PCO Syndrome and Sleep-related Breathing Disorders
A Case Study

Martin Konermann, Sabine Peine, Hilka Rehling and Berthold Rawert

Medical Department, Marienkrankenhaus Kassel
Akademisches Lehrkrankenhaus of the University of Marburg, Germany

A study was conducted on two female patients long suffering from progressive daily somnolence and a decrease in physical performance. Both patients were considerably overweight and had been since childhood, and both had a history of severe menstrual disorders. The patients were childless, despite one of the female’s exhaustive attempts to conceive. Each patient suffered from hypertestosteronemia, a metabolic syndrome, obstructive sleep apnea at polysomnography, and an obesity-related hypoventilation syndrome. Diagnoses of PCO Syndrome, metabolic syndrome, overlap syndrome (obstructive sleep apnea and obesity-related hypoventilation) were established. One patient received nocturnal nCPAP treatment and the other received nBiPAP treatment. The PCO Syndrome was treated by applying a combination of estrogen and gestagen. Polysomnographic findings and a daily sense of well-being were considerably improved with therapy.

CURRENT CLAIM: Patients with PCO Syndrome often have a combination of obesity, hypertestosteronemia, and a metabolic syndrome, all leading to the development of sleep-related respiratory disorders, which must receive consideration during diagnosis and treatment.

Polycystic Ovary Syndrome (PCO Syndrome, Stein-Leventhal Syndrome) is the most common endocrine disturbance in women of reproductive age (Sozen and Arici, 2000; Dewailly, 2000). The condition is a complex functional disturbance that may be associated with virilization, oligomenorrhea or amenorrhea, infertility, metabolic disturbances, hyperinsulinism, and obesity in about 50% of the cases (Dewailly, 2000; Goudas and Dumesic, 1997) (Table 1). In the majority of patients, the disease has its onset prior to puberty, and obesity appears to play a major role (Sozen and Arici, 2000; Goudas and Dumesic, 1997; Geisthövel, 1995). Besides hypertestosteronemia (Dexter and Dovre, 1998; Cistulli et al., 1994), obesity is a factor that predisposes patients with PCO Syndrome to develop sleep-related breathing disorders as well—a point that has, so far, hardly found mention in the literature. On the basis of two cases, the relationships will be described and discussed.

Table 1
Frequent Findings in PCO Syndrome

<table>
<thead>
<tr>
<th>Hirsutism</th>
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<td>Oligomenorrhea/Amenorrhea</td>
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<td>Infertility</td>
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<td>Obesity (body mass index &gt;27kg/m², waist-hip ratio &gt;0.8)</td>
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<td>Metabolic Syndrome (hypertension, hyperlipidemia, insulin resistance)</td>
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<td>Hypertestosteronemia (&gt;0.7 ng/dL)</td>
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CASE I (G.R., 33 years old)

History
Massive obesity since early childhood. Repeated failed attempts to lose weight. Menarche at age 13, irregular menses, periods of amenorrhea up to a six-month duration. No children, despite all attempts to conceive. Ovulation inhibitors for the past 12 months, with complete amenorrhea for the past nine months. Hypertension and hypercholesterolemia of six years standing, the former treated with amlodipine.

Over many years, progressive loud snoring, reportedly with periods of cessation of breathing. For the past two years, progressive loss of vigilance and diurnal sleepiness, associated with decreased physical performance.

Results of Physical Examination
Height 162 cm, weight 122.6 kg, body mass index 64.5 kg/m², waist-hip ratio 1.12. General state of health normal, virile alopecia, otherwise no pathological findings affecting the head and neck, in particular no pathology in the throat. Percussion and auscultation of heart and lungs unremarkable. Evaluation of the abdomen impossible due to massive obesity. Congestive dermatosis affecting both calves. Sparse pubic hair, otherwise typical female phenotype. No further abnormalities.

Normal Examination Findings

Laboratory Investigations: blood count, electrolytes,
Pathological Findings

**Laboratory Investigations:** Cholesterol 258 mg/dL; HDL 42.9 mg/dL, LDL 182 mg/dL; triglycerides 296 mg/dL; testosterone 74 ng/dL.

**24-hour Blood Pressure Monitoring:** Mean pressure 145/92 mmHg, loss of night dipping.

**Ultrasonography of the Abdomen:** Hepatic steatosis; evaluation of the ovaries not possible due to massive obesity. No other pathological findings.

**Epworth Sleepiness Scale:** 16 points, indicating high-grade diurnal sleepiness.

**Computer Vigilance Test** (fly catching, 3x20 minutes): Correct reactions in 82% (normal value >90%), no reactions in 18% (<10%). Thirty-four inappropriate reactions (<10). Reaction time (250-400 msec) minimum 285 msec, maximum 896 msec, average 419 msec (standard deviation 79.9%). Overall, signs of considerably reduced vigilance and rapid tiring.

**Cardiorespiratory Polysomnography:** Sleep-onset latency six minutes, sleep efficiency 81%, one complete and three incomplete sleep cycles. REM sleep and slow-wave sleep considerably shortened with increase in the wake time. Considerably disrupted sleep architecture with massive sleep fragmentation caused by 297 arousals and awakenings with an index of 56.3/h. Loud snoring, overall 76 apneas and hypopneas, one central and 75 obstructive. RDI 15.2/h. Mean oxygen saturation in the wake state 95%, during sleep 92%, in part prolonged oxygen desaturations, minimum 84%. For 34.8% of the sleep time, oxygen saturation below 90%. No increase in motoric events.

**Assessment:** Combined sleep-related breathing disorder with obstructive sleep apnea and obesity-hypoventilation syndrome.

Diagnoses

Overlap syndrome with obstructive sleep apnea and obesity-hypoventilation syndrome, PCO Syndrome with hypotestosteronemia and metabolic syndrome (massive obesity, arterial hypertension, hypercholesterolemia).

Treatment and Course

On the basis of the clinical symptoms and the polysomnographic findings, the patient was fitted out with a respiratory aid for use at night. With nCPAP treatment, adequate suppression of the respiratory disturbances could not be achieved. Under nBiPAP treatment with a pressure of 17/5 mbar, breathing during sleep was regular, snoring suppressed, and sleep quality considerably improved. Diurnal well-being was also considerably improved. Despite comprehensive counseling, a weight reduction in the first three months after initiative of nBiPAP treatment was not achievable. The PCO Syndrome was treated with an estrogen/gestagen combination (ethinylestradiol 0.05 mg, norethisteronacetate 1 mg=Non-Ovlon® 1/day), and hypertension treatment supplemented by an ACE inhibitor.

**CASE II (J.F., 25 years old)**

**History**

Overweight since childhood. Weight reduction of 10 kg over the past two years. Menarche at age 18, irregular menses, approximately one menstruation a year. Single, no sexual partner, childless.

Since the age of 12, progressive snoring and diurnal somnolence with an irresistible urge to sleep during the day. Currently, repeated episodes of falling asleep during the day in quiet situations. Total sleep time 16-18/24 hours. Occupation not possible because of tiredness.

**Results of Physical Examination**

Height 170 cm, weight 118.4 kg. Body mass index 40.9 kg/m², waist-hip ratio 0.98. Normal general state of health. Hirsutism. No pathological findings affecting the head, neck or throat. Heart and lungs unremarkable on percussion and auscultation. Abdomen soft with no pathological resistances, striae present. Sparse pubic hair, otherwise typical female phenotype. No other pathological findings.

**Normal Examination Findings**

**Laboratory Investigations:** Blood count, electrolytes, creatinine, urea, CK, GOT, GPT, LDH, gamma-GT, TSH basal, blood sugar daily profile, HbA1c, urinary status, catecholamines in 24-hour urine, dexamethasone suppression test, arterial blood gas analysis and acid-base balance. Exercise and resting ECG, two-dimensional echocardiography and whole body plethysmography.
part, long-duration desaturations to a minimum of 81%. For 24% of the total sleep time, O₂ saturation was less than 90%. No relevantly increased motoric events.

Assessment: Combined sleep-related breathing disorder with obstructive sleep apnea and obesity-hypoventilation syndrome.

Diagnoses
Overlap syndrome with obstructive sleep apnea and obesity-related hypoventilation syndrome, indicative of narcolepsy. PCO Syndrome with hypertestosteronemia and metabolic syndrome (massive obesity, hypercholesterolemia, insulin resistance).

Treatment and Course
With the aid of a nCPAP device, the sleep-related respiratory disorder was well suppressed and the quality of sleep appreciably improved. Nevertheless, an irresistible desire to sleep persisted during the day. Since concomitant narcolepsy was suspected, the patient was referred to a neurological sleep laboratory, where the diagnosis could be clarified and a successful treatment with modafinil (Vigil® 2/day) was initiated. The PCO Syndrome was treated with an estrogen/gestagen combination (ethinylestradiol 0.05 mg, norethisteronacetate 1 mg=Non-Ovlon® 1/day), but there was no influence on the patient’s body weight and the severity of nocturnal breathing disorder in the first six months.

DISCUSSION
Polycystic Ovary Syndrome (PCO Syndrome) is associated with a wide range of manifestations, which can be very burdensome and carry an unfavorable prognoses for those affected (Table 1). Obesity, virilization, and infertility together represent a powerful psychological stress which, in turn, may cause a psychoactive disturbance of eating habits and thus perpetuate the obesity (Gortmaker et al., 1993). Hypertension, hypercholesterolemia, hyperinsulinemia and, again, obesity, are factors that negatively affect the morbidity and mortality of the patients (Wild et al., 2000; Lerner and Kannel, 1986).

Our two cases show that sleep-related breathing disorders, which in turn worsen the prognoses (He et al., 1988; Young et al., 1993), may also commonly occur, a point that, so far, has been described only once in the literature (Cistulli et al., 1994).

Obesity, in particular the android form with a waist-hip ratio >0.8, appears to be one of the major factors for the comorbidity of PCO Syndrome and sleep-related respiratory disturbances. An increased incidence of sleep-related respiratory disorders in obesity is well-known. Sixty to eighty percent of patients with obstructive sleep apnea are overweight which, although not the sole causal factor for this condition, is nevertheless of substantial importance (Kopelman, 1992; Borys and Boute, 1994). But, there are no data about the prevalence of sleep-related breathing disorders in PCO patients without obesity.

Furthermore, as in our first case, massive obesity results in nocturnal alveolar hypoventilation, formerly known as the Pickwickian Syndrome, but now referred to as obesity-hypoventilation syndrome (Kopelman, 1992; Borys and Boute, 1994). Those affected suffer, in common with sleep apnea patients, from appreciable diurnal somnolence and concomitant or consecutive cardiovascular diseases (Konermann et al., 1995).

For the onset and perpetuation of PCO Syndrome, the patient's weight also plays an important role (Sozen and Arici, 2000; Goudas and Dumesic, 1997; Geisthövel, 1995). The fat is an endocrine organ in which C19 steroids are converted from less to more strong acting androgens (androstendione), and C18 steroids (estrone) are synthesized (Geisthövel, 1995). Via these mechanisms, the prepubertal obesity has a decisive influence on the development of PCO Syndrome (Goudas and Dumesic, 1997; Geisthövel, 1995). Figure 1 shows some of the known underlying endocrinological pathways.
androgens and android obesity have been demonstrated (Sozen and Arici, 2000; Geisthövel, 1995; Wang et al., 1998).

PCO Syndrome can be treated surgically by ovariectomy or ovarotomy, but this is rarely curative (Dewailly, 2000; Goudas and Dumesic, 1997; Geisthövel, 1995). Otherwise, treatment is, as in our two patients, symptomatic by the administration of ethinylestradiol and cyproterone acetate, which inhibit the secretion of gonadotropins by the hypophysis and suppress ovarian production of testosterone (Dewailly, 2000; Geisthövel, 1995; Creatas et al., 2000). Modern alternatives are the use of LH-RH antagonists and anti-androgens (Dewailly, 2000; Goudas and Dumesic, 1997; Geisthövel, 1995; Diamanti-Kandarakis and Zapanti, 2000). With this approach, however, adequate treatment of the concomitant components of the metabolic syndrome (hypertension, hyperinsulinemia, hyperlipidemia, obesity) cannot be achieved so that, in addition to hormone therapy, a holistic-internistic treatment concept should be applied. Here, treatment of hyperinsulinemia with insulin sensitizers, is a simultaneous treatment for hyperandrogenism, on account of the synthesis interactions (Sozen and Arici, 2000; Wang et al., 1998; Diamanti-Kandarakis and Zapanti, 2000; De Leo et al., 2000). When the internistic treatment concept is being considered, however, it is imperative that sleep-related breathing disorders also be taken into account.

The treatment of sleep-related respiratory disorders is oriented to the usual therapeutic guidelines. Apart from the consideration of the general rules of sleep hygiene and, if possible, weight reduction, treatment of severe obstructive sleep apnea consists in the nocturnal application of nCPAP or nBiPAP. Treatment of obesity-related hypoventilation requires —occasionally in combination with nCPAP or nBiPAP— nocturnal O₂ insufflation of 2–4 liters/minute (Sampol et al., 1996). Using this approach, an appreciable improvement in ventilation during sleep and daytime vigilance can be achieved in almost all cases.

In our second patient, the medical history together with the results of the sleep-laboratory examination and HLA typing, aroused suspicion of narcolepsy, with which HLA-DR 15 and HLA-DQ 6 are associated. The diagnosis was clarified and a successful treatment was initiated.

Conclusion

PCO Syndrome is an endocrine/metabolic disease comprised of complex symptoms: virilization, oligomenorrhea/amenorrhea, infertility, obesity, hypertension, hyperlipidemia, and hyperinsulinemia. Our two cases also indicate that sleep-related breathing disorders may also form part of the Syndrome, and thus need to be taken into account for the diagnostic work-up and treatment.

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REFERENCES


