doi: http://dx.doi.org/10.11606/issn.1679-9836.v100i3p294-298 Rev Med (São Paulo). 2021 May-June;100(3):294-8.

Sleep hyperhidrosis associated with obstructive sleep apnea in the context of systemic lupus erythematosus - case report

Hiperidrose do sono associada à apneia obstrutiva do sono em paciente portadora de lúpus eritematoso sistêmico - relato de caso

Farley Carvalho Araújo[1], Fabiana Souza Máximo Pereira[2], Tainá Giovanna Batista Brandes[3]

Araújo FC, Pereira FSM, Brandes TGB. Sleep hyperhidrosis associated with obstructive sleep apnea in the context of systemic lupus erythematosus - case report / *Hiperidrose do sono associada à apneia obstrutiva do sono em paciente portadora de lúpus eritematoso sistêmico: relato de caso*. Rev Med (São Paulo). 2021 May-June;100(3):294-8.

ABSTRACT: This is an 81-year-old patient referred to a rheumatologist due to positive ANA in addition to intense night sweating and nighttime awakenings throughout a period of four months, as well as non-restorative sleep, fatigue and excessive daytime sleepiness, hyporexia and significant weight loss (19,8 pounds during the referred period). Tests were requested to exclude more serious causes, such as lymphoma, tuberculosis and pheochromocytoma. In addition, polysomnography was requested, which showed a severe apnea hypopnea index due to obstructive events (AHI = 45.2/ hour), an increased rate of awakenings (awakening index = 27.9/ hour) and oxyhemoglobin desaturation associated with respiratory events with a minimum saturation of 84% and the presence of snoring, therefore compatible with severe obstructive sleep apnea syndrome. Furthermore, it is important to note that during subsequent consultations the patient was also identified as having Systemic Lupus Erythematosus (SLE). Night hyperhidrosis, a clinical condition characterized by exacerbated and unregulated sweat production that interferes with sleep quality, is correlated with obstructive sleep apnea syndrome (OSAS), when untreated, is responsible for an increase in sympathetic activity that affects sleep and awakening, in a feedback loop. The first condition, SLE, little discussed in literature, has its diagnosis dependent on clinical suspicion and the recognition of possible secondary causes. The SAOS treatment proposal for the patient was the introduction of positive airway pressure treatment, with a nasal mask, in addition to conservative measures. The treatment for SLE was also instituted. In two months, the patient has been able to present control of that disease and of the hyperhidrosis, as well as the night symptoms associated with SAOS.

Keywords: Hyperhidrosis; Sleep apnea, obstructive; Lupus Erythematosus, Systemic.

RESUMO: Trata-se de uma paciente de 81 anos encaminhada ao reumatologista em função de sudorese noturna intensa há 04 meses associada a despertares noturnos, assim como sono não restaurador, fadiga e sonolência excessiva diurna, hiporexia e perda ponderal importante (09 quilos no período referido) além de positividade do FAN. Em consulta, levando-se em conta as principais hipóteses diagnósticas de hiperidrose noturna e síndrome da apneia obstrutiva do sono, foram solicitados exames para exclusão de causas mais graves, como linfoma, tuberculose e feocromocitoma. Ademais, foi solicitada polissonografia que evidenciou aumento severo do índice de apneia-hipopneia às custas de eventos obstrutivos (IAH = 45,2 eventos/hora), índice de despertares aumentado (Índice de despertar = 27,9/ hora) e dessaturação da oxi-hemoglobina associada aos eventos respiratórios com saturação mínima de 84% e presença de roncos, por conseguinte compatível com síndrome da apneia obstrutiva do sono de grau grave. Outrossim, faz-se importante ressaltar que durante consultas posteriores a paciente também foi identificada como portadora de Lúpus Eritematoso Sistêmico (LES). Correlaciona-se, portanto, a hiperidrose noturna, condição clínica caracterizada pela produção exacerbada e desregulada do suor que interfere na qualidade do sono, com a síndrome da apneia obstrutiva do sono (SAOS), responsável, quando não tratada, por um aumento da atividade simpática que afeta o sono e o despertar, em um ciclo retroalimentativo. A primeira condição, pouco discutida no meio médico, tem seu diagnóstico dependente da suspeita clínica e do reconhecimento de possíveis causas secundárias. A proposta de tratamento para a paciente foi a terapia com pressão positiva, além de medidas conservadoras. O tratamento para o Lúpus Eritematoso Sistêmico (LES) também foi instituído. Em dois meses, a paciente passou a apresentar controle do quadro lúpico e da hiperidrose noturna, assim como dos sintomas noturnos associados ao quadro de SAOS.

