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Case Report

Cheyne - Stokes Respiration with Central Sleep Apnea in a Patient with a Heterozygous Mutation in Exon 24 of ABCC6 Gene

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ABSTRACT

We present the case of a patient with Cheyne-Stokes respiration with central apnea while sleeping and during wakefulness and a heterozygous mutation in the ABCC6 as a clinical manifestation of pseudoxanthoma elasticum. The presentation of this disease is unusual and it probably reflects more widespread involvement at the onset. With this case, we show the importance of considering this kind of disease in the differential diagnosis of central sleep apnea syndromes.

Keywords: Cheyne-stokes, Central apnea, Genetic disorders, Pseudoxanthoma elasticum

Abbreviations

EEG: Electroencephalogram; FIRDA: Frontal Intermittent Rhythmic Delta Activity; VPSG: Video-Polysomnography Study; EKG: Electrocardiogram; CSR-CSA: Cheyne-Stokes Respiration with Central Sleep Apnea; REM: Rapid Eyes Movement; NREM: Non Rapid Eyes Movement; CPAP: Continuous Positive Airway Pressure; PXE: Pseudoxanthoma Elasticum; $PaCO_2$: Partial Pressure of Carbon Dioxide in Arterial Blood

Introduction

Pseudoxanthoma elasticum is a genetic, multisystem connective tissue disorder, which primarily affects the skin, eyes, and the cardiovascular system. Even though Cheyne-Stokes respiration is common in heart failure and cerebrovascular disease, the relationship between Cheyne-Stokes respiration and central sleep apnea with a normal left ventricular ejection fraction and pseudoxanthoma elasticum has not been published yet [1,2].

Here we present the case of a patient with a heterozygous mutation in the ABCC6 gene and Cheyne-Stokes respiration during wakefulness and with central sleep apnea as a presentation of pseudoxanthoma elasticum.

Case Report

We present the case of an 80-year-old man, non-smoker with cardiovascular risk factors: controlled arterial hypertension with two antihypertensive drugs, dyslipidemia and type II diabetes. He reported a clinical history of acute myocardial infarction in 2002 which required the placement of two stents in the anterior descending artery. In 2010 the patient experienced an increase of dyspnea and an aortic valve replacement was needed. An echocardiogram was performed in each routine control visit in the cardiology consultation. In the last visit, attended in 2018, results showed a type II diastolic dysfunction, severe left atrial dilatation, moderate ischemic mitral insufficiency, and mild tricuspid regurgitation, but with a left ventricular ejection fraction of 55%.

In 2018, the patient suffered a confusional syndrome with aphasia of comprehension and disconnection of the medium of three minutes. Electroencephalogram(EEG) was performed in the

emergency box showing the presence of occasional outbreaks of bilateral frontal waves. It was compatible with a frontal intermittent rhythmic delta activity (FIRDA) pattern with a nonspecific meaning. Cranial computed tomography scan was also performed with administration of contrast. It showed moderate cortico-subcortical parenchymal atrophy leukoaraiosis and extensive patchy hypodense areas in supratentorial white matter in a probable relationship with small vessel disease. A lacunar infarction in the left thalamus and a small area of encephalomalacia in the right cerebellar hemisphere were found too, probably related to the chronic ischemic event. The neurologist also observed severely calcified atheromatosis of both cavernous carotid arteries and vertebral arteries. After this episode, the patient was referred to the respiratory consultant for habitual sleepiness and snoring. The patient did not present dyspnea. The patient and his wife related a clinic history of parasomnias with important movements of legs and arms during sleep time. Although he did not mention a family background of sleeping disorders, he had a history of marriages between family members in the family tree. In fact, his parents were related to each other (second cousins).

The physical examination showed that pupils were equal and reactive, with normal cranial nerve examination and field of vision. Strength and proprioception were normal in the 4 extremities. There was no evidence of dysarthria or dysdiadochokinesia. Gait remained stable, with no resting or action tremors and a negative Romberg test. The remainder of the physical examination was also normal; oxyhemoglobin saturation was 97%, and there was evidence of sleepiness (Epworth Sleepiness Scale score 20).

A video-polysomnography study (VPSG) was carried out. The study included: a nighttime recording of the patient by means of a video system, digitalized EEG, and electrodes attached to the surface of the scalp with collodion, following AASM guidelines (F3-M2, C3-M2, O1-M2, F4-M1, C4.M1, O2-M1); a study of eye movements (left eye M2, right eye M2), EMG (chin and right and left anterior tibialis), Electrocardiogram (EKG), thermistor and pressure cannula, thoracic and abdominal effort, pulse oximetry, snoring level, and body position. The respiratory events during sleep were scored according to AASM guidelines, showing 64 central apneas (Figure 1; central apnea index: 91.1/h) (45 events in NREM1 [67.5/h] with 80.2% of sleep time, 1 in NREM2 [30/h] with 19.8% of sleep time and 0 in NREM3 [0/h]), 1 mixed apnea (1.4/h), 1 obstructive apnea (1.5/h) in NREM2, and 1 hypopnea (1.4/h) The patient failed to consolidate a stable sleep throughout the record and although he apparently failed asleep after 38 minutes of the start of the record, he was not able to complete a sleep cycle at any time. He remained in wakefulness most of the record, with brief periods of superficial sleep without reaching neither deep rapid eye movement (REM) sleep nor REM. The Cheyne-Stokes respiration was observed in all the VPSG registry during wakefulness. The efficiency of sleep (69%), with a total sleep time of 256 minutes, was severely diminished. The few periods of sleep appeared very fragmented by frequent arousals, motivated by respiratory events. The patient was treated with positive pressure device by an oronasal mask with a good response, improvement of ESS (score of 3) and 14 central events while continuous positive airway pressure (CPAP) treatment in the control VPSG, with a sleep efficiency of 88% and without Cheyne-Stokes respiration during wakefulness.

Considering the results obtained and the previous family tree and cardiovascular disease, a family genetic study was carried out. The patient's DNA was obtained from a peripheral blood sample. Roche-454 technology was used as DNA amplification method. Roche-454 technology is the first next-generation sequencing technology that utilizes a DNA amplification method known as emulsion PCR (EmPCR). This technique was performed to sequence ABCC6 gene including exon 24. The patient presented a heterozygous mutation (only in one of the 2 copies of the gene), the mutation p.Arg1141Ter (p.R1141X) at position 3421 (c.3421C> T) of exon 24

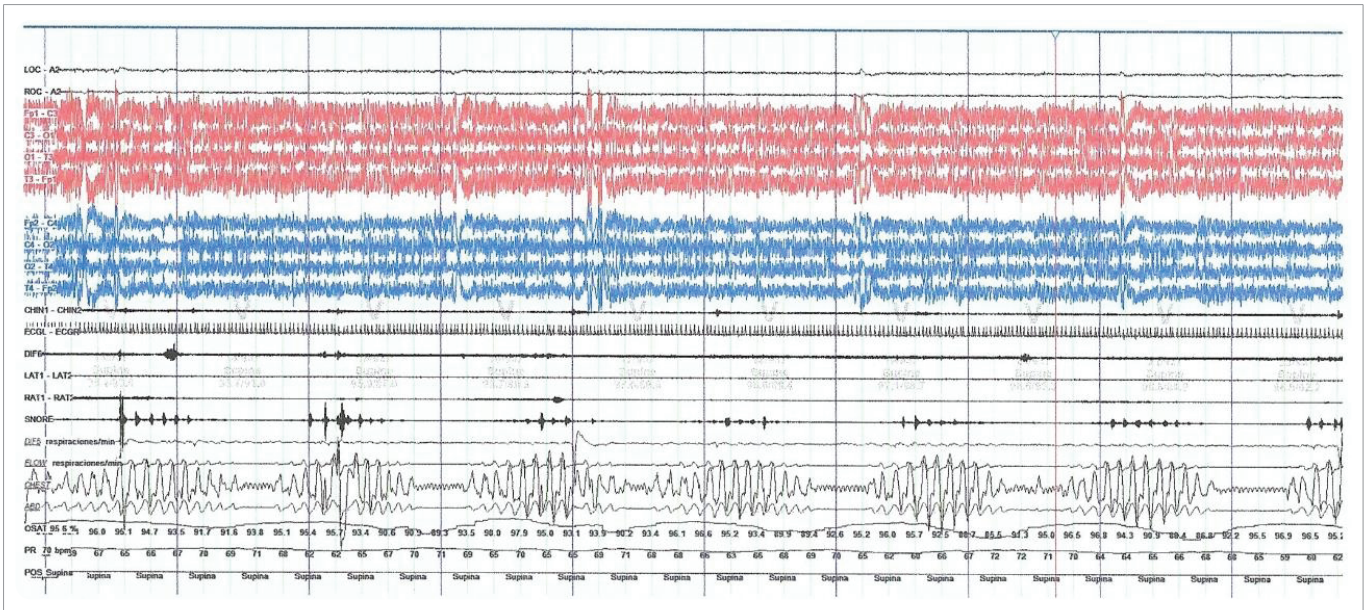

Figure 1: PSG showing a Cheyne-Stokes respiration with central sleep apnea.

of the ABCC6 gene. No other exon mutation of ABCC6 gene was found.

The patient did not have offspring but genetic tests were performed in the patient ´s siblings. The patient's brother reported skin manifestations of pseudoxanthoma elasticum (PXE) consisting of small yellow papules on the nape and sides of the neck and in flexural areas. He had never consulted a doctor because of this skin problem. A homozygous mutation of c.3421C> T (p.Arg1141Ter) in exon 24 of the ABCC6 gene was found in her blood test. The patient´s sister had a heterozygous mutation but she did not develop symptoms of this disease at all.

Discussion

Pseudoxanthoma elasticum (PXE) is a rare, genetic, multisystem connective tissue disorder primarily affecting the skin, eyes, and the cardiovascular system. PXE is caused by mutations in the ABCC6 gene which encodes ABCC6, a transmembrane transporter protein. PXE is characterized by progressive pathologic calcification and fragmentation of the elastic tissue in the affected organs. In different reports, the prevalence is given to range between 1:25,000 and 1:100,000. Due to the lack of adequate knowledge among patients and physicians, delay in diagnosis, and genetic heterogeneity, the exact prevalence of PXE might be underestimated [1]. Although autosomal recessive inheritance patterns have been frequently reported, some families show autosomal dominant inheritance and some cases are sporadic. There is considerable interfamilial heterogeneity. As a result, in some families, the skin manifestations may be predominant with relatively little eye or cardiovascular involvement, while in other families involvement of the heart and the cerebrum that may have severe clinical consequences with considerable morbidity and occasional early mortality. The reasons for this phenotypic heterogeneity are currently unclear, and attempts to establish genotype/phenotype correlations in different populations have mostly yielded negative results. There are suggestions, however, that the contribution of genetic modifier genes, epigenetics, dietary factors, and lifestyle variables contribute to the variable phenotypes [2-6]. The most frequent complications are a reduction of the presence of peripheral pulses, intermittent claudication, arterial hypertension, coronary occlusion, and hemorrhages, mainly digestive [7,8].

It is generally accepted that heterozygous carriers of a mutation in one ABCC6 allele do not develop PXE, due to this is an autosomal recessive disease. However, some heterozygotes seem to display clinical and histopathological features of PXE [9-11]. It has been defined as a "forme fruste" of PXE (OMIM #177850) a p.R1141X mutation in ABCC6 and a p.V255M mutation in GGCX (coding for gamma-glutamyl carboxylase) in a patient with abnormally mineralized skin areas [12]. It has been suggested that the nonsense mutation of our patient (p. Arg1141*) might predispose patients to cardiovascular disease and that the ABCC6 p. Arg1268Gln polymorphism is associated with angioid streaks and early manifestation of this disease [13,14]. This could be the reason for the cardiovascular manifestations in our patient that predispose to Cheyne-Stokes respiration with central sleep apnea (CSR-CSA).

Central sleep apneas and hypopneas arise from complete or partial reductions in central neural outflow to the respiratory muscles during sleep leading to complete or partial cessation of airflow for at least 10 seconds, respectively [15]. CSR-CSA is a form of periodic breathing into the central sleep apnea group, commonly observed in patients with heart failure, in which central apneas alternate with hyperpnoea that have a waxing-waning pattern of tidal volume. CSR-CSA is caused by respiratory control system instability characterized by a tendency to hyperventilate (high loop gain). Central apnea occurs when the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) falls below the threshold for apnea during sleep due to ventilatory overshoot. CSR at daytime is easily detectable in an objective way in chronic heart failure patients. It is a frequent manifestation and it is associated with adrenergic activation and increased natriuretic hormone plasma level.

Controversy remains as to whether CSR-CSA is simply a reflection of heart failure severity, or whether it exerts unique adverse effects on prognosis. A number of studies have examined the potential relationship between CSR-CSA and mortality. Most of them reported that CSR-CSA was associated with an increased risk for mortality, but these studies were limited. Further research is therefore needed to elucidate mechanisms that contribute to the pathogenesis of CSR-CSA [16]. Only a few studies investigated CSR during wakefulness and all of them have been performed in patients with chronic heart failure. CSR during wakefulness is found less often than CSR during sleep and appears to be a marker for CHF severity. He also reported a clinical history of acute myocardial infarction and a valve replacement however the left ventricular ejection fraction was 55%. Our patient reported neurological sequels that could contribute to the respiratory control system instability [17,18].

There is no evidence of the association between sleep apnea and the pseudoxanthoma elasticum. Our hypothesis is that CRS in this disorder may be explained by a number of chronic heart failure and neurological damage but it remains unclear if this respiration pattern could be an initial manifestation of this disease, especially due to the phenotypic heterogeneity that has not been clarified.

This case shows the importance of including these genetic disorders in the differential diagnosis of central apnea syndromes, mainly when they coexist with cardiovascular and cerebrovascular complications.

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Conflicts of Interest

The authors declare no conflict of interest

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