson disease	1 (1.2)
Parkinsonism of unknown cause	1 (1.2)
Spinocerebellar ataxia type 1	1 (1.2)
Amyotrophic lateral sclerosis	1 (1.2)
Arnold-Chiari malformation	1 (1.2)
Medullar hemorrhage	1 (1.2)
Brainstem glioma	1 (1.2)
Lesion in the peripheral nervous system	
Laryngeal nerve injury after thyroidectomy	6 (7.4)
Idiopathic vocal cord abductor pasly	3 (3.7)
Vagus nerve stimulation	1 (1.2)
Lesion in the larynx/hypopharynx	
Radiotherapy for laryngeal cancer	3 (3.7)
Orotraqueal intubation	1 (1.2)
Cervical osteophyte	1 (1.2)
Retropharyngeal neoplasm	1 (1.2)
Achondroplasia	1 (1.2)

Values are expressed as number and percentatges.

SDS in MSA

SDS occurred in 49 subjects with MSA, 25 (51.0%) with the cerebellar subtype (MSA-C) and 24 (49.0%) with the parkinsonian subtype (MSA-P). There were no differences in demographic, V-PSG, and laryngoscopic data between MSA-C and MSA-P except that SDW was only seen in subjects with the parkinsonian subtype and in none with the cerebellar subtype (Table 3). SDS was the first manifestation of MSA in four patients. All these 49 MSA patients with SDS had REM sleep behavior disorder confirmed by V-PSG. Laryngoscopy during wakefulness was performed in 42 (85.7%) MSA patients and was abnormal in 39 (92.9%) of them showing vocal cord abductor restriction during inspiration in all of them. A total of 42 MSA patients received CPAP therapy with a mean optimal pressure of 8.7 ± 2.3 (range, 4–13) cm H_2O. Tracheostomy was performed in 13 patients because SDS coexisted during wakefulness (*n* = 7), respiratory failure (*n* = 5), and poor adherence to CPAP (*n* = 1).

SDS in amyotrophic lateral sclerosis

A 58-year-old man developed SDS and SDW 2 years after the diagnosis of amyotrophic lateral sclerosis. V-PSG showed AHI of 7.7 and CT90 of 0. Laryngoscopy demonstrated BCAR. Tracheostomy eliminated stridor and apneic events.

SDS in spinocerebellar ataxia type 1

A 35-year-old woman was diagnosed with spinocerebellar ataxia type 1 at the age of 24 and developed SDS and SDW at the age of 34. V-PSG demonstrated AHI of 28.4 and CT90 of 10. Laryngoscopy found BCAR. The patient declined therapy for stridor.

SDS in Arnold–Chiari malformation

A 69-year-old woman with Arnold–Chiari malformation type 1 and cervical and dorsal syringomyelia developed SDS since the age of 63 (Figure 2). V-PSG showed AHI of 19.6 and CT90 of 1. Laryngoscopy found UCAR. CPAP at the pressure of 12 cm H_2O eliminated SDS and apneas.

SDS in anti-IgLON5 disease

SDS occurred in five patients with this condition. SDS was continuous in four and intermittent in one. The mean AHI was 33.7 ± 11.5 and the mean CT90 was 15.0 ± 17.4. Laryngoscopy showed BPAR in two patients, UPAR in two, and normal mobility of the vocal cords in one. CPAP in four patients (optimal pressures from 11 to 12 cm H_2O) abolished SDS and obstructive sleep apnea. Tracheostomy had to be performed in one patient with respiratory insufficiency and BPAR, continuous SDS, and AHI of 23.

SDS in fatal familial insomnia

SDS was found in two patients in whom stridor was intermittent. V-PSG showed AHI of 69 and 7, and CT90 of 24.8 and 0, respectively. Laryngoscopy was not performed in any of these two patients. Therapy for SDS was disregarded due to severe neurological disability.

SDS associated with brainstem glioma

A 39-year-old woman with brainstem glioma involving the medulla developed SDS (Figure 3). V-PSG showed intermittent SDS, obstructive AHI of 4.8, central apnea index of 16.6 and CT90 of

Table 3. Findings in patients with MSA

	MSA-C (*n* = 25)	MSA-P (*n* = 24)	*P* value
Male sex, *n* (%)	20 (80.0)	13 (54.1)	0.054
Age at disease onset, y	57.6 ± 6.7	59.7 ± 11.2	0.483
Age at stridor onset, y	60.1 ± 7.1	63.1 ± 11.7	0.335
Stridor as the first manifestation of the disease, *n* (%)	1 (4.0)	3 (12.5)	0.257
Age at V-PSG, y	61.5 ± 6.9	63.2 ± 10.8	0.555
Inspiratory stridor, *n* (%)	25 (100)	22 (91.7)	0.141
Expiratory stridor, *n* (%)	2 (8.0)	2 (8.3)	1.000
Inspiratory and expiratory stridor, *n* (%)	2 (8.0)	0 (0)	0.149
AHI, *n*	16.8 ± 17.0	20.9 ± 19.9	0.472
AHI > 5, *n* (%)	19 (76.0)	21 (87.5)	0.480
AHI > 10, *n* (%)	11 (44.0)	17 (70.8)	0.087
AHI > 30, *n* (%)	4 (16.0)	4 (16.6)	1.000
Obstructive apnea index, *n*	16.2 ± 16.8	20.7 ± 19.8	0.383
Central apnea index, *n*	0.5 ± 1.2	0.2 ± 0.7	0.850
CT90, *n*	13.0 ± 21.8	15.4 ± 22.9	0.780
Nadir O_2Hb, *n*	84.2 ± 8.1	83.2 ± 7.1	0.580
Stridor during wakefulness, *n* (%)	0 (0)	7 (29.2)	**0.004**
Laryngoscopy, *n* (%)	23 (92.0)	19 (79.2)	0.199
Abnormal vocal cord mobility in laryngoscopy, *n* (%)	21 (91.3)	18 (95.0)	0.667
Vocal cord bilateral impairment, *n* (%)	13 (61.9)	14 (77.8)	0.284
Vocal cord unilateral impairment, *n* (%)	8 (38.1)	4 (22.2)	0.284
Vocal cord flickering, *n* (%)	3 (14.3)	1 (5.5)	0.393
CPAP therapy, *n* (%)	23 (92.0)	19 (79.1)	0.123
CPAP pressure, cmH_2O	8.7 ± 2.3	7.9 ± 2.4	0.255
Tracheostomy, *n* (%)	5 (20.0)	8 (33.3)	0.291

