



Wake-Up Right-Sided Hemiparesis and Dysarthria in a Heavy Snorer

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CASE PRESENTATION: A 57-year-old man was referred to the ED for wake-up right-sided hemiparesis, hypoesthesia, dysarthria, and a National Institutes of Health Stroke Scale score of 7. Urgent CT brain scanning showed an ischemic lesion of the left temporal and insular lobes. The patient was admitted to the stroke unit, and acetylsalicylic acid 300 mg and low-molecular-weight heparin 6,000 IU were administered. CHEST 2018; 153(1):e13-e17

Physical Examination Findings

The patient was obese (BMI, 39.45 kg/m²) and a heavy snorer; he reported two previous episodes of thrombophlebitis of the lower limbs (12 years and 5 months, respectively, before the current admission). The family medical history was suggestive for thrombophilia: The patient's father and nephew died of pulmonary embolisms, and his sister had recurrent episodes of DVT. Three days after admission, the patient had syncope associated with severe bradycardia, dyspnea, and severe hemoglobin desaturation, suggestive of a pulmonary embolism.

Diagnostic Studies

CT brain imaging and CT angiography (on day 2 after the onset of symptoms) confirmed ischemic stroke and did not identify arterial occlusions. Urgent pulmonary CT angiography revealed subtotal occlusion of both pulmonary arteries (Fig 1).

Venous Doppler ultrasonography of the lower limbs showed bilateral DVT extending to the common femoral veins. Transcranial Doppler ultrasonography showed microembolic signals at rest (Spencer grade 1/2), which

markedly increased after a Valsalva maneuver (grade 5). The presence of a patent foramen ovale (PFO) was further confirmed by transesophageal echocardiography. At transthoracic echocardiography, the left ventricular ejection fraction was 62% and the left ventricular telediastolic diameter was 57 mm. Both right ventricular function (tricuspid annular plane systolic excursion, 26 mm) and dimensions were normal.

Polysomnography (PSG) on day 15 showed snoring and prolonged apnea associated with hemoglobin desaturation events, consistent with severe OSA. Detailed PSG results are shown in Table 1. A 5-min recording of the patient's polysomnogram is shown in Figure 2.

Screening for thrombophilia showed a deficit of antithrombin III (ATIII) (55% normal range 70-140).

Analysis of the antithrombin III gene (AT3) showed a heterozygous mutation in exon 4, which converts tryptophan in a stop codon at position 307. Brain MRI could not be performed, because the patient was claustrophobic. An extended autoimmune screening test and 24-hour Holter ECG monitoring were unremarkable.

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DOI: <http://dx.doi.org/10.1016/j.chest.2017.08.006>

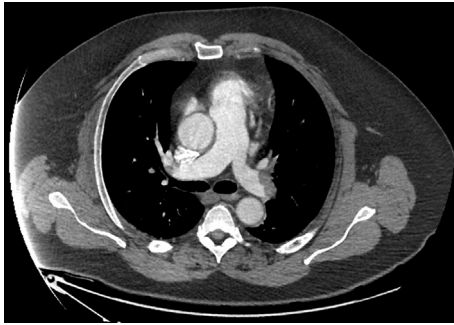


Figure 1 – Pulmonary CT angiography shows subtotal occlusion of both pulmonary arteries.

TABLE 1] Detailed PSG Results at Baseline and During CPAP Treatment

Sleep Macrostructure	Baseline	CPAP
TIB, min	414.0	412.5
Total sleep time, min	397.0	382.5
SPT, min	406.5	403.0
Sleep efficiency on SPT, %	97.5	94.9
Sleep efficiency on TIB, %	95.9	92.7
Sleep onset latency, min	7.0	6.5
REM/SPT, %	12.8	25.6
Stage 1/SPT, %	8.2	6.3
Stage 2/SPT, %	68.3	50.7
Stage 3/SPT, %	8.2	12.3
Wake/SPT, %	2.5	5.1
Awakenings, No.	2.0	7.0
Wake after sleep onset, min	10.5	23.5
Respiratory events		
Central AHI	1.2	3.0
Obstructive-mixed AHI	71.2	6.5
NREM AHI	75.0	3.2
REM AHI	64.6	8.2
Nonsupine AHI	67.3	2.8
Supine AHI	78.1	14.3
Longest obstructive apnea, s	66.4	15.3
ODI	73.6	4.7
t90, %	46.8	8.7
Awake SpO ₂ , %	95.0	95.0
Lowest SpO ₂ , %	79.4	84.0

AHI = apnea-hypoxia index; NREM = non-rapid eye movement; ODI = oxygen desaturation index; PSG = polysomnography; REM = rapid eye movement; SpO₂ = oxygen saturation; SPT = sleep period time; TIB = time in bed; t90 = percentage of sleep with hemoglobin saturation < 90%.

