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SLEEP APNEA, PULMONARY HYPERTENSION AND NEPHROTIC SYNDROME *

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Summary

Many cardiopulmonary abnormalities have been described in patients with sleep apnea syndrome. We are reporting a patient with severe obstructive sleep apnea who had severe episodic pulmonary hypertension, hypoxemia, and nephrotic syndrome. We are postulating that nephrotic syndrome was causally related to sleep apneas.

Introduction

Sleep-apnea syndromes are characterized by obesity, excessive daytime somnolence, snoring, and many episodes of apneas at night[1]. Apneic episodes may cause pulmonary hypertension and right heart failure (Pickwickian syndrome). Repeated episodes of acute pulmonary edema and many other cardiovascular abnormalities may occur in patients with sleep apnea syndrome [2,3]. Hypoxemia and pulmonary hypertension have been implicated in the pathogenesis of pulmonary edema in patients with sleep apnea. It is likely that hypoxemia and pulmonary hypertension (and consequent systemic venous hypertension) may lead to dysfunction of other organs. We report a patient with sleep apnea syndrome who had severe episodic nocturnal pulmonary hypertension and was found to have nephrotic syndrome.

Case Report

A 29-year-old white male was referred to the sleep disorder center of the Talmadge Memorial Hospital — Medical College of Georgia (TMH-MCG) for evaluation for sleep apnea syndrome.

The patient weighed 180 lbs. at 22 years of age when he started gaining weight and during the next seven years his weight increased to 347 pounds. He began having progressive daytime somnolence and shortness of breath four years prior to his evaluation at TMH-MCG. The patient had fallen asleep many times during conversation, eating his food, driving the car, and during other activities. He had quit his job because of his inability to stay awake. His shortness of breath had been mainly at night; he would get up on multiple occasions each night with a choking sensation and struggling for breath. Many times, the patient had spent the whole night sitting to relieve his shortness of breath. During the two years prior to this evaluation, he started having swelling of his legs and progressive shortness of breath with exertion. He also had a history of loud snoring. The patient was admitted to his local hospital on multiple occasions because of shortness of breath. During these hospitalizations, no evidence of cardiac disease was found. He had high hemoglobin level (up to 21 G/dl), hypoxemia (PaO_2 in 40s) and 3 to 4 + proteinuria during these hospitalizations. The patient was being treated with a diuretic, bronchodilators and digitalis.

When evaluated at the TMH-MCG pulmonary clinic, the patient was extremely drowsy, and fell asleep many times during the interview, but was not in acute distress. His blood pressure was 128/90 mmHg, respiration 20/minutes, and he weighed 326 pounds. The remainder of the physical examination was normal except for slight edema of his lower legs. Pulmonary function tests showed mild restrictive ventilatory impairment and the arterial blood gases showed hypoxemia (PaO_2 52 mmHg, SaO_2 78%) and hypercapnia ($PaCO_2$ 48 mmHg). The patient was admitted to the TMH-MCG for further work up and treatment.

Urinalysis showed specific gravity of 1,024, 4 + proteinuria, oval fat bodies, and maltese crosses - all characteristic of nephrotic syndrome. Twenty-four hour urine excretion of protein was 4.5 G (84% albumin on protein electrophoresis). The creatinine clearance was 119/ml/min. No other evidence of renal abnormality was found.

A Swan-Ganz catheter was inserted to monitor pulmonary artery pressure. In the awake state, the pulmonary artery pressure was 44/22 mmHg (mean 33 mmHg). The catheter could not be wedged in the pulmonary artery and hence the wedge pressure could not be obtained. The pulmonary artery pressure repeatedly increased during the apneic episodes and reached a level as high as 152 / 72 mmHg (mean 100 mmHg). In addition, the patient coughed many times during sleep. During these coughing episodes the pulmonary artery pressure showed further elevations and maximal systolic pulmonary artery pressure of 320 mmHg was recorded. The patient had an arterial line to monitor systemic arterial pressure, and arterial pressure remained in the normal range (110/70—122/80 mmHg) during the episodes of pulmonary artery hypertension. Radionuclear ventriculography with 99mTC-PYP showed a left ventricular ejection fraction of 66% and a right ventricular ejection fraction of 18%. In addition, paradoxical motion of the interventricular septum was noted during each systole.

A six hour nocturnal polysomnographic recording of electroencephalogram, chest wall and abdominal expansion, airflow at the mouth and nostrils, and oxygen

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saturation was made. The patient awakened repeatedly, many times coughing, but fell asleep again. He spent 2 hours and 19 minutes in sleep during the study and had 193 apneic episodes. The apneic episodes varied from 10-36 seconds in duration (mean 18.5 seconds). His apnea index (number of apneas/hour of sleep) was 95 and he spent 43% of his sleep time in an apneic state. All of these apneic episodes were obstructive in type, i.e., the chest wall and abdominal expansion continued during the apneic episodes (Fig. 1). The oxygen saturation was 95% at the beginning of the study, but fell repeatedly; the lowest oxygen saturation was 26% following a 36 second apneic episode. He had occasional premature cardiac beats, but no serious arrhythmias were noted.

The patient underwent tracheostomy. His postoperative course was uneventful. The daytime somnolence and shortness of breath slowly improved over the next few weeks.

Discussion

In patients with obstructive sleep apnea syndromes, many pulmonary, cardiovascular, neurologic and psychiatric problems have been described. We have not seen any reports describing renal abnormalities in patients with sleep apnea syndromes. We believe this is the first report of nephrotic syndrome occurring in a patient with documented obstructive sleep apnea syndrome.

The diagnosis of both the obstructive sleep apnea and the nephrotic syndrome was well established in this patient. This patient had very severe obstructive sleep apnea syndrome as evident by the frequency and duration of the apneic episodes. The patient was spending 43% of his sleep time in an apneic state. These apneic episodes were associated with severe hypoxemia and severe episodic pulmonary hypertension. This patient had many characteristics of nephrotic syndrome; his urine contained 4 + proteins, oval fat bodies and maltese crosses. The 24 hours urine excretion of proteins was 4.5G which was 84% albumin on protein electrophoresis. There was no clinical or laboratory evidence of any other disease causing nephrotic syndrome.

Proteinuria has been reported in patients with Pickwickian syndrome (4-6). Many of these patients had evidence of polycythemia suggesting they had severe hypoxemia. Proteinuria improved in many patients when they lost weight. It is likely that many of these patients had sleep apnea, however, nocturnal monitoring for apneas was not performed.

Weisinger, *et al*, have reported four patients with massive obesity who had nephrotic syndrome.[7] They suggested that obesity was responsible for the nephrotic syndrome. It is quite possible, however, that these obese patients had sleep apnea syndrome. Three of the four patients had daytime hypersomnolence, disturbed nocturnal sleep and nocturnal restlessness — all characteristics of sleep apnea syndrome. The fourth patient had poliomyelitis. Poliomyelitis has been reported to cause sleep apnea syndrome.[8] Sleep studies, however, were not performed in the patients described by Weisinger, *et al*.

Severe, episodic, nocturnal pulmonary hypertension associated with apneic episodes was well documented in our patient. Pulmonary hypertension has been described in patients with sleep apnea syndrome.[9, 10] Tilkian, *et al*, studied pulmonary artery pressure in 12 men with obstructive sleep apnea during wakefulness and sleep.[9] Few abnormalities were present during wakefulness, but mild pulmonary hypertension occurred in five patients with exercise. During sleep, elevation of pulmonary artery pressure occurred in 10 of 12 patients and in five patients the systolic pressure exceeded 60mmHg. Motta, *et al*, studied pulmonary artery pressure in six obstructive sleep apnea patients before and after tracheostomy.[10] Significant improvement was noted in both nocturnal pulmonary hypertension and hypoxemia in these patients following tracheostomy.

The pathogenesis of nephrotic syndrome due to sleep apnea is speculative at the present time. Many changes, eg hypoxemia, pulmonary hypertension, cardiac arrhythmias occur during apneic episodes and may contribute to the pathogenesis of nephrotic syndrome. Elevated renal vein pressure secondary to pulmonary hypertension may be responsible for proteinuria. Many cardiopulmonary diseases that cause systemic venous hypertension eg polycythemia[11], tricuspid valve insufficiency,[12] constrictive pericarditis,[13] primary pulmonary hypertension[14] have been associated with proteinuria and nephrotic syndrome. Renal venous thrombosis in an obese patient has been reported to cause nephrotic syndrome.[15] Our patient did not have any clinical evidence of other renal abnormalities or thromboembolism that might suggest renal vein thrombosis.

Another possible cause of nephrotic syndrome may be renal ischemia due to hypoxemia and/or reduced cardiac output. Severe, intermittent, nocturnal hypoxemia associated with apneic episodes occurs commonly in patients with obstructive sleep apnea. Extremely elevated pulmonary artery pressure might reduce left ventricular filling and reduced cardiac output. Evaluation of left ventricular function during apneas, however, has not been reported.

There are no studies evaluating the frequency of proteinuria and nephrotic syndrome in patients with sleep apnea syndrome. Since hypoxemia and pulmonary hypertension are common in patients with sleep apneas, renal abnormalities may also be frequent. Prospective studies are needed to evaluate the frequency of renal abnormalities, characterize the renal histologic abnormalities and the effect of therapy for sleep apneas on proteinuria.

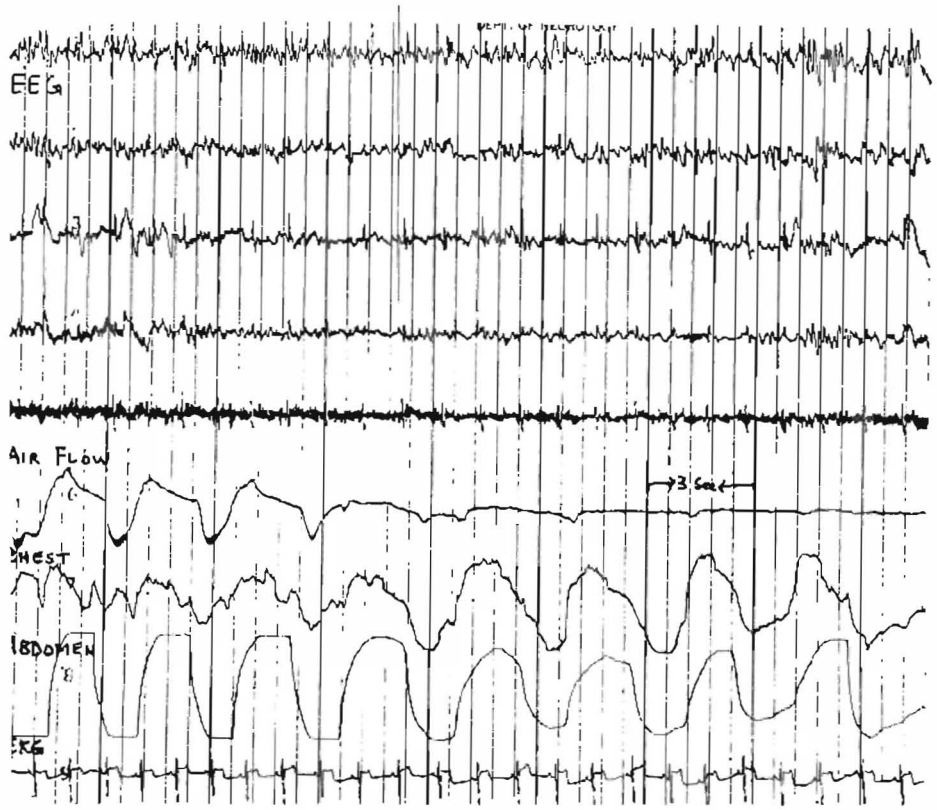

Figure 1

Polysomnogram consisting of EEG (line 1-5), airflow (line 6), thoraco-abdominal movements (line 7, 8) and EKG (line 9). After 9 seconds of airflow a 15 second obstructive apnea is seen.

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