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Obstructive sleep apnea syndrome and nocturnal epilepsy with tonic seizures

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ABSTRACT – Some ambiguous symptoms may delay or lead to an erroneous diagnosis. We present a case of pure sleep, generalized tonic seizures in a patient with concomitant sleep apnea syndrome. The prolonged apneic periods with tonic muscle contracture lasting minutes and occurring exclusively at night with ensuing confusional state posed diagnostic difficulties because of the negative EEG at the beginning of the workup and the absence of other epilepsy symptoms (*i.e.* clonic phase, tongue biting, enuresis, seizures while awake). Numerous apneas on polysomnography led to the diagnosis of sleep apnea syndrome. No effect of continuous positive airways pressure (CPAP) treatment on frequency of the nocturnal tonic epileptic fits and the repetitive character of the clinical presentation combined with the typical pathologic changes on subsequent EEGs permitted to suggest the epileptic nature of the paroxysmal events. Episodes stopped following administration of clonazepam. However, spontaneous, coincidental remission of seizures cannot be excluded since the patient remained seizure free even after discontinuation of the drug.

Key words: pure sleep tonic epilepsy, sleep apnea

A prolonged apnoeic period with subsequent state of confusion with blunted response to external stimuli observed during sleep, may pose diagnostic difficulties particularly in patients referred due to presumptive diagnosis of obstructive sleep apnea syndrome (OSAS). Epilepsy, because of various clinical presentations, should be included in the differential diagnosis of witnessed prolonged apnea.

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Case report

In 2003, a 38-year-old male was referred to the Sleep Centre with a presumptive diagnosis of OSAS. The symptom that made him seek medical attention, was a nocturnal prolonged apnea with "loss of consciousness" (according to his spouse) that first occurred in May of the same year. The patient fell asleep around 11:00 pm; was later awoken by an ambulance crew at approximately 03:00 am. His spouse described what appeared to be an episode of prolonged apnea (lasting more than 5 min) accompanied by a generalized tonic contraction of muscles with eyes partially open. No clonic phase, tongue biting, or enuresis was reported. The patient was unresponsive to stimuli (including pain) and remained in a semi-comatose state for approximately 30 minutes subsequent to ces-

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sation of the episode. Upon admission to a hospital blood gases assessment revealed mild respiratory acidosis that subsided by morning. As sequels of the episode, the patient complained of generalized muscle pain, and presented, for a few days, with petechiae over the neck and trunk. The neurological diagnostic workup (EEG, CT, and NMR) revealed no obvious pathology; therefore he was referred to the Sleep Centre for further evaluation.

The clinical presentation was somewhat typical: not refreshing sleep and witnessed apneas but without daily somnolence (4