Descritores: Hiperidrose; Apneia obstrutiva do sono; Lúpus Eritematoso Sistêmico.

1. Rheumatologist, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Faculdade de Medicina. ORCID: https://orcid.org/0000-0003-4679-323X. E-mail: farleycarvalhomed@hotmail.com
2. Geriatric medicine, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Faculdade de Medicina. ORCID: https://orcid.org/0000-0002-5279-7643. E-mail: fabiana.geriatria@gmail.com
3. Medical student, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Faculdade de Medicina. ORCID: https://orcid.org/0000-0003-4660-9658 E-mail: brandestaina@gmail.com

Correspondence: Tainá Giovanna Batista Brandes. Rua do Amparo, 235, Centro. Diamantina, MG, Brasil.

INTRODUCTION

Sleep hyperhidrosis is an entity not fully explained and open to many interpretations. In addition, it is a subject little discussed in medical courses and among health professionals, despite being a common concern both in primary care and in specialized offices. Hyperhidrosis is a condition that includes a deregulation in the production of suor, due to dysfunctions in the autonomic sympathetic nervous system, in the muscarinic receptors in the exocrine glands - responsible for controlling the reaction to emotions - or for secondary reasons, systemic conditions such as pregnancy, menopause, tuberculosis, HIV, lymphomas and other malignancies, endocrinopathies, psychic disorders and medications that can contribute to the hormonal and neuronal imbalance of the body[1].

This article connects a condition of nighttime hyperhidrosis with obstructive sleep apnea syndrome, which for the American Academy of Sleep Medicine can be understood as a disorder where recurrent episodes

of upper airway obstruction occur for more than 10 seconds therefore resulting in micro-awakenings with negative interaction in neurocognitive and psychosocial functions, generating impairments in mood, memory, concentration and causing fatigue and drowsiness throughout the day[2].In this situation, it is essential, in addition to the clinical history and physical examination, to perform polysomnography, which provides useful information about abnormal respiratory events and their impact on sleep stages. In addition, systemic lupus erythematosus is the condition responsible for the increase in cytokines and inflammatory markers that interacts helping to increase the prevalence of OSAS, in an integrated feedback chain that contributes a lot to the appearing of nocturnal symptoms, such as hyperhidrosis.

CASE REPORT

MCAP, 81, retired and widow. In follow-up with a geriatrician, she was referred to the rheumatologist due to a positive ANA and a history of night sweats beginning four months ago, hyporexia, prostration, reduced appetite and loss of 19,8 pounds in this period. She reports that sweating occurs when she sleeps and it is important to the point of soaking the sheets during the night. She has nightmares with nighttime awakenings, a period when she even checks her temperature, but denies fever at any time. She sleeps with the lights on, refers fear of dying and being alone. In addition, she reports non-restorative sleep that results in intense fatigue and daytime sleepiness. She performs follow-up with a psychiatrist. Preserved intestinal and urinary habits.

In use of: Venlafaxine 75mg/day, Amlodipine 5mg/day, Quetiapine 100mg/day, Glucophage XR 850mg/day, Losartan 50mg/day and vitamin D 7000 IU/week.

Obstetric and gynecologic history: G4P4A0, uneventful pregnancies and deliveries. Previous myomectomy and partial hysterectomy.

Initial exams brought for consultation: Hb 11,4; MCV 84; WBC 5040; Platelet count 244.000; RPTU 0,28; CRP 48; Calcium (serum) 8,9; Cr 0,81; Urea 38; ALP 198; GGT 19; glucose levels: 151; AST 17; ALT 9; potassium 4,8; sodium 136; fecal occult blood test - negative; urine sodium:89; T4L 1,16; TSH 2,42; HBA1C 5,7; CA125 17,27; CEA 1,44; B12 278; Vitamin D 33; positive ANA.

Clinical examination: The patient was hydrated, anicteric and acyanotic. Malar erythema on inspection. Blood pressure: 130/80. Heart rate: 72. Respiratory rate: 13. Cardiac auscultation: Aortic heart murmur. Normal respiratory sounds. Normal bowel sounds. Left wrist deformities (possible fracture sequelae); limitation to the range of motion of the shoulder (previous report of tendon rupture).

The following diagnostic hypotheses were suggested: secondary sleep hyperhidrosis, Obstructive Sleep Apnea Syndrome and Systemic Lupus Erythematosus. In order to discard most serious differential diagnoses - tuberculosis, lymphoma and pheochromocytoma - several tests were requested.