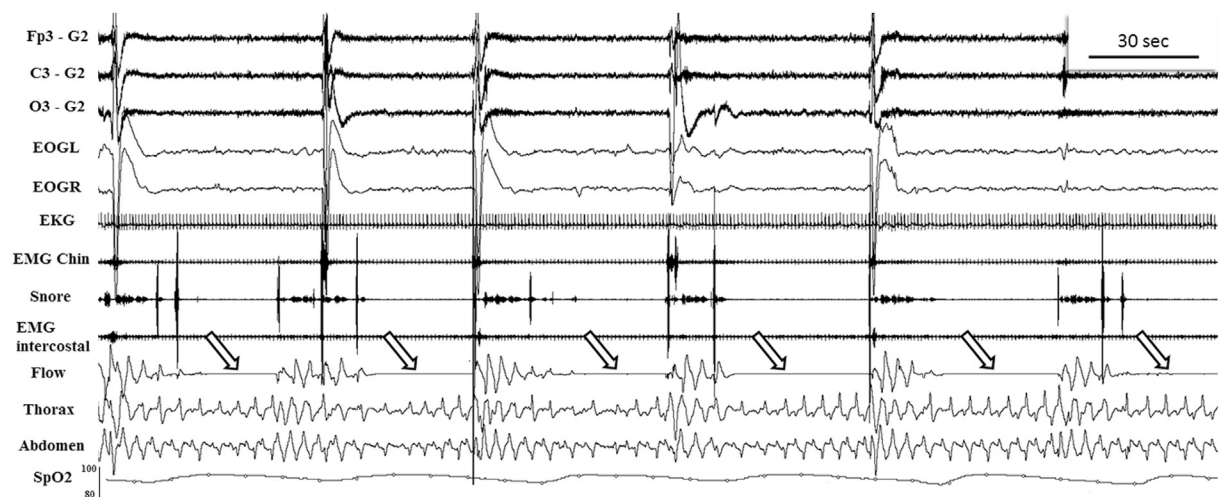


Figure 2 – Five-min polysomnography recording showing periodic obstructive apneas. ECG = electrocardiogram; EMG = electromyography; EMG Chin = electromyography recorded from submental muscle; EOGL = left electrooculogram; EOGR = right electrooculogram; SpO₂ = oxygen saturation.

What is the diagnosis?

What three mechanisms contributed to his stroke?

How could untreated OSA influence flow across a PFO?

Diagnosis: Ischemic stroke and pulmonary embolism in a patient with PFO, ATIII deficiency, and OSA.

The combination of PFO, ATIII deficiency, and OSA concurred in the etiopathogenesis of the ischemic stroke in the patient. ATIII deficiency was responsible for the DVT.

During sleep, prolonged obstructive apneas induced the Valsalva and Müller maneuvers, which in turn caused an increase of pressure in the right atrium and a massive right to left shunt across the PFO, resulting in paradoxical embolism and ischemic stroke

Discussion

PFO is a remnant of the fetal foramen ovale, a hole in the interatrial septum, that allows blood to bypass the pulmonary circulation, because fetal lungs do not participate in oxygen exchange. At birth, as the lungs begin working, pulmonary vascular resistance drops, and there is a reversal of blood flow through the foramen ovale as it closes. In about 25% of people it stays open as a PFO.

PFO has a high prevalence in cryptogenic stroke, especially in younger patients. Moreover, patients with PFO and previous cryptogenic ischemic stroke are at risk for recurrence of cerebrovascular events. It is important to remark that patients with a PFO who have not had a previous stroke do not have increased cerebrovascular risk compared with the general population. Results on these studies are still controversial.

The most recent guidelines from the American Heart Association/American Stroke Association on PFO management, recommend:

1. Antiplatelet therapy for patients with ischemic stroke or transient ischemic attack (TIA) and PFO (*Class I; Level of Evidence B*)
2. Anticoagulation for patients with ischemic stroke or TIA and both an PFO and a venous source of embolism, depending on stroke characteristics (*Class I; Level of Evidence A*)
3. For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence of DVT, available data do not support a benefit for PFO closure (*Class III; Level of Evidence A*)
4. PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (*Class IIb; Level of Evidence C*)

The most widely accepted mechanism of PFO-related stroke being considered is the paradoxical embolism. A massive right to left shunt across a PFO is normally prevented by the higher pressures in the left-sided heart chambers; all conditions that increase pressure in the right side of the heart exceeding left atrial pressure (such as coughing, exercise, heavy lifting, Valsalva maneuvers) determine a right to left shunt, causing paradoxical embolism through a PFO. OSA is one of the conditions in which pressure can rise in the right-sided chambers.