Values are expressed as mean, standard deviation, number, and percentatges. MSA, multiple system atrophy; MSA-C, cerebellar subtype of multiple system atrophy; MSA-P, parkinsonian subtype of múltiple system atrophy; V-PSG, video-polysomnography; AHI, apnea–hypopnea index; CT90, cummulative percentatge of total sleep time with oxyhemoglobin saturation below 90; O2Hb, oxyhemoglobin saturation; CPAP, continuous positive airway pressure.

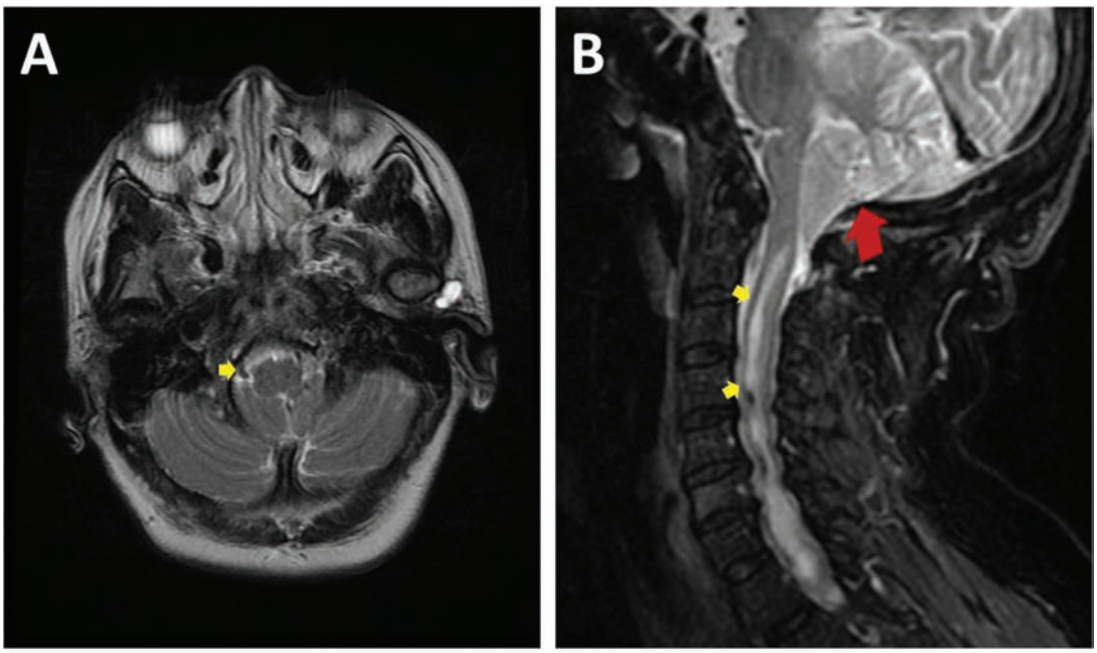

Figure 2. Arnold–Chiari malformation (red arrow) and cervical syringomyelia (yellow arrows). (A) Brain MRI axial T2 sequence. (B) Cervical spinal cord MRI sagittal T2 sequence.

0. Laryngoscopy showed UCAR. CPAP eliminated SDS and obstructive sleep apnea with a pressure of 12 cm H_2O, but not the central apneic events.

SDS associated with medullar hemorrhage

. A 47-year-old woman suffered a medullar hemorrhage during surgery for a cavernous malformation located in the medulla (Figure 4). At discharge, the patient's bed partner noticed an abnormal respiratory sound during sleep different from snoring. V-PSG showed intermittent inspiratory SDS, AHI of 10, and CT90 of 0. Laryngoscopy found UCAR. CPAP eliminated SDS and obstructive sleep apneic events with a pressure of 7 cm H_2O.

SDS after thyroidectomy

This was detected in six women with a mean age of 59.7 ± 11.8 years. In three subjects, SDS was noted by their bed partner

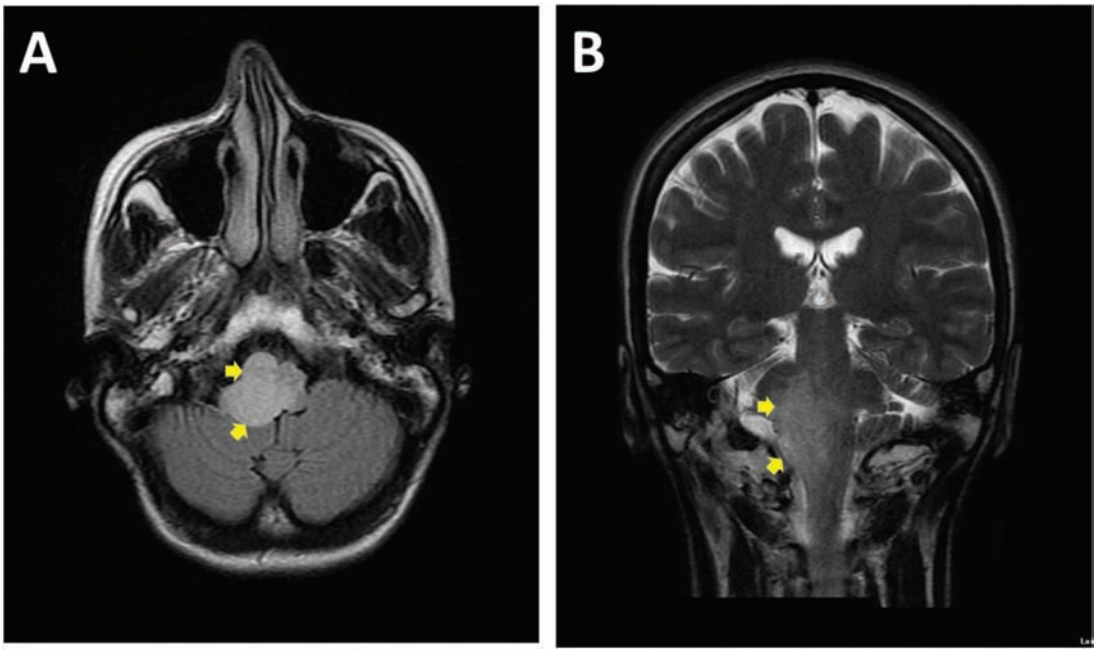

Figure 3. Brainstem glioma predominantly involving the right side of the pons and the medulla (yellow arrows). In this patient, laryngoscopy demonstrated UCAR of the right vocal cord and normal motility of the left vocal cord. (A) Brain MRI axial FLAIR sequence. (B) Brain MRI coronal T2 sequence.

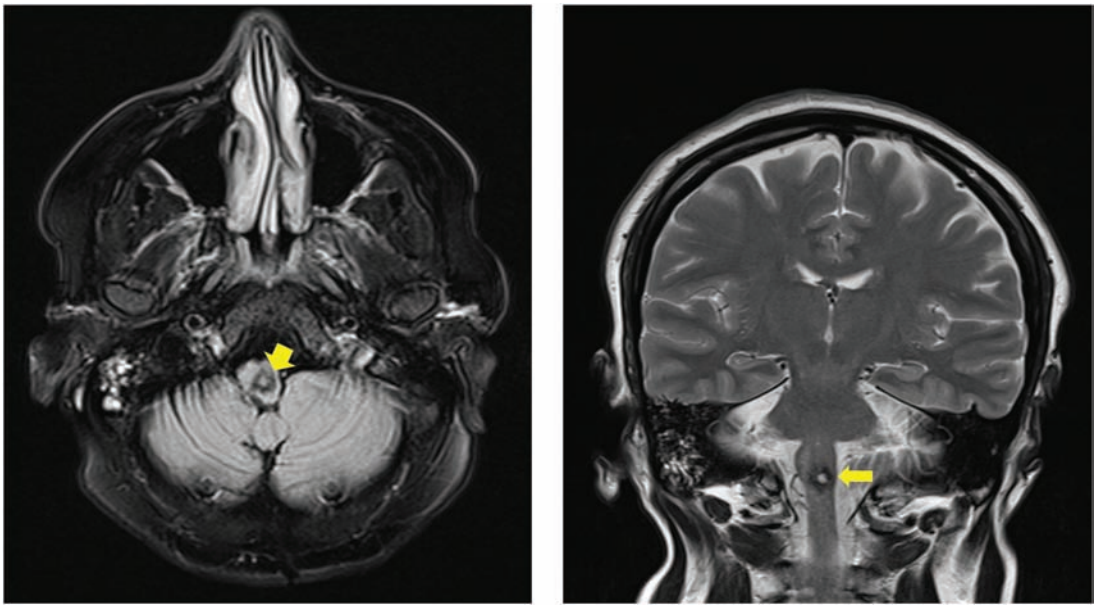

Figure 4. Chronic hemorrhage in the medulla (yellow arrows) secondary to cavernous malformation. (A) Brain MRI axial FLAIR sequence. (B) Brain MRI coronal T2 sequence.

after discharge. In the other three cases, SDS was an incidental finding when patients underwent V-PSG to rule out obstructive sleep apnea. In these three incidental cases, V-PSG was performed 13, 18, and 19 years after thyroidectomy. In all the six cases with SDS related to thyroidectomy, the mean AHI was 8.6 ± 3.4 and the mean CT90 was 4.0 ± 7.5. SDS was only inspiratory in all six, continuous in three, and intermittent in three. Laryngoscopy found BCAR in one, UCAR in one, BPAR in two, and UCAR in one vocal cord plus UPAR of the contralateral vocal cord in the remaining two individuals. All six patients had dysphonia during wakefulness and the patient with BCAR had mild intermittent SDW. Of these six subjects, two were treated only with CPAP (pressures of 9 and 11 cm H_2O), two with CPAP (pressures of 9 and 11 cm H_2O) plus posterior cordotomy, one with posterior cordotomy plus subtotal arytenoidectomy, and the remaining patient declined therapy.