The exams that drew attention, brought in later medical appointment, were the following: ESR 56, Cr 0.84, 24 hour urine protein 282, protein/creatinine ratio in 24 hour urine protein 0,63, anti-RNP, Anti-SM, Anti-Ro/SSA, Anti-La/SSB and IgG and IgM anticardiolipin antibodies negative, B2 microglobulin antibodies 4,4 (normal levels: 0,61-2,17), complement C3 110 and C4 28,8, ANA NH 1/1280 ANTI-DNA 1/40 (CRITHIDIA ELIS 2,2 - positive if >1,0). Urinary metanephrines were also requested to search for possible pheochromocytoma, which came within normal reference values.

The patient in question also brought polysomnography, an exam considered the gold standard for confirming the diagnosis of OSAS, which showed: Latency for sleep of 27 minutes and latency for REM sleep of 349 minutes. The total sleep time was 513.5 minutes, with sleep efficiency of 79.1%. The exam started at 20:14:04 hours and ended at 07:00:59 hours and the distribution of the sleep stages showed:

Table 1 - Sleep stages found and predicted for the patient in question

Sleep Stage	% found	% foreseen
Stage 1	7,4%	Until 5%
Stage 2	72,8%	45-55%
Stage 3	9,5%	>15%
REM sleep	10,2%	20-25%
Sleep efficiency	79,1%	>85%

During the total sleep period, she remained awake for 135.5 minutes and there were 239 micro-awakenings (index of 27.9 / hour). There were 387 respiratory events, 0 central, 387 obstructive and 0 mixed. The total apnea / hypopnea index was 45.2 events / hour, with 13.8 apnea / hour and 31.4 hypopnea / hour. The apnea / hypopnea index in REM sleep was 11.4 / hour, with 2.3 apnea / hour and 9.1 hypopnea / hour. The rate of respiratory disturbance was 45.2 / hour. The baseline saturation of oxyhemoglobin was 93%, with an average saturation of 92%, the highest of 99% and the minimum of 84%, remaining 17.0 minutes (2.6%) of record with saturation below 90% and 0.0 minutes (0.0%) with saturation below 80%. There were 311 desaturations. The classification of the severity of the condition is generally based on the apnea-hypopnea index (AHI), which would be the sum of apneas and hypopneas divided by the number of hours of sleep. The severity classification is established by means of the AHI: Mild OSAS - AHI 5-14.9; Moderate OSAS - AHI 15 29.9; Severe OSAS - AHI> 30. Thus, the polysomnographic examination was compatible with severe obstructive sleep apnea syndrome.

Table 2 - Distribution of respiratory events and association with micro-arousals and desaturation

Events	Quantity	(Index/ hour)	Average (Seconds)	Major (Seconds)	With micro-awakening	With desaturation	With micro-awakening and desaturation
Apnea	118	13,8	14,9	25,8	51	95	42
Obstructive	118	13,8	14,9	25,8	51	95	42
Central	0	0,0	0.0	0,0	0	0	0
Mixed	0	0,0	0,0	0,0	0	0	0
Hypopnea	269	31,4	23,0	50,9	166	172	85
Total	387	45,2	20,5	50,9	217	267	127
RERA	0	0,0	0,0	0,0	0	0	0
IDR	387	45,2	20,5	50,9	217	267	127

Events	REM Quantity	REM (Index/hour)	NREM Quantity	NREM (Index/hour)
Apnea	2	2,3	116	15,1
Obstructive	2	2,3	116	15,1
Central	0	0,0	0	0,0
Mixed	0	0,0	0	0.0
Hypopnea	8	9,1	261	34,0
Total	10	11,4	377	49,1
RERA	0	0,0	0	0,0
IDR	10	11,4	377	49,1

Therefore, the main diagnostic hypotheses for this patient are: Systemic Lupus Erythematosus (ANA positive, Anti-DNA positive, P / C ratio 24 hours 0.6, anti beta-2-microglobulin and elevated ESR, acute skin lesion malar erythema) and severe obstructive sleep apnea-hypopnea syndrome associated with nocturnal hyperhidrosis.

Accordingly to this, treatment for systemic lupus erythematosus was instituted with hydroxychloroquine and

prednisone 20mg per day. The patient also started using CPAP at night to sleep associated with behavioral measures: sleep hygiene and the adoption of lateral decubitus position when sleeping.

In a return appointment, two months after the measures were taken, there was a report and evidence of improvement in nocturnal hyperhidrosis, fatigue and daytime sleepiness, as well as malar erythema.