In fact, during obstructive apneas, patients breathe against resistance, thus performing Müller and Valsalva maneuvers. Direct evidence of the occurrence of a right to left shunt during OSA has been provided by Beelke et al. On transcranial Doppler ultrasonography, these authors observed that right to left shunting was present in nine of 10 patients and appeared during obstructive apneas longer than 17 s. The number of microembolic signals detected during apneas was directly related to the number detected during Valsalva maneuvers in wakefulness. In a large cohort of 100 patients, Guchlerner et al. observed that the prevalence of PFO is high in OSA and that right to left shunting occurs frequently in these patients.

On these grounds, it could be hypothesized that OSA contributes to the reopening of a patent, but formerly closed, foramen. The repeated transient episodes of hypoxemia caused by OSA cause pulmonary vasoconstriction and eventually pulmonary hypertension. The result is a permanent increase in right-sided cardiac pressures and in turn an increased risk of paradoxical embolism. An Italian multicenter trial (DARIA [Detection of Sleep Apnea as Risk Factor in Acute Stroke]) evaluated the association among OSA, PFO, and wake-up cerebrovascular accidents (stroke and TIA). The results of this study suggested that even single long-lasting (20 s or more) obstructive events can facilitate a right to left shunt and that the combination of long episodes of apnea and PFO could be a risk factor for cerebrovascular ischemic events. More recently, Siarnik et al reported that wake-up stroke is associated with higher apnea/hypopnea and desaturation indexes.

The suspicion of paradoxical embolism also implies a venous source. ATIII is a natural anticoagulant. It is a serine protease inhibitor, acting on factor IIa, factor Xa, and other serine proteases in the coagulation cascade. Deficiency of ATIII can be inherited or acquired. Inheritance of ATIII deficiency is in an autosomal dominant fashion with variable penetrance. The resulting phenotypes are divided into type I and type II deficiencies, corresponding to reduced levels of ATIII

antigen and activity or to functionally defective ATIII presenting at normal levels, respectively. In the patient, there was a type I phenotype caused by a single base substitution (mutation) in exon 4 that determined a deficiency of ATIII. This deficiency is associated with an increased risk of DVT and pulmonary embolism; arterial thrombosis has been reported but is not characteristic of ATIII deficiency.

Clinical Course

The patient was treated with IV heparin and ATIII replacement (50 IU/kg), because heparin is an indirect inhibitor of thrombin and factor Xa and requires adequate levels of circulating ATIII to be effective. When heparin was replaced with an oral anticoagulant, ATIII implementation was interrupted. Oral anticoagulation (target international normalized ratio, 2.5; range, 2.0-3.0) and CPAP (10 cm H₂O) were initiated, and percutaneous closure of the PFO was performed. Detailed PSG results during CPAP treatment are shown in Table 1. The patient progressively recovered, and at discharge on day 25, the National Institutes of Health Stroke Scale score was 0.

In conclusion, the combination of these three risk factors concurred in the etiopathogenesis of ischemic stroke in the patient: ATIII deficiency was responsible for DVT; during sleep, prolonged sleep apnea induced a massive right to left shunt across the PFO, and this in turn resulted in paradoxical embolism and ischemic stroke. This pathogenic mechanism suggested a peculiar therapeutic strategy, consisting of a combination of anticoagulation treatment, nocturnal positive-pressure ventilation, and surgical closure of the PFO.

Clinical Pearls

1. OSA is a well-known risk factor for stroke and has a high prevalence in stroke; in particular, OSA is associated with wake-up cerebrovascular events.
2. OSA can induce paradoxical embolism in patients with PFO because obstructive apneas can increase right atrial pressure and facilitate right to left shunting.
3. PFO alone is not a risk factor for ischemic stroke. Instead the risk of ischemic stroke is increased in patients with PFO and a previous cryptogenic stroke. The

paradoxical embolism is the most reliable mechanism but probably not the only one.

4. The best medical treatment for secondary prevention in patients with PFO and ischemic stroke is antiplatelet therapy. Anticoagulation can be taken into consideration when there is a venous source of the embolism, depending on the stroke characteristics. PFO closure has to be taken into consideration when there is a high risk of recurrence of DVT.

Acknowledgments

Author contributions: V. B. contributed to the study concept and design, drafting of the manuscript, and interpretation of data and accepts responsibility for the conduct of research and acquisition of data. M. A. N. F., C. V., and A. D. contributed to the interpretation of data and accept responsibility for the conduct of research and acquisition of data. G. D. M. contributed to the interpretation of data and accepts responsibility for the conduct of research, study supervision, revising the manuscript, and final approval.

Financial/nonfinancial disclosures: None declared.

Other contributions: CHEST worked with the authors to ensure that the Journal policies on patient consent to report information were met. The patient's mother (in consultation with the patient) consented to the publication of this Clinical Pearl.

Suggested Readings

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