SDS associated with vagal nerve stimulation

A 55-year-old man with refractory epilepsy suffered *status epilepticus* that required sedation and oral intubation at the age of 50 years. At discharge, the patient had dysphonia but laryngoscopy and V-PSG were not performed. At the age of 55, the patient

was treated with left vagal nerve stimulation for drug-resistant epilepsy and after the procedure he developed mild and intermittent SDW. V-PSG showed inspiratory and continuous SDS, AHI of 35.5, and CT90 of 20. V-PSG showed that SDS and obstructive apneic events were not synchronized with the activation of the vagal stimulation. Laryngoscopy found BCAR. CPAP at the pressure of 12 cm H_2O abolished SDS and apneic events.

SDS associated with neck tumors

SDS occurred in four patients with neck tumors. Three patients with squamous cell carcinomas of the larynx were treated with laryngeal surgery plus adjuvant chemotherapy and neck radiotherapy. After completion of radiotherapy, these three patients developed SDS. Laryngoscopy showed BPAR in two patients and UCAR in one patient with severe edema impairing its mobility (Figures 5 and 6). In these three subjects with laryngeal cancer, SDS was abolished with tracheostomy in one, and first with CPAP (with pressures of 10 and 12 cm H_2O) and later with tracheostomy in two when SDW later appeared. In the fourth patient, AHI was 11.5 and laryngoscopy demonstrated normal movements of the vocal cords but identified a retropharyngeal tumor of 18 × 16 mm that partially obstructed the upper airway at the level of the larynx (Figure 7). This fourth patient refused therapy with CPAP for stridor.

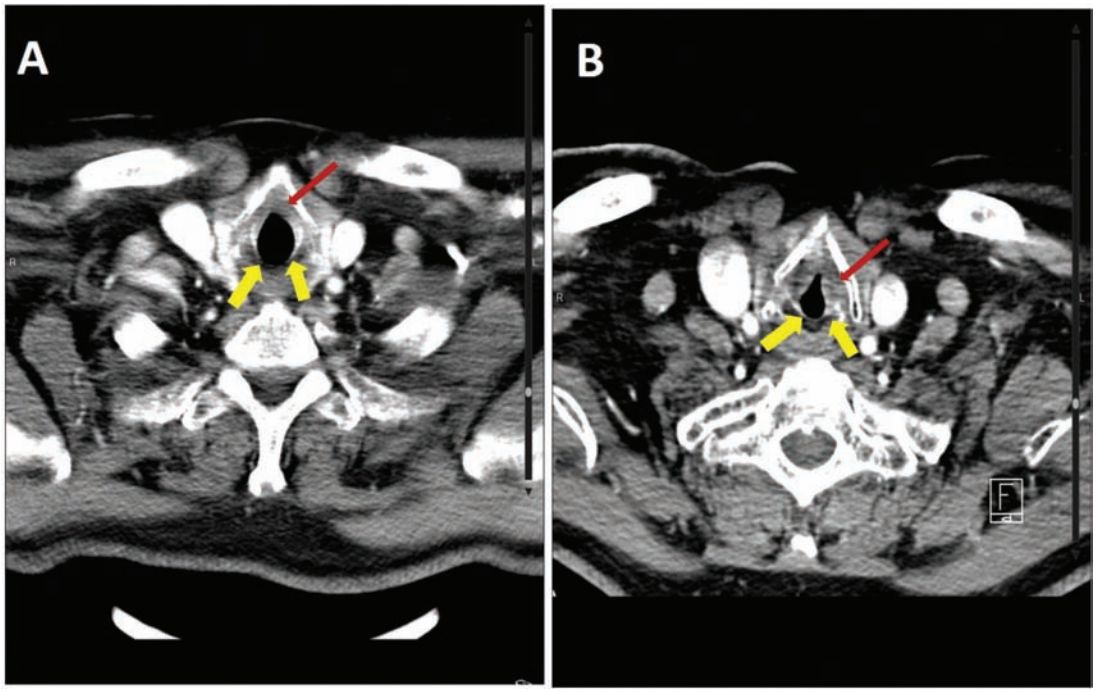

Figure 5. Laryngeal carcinoma and narrowing of the glottis after cervical radiotherapy. (A) CT scan with contrast performed before surgery and before radiotherapy showing a carcinoma located in the anterior third of the vocal cords (red arrow) with normal size of the glottic space (yellow arrows). (B) CT scan with contrast performed after surgery and after radiotherapy (when the patient developed stridor during sleep). The glottic space is narrower compared with prior radiotherapy (yellow arrows). Laryngoscopy showed bilateral edema (red arrow) and vocal cord abduction restriction.