DISCUSSION

Hyperhidrosis has multiple definitions, but in theory it can be synthesized as a deregulation in the production of sweat at a specific moment. In addition to having a range of precedent causes, it clinically draws attention when it impacts the patient's functionality, causing emotional, social and physical consequences, directly affecting the individual's quality of life. Other factors that permeate this theme and require focus: the lack of knowledge or awareness of the subject by health professionals, as well as inconsistent methodologies used in its diagnosis and in epidemiological studies.

Hyperhidrosis is a condition that can be divided into primary, resulting from a dysfunction in the autonomic sympathetic nervous system, which participates in thermoregulation, taking signals from the cortex / hypothalamus control center to the efferent sympathetic nerve fibers that, dysfunctional, overactivate through their muscarinic receptors the glands exocrine responsible for sweat.

Another hypothesis points out that there may be a lack of control in the patient's center of emotions, commanded by the limbic system, hypothalamus and the frontal part of the cingulate cortex, responsible for controlling the reactional sweat to emotions, which occurs primarily in the armpits, palms and soles of the feet and scalp. There seems to be an interference from the thermoregulatory system and its cholinergic sympathetic nerve fibers, increasing the amount of sweat produced.

Primary hyperhidrosis is usually focal, bilateral and symmetrical, typically affecting the armpits, hands, feet and regions of the face. It can be induced by climatic changes, emotional or physical activities. Secondary hyperhidrosis, on the other hand, refers to a condition associated with a specific cause, whether due to physiological, pathological conditions or the use of medications. It is usually widespread and less common than the primary. Possible causes are: fever, pregnancy, menopause, malignancies such as lymphoma and other myeloproliferative disorders, infections, such as tuberculosis and HIV, endocrinopathies, such as diabetes mellitus and pheochromocytoma, psychiatric disorders, among others. Some drugs associated with secondary hyperhidrosis include tricyclic antidepressants, serotonin reuptake inhibitors and antivirals, such as acyclovir. It is also worth remembering that secondary hyperhidrosis can be focal, when caused by peripheral neuropathies and spinal cord injuries[3,4,5].

The clinical history should be investigated and is usually sufficient to differentiate both definitions. It is important to exclude secondary causes before primary hyperhidrosis can be diagnosed. Therefore, it is an essential part of the anamnesis to ask about the sweat pattern, duration and frequency, and any symptoms that point to secondary causes. Type B symptoms, such as weight loss, fever, and lymphadenopathy, can raise suspicions of secondary causes.

Normally, laboratory tests are not required, however, they can be used when secondary causes are suspected. In this situation, screening is recommended, with a complete blood count, white blood cell count, hepatogram, thyroid test, serum metanephrines (pheochromocytoma) and a chest X-ray, in order to cover the main hypotheses of secondary hyperhidrosis.

Some findings that increase the suspicion of secondary hyperhidrosis are found in the generalized, asymmetric, unilateral distribution, beginning after 25 years of age, negative family history and nocturnal symptoms.

An addendum to be made concerns to the correlation between nocturnal hyperhidrosis and sleep quality. Furthermore, it is pointed out as another cause of secondary hyperhidrosis, obstructive sleep apnea, which, untreated, presents an expressive, pathophysiological increase in sympathetic activity, which affects sleep and awakening. Individuals with nocturnal hyperhidrosis usually complain of daytime tiredness and insomnia. A variable pointed out in the literature shows that patients with a poor quality of sleep are more likely to have nighttime awakenings and notice that they are sweating, and therefore, they are more likely to report such symptom. Sleep disorders and night sweats may be associated with a third factor in question, such as anxiety, depression and medication use, that can worsen hyperhidrosis, resulting in a cycle that is activated through its own components[6].

The patient in question, although she used serotonin and norepinephrine reuptake inhibitors, reported that the symptoms started before the medication. She presented obstructive sleep apnea on polysomnography and insomnia, which alone may be responsible for nocturnal hyperhidrosis[7]. She was also diagnosed with a rheumatological autoimmune disease, systemic lupus erythematosus, whose association with sleep disorders has been studied as a marker of disease activity. There is a bidirectional relationship between sleep disorders, pain and fatigue in rheumatological diseases. Changes in the regulation of cytokines and inflammatory markers are pointed out as having important roles in the context of sleep disorders. Sleep apnea appears to be present in 26-50% of patients with lupus. In short, sleep disorders are present in

more than half of the patients who have lupus, with a higher prevalence than in the general population[8].

