OBSTRUCTIVE SLEEP APNEA MANIFESTED AS AN ATYPICAL MAJOR DEPRESSIVE DISORDER: A CASE REPORT AND REVIEW OF THE LITERATURE

Rui Lopes¹, Jacinto Azevedo¹,², Rosário Curral¹,², Manuel Esteves¹,², Rui Coelho¹,², António Roma-Torres¹

ABSTRACT

BACKGROUND: Sleep disorders can be related to loss, disruption or inappropriate day-night rhythm of sleep and represent a great economic burden, involving morbidity and mortality. The insomnia or hypersomnia, secondary to a psychiatric disorder such as depression or psychosis, is frequent in psychiatric practice. Moreover, although uncommon, primary sleep disorders can also cause psychological or psychiatric problems, with some interdependence, which is not completely understood.

CASE PRESENTATION: A 48-year-old woman presented atypical depressive symptoms resistant to antidepressants. In this atypical state, she also showed excessive daytime sleepiness (EDS), snoring, daytime naps and cognitive symptoms. After a sleep study with polysomnography, an obstructive sleep apnea (OSA) manifested as atypical depression was diagnosed. Remission of depressive symptoms was verified with additional continuous positive airway pressure (CPAP) therapy.

CONCLUSION: The awareness that OSA could be presented as an atypical depression allows its early detection and treatment, and possibly the prevention of numerous medical disorders. Psychiatrists and General Practitioners should be familiar with sleep disorders and psychiatric co-morbidities.

KEY-WORDS: SLEEP DISORDERS, OBSTRUCTIVE SLEEP APNEA, DISORDERS OF EXCESSIVE SOMNOLENCE, DEPRESSION, MENTAL DISORDERS

APNEIA OBSTRUTIVA DO SONO MANIFESTADA COMO EPISÔDIO DEPRESSIVO ATÍPICO: UM CASO CLÍNICO E REVISÃO DA LITERATURA

RESUMO

CONTEXTO: As perturbações do sono podem estar relacionadas com a perda, desregulação ou inadequação do ritmo do ciclo sono-vigília, traduzindo-se em consequências econômicas importantes a nível de morbidade e mortalidade. A insônia ou hiperinsônia secundárias a uma doença psiquiátrica, como a depressão ou a psicose, são frequentes na prática clínica em psiquiatria. Por outro lado, e embora incomum, as perturbações do sono primárias também podem originar problemas psicológicos ou psiquiátricos, numa interdependência ainda não totalmente esclarecida.

CASO CLÍNICO: Mulher de 48 anos apresenta sintomatologia depressiva atípica resistentes a antidepresivos, acompanhada por sonolência excessiva diurna, ressonar (roncopatia), adormecimentos diurnos e sintomas cognitivos. Após a realização de estudo do sono com polissonografia foi diagnosticado apneia obstrutiva do sono (AOS) manifestada como depressão atípica. A instituição adicional de terapia por pressão positiva contínua nas vias aéreas (continuous positive airway pressure, CPAP) originou a remissão dos sintomas depressivos.

CONCLUSÃO: A sensibilização para a apresentação da AOS como depressão atípica permite a sua detecção e tratamento precoces e, possivelmente, a prevenção de várias condições médicas. Os Psiquiatras e Médicos de Família devem estar familiarizados com as perturbações do sono e comorbidades psiquiátricas.

PALAVRAS-CHAVE: PERTURBAÇÕES DO SONO, APNEIA OBSTRUTIVA DO SONO, PERTURBAÇÕES DO SONO POR SONOLÊNCIA EXCESSIVA, DEPRESSÃO, PERTURBAÇÕES MENTais

BACKGROUND

There is an inherent need for sleep recognized in almost every mammal and humans spend almost one third of their life sleeping. This normal yet altered state of consciousness is defined by a complex physiologic pattern of sleep phases.¹ The changes in the sleep - wake cycle can have an impact on health and on people's day-time living.² At least one in 10 persons suffer with a sleep-related problem.³ ⁴ Sleep disorders can affect mental and emotional functions, causing fatigue, poor concentration and depressive symptoms.⁵⁻⁷ A prolonged sleep disturbance can cause disorientation, illusions, hallucinations, persecutory ideas and cognitive impairments.⁷ Mental disorders and their treatment can interfere with the sleep-wake cycle as well. Initial insomnia, early morning wakening, disturbing dreams and day-time fatigue are frequently observed in major depression.⁸ Sometimes hypersonmia can also appear in atypical depressive cases, bipolar affective disorder and seasonal affective disorder.⁶ Alterations on rapid eye movement (REM) sleep latency are frequently noticed in certain forms of severe depression⁷ and sleep deprivation is reported as having an antidepressant effect and may precipitate the onset of a manic episode.⁹ Interestingly, the symptoms of sleep disorders are sometimes wrongly evaluated as psychiatric disorders, such as depression. This fact, together with the non-recognition of sleep disorder symptoms, can compromise their appropriate diagnosis and treatment.

We present a clinical case of an OSA with an atypical major depressive disorder symptoms presentation. The appreciation of depression in OSA has been reported earlier in the literature,⁹ but its aetiology remains unclear.¹⁰ Although there is a higher prevalence of depression in OSA,¹⁰¹³ the underappreciation of this association in medical practice can sometimes cause undesirable medical disorders, such as high blood pressure, that could otherwise be treated.

The importance of this connection for primary care and for mental health clinicians is related to the overlap of symptoms and consequently to the under-diagnosis of OSA and other sleep disorders in depressed patients.¹⁰ ¹⁴ Besides, this overlap of symptoms represents a challenge for correct diagnosis and management.¹⁵ This case report illustrates
that the non-identification of OSA in a depressive patient can influence the process of treatment and/or contributes to its antidepressant treatment failure, thus highlighting for the importance of assessment using a sleep study with polysomnography in a more regular basis.

CASE REPORT

Our patient is a 48-year-old woman, single, living with her two children, office assistant. She is the second of four sisters and a brother, in a family of middle socioeconomic status. She was born by eutocic birth and had a normal psychomotor development with no reports of relevant health problems. At the age of six, she enrolled in elementary school, completed the 4th grade when she was 11 years old and was a sociable girl. She began working at the age of 13 in a shoe factory till she was 26, when she started working as an office assistant. She had her first daughter when she was 28 years old and her second daughter five years later.

She has no personal history of smoking, alcohol or toxic substance misuse. She suffers from hypertension, being medically treated with losartan 50 mg/day. Concerning psychiatric antecedents, she had two previous reactive depressive episodes related to important life-events; the first one occurred when patient was 15 years old after her best friend suddenly died by a cerebral neoplasm, and the second depressive episode occurred at 34 years old when his brother suddenly hanged by suicide. Both episodes remitted following a brief course of antidepressant treatment of 9 months. The patient denied hypomanic or manic episodes.

Recently, by the age of 46, she started feeling progressively sad, with anhedonia, fatigue, hyperphagia (with a weight gain of 10 kg in one year), leaden paralysis, dizziness with sensation of fainting, subjective experience of amnesia complains (she often forgot names and codes related to work), morning headaches and difficulties in attention and concentration at work. She also reported snoring (identified by her daughters), EDS and unintentional sleep episodes occurring while watching television, reading, or even when working. After beginning to miss days at work, she started complaining to her General Practitioner, who diagnosed a recurrence of her depression and started treatment, first with sertraline 50 mg/day and then with fluoxetine 20 mg/day. Because of symptoms unimprovement, she was sent to psychiatric ambulatory treatment by her General Practitioner (Figure 1).

On the mental examination, the patient was alert, cooperative and calm and showed time and space orientation. Her speech was coherent and logical. There was good emotional resonance but she had a depressive mood. She did not have any changes in thought content, such as suicidal or delusional ideas. No sense-perception changes were observed either. Insight and critical appraisal were preserved. She described herself as being shy, quiet, introverted and sensitive to interpersonal rejection.
The physical examination showed an overweight woman with a body mass index (BMI) of 31.3 Kg/m². Neurological examination was normal, the same happening with blood investigations (hemogram, basic biochemical investigations, illicit drug screen and thyroid function). There were no relevant alterations in the electroencephalogram (EEG) and in cerebral magnetic resonance imaging (MRI) results, as well as in the mini-mental state examination (MMSE).

We switched the antidepressant treatment to escitalopram 20 mg/day. Although there was some slight improvement in sadness and anhedonia after three months, the patient maintained the symptoms of snoring, EDS, unintentional napping episodes, cognitive symptoms and morning headaches, and was referred for a sleep study. Here, on a more detailed physical examination, the patient revealed a partial obstruction of the nose and a Mallampati score of 4. She scored 23 on the Epworth sleepiness scale (ESS), had a desaturation index of 18.8/h on overnight pulse oximetry (min. of 84%, average of 95%), and had an apnea-hypopnea index (AHI) of 16.3/h on polysomnography. There were no reports of circadian rhythm alterations, nocturnal insomnia, sleep fragmentation or restless legs symptoms.

She started the treatment with nightly CPAP therapy (10cm of H2O pressure), and carried out lifestyle changes and weight-loss education and diet. Although patient had some initial difficulties in the adherence due to leakage and nocturnal awakenings (median use = 2 hours; use above 4 hours = 12%), a progressive and substantial improvement occurred during the next 8 weeks after ventilation mask readjustment (Figure 1). Sadness and anhedonia were now in remission. The patient had lost 5 kg (BMI of 29.3 Kg/m²) and there was also a symptomatic improvement in EDS (ESS = 12), snoring, napping, morning headaches and also an increase in attention and concentration. The patient mentioned a better subjective quality of life and had now no work absence and after six months, our patient remained euthymic.

**DISCUSSION**

Our presumptive diagnosis is OSA, presenting as an atypical depression episode. Several studies have identified depressed mood has a symptom of untreated OSA. Although it has been documented higher prevalence of depression in patients with OSA, an etiological link between the two entities has not entirely demonstrated. OSA is a sleep-related breathing disorder and is one the most commonly diagnosed sleep problems (lifetime prevalence is between 4% and 9%), although still under-diagnosed. It is associated with several medical conditions and increases motor vehicle accidents. Besides, it represents an important impact in terms of healthcare burden and also in morbidity and mortality. Severe and untreated OSA (AHI ≥ 30) can increase 3 to 6 times the risk of all-cause mortality, compared with individuals without OSA. Typically, a transient upper airway complete or partial occlusion occurs as sleep deepens, resulting in oxygen deprivation. The subsequent arousal prevents the deeper stages of slow wave sleep, a condition that may happen hundreds of times a night. The patient is usually unaware of snoring, respiratory pauses and their severity. Sometimes this information is provided by family or bedpartners.

Our patient had two previous episodes of major depression with characteristic mood reactivity for life-events that were successfully treated with antidepressants. In the present depressive episode, along with features of atypical depression (such as sadness, anhedonia, EDS, leaden paralysis, hyperphagia and oversensitivity to interpersonal rejection), she also showed snoring, unavoidable episodes of napping during the day, difficulties in attention and concentration and morning headaches. Although there was an improvement in some depressive clinical features with the escitalopram 20 mg/day treatment, the persistence of EDS associated with snoring, morning headaches, naps during the day and cognitive symptoms made us consider another possible aetiology or comorbid condition.

In the presence of EDS several common disorders must be considered, but the most frequent are sleep disorders. The first step towards the evaluation of a sleep disorder is a complete throughout physical, medical, psychiatric assessment and also a vigorous evaluation of sleep complaints. A sleep diary can be useful in providing information about daily sleep patterns.

A polysomnography with respiratory variables is a first-line diagnostic approach when suspecting of a sleep disorder. OSA can be diagnosed in asymptomatic adults if the AHI is greater than 15 events per hour, and in symptomatic adults (loud snoring, daytime sleepiness, apneic episodes, frequent arousals, impaired cognition) if the AHI is greater than five events per hour. Subgroups based on OSA severity were categorized into three groups according to the AHI: AHI < 15/h (mild OSA), AHI < 30/h (moderate OSA) and AHI ≥ 30/h (severe OSA). The patient had and an
AHI of 16.3/h on polysomnography, corresponding to a moderate OSA.

Several signs in the patient’s physical examination were also suggestive of OSA, such as mouth breathing and partial nasal obstruction during inspiration, revealed by the bilateral collapse of the nasal rim. This is often a sign of OSA-associated nasal resistance, due to higher inspiratory upper airway pressure and increased collapsibility of pharyngeal walls, and a potential cause of sleep apnea due to a predisposition to mouth breathing and the downward and backward displacement of the mandible. The patient also had the Mallampati’s score of 4, which is a classification system based on visualization of posterior oropharyngeal structures. The highest Mallampati’s score of 4 indicates a not visible soft palate and a crowded oropharyngeal space, predisposing to obstruction during sleep. The combination of nasal obstruction and a high Mallampati’s score (3 or 4) is associated with an increased risk of sleep apnea. She was also overweight (BMI of 31.3kg/m²), which is a predisposing factor for the development of OSA. Middle age, hypothyroidism, maleness, neurological conditions and malformations that impair upper airway muscle tone are other predisposing factors.

The repeated periods of hypoxia, hypercapnia and sleep fragmentation of OSA can lead to cardiovascular complications, such hypertension, heart arrhythmias and sudden death, cerebrovascular disease and poor cognitive performance, especially when AHI > 30 per hour of sleep. These events during sleep can also be an explanation to the EDS and the cognitive symptoms, as well as to the morning headaches reported by the patient. OSA can possibly represent an increased risk for the development of the patient’s hypertension. The variability of symptoms presentation does not necessarily reflect the duration and severity of OSA. The severity of EDS due to OSA does not necessarily reflect a high AHI either, but can be more associated with depressive symptoms. Also, although fatigue might be present in OSA or in depression, depressive symptoms have been independently associated with more expressive levels of fatigue in OSA patients.

EDS can be assessed by a multiple sleep latency test, used to diagnose narcolepsy, or using questionnaire scales. Our patient had 23 on ESS (maximal value is 24 and a score > 10 is considered sleepy). This apparently severe EDS can be responsible for mood and behavioural consequences, interpersonal difficulties, impaired driving ability, and lowered health-related quality of life (QoL). Further, it has been found a positive association between depression and obesity with sleepiness and QoL scores in patients with OSA. OSA has been associated with depression and also to other psychiatric diagnosis. Emerging evidence points to a high prevalence of depressive symptoms in patients with OSA, suggesting a mutual relationship. According to recent revisions, it may ranges from 5 to 63% in males and 19, 42, 43 cerebrovascular disease and metabolic syndrome, founding factors such as obesity, hypertension, and sleep fragmentation of OSA can lead to cardiac complications, such arrhythmias and sudden death, cerebrovascular disease and poor cognitive performance, especially when AHI > 30 per hour of sleep. These events during sleep can also be an explanation to the EDS and the cognitive symptoms, as well as to the morning headaches reported by the patient. OSA can possibly represent an increased risk for the development of the patient’s hypertension. The variability of symptoms presentation does not necessarily reflect the duration and severity of OSA. The severity of EDS due to OSA does not necessarily reflect a high AHI either, but can be more associated with depressive symptoms. Also, although fatigue might be present in OSA or in depression, depressive symptoms have been independently associated with more expressive levels of fatigue in OSA patients.

An hypothetical link between OSA and depression is still not demonstrated and, despite studies reporting a mutual connection, the pathophysiological mechanisms of that relationship remain unclear and seem complex. Disturbance of the sleep/wake cycle, wakefulness and regulation of mood in both entities can be interrelated with abnormalities in neurotransmitters (serotonin, norepinephrine and gamma-aminobutyric acid - GABA), neurotransmission, neuroplasticity and to inflammatory substances and cytokines. It has also been suggested that serotonin can influence upper airway patency through the hypoglossal nucleus.

In our patient, depressive symptoms presented at the same time with other symptoms of OSA, and the overlapping symptoms of both entities, such as EDS, fatigue, poor concentration, psychomotor retardation and weight gain can represent a diagnostic challenge and lead to misdiagnosis. Due to the overlap of symptoms, we cannot affirm that OSA was solely the cause of the depressive mood itself, or that some symptoms of OSA were independent of the atypical depression. Nevertheless, a hypothetical comorbid and synergistic action of both entities can be present. Moreover, it can be the result of repeated episodes of hypoxia or to fragmentation of sleep, or to multivariable confounding factors such as obesity, hypertension, cardiovascular disease and metabolic syndrome, associated with both entities. Nevertheless, in this patient and after CPAP institution, the depressive symptoms and EDS, snoring, masts, morning headaches and cognitive symptoms had a...
great improvement. After eight weeks, depressive symptoms were in remission and the others have improved substantially, the patient returned to work at full time, suggesting that OSA could be the cause of previous antidepressant treatment failure and possibly contributed to exacerbate the depressive symptoms. Therefore, awareness of this relationship is still important for a better diagnosis and treatment in both entities. A study also reported that in depressed patients following an acute myocardial infarction (MI) and with OSA, cognitive behaviour therapy is less efficacious compared to patients without OSA, therefore highlighting that OSA could decrease the antidepressant treatment response.

The subjective neurocognitive symptoms presented by the patient, such as impaired attention and memory together with poor concentration, reversed mostly after treatment. Deficits in executive functions in OSA patients are sometimes not completely reversed when sleepiness is relieved by treatment due to irreversible anoxic brain changes (neuronal cell injury, neurodegeneration, and cell death) and vasculopathy. This may be associated to hippocampus atrophy and abnormalities in white matter, particularly in frontal lobes. Cases of dementia due to grey-matter loss and alterations in markers of neuronal integrity were also evidenced by neuroimaging studies. It has been also documented that depression in OSA patients seems to add additional damage in affective, cognitive, respiratory, and autonomic control brain regions.

Other conditions can be responsible for the EDS, which should be considered in the differential diagnosis. But, the normal findings on thyroid-stimulating hormone, ferritin, cobalamin, folate, full blood cell count, EEG, cerebral MRI and MMSE make a possible medical, neurological or substance abuse sleep related disorder less likely to be present. In this patient, the apneas or hypopneas could be a manifestation of central apnea, a condition involving impairment of the respiratory drive, but in this situation there is usually an absence of snoring, the respiratory pauses are not accompanied by respiratory efforts and insomnia is present more often than EDS. There is an absence of sleep attacks, cataplexy, hypnagogic hallucinations and sleep paralysis suggestive of narcolepsy, and an absence of an actual external oscillator, responsible for a circadian rhythm disorder. Besides, there are not clinical elements suggestive of parasomnias or of a psychophysiological, paradoxical and idiopathic hypersonmia, or restless legs syndrome.

**TREATMENT**

The treatment goals for OSA include measures towards reducing the number of apneic episodes, improvement of symptoms and oxygen saturation. Night-time nasal CPAP, maintaining the patency of the oropharynx through an air stream under pressure, is the most successful treatment. It can greatly improve the patient’s functional status, providing efficient oxygenation and restorative sleep, reducing blood pressure, improving cognitive deficits and raising the number of years of good health by 5.5 quality-adjusted life-years. There is also evidence that positive pressure therapy may be an appropriate treatment for mood disorders when they are related to sleep disordered breathing. Some authors even suggest that CPAP should be tried first, before starting other treatment modalities for depression. Nevertheless, there have also been trials, though with negative findings on the improvement of depression, with treatment of apnea, but CPAP adherence in these last studies was not monitored. In fact, high scores on depression and anxiety in OSA patients have been associated to non-compliance with CPAP therapy. Patients tend to abandon CPAP therapy early, so monitoring, support and mask education should be directed towards sustaining adherence, as occurred with this patient. Recent evidence shows that telemonitoring, in a self-management and self-behaviour approach can be effective by increasing adherence.

Apparently no pharmacotherapy is consistently effective in normalizing sleep in these patients. Central nervous system depressants (alcohol, benzodiazepines, zolpidem) should be avoided, due to respiratory depression and weaker respiratory response to hypoxia. Other measures such dental devices or oropharyngeal exercises have also been reported to be useful, although with limited evidence.

The usefulness of antidepressants in patients with OSA and comorbid depression is not extensively studied. Nonetheless, the improvement of sleep apnea (reduction of the frequency of apneas and increase in oxygen saturation) with some antidepressants is related to their REM-suppressant activity, the sleep stage in which most apneas occur. Evidence of these properties was demonstrated with tricyclic antidepressants, protriptyline and imipramine. Fluoxetine and paroxetine (serotonin-specific reuptake inhibitors - SSRIs) have shown similar results, yet causing fewer adverse effects. The treatment of EDS is better with more stimulating antidepressants, such as...
SSRIs, reboxetine or bupropion. Mirtazapine and trazodone are not recommended98 because of their sedating properties.98

Because of their sedative effects, antihistamines should not be used either, but some non-sedating antihistamines, however, can be useful for allergic rhinitis and relieve obstruction.99 Modafinil, a wakefulness-promoting agent,100, 101 improves the quality of episodic memory and attention, but should be used only after CPAP has been instigated and maximized and after the exclusion of other causes of sleepiness.102 More recently, it has been also demonstrated the usefulness of armodafinil, another nonamphetamine wakefulness-promoting agent, for treating excessive sleepiness in patients with OSA and comorbid depression.103

Surgical procedures are reserved for CPAP treatment failures or anatomic correction of selected cases to increase posterior airway space (nasal reconstruction, tonsillectomy, uvulopalatopharyngoplasty, mandibular advance and rarely tracheostomy).104 Lifestyle changes, particularly weight loss, or avoidance of a supine sleeping position may affect the severity of OSA.105 Education about normal sleep and habits of good sleep hygiene are also important measures.106

CONCLUSION

Sleep disorders are not still well recognized and treated, representing important sources of disease, disability and even death. A case with an improvement in depressive symptoms after treatment with escitalopram but with the persistence of EDS, snoring, naps and cognitive symptoms led us to a careful evaluation of a possible sleep disorder. After the diagnosis of OSA, an additional treatment with CPAP was initiated. Then, the clinical picture ameliorated towards a full remission of depressive symptoms and a substantial improvement of the others, making us consider an OSA case with an atypical depressive syndrome presentation.

A detailed diagnostic interview and a physical examination, complemented with a polysomnography, were essential for diagnosis of OSA. Careful management of OSA together with depression should regard to sleep disorder itself but also to depressive symptoms. For that, CPAP is essential, but treatment requires particularly careful consideration, when choosing antidepressants. A behaviourial approach, including lifestyle modifications (weight loss) and hygiene sleep measures must also be considered. Benzodiazepines and sedating anti-depressants should be avoided. Other drugs such as modafinil may be a promise in the future. Surgery is used in special anatomical situations.

An early intervention and prevention are essential to an easier and well-succeeded recovery, as well as for costs reduction and improvement in life quality, avoiding undesirable medical and social consequences. In particular, the early recognition and assessment of atypical depressive symptoms refractory to different antidepressants, along with other symptoms suggesting the presence of an OSA should prompt to a sleep study investigation. This case highlights the relationship between OSA and depressive disorders, a field that needs more investigation and General Practitioners and Psychiatrists should be familiar with this health problem.

ACKNOWLEDGEMENTS

We would like to thank the patient for her collaboration. The authors also wish to thank Professor Leonor Duarte for her kind help in revising the english in the article.

REFERENCES