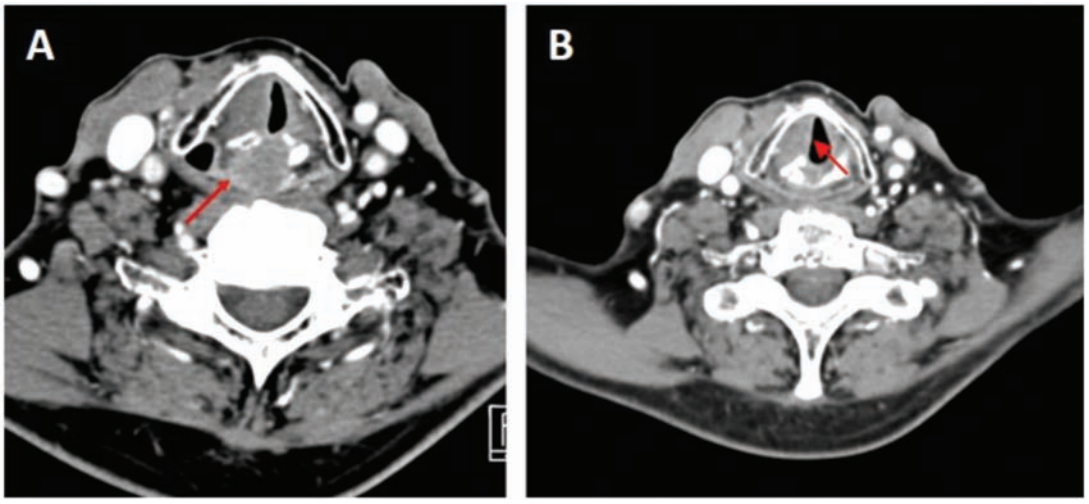

Figure 6. Retrocricoid carcinoma and narrowing of the glottis after radiotherapy. (A) CT scan performed before surgery and before radiotherapy showing a carcinoma located in the posterior commissure (red arrow). (B) CT scan performed after surgery and after radiotherapy (when the patient developed stridor during sleep). The tumor was removed but the right vocal cord is fixed in the middline and the glottic space is reduced (red arrow).

SDS associated with cervical osteophyte.

A 79-year-old man with Parkinson disease underwent V-PSG to rule out obstructive sleep apnea. V-PSG demonstrated intermittent inspiratory SDS, AHI of 26.5, and CT90 of 8. Laryngoscopy showed normal vocal cord mobility but demonstrated a nonpulsatile protrusion of the left retropharyngeal area that narrowed the glottic space. A cervical magnetic resonance imaging found prominent cervical osteophytes at the C3–C6 vertebra levels (Figure 8). The patient declined therapy for obstructive sleep apnea and SDS.

SDS associated with achondroplasia.

Loud and intermittent SDS was detected in a 37-year-old man with achondroplasia who underwent V-PSG because of a 4-year history of a "heavy respiratory sound in sleep" and witnessed apneas. The AHI was 17.7 and CT90 was 0. Laryngoscopy showed normal vocal cord mobility. Drug-induced video-endoscopy with propofol showed partial collapse of the larynx associated with stridor with normal motility of the vocal cords. The patient declined therapy for SDS.

There were no demographic, clinical, V-PSG, and laryngoscopic differences between patients with lesions located in the central nervous system versus patients with lesions in the peripheral nervous system and intrinsic to the larynx, except that central conditions showed higher CT90 and needed lower pressure of CPAP to eliminate SDS (Table 4).

Video-polysomnographic findings

SDS was only inspiratory in 70 (86.4%) patients, only expiratory in 2 (2.5%), and combined inspiratory and expiratory in 9 (11.1%).

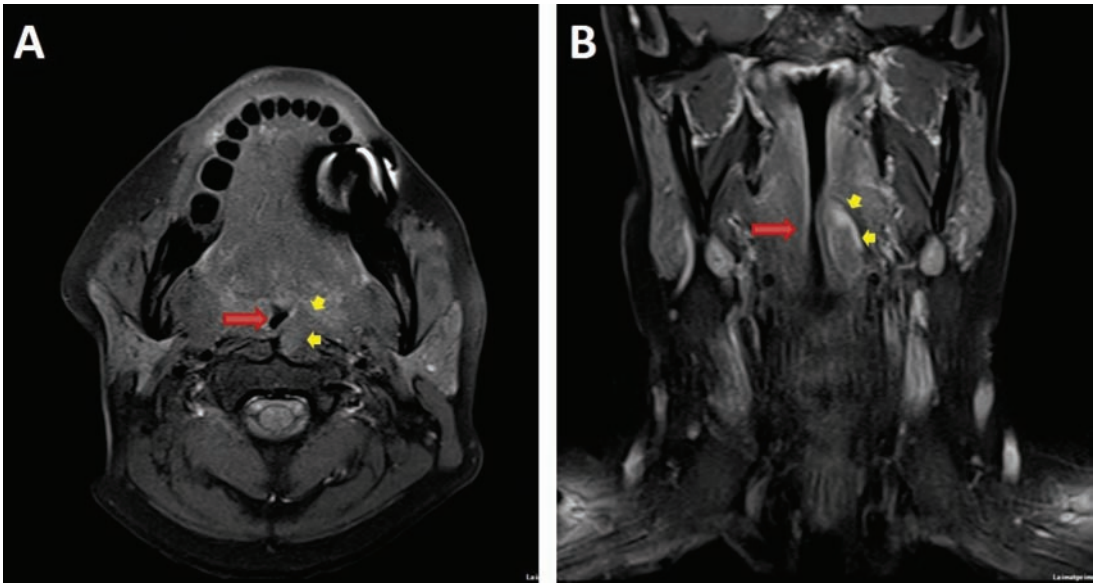

Figure 7. Retropharyngeal tumor compressing the glottis. (A) Cervical MRI axial T1 sequence showing a retropharyngeal tumor (yellow arrows) narrowing the supraglottic space (red arrow). (B) Cervical MRI coronal T2 sequence showing contrast enhancement of the tumor (yellow arrows) narrowing the supraglottic space (red arrow).

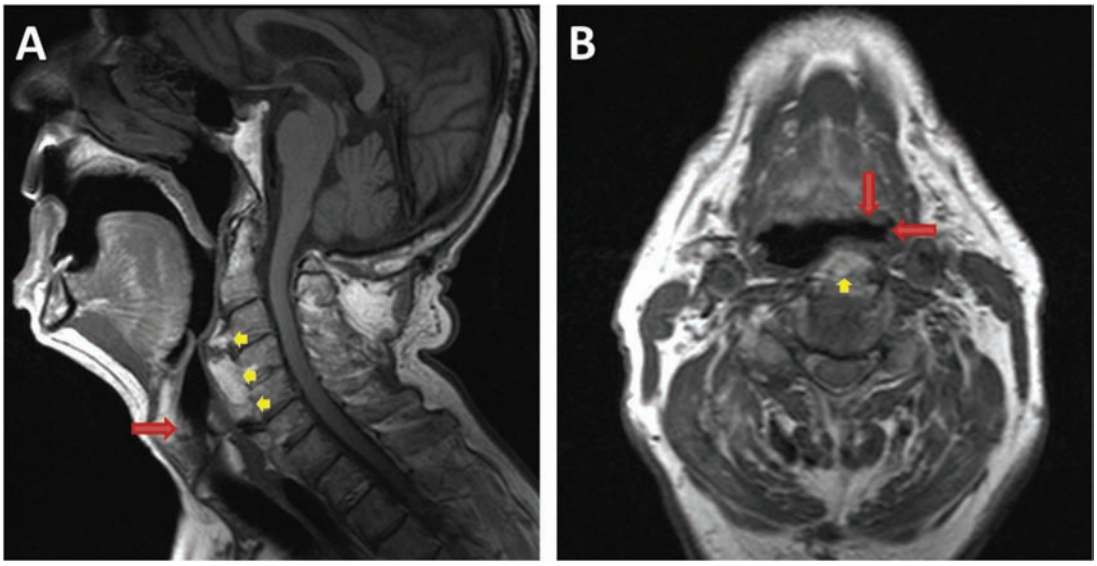

Figure 8. Cervical vertebrae osteophytes. (A) MRI sagittal T1 seguence showing cervical vertebrae osteophytes from C3 to C6 (yellow arrows) protrusing the posterior wall of the pharynx and reducing the supraglottic and glottic spaces (red arrow). (B) MRI axial T1 sequence showing a cervical vertebrae osteophyte (yellow arrow) protrusing the posterior wall of the pharynx and reducing the supraglottic space (red arrows).

Table 4. Findings according to the location of the lesion

	Lesion in the CNS (n = 64)	Lesion in the PNS and intrinsic to the larynx (n = 17)	P value
Male sex, n (%)	39 (60.4)	7 (41.2)	0.144
Age at disease onset, y	57.7 ± 11.4	52.8 ± 20.5	0.155
Age at estimated stridor onset, y	61.1 ± 10.9	58.4 ± 16	0.802
Stridor as the first manifestation, n (%)	4 (6.2)	0 (0)	0.366
Age at V-PSG, y	62 ± 10.5	60.9 ± 14.1	0.921
Inspiratory stridor, n (%)	63 (98.4)	17 (100)	0.460
Expiratory stridor, n (%)	7 (10.9)	4 (23.5)	0.178
AHI	21.3 ± 18.5	22 ± 19.6	0.885
AHI >5, n (%)	53 (82.8)	15 (82.2)	0.588
AHI >10, n (%)	41 (64.1)	11 (64.7)	0.961
AHI >30, n (%)	14 (21.9)	5 (29.4)	0.514
Obstructive apnea index, n	19.7 ± 17.6	20.7 ± 20.4	0.903
Central apnea index, n	1.6 ± 7.7	0.34 ± 0.5	0.212
CT90, n	13.4 ± 20.9	4.5 ± 7.1	**0.022**
Nadir O_2Hb, n	83.7 ± 7.8	86 ± 5.2	0.353
Stridor during wakefulness, n (%)	9 (14.1)	4 (23.5)	0.345
Laryngoscopy, n (%)	55 (85.9)	17 (100)	0.101
Abnormal vocal cord mobility in laryngoscopy, n (%)	51 (92.7)	14 (82.3)	0.207
Vocal cord bilateral impairment, n (%)	33 (64.7)	9 (64.4)	0.977
Vocal cord unilateral impairment, n (%)	18 (35.3)	5 (35.7)	0.977
Vocal cord flickering, n (%)	6 (11.8)	0 (0)	0.167
CPAP pressure, n	8.7 ± 2.4	10.4 ± 1.3	**0.035**
Tracheostomy, n (%)	16 (25)	2 (11.8)	0.243

CNS, central nervous system; PNS, peripheral nervous system; V-PSG, video-polysomnography; AHI, apnea–hypopnea index; CT90, percentatge of total sleep time with oxyhemoglobin saturation below 90; O2Hb, oxyhemoglobin saturation; CPAP, continuous positive airway pressure.

SDS was continuous in 42 (51.9%) and intermittent in 39 (48.1%). The mean AHI was 21.4 ± 18.6 (range, 0–73.9) and AHI > 10 was found in 52 (64.2%) subjects. The mean CT90 was 11.5 ± 19.1 (range, 0–96) (Table 1).

Overall, most apneic events were obstructive with a mean of obstructive AHI of 19.9 ± 18.1. A central apnea index >10 was found in only two (2.4%) patients. One patient with brainstem glioma involving the medulla had a central apnea index of 16.6, obstructive apnea index of 4.8, and CT90 of 0. The other patient with central sleep apnea had fatal familial insomnia with central apnea index of 50.0, obstructive apnea index of 6.5, and CT90 of 24.8.

Laryngoscopic findings

Laryngoscopy during wakefulness was performed in 72 (88.9%) subjects and showed abnormal mobility of the vocal cords in 65 (90.3%) (Table 1). Abnormal vocal cord abduction during inspiration was bilateral in 42 (64.6%) and unilateral in 23 (35.4%). Of these 65 patients with vocal cord abductor impairment, BCAR occurred in 15 (23.1%), UCAR in 11 (16.9%), BPAR in 23 (35.4%), UPAR in 12 (18.4%), and UCAR in 1 vocal cord plus UPAR in the contralateral vocal cord in 4 (6.2%) patients. Flickering movements of the arytenoid cartilage were detected in six patients (9.2%); two with bilateral flickering, two with unilateral flickering and contralateral normal mobility, and two with unilateral flickering and contralateral UCAR.

In patients who had laryngeal cancer and were treated with radiotherapy, laryngoscopy showed fibrosis and edema of the vocal cords plus abductor dysfunction (Supplementary Video 5). In one patient, laryngoscopy showed normal mobility of the vocal cords but prominent retropharyngeal cervical osteophytes that obstructed the glottic space leading to SDS (Supplementary Video 6). In another subject, laryngoscopy documented a retropharyngeal lesion that caused supraglottic airway compromise while vocal cord movements were normal. In one patient with achondroplasia, laryngoscopy showed normal vocal cord mobility but drug-induced video-endoscopy with propofol showed partial collapse of the larynx associated with stridor. Wakefulness laryngoscopy was normal in four patients with SDS (three with MSA and one with anti-IgLON5 disease) in whom drug-induced video-endoscopy was not performed. In our series, laryngoscopy did not detect a floppy epiglottis.

Stridor during wakefulness

SDS coexisted with SDW in 13 (16.0%) patients; 7 with MSA (all with the parkinsonian subtype), 1 with amyotrophic lateral sclerosis, 1 with spinocerebellar ataxia type 1, 1 after the surgical placement of vagal nerve stimulator for epilepsy, 1 secondary to orotracheal intubation, 1 due to nerve injury after thyroidectomy, and 1 with idiopathic vocal cord palsy. In these 13 patients V-PSG showed a mean AHI of 18.7 ± 15.4 and mean CT90 of 10.2 ± 12.8. SDS was continuous in 10 patients and intermittent in 3. Laryngoscopy was performed in 12 of these 13 subjects with SDW and demonstrated BCAR in 8, BPAR in 3, and UPAR in 1.

Management of stridor

CPAP was titrated in 60 (74.1%) patients. In 55 subjects, CPAP abolished both SDS and sleep-disordered breathing with a mean optimal pressure of 9.0 ± 2.3 (range, 4–13) cm H_2O (Supplementary Video 7). In three MSA patients with chronic respiratory insufficiency, bi-level positive airway pressure (BiPAP) ventilation was

needed to eliminate SDS. In two patients with MSA, CPAP decreased but could not eliminate SDS.

Tracheostomy at baseline or at follow-up was done in 19 (23.4%) subjects; 13 with MSA, 3 that received radiotherapy for laryngeal cancer, 1 with amyotrophic lateral sclerosis, 1 with anti-IgLON5 disease, and 1 with Niemann–Pick type C disease. According to bed partners report, tracheostomy abolished SDS in all patients. A total of 14 of the 19 patients that underwent tracheostomy were previously treated with CPAP (18 successfully treated and 1 unsuccessfully treated with CPAP). Reasons to perform tracheostomy were the development of SDW after SDS onset (n = 10), subacute or acute respiratory failure (n = 8), and poor adherence to CPAP (n = 1). Tracheostomy was elective in 17 patients and was performed in an urgent situation in 2 who presented to the emergency department with respiratory failure.

Unilateral posterior cordotomy with or without partial arytenoidectomy was performed in three patients who had SDS secondary to recurrent laryngeal nerve injury after thyroid surgery. These three subjects had bilateral vocal cord abductor dysfunction. According to bed partners report, laryngeal surgery abolished SDS completely in all three patients.

Discussion

To the best of our knowledge, this is the first descriptive study of consecutive adults with SDS that were identified by V-PSG in a tertiary sleep disorders center during a long period of 20 years.

Clinical findings

Like in snoring, patients were unaware of displaying SDS and this abnormality was suspected only after the report from a reliable informant. Subjects in whom SDS was an incidental finding during V-PSG lacked a bed partner. This highlights the importance in sleep medicine of performing clinical history with individuals able to provide information on sleep and the availability of audio recording in a polysomnographic study.

SDW was associated with severe laryngeal obstruction. We do not know why SDW was only observed in MSA-P and not in MSA-C. MSA-P patients needed higher CPAP pressure to control SDS than those with MSA-C despite having similar age and duration of the disease, suggesting different degrees of impairment of the brainstem in these two forms of MSA.

Associated conditions and related mechanism of stridor

We found a number of different etiologies associated with SDS. They impaired the neuronal and laryngeal structures that modulate the motility of the vocal cords, namely (1) the nucleus ambiguus in the medulla (e.g. glioma, hemorrhage located in the medulla, anti-IgLON5 disease, and fatal familial insomnia), (2) the laryngeal recurrent nerve (e.g. iatrogenic injury after cervical surgery), (3) the vocal cords themselves (edema as complication of radiotherapy and traumatic tracheal intubation), and (4) external mechanical compression of the laryngeal space (adjacent neoplasm). In MSA, the origin of laryngeal narrowing is thought to be related to hypoactivity of the abductors (due to denervation of the recurrent laryngeal nerve secondary to Wallerian degeneration caused by neuronal loss in the nucleus ambiguus) and unbalanced hyperactivation of the adductors in response to an increased upper airway resistance [17–45]. It is speculated that the same mechanism explains SDS in spinocerebellar ataxias, amyotrophyc lateral sclerosis, and Arnold–Chiari malformation with syringomyelia and other conditions of central origin [46–64]. In left vagal nerve stimulation for drug-resistant epilepsy, the mechanism underlying SDS is related to either injury of the vagal nerve during the surgical implantation of the electrodes or to excessive activation of the adductors of the left vocal cord due to excessive stimulation of the left recurrent laryngeal nerve [65–69]. In a few cases, SDS was caused by an adjacent extrinsic mass that reduced the glottic inlet (a retropharyngeal tumor and cervical osteophytes) and by increased collapsibility of the glottic cartilages (laryngomalacia associated with achondroplasia) [70–72].

