CASE REPORTS

Acute Confusional Syndrome Associated With Obstructive Sleep Apnea Aggravated by Acidosis Secondary to Oral Acetazolamide Treatment

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Acute confusional syndrome, or delirium, is a transitory mental state characterized by the fluctuating alteration of awareness and attention levels. We present the case of a patient with acute confusional syndrome associated with obstructive sleep apnea syndrome (OSAS) aggravated by metabolic acidosis induced by oral acetazolamide treatment.

A 70-year-old man with no history of neurological disease was referred with a clinical picture consistent with acute confusional syndrome presenting between midnight and dawn. During the admission examination infectious, toxic, and neurologic causes, or those related to metabolic or heart disease were ruled out. Arterial blood gases measured during one of the nighttime episodes of acute confusional syndrome showed mild hypoxia and hypercapnia with mixed acidosis. Signs and symptoms suggestive of OSAS had been developing over the months prior to admission, with snoring, sleep apnea, and moderate daytime drowsiness. Polysomnography demonstrated severe OSAS with an apnea-hypopnea index of 38. Mean arterial oxygen saturation was 83%; time oxygen saturation remained below 90% was 44%. The attending physician ordered the withdrawal of oral acetazolamide, which was considered the cause of the metabolic component of acidosis. Treatment with continuous positive airway pressure was initiated at 9 cm H_2O after a titration polysomnographic study. The patient continued to improve.

OSAS, for which very effective treatment is available, should be included among diseases that may trigger acute confusional syndrome.

Key words: *Acute confusional syndrome. Delirium. Obstructive sleep apnea syndrome. Metabolic acidosis. Acetazolamide.*

Síndrome confusional agudo asociado a apnea-hipopnea obstructiva del sueño y agravado por acidosis metabólica secundaria a acetazolamida oral

El síndrome confusional agudo o *delirium* es un trastorno transitorio del estado mental caracterizado por la alteración fluctuante del nivel de conciencia y atención. Presentamos el caso de un paciente con síndrome confusional agudo asociado a síndrome apnea-hipopnea obstructiva del sueño (SAHOS), agravado por una acidosis metabólica secundaria al tratamiento con acezatolamida.

Se trataba de un varón de 70 años de edad, sin antecedentes de enfermedad neurológica previa, remitido por un cuadro confusional agudo de inicio en la madrugada. Durante el ingreso se descartaron causas de origen infeccioso, tóxico, neurológico o secundarias a enfermedad metabólica o cardíaca. Los gases arteriales obtenidos en la madrugada durante uno de los episodios de síndrome confusional agudo mostraron una ligera hipoxia e hipercapnia con acidosis de tipo mixto. El paciente había presentado en los meses previos al ingreso síntomas indicativos de SAHOS (ronquido, pausas respiratorias durante el sueño y somnolencia diurna moderada). Se efectuó una polisomnografía diagnóstica que puso de manifiesto un SAHOS de carácter grave. El índice de apnea-hipopnea/h era de 38, la saturación de oxígeno media del 83% y el tiempo de saturación de oxígeno por debajo del 90%, del 44%. Se retiró la acetazolamida oral, que se consideró la causa del componente metabólico de la acidosis, y tras un nuevo estudio polisomnográfico de titulación se inició tratamiento con presión continua en la vía aérea a 9 cmH_2O. El paciente siguió un curso clínico favorable.

El SAHOS, entidad con un tratamiento muy eficaz, ha de incluirse entre las enfermedades que pueden precipitar un síndrome confusional agudo.

Palabras clave: *Síndrome confusional agudo.* Delirium. *Síndrome de apnea-hipopnea obstructiva del sueño. Acidosis metabólica. Acetazolamida.*

Introduction

Acute confusional syndrome, or delirium, is a transitory mental state characterized by various clinical manifestations, principally alterations in levels of awareness and attention, with an acute or subacute onset and fluctuating course. Although confusional syndrome

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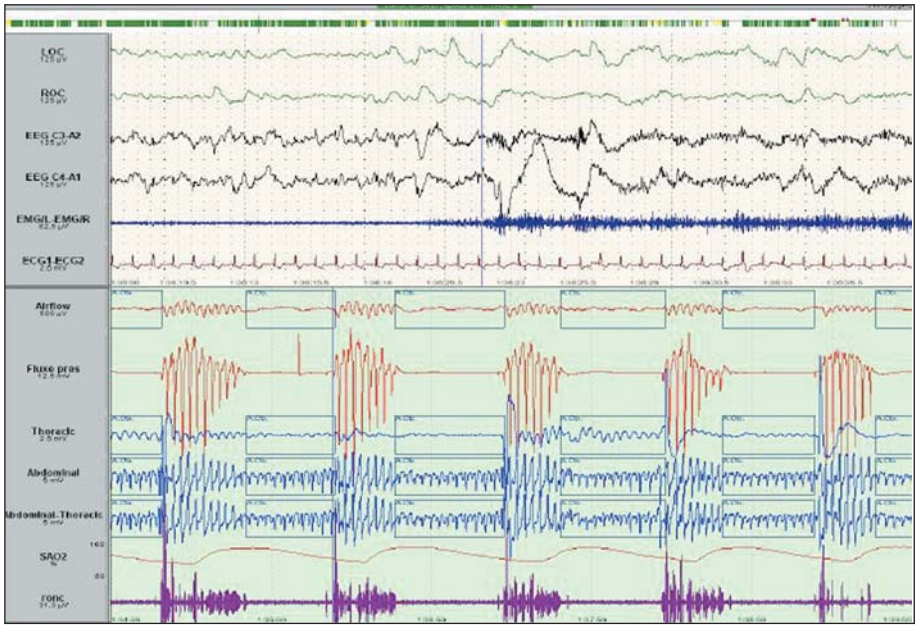

Figure. Polysomnography tracings. Upper panel (white background): neurophysiological parameters and electrocardiogram. Time constant: 30 seconds. Lower panel (green background): respiratory parameters. Time constant: 5 minutes. Episodes of oronasal airflow cessation accompanied by thoracoabdominal movements (obstructive apnea) were observed, and resulted in arterial oxygen desaturation, snoring, and cortical arousal (upper panel).

arises for multiple reasons, it is usually secondary to a medical disease or associated with the consumption of alcohol, tobacco, street drugs, or medication. However, it may also be the mode of presentation of serious diseases of the central nervous system.[1]

We present the case of a patient with an episode of acute confusional syndrome associated with obstructive sleep apnea syndrome (OSAS) and aggravated by the coexistence of metabolic acidosis secondary to treatment with oral acetazolamide. The interest of the case lies in the uncommon mode of presentation of OSAS.

Case Description

A 70-year old man was sent to the emergency room with acute confusion. The patient's symptoms began sometime between midnight and dawn, when he got up confused and disoriented, and lay on the floor of his house for several hours. He apparently remained conscious, experienced no transitory incontinence, and had difficulty calling for help.

He had no known history of alcohol, tobacco, or street drug use and his medical history was most significant for high blood pressure controlled with doxazosin and quinapril; hypertensive cardiomyopathy; type 1 diabetes mellitus with retinopathy, nephropathy, sensory polyneuropathy, and peripheral vascular disease in both lower extremities as late complications; and glaucoma treated with brimonidine tartrate, topical timolol, and oral acetazolamide (500 mg/d). Prior to the episode in question, the patient had been completely autonomous in basic activities of daily living, and showed no impairment of higher cognitive functions. He was scheduled to undergo polysomnography for snoring, pauses in breathing observed during sleep, and moderate daytime drowsiness.

Upon admission to the emergency room, the patient was afebrile, and hydration and color were normal. Blood pressure was 130/70 mm Hg, heart rate was 90 beats/min, and respiratory rate 20 breaths/min; body mass index was 34 kg/m^2. Heart sounds were rhythmic, with no heart murmur or carotid bruits. Lung auscultation revealed diminished lung sounds, with no added sounds. The rest of the examination showed no alterations except in lower extremities, where trophic changes due to chronic venous insufficiency with a lesion on the dorsal surface of the left foot were observed. The patient was conscious, but disoriented to time and place. There was no evidence of previous injury or tongue biting. Some sluggishness was observed, as well as paucity and slowness of speech, which was incoherent at times. The patient also had difficulty sustaining attention. The rest of the neurological examination showed no other alterations except for the loss of vibratory sensation up to both knees.

A hemogram, white blood cell count, and biochemistry were normal, except for a blood glucose level of 14.1 mmol/L. Thyroid function tests (thyrotropin and thyroxine levels) and creatine kinase, troponin, aldolase, vitamin $B_{12,}$ and folic acid levels were within normal range. No ketosis was detected. Arterial blood gas analysis showed the following values (fraction of inspired oxygen, 0.21): pH, 7.33; PaO_2, 61 mm Hg; $PaCO_2$, 49 mm Hg; and standard bicarbonate, 23 mEq/L. Cerebrospinal fluid analysis showed no pathological findings. Chest x-ray, electrocardiogram, and cranial computed tomography showed no abnormalities. Urinalysis showed no bacteria or ketones present, but did show an elevated microalbumin level, previously detected, secondary to diabetes. Urine drug tests (for ethanol, benzodiazepines, antidepressants, cocaine, and opiates) were negative. Serologies were performed for toxoplasmosis, syphilis, hepatitis C and B viruses, cytomegalovirus, herpes, Epstein-Barr virus, herpes zoster, and human immunodeficiency virus, all with negative results.

During the first 2 days following admission the patient remained afebrile and hemodynamically stable, but showed fluctuating confusion and disorientation. Episodes of disorientation occurred mainly in the early morning hours. Arterial blood gas values obtained at that time showed deterioration compared with those of the previous evening

(pH, 7.25; PaO_2, 58 mm Hg; $PaCO_2$, 66 mm Hg; standard bicarbonate, 27 mEq/L). Finally, a polysomnography was performed showing numerous obstructive apnea and hypopnea events, with severe arterial oxygen desaturation and sleep disturbance (Figure). The apnea-hypopnea index was 38.3, mean arterial oxygen saturation was 83%, and time oxygen saturation remained below 90% was 44%. After a continuous positive airway pressure (CPAP) titration study, treatment was initiated at 9 cm H_2O. Clinical response was good and arterial blood gases improved, although mixed acidosis persisted. Oral acetazolamide was withdrawn and replaced by topical brinzolamide. The patient improved clinically, and his level of awareness quickly returned to normal. In subsequent outpatient follow-up visits, he remained asymptomatic, and arterial blood gas analysis performed after the first month of treatment yielded the following results: pH, 7.37; PaO_2, 69 mm Hg; $PaCO_2$, 44 mm Hg; and standard bicarbonate, 26 mEq/L.

Discussion

Acute confusional syndrome or delirium, an organic brain syndrome that is highly prevalent in elderly hospitalized patients, is associated with considerable morbidity and mortality.[1,2] Alterations in consciousness and attention and disorganized thought, with acute onset and fluctuating course, are the most useful diagnostic criteria.[3,4] The pathophysiology of delirium is not well established, but alterations of neurotransmitters and a decrease in cholinergic function, or an excess of dopamine, adrenaline, or glutamate have been suggested. Alterations in γ-aminobutyric acid and serotonin have also been implicated.[2]

The etiology of delirium is usually multifactorial (Table). It is associated with primary neurological disorders, systemic diseases that can affect neurological function, the use of certain drugs, particularly those with anticholinergic activity, intoxication with exogenous substances, and withdrawal from alcohol or certain drugs, such as benzodiazepines. It is important to identify the underlying causes of the confusional syndrome, as in many cases they can be treated easily.[1,2,4]

OSAS has been described as triggering the onset of acute confusional syndrome.[5] It is characterized by partial (hypopnea) or total (apnea) obstruction of the upper airway during sleep that may cause alterations in gas exchange and sleep disturbances. It has been associated with cognitive deficits and psychiatric disorders, alterations that can be reversed by administering CPAP. Muñoz et al[6] described the case of a patient with delirium that developed suddenly during the night and impelled him to jump out of the window of his home. His state was attributed to severe OSAS that responded well to CPAP.

In the case we present, while the patient had a history of systemic diseases that could cause a state of acute confusion, no signs of exacerbation of any of them were detected upon admission. His symptoms, which fluctuated and occurred mostly at night, ceased only after CPAP treatment was initiated and oral acetazolamide withdrawn. Acetazolamide is a carbonic anhydrase inhibitor that increases the excretion of bicarbonates, together with sodium, potassium, and water, producing an increase in alkaline urine flow and moderate metabolic acidosis.[7] It acts on the peripheral and central chemoreceptors causing local changes in the brain and systemic changes in pH. It has been used to stimulate ventilation and as a treatment for central sleep apnea syndrome.[8,9] In some patients with this syndrome its use has been associated with prolonged episodes of obstructive apnea and worsened nocturnal hypoxemia.[10] In our opinion, the drug contributed to the worsening of

TABLE
Etiology of Acute Confusional Syndrome

Medical diseases
Intrinsic neurological diseases
Localized diseases: vascular, primary and metastatic neoplasms, infections, demyelinating diseases
Diffuse or multifocal diseases: vascular, neoplasms, infections, demyelinating diseases, hypoxic encephalopathy, brain injury, epilepsy
Systemic diseases
Metabolic changes: electrolytes, hypoxia, hypercapnia, acidosis/alkalosis (metabolic/respiratory)
Nutritional deficiencies: thiamine, vitamin B_{12}/folic acid
Endocrine disorders: hypo/hyperthyroidism, uncontrolled diabetes
Hematological disorders: severe anemia, polycythemia
Cardiovascular diseases: heart disease, cardiac insufficiency, hypertensive encephalopathy
Lung diseases: pulmonary embolism
Digestive diseases: liver diseases (hepatic encephalopathy), pancreatic diseases
Kidney diseases: renal insufficiency
Infectious diseases: infectious endocarditis, urinary tract infections, pneumonia
Environmental factors: disturbances in thermoregulation, electrocution, burns
Surgery (postoperative state)
Substance-induced
Intoxications: ethyl and methyl alcohol, amphetamines, anxiolytics, antidepressants, cannabis, cocaine, opiates
Withdrawal: alcohol, anxiolytics, barbiturates, hypnotics, sedatives
Absence of intoxication/withdrawal: antibiotics, antihistamines, corticosteroids, H_2 receptor antagonists, industrial toxins, poisonous animals and plants
Unknown causes

gas exchange in this patient. Increased acidosis during the night was due to insufficient metabolic compensation for the increase in $PaCO_2$ caused by the apnea episodes.

In conclusion, the presence of OSAS should be considered among the differential diagnoses considered when a patient presents with delirium. It is important when taking the medical history to include questions directed at discovering symptoms of OSAS and to perform a full diagnostic study in cases of high clinical suspicion.

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