In the study by Iaboni et al.[9], a pattern of poor sleep quality was demonstrated through polysomnography, which showed deficits in non-REM sleep, high excitatory frequency during sleep and high levels of alpha waves in the electroencephalogram compared to healthy individuals, which was comparable to the non-restorative sleep pattern of patients with fibromyalgia.

Psychological and social factors, particularly depression, are suggested as one of the main causes of sleep disorders in SLE. Active disease itself is associated with reduced sleep quality and increased fragmented sleep, pain and fatigue, as shown by Grenwood, Lederman and Lindner[10]. In an additive way, Baglioni and Riemann[11] shows that sleep deprivation impacts cytokines and the inflammation process, as it is linked to a reduction in the proportion of natural killer cells and IL-2, while increasing the levels of inflammatory cytokines such as IL -6 and TNF in the morning.

CONCLUSION

We report a case of sleep hyperhidrosis related to obstructive sleep apnea and SLE. There seems to be a strict association between hyperhidrosis, sleep disorders and rheumatological diseases, and further studies on the topic are needed. These disorders, as well as treatments, can affect patients' quality of life and should be carefully evaluated in clinical practice. The development of evidence-based guidelines is necessary to better understand the problem and improve the diagnosis of hyperhidrosis, as well as more complete and longitudinal studies should be proposed for better definition of the issue, in addition to more definitive evidence.

Conflicts of interest: All authors declare no conflicts of interest.

Authors participation: *Farley Carvalho Araújo* - Responsible for the outpatient care of the patient reported in the case and for the review of the article; *Fabiana Souza Máximo Pereira* - Responsible for the outpatient care of the patient reported in the case and for the review of the article; *Tainá Giovanna Batista Brandes* - Responsible for carrying out the bibliographic review of the case, write the report and submit it for publication.

REFERENCES

1. Rystedt A, Brismar K, Aquilonius SM, Naver H, Swartling C. Hyperhidrosis: an unknown widespread "silent" disorder. J Neurol Neuromed. 2016;1:4:25-33. https://doi.org/10.29245/2572.942x/2016/4.1037_
2. Silva GA, Sander HH, Eckeli Al, Fernandes RMF, Coelho EB, Nobre F. Conceitos básicos sobre síndrome da apneia obstrutiva do sono. Rev Bras Hipertens. 2009. 2009:150-7. Disponível em: http://departamentos.cardiol.br/dha/revista/16-3/05-conceitos.pdf
3. Hasimoto FN. Radiofrequência no tratamento da hiperidrose primária. Revisão sistemática [tese]. Botucatu: Universidade Estadual Paulista Júlio de Mesquita Filho, Faculdade de Medicina de Botucatu; 2017.
4. Lee JH, Kim DW, Sim WS. Lumbar sympathetic radiofrequency thermocoagulation using bipolar probe in the hyperhidrosis patient: a case report. Korean J Pain. 2005;18:92-5. doi: 10.3344/kjp.2005.18.1.92.
5. Haider A, Solish N. Focal hyperhidrosis: diagnosis and management. Can Med Assoc J. 2005;172:69-75. doi: https://doi.org/10.1503/cmaj.1040708.
6. Mold JW, Holtzclaw BJ, McCarthy L. Night sweats: a systematic review of the literature. J Am Board Fam Med. 2012;25:878-93. doi: 10.3122/jabfm.2012.06.120033.
7. Arnardottir ES, Janson C, Bjornsdottir E, Benediktsdottir B, Juliusson S, Kuna ST, Pack AI, Gislason T, et al. Nocturnal sweating: a common symptom of obstructive sleep apnoea: the Icelandic sleep apnea cohort. BMJ Open .2013;3:e002795. doi: 10.1136/bmjopen-2013-002795.
8. Palagini L, Tani C, Mauri M, Carli L, Vagnani S, Bombardieri S, Gemignani A, Mosca M. Sleep disorders and systemic lupus erythematosus. Lupus. 2014;23:115-23. doi: 10.1177/0961203313518623 8.
9. Iaboni A, Ibanez D, Gladman DD, Urowitz MB, Moldofsky H. Fatigue in systemic lupus erythematosus: contributions of disordered sleep, sleepiness, and depression. J Rheumatol. 2006;33:2453-7. Available from: https://pubmed.ncbi.nlm.nih.gov/17143980/.
10. Greenwood KM, Lederman L, Lindner HD. Self-reported sleep in systemic lupus erythematosus. Clin Rheumatol. 2008;27:1147-51. doi: 10.1007/s10067-008-0884-2.
11. Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. Curr Psych Rep. 2012;14:511-8. doi: 10.1007/s11920-012-0308-5.

Submetido:
Aceito: