Case Report

Multifactorial sleep disturbance in Klinefelter syndrome: a case report

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Background: Klinefelter syndrome (KS), which is related to the presence of an additional X chromosome in a man, is associated with a broad variety of physical and psychosocial impairments. While the focus is usually placed on symptoms related to hypogonadism, such as infertility, recent studies have noted evidence of poor sleep in those patients.

Case Description: We report on the case of a 44-year-old man with KS who consulted in our Sleep medicine center for excessive daytime sleepiness and delayed sleep with irregular patterns. Polysomnography (PSG) revealed sleep apnea syndrome, with both obstructive and central apnea. Peripheral temperature monitoring revealed patterns indicative of altered melatonin secretion. The present case report suggests that sleep disturbance in patients with KS appears multifactorial with the occurrence of: obstructive sleep apnea (OSA), iatrogenic central apnea due to testosterone therapy, and circadian sleep/wake disorder.

Conclusions: While this topic warrants larger studies with control groups, this case report suggests there might be specific sleep impairments, associated with three different mechanisms, in patients with KS. Those sleep disorders can worsen psycho-social and cognitive difficulties in those patients, and should therefore be screened for and treated.

Keywords: Klinefelter syndrome (KS); sleep; sleep apnea; circadian rhythm; case report

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Introduction

First described in 1942, Klinefelter syndrome (KS) is caused by the existence of an additional X chromosome in a man, leading in most cases to a 47,XXY karyotype (1). The additional X chromosome is related to a sex chromosome non-disjunction, either during spermatogenesis or oogenesis (roughly 50% each) (2). The prevalence of KS diagnosed in newborns ranges from 0.1% to 0.2%, but it is probably much higher, since it is much more commonly found among infertile (3–4%) and azoospermic men (10–12%) (3).

The typical phenotypical presentation of KS includes tall stature, gynecomastia, small testes, gynoid aspect of the hips, sparse body hair, dysmetabolic syndrome, abnormal BMI (ranging from overweight to obesity), impaired sexual desire, impaired erectile function, and mood disturbances. On a hormonal level, KS patients present with hypergonadotropic hypogonadism (high FSH and LH, low testosterone). It has been hypothesized that a large portion of KS patients actually have a much milder phenotype, and therefore remain undiagnosed (4). The phenotype may vary based on multiple parameters: number of CAG repeats on the androgen receptor gene, X-chromosome inactivation pattern, and mosaicism (5). Additional KS forms exist, with supernumerary X chromosomes (e.g., 48,XXXY),

associated with more severe phenotypes, including language and speech disabilities (5). It has been suggested that only 26% of KS individuals are eventually diagnosed (6). Future efforts should aim at increasing diagnosis, since KS patients are at higher risk of psychological, cognitive, and socioeconomic hardships (7,8).

A small number of studies have reported on the existence of sleep disturbance in KS. In one study, KS men self-reported lower scores on the Pittsburgh Sleep Quality Index, which includes subjective sleep quality, sleep disturbance, daytime functioning, and sleep medication use (9). Additionally, in this study, roughly 25% of patients reported improved sleep after testosterone therapy initiation. A subsequent study analyzed actimetry data on KS patients, and found significantly longer night wakes (10).

The present case report suggests that sleep disturbance in KS patients is multifactorial. We present this case in accordance with the CARE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-587/rc).

Case presentation

We report on the case of a 44-year-old patient whose KS was diagnosed at the age of 26 when being assessed for infertility. The patient exhibited typical KS signs, with gynecomastia, small testes, sparse body hair, erectile dysfunction, low sexual desire, and infertility (azoospermia). He also showed signs of metabolic syndrome: obesity (BMI =40 kg/m^2), hypertriglyceridemia (3.28 g/L), and borderline hyperglycemia (1.15 g/L). He was subsequently treated with intra-muscular testosterone, from 2003 to 2014 (discontinued because the patient considered its efficiency waned with time), and then from January 2021, with improvement of both erectile function and sexual desire. No psychological or psychiatric disorders were evidenced.

He consulted at our Sleep medicine department (Centre du Sommeil et de la Vigilance, Hôtel-Dieu, Paris) a year after the second initiation of testosterone therapy for increased daytime sleepiness, with an average total sleep time (TST) at night of 10 hours on his sleep log, in addition to daytime naps. In addition, wake-sleep patterns appeared irregular.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Full night polysomnography (PSG) revealed an altered sleep architecture, with a low TST (3 h 4 min), a decreased sleep efficiency (48.5%), sleep onset insomnia (sleep latency: 70 min) and delayed slow wave sleep (4 h 35 min). Notably, severe sleep apnea was evidenced (apnea-hypopnea index or AHI: 47/h), and more than half of the respiratory events were central (26.7/h) (*Table 1*). Central apnea was identified on the basis of cessation of airflow for 10 s or longer without an identifiable respiratory effort. Normal polysomnographic parameters are provided (11).

Besides PSG, the patient also had six consecutive nights recorded with a new wearable ring device assessing activity and cutaneous temperature continuously (Circular, Paris, France). The circular ring is a commercial finger-worn wellness tracker device that uses acceleration, photoplethysmogram signal, and body temperature to estimate biometric parameters such as heart rate variability, SpO_2, respiratory rate, movement intensities and other physiological parameters aimed at assessing sleep and activity. The data are automatically sent to a mobile app and transferred to a cloud server.

Data analysis showed (*Figure 1*):

- ❖ Irregular sleep wake patterns with varying sleep onset and waking up times, with total sleep times ranging from 380 to 588 min.
- ❖ Absence of significant nocturnal circadian cutaneous temperature variations throughout the 6 nights, with a mean distal temperature standard deviation of 0.48 ℃.

Highlight box

Key findings

- Klinefelter syndrome (KS) is associated with a specific combination of sleep disturbances, which should be screened for and potentially treated.

What is known and what is new?

- Other studies have showed that could KS could be associated with obstructive apnea, central apnea, and melatonin secretion abnormalities.
- The present case report exhibits that those three mechanisms can be present in a single KS patient.

What is the implication, and what should change now?

- This case reports suggests the need for physicians to evaluate sleep in KS patients, at least clinically, and refer to a sleep medicine clinic/specialist when needed.

Table 1 Polysomnography results

Parameter	Value in the patient	Normal values
Total sleep time (min)	184	388–401
Sleep efficiency (%)	48.5	84.8–86.6
Sleep onset latency (min)	70.5	14.2–16.7
REM latency (min)	43.5	93.9–100.8
Stage REM (min)/(%)	42.5/23.1	18.5–19.6%
Stage N1 (min)/(%)	19/10.3	7.3–8.5%
Stage N2 (min)/(%)	90/48.9	50.2–52.6%
Stage N3 (min)/(%)	32.5/17.7	19.0–21.8%
AHI (total)	47/h	<5/h
AHI (central)	26.7/h	NA
Mean SpO_2	96.70	94.7–95.3

Polysomnography in this patient shows sleep onset insomnia (increased sleep latency and low total sleep time), low sleep efficiency, decreased REM latency, as well as mixed (central and obstructive) apnea. Normal parameters are provided (11). REM, rapid eye movement; AHI, apnea hypopnea index; N1–N3, non-rapid eye movement; SpO_2, saturated pulse oximetry; NA, not available.

In order to assess central sleep apnea etiology: brain MRI, echocardiography, and blood gas analysis were conducted, and were all within normal limits. No opioid intake was noted.

CPAP therapy was initiated, and significantly improved sleep continuity and daytime vigilance. CPAP reports showed normalization of AHI and satisfactory observance. Secondarily, melatonin therapy (3 mg, at bed-time) was started, and allowed for a stabilization of bed-time hours. The patient noted improvement of both day-time vigilance and sleep quantity and quality. Adherence to and efficiency of CPAP therapy was assessed from the CPAP device automatic reports.

Discussion

KS is classically associated with a broad variety of physical, psychological, and social difficulties that may impact sleep. With the present case, we hypothesize that sleep impairments may also be multifactorial and related to: obstructive apnea, iatrogenic central apnea due to testosterone therapy, and sleep-wake circadian disorder associated with an altered melatonin secretion.

Obstructive apnea

KS is associated with an increased risk of visceral obesity, alongside other metabolic anomalies (dyslipidemia, insulin resistance) (12).

Obesity is the main risk factor for obstructive sleep apnea (13). Indeed, it affects both the function and structure of the upper airway. Upper airway narrowing is related to subcutaneous and periluminal fat, thus promoting airway collapse. It was found that a 10% weight gain resulted in a 32% increase in AHI (14). It appears that obstructive sleep apnea is most correlated with visceral fat, as opposed to subcutaneous and total body fat (15). Additionally it has been shown that serum leptin levels are correlated with OSA, independently of weight (16). Leptin is a hormone produced by adipose tissue playing a key role in the regulation of body weight. It has been evidenced to be elevated in patients with KS (17). Leptin was however not measured in the present case.

Previous cases of KS patients with obstructive apnea were reported: (I) one with type 2 diabetes, stage 3 chronic kidney disease, hypertension, and a 48,XXXY karyotype, (II) one with type 2 diabetes, obesity, and dyslipidemia, (III) and one with obesity and binge eating disorder (18-20). Obstructive sleep apnea has also been noted in hypogonadism of other etiologies besides KS (21).

Iatrogenic central apnea

Central apneas are far less common than obstructive apnea and are usually related to neurological disease (stroke history, tumors), heart failure, high altitude, or opioid use. In the present case, all those etiologies were ruled out.

Killick *et al*. in 2013 have reported on the effect of testosterone therapy on O_2 chemoreceptor function, affecting ventilatory response (22). In a group of patients with testosterone deficiency treated with exogenous testosterone, compared to a placebo group, they found a dampened response to hypercapnea, with an increase of the hyperoxic (as well as hypoxic) carbon dioxide ventilatory recruitment threshold. This phenomenon led in that study to an increase in the time spent below an oxygen saturation of 90% during sleep. This effect was maximal at 6–7 weeks, and waned after the 18th week.

The patient has been treated with testosterone therapy for several years upon KS diagnosis, before being discontinued, and started again 12 months prior to the present report. His sleepiness worsened after testosterone re-initiation.

We hypothesize that the central component of the

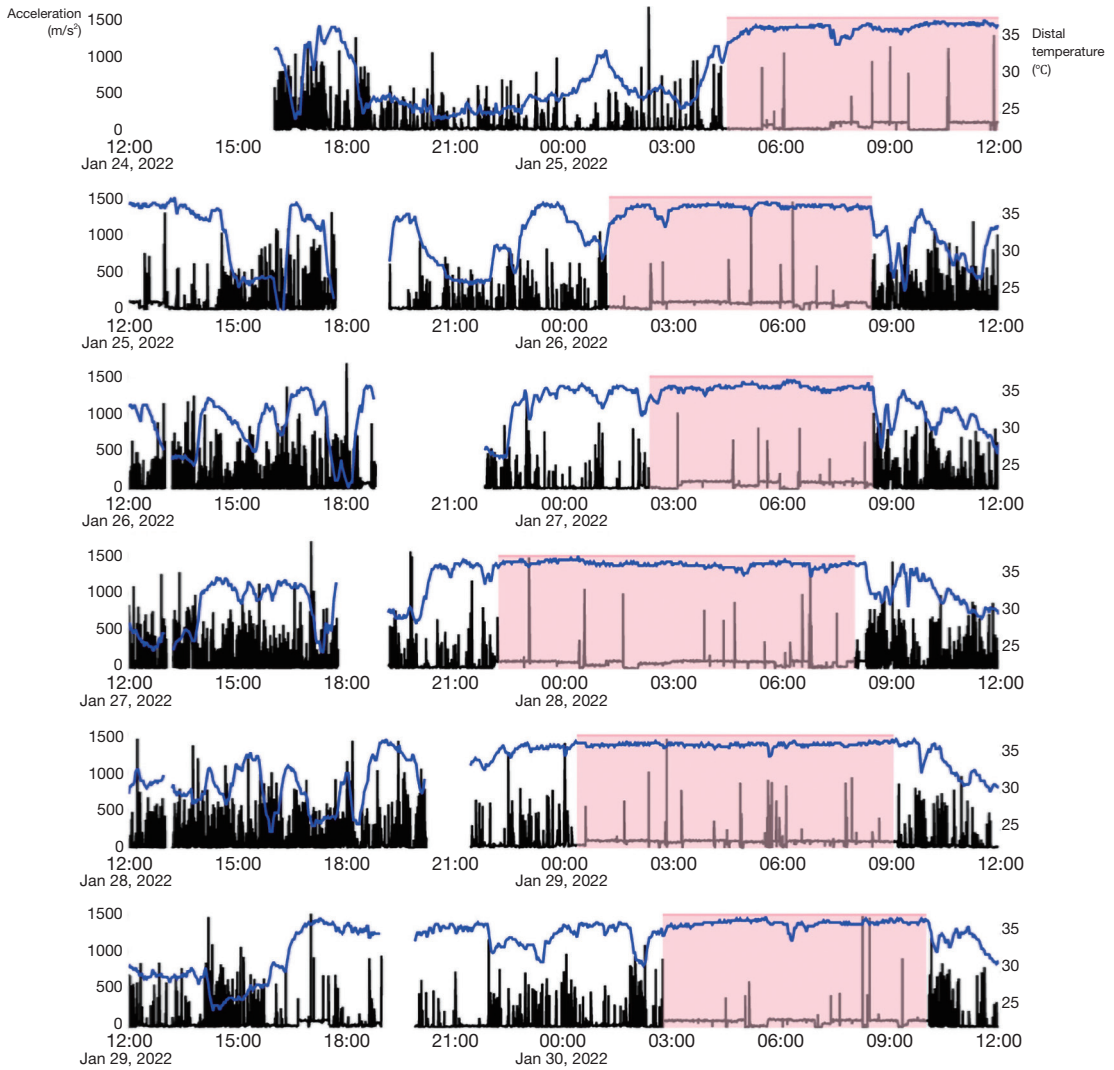

Figure 1 Actimetry and distal body temperature (°C) obtained from a wearable ring device (Circular, Paris, France) over a 6 nights and days period. X-axis shows time, from 12:00 to 12:00 (24-h time frame). Left y-axis shows movement velocity (m/s^2), and right y-axis shows distal body temperature (°C). The sporadic white spaces correspond to the times the ring had to recharged. Actimetry (black bars) shows signs of sleep-phase disorder, with varying sleep times (periods of inactivity are marked in pale red). Temperature (blue line) analysis shows stable temperature during the night time, evocative of wake sleep-cycle disorder and abnormal melatonin secretion.

patient's sleep apnea could be related to an altered ventilatory response, caused by testosterone therapy. Furthermore, this case suggests that central apnea related to testosterone therapy can continue longer than originally thought (18 weeks).

Wake-sleep cycle disorder

A decreased melatonin nocturnal secretion has been evidenced in patients with KS and low testosterone levels, and more broadly in men with hypergonadotropic hypogonadism (23-25). Men with KS were found to have an altered sleep architecture, with almost twice as less REM sleep, and a longer REM latency. Those differences were partially normalized upon testosterone therapy (25).

Indeed, melatonin plays a role in normal sleep wake regulation, with correlations between the nocturnal melatonin onset and changes in body temperature (26). It has been shown that while core body temperature decreases at night, distal temperature increases, which is related to a

peripheral temperature dissipation phenomenon (27,28). It is believed that nocturnal melatonin secretion increases blood flow and heat loss at the periphery, leading to a drop in core body temperature, and eventually to sleep initiation (29). The magnitude of this phenomenon was reported by Herberger *et al*. in 2020, with an increase from 32.5–33.25 ℃ in distal temperature during the day to 33.5–34.5 ℃ upon sleep onset and throughout the night (30). Additionally, Gompper *et al*. in 2010 showed an increase of roughly 3 ℃ between day and night (31). Distal temperature normally exhibits a gradual increase over the evening, reaching a plateau between midnight and 8:00, and then slowly decreasing over the morning (28). In the present case, distal temperature remains stable throughout the evening and night. However, peripheral temperature measurement, with a connected ring in the present case, has limitations. It is likely that outside temperature, when the patient leaves his home in the morning, has an influence on the measured temperature. Further studies should look at central temperature, and/or include controls.

One also has to take into account the differences between men and women on the effect of melatonin on nocturnal temperature and haemodynamics (32,33). Besides, sleep apnea and melatonin are interrelated, and sleep apnea itself has been correlated to obesity, with a strong correlation between BMI and AHI (34). Additional studies should be conducted looking at distal body temperature in KS patients and control subjects, as well as controlling for sex, AHI, and BMI—which can all play a role in melatonin secretion and effect.

Conclusions

With the present case, we want to alert clinicians on the fact that KS patients might exhibit multifactorial sleep abnormalities, including insomnia, obstructive apnea, iatrogenic central apnea, and sleep/wake circadian disorder resulting from an abnormal melatonin secretion. Other studies have suggested the existence of sleep disorders in KS. With this case report, we emphasize the multifactorial aspect of those sleep disorders, with intertwined causes. While a larger number of cases should be studied alongside controls, we suggest that patients with KS should be appropriately screened for sleep disorders.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-587/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-587/coif). ME consulted as a scientific advisor (non-compensated) to Circular (Lyon, France). Edouard Duquesne works for Circular (Lyon, France). The other authors have no conflicts of interest to disclose.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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