The role of V-PSG

V-PSG identified SDS and distinguished its sound from others that occur during sleep such as snoring, bruxism, and catathrenia. V-PSG was useful to describe that SDS was mainly inspiratory, continuous, or intermittent in a similar proportion, and often associated with obstructive apneas and oxyhemoglobin desaturations. Central sleep apnea was much less frequent only occurring in neurological conditions that damaged the medulla (brainstem glioma and fatal familial insomnia).

The role of laryngoscopy

Laryngoscopy during wakefulness identified the cause of SDS in most of the cases showing a stenotic glottic space secondary to impaired vocal cord abduction, and more rarely to extrinsic compressive lesions or to increased intrinsic laryngeal collapsibility. In one patient with achondroplasia, laryngoscopy during wakefulness showed normal vocal cord mobility but drug-induced video-endoscopy showed partial collapse of the larynx and stridor. This situation has also been described in patients with MSA where paradoxical adduction during sleep may occur [12, 27, 30, 31].

The role of therapy

Treatment for SDS was individualized based on clinical judgment according to the nature of the underlying condition, patient's prognosis, laryngoscopic findings, and severity of obstructive sleep apnea. We used CPAP, tracheostomy, and laryngeal surgery, and all three procedures were capable to eliminate SDS and sleep-disordered breathing.

The mechanism of action of CPAP is thought to preserve the upper airway patency thereby reducing overall collapsibility. In patients with MSA, CPAP probably eliminates SDS by decreasing the paradoxical activation of the vocal cord adductors during inspiration which results from an increased upper airway pressure secondary to laryngeal narrowing [13–16, 35, 36]. In our series, CPAP was the most used therapeutic alternative and eliminated SDS in the majority of subjects. We did not detect floppy epiglottis which is a contraindication for CPAP [18–20]. In three MSA patients with chronic respiratory insufficiency, however, we needed to use BiPAP to abolish SDS, as previously described

[30]. Despite the elimination of SDS with CPAP, some MSA patients have died while sleeping, presumably due to respiratory failure of central origin or cardiac arrest related to autonomic failure [41, 42].

Tracheostomy produces immediate relief bypassing the upper airway obstruction. In MSA, tracheostomy ceases the tonic activity of the adductors during inspiration [36]. Tracheostomy requires long-term care, is linked to psychological and social problems, is often refused by the patients, and is associated with long-term complications [6]. Central apneas without important desaturations may appear after tracheostomy and CPAP [40] probably because pre-existing central apneas were unmasked after obstructive apneas were corrected [41]. We performed tracheostomy only in patients with severe occlusion of the glottis who developed SDW, respiratory insufficiency or in selected cases who could not tolerate the CPAP mask.

Laryngeal surgery enlarges a stenotic larynx [6]. Cordotomy and arytenoidectomy, though, are not recommended in individuals with dysphagia because an increased risk of aspiration [31, 43, 44]. Side effects of surgery include dysphonia, aspiration, granulation, and formation of scar tissue. In our series, three subjects with SDS secondary to thyroid surgery and bilateral vocal cord abductor dysfunction underwent posterior cordotomy (with or without subtotal arytenoidectomy) for widening the posterior area of the glottis.

Our study has several limitations. First, there is an important referral bias in our series as our sleep disorders center is part of the Neurology service in a tertiary hospital. Our institution is a referral hospital for neurodegenerative diseases, prion diseases and autoimmune disorders. This may explain why a number of patients of our series had neurological diseases, particularly MSA, anti-IgLON5 disease, and fatal familial insomnia, which are not common in the general population. Second, the design was retrospective and this implies the existence of missing data (e.g. the occurrence and intensity of SDS in different sleep stages or body positions in those in whom SDS was intermittent, the coexistence of snoring and SDS in some patients, the respiratory signs profile during V-PSG). Third, we did not provide information of the follow-up and outcome of our patients, and of the long-term efficacy of CPAP, tracheostomy, and laryngeal surgery for SDS. Fourth, in subjects that underwent tracheostomy and laryngeal surgery for SDS a second V-PSG was not performed to confirm the elimination of SDS and to determine their effect on obstructive sleep apnea and oxyhemoglobin desaturations. Finally, our study only included subjects in whom SDS was diagnosed by V-PSG. Many patients with SDW or dysphonia after neck surgery are usually not referred to a sleep center to rule out SDS. It should be noted that in some instances SDS and SDW develop acutely requiring emergency therapy to secure the airway, and these patients are not referred to undergo V-PSG before treatment. Strengths of our study are the analysis of a large sample of individuals in a long period of observation, the comprehensive characterization of SDS by V-PSG, and the performance of laryngoscopy in most of the patients.

In summary, SDS in adults is associated with conditions that damage the brainstem, recurrent laryngeal nerve and vocal cords. V-PSG is essential to document the typical sound of stridor and associated sleep-disordered breathing while laryngoscopy during wakefulness frequently shows vocal cord abductor dysfunction narrowing the glottis. CPAP, tracheostomy, and laryngeal surgery are therapeutic strategies capable to prevent SDS.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Disclosure statements

Financial disclosure: none.

Non-financial disclosure: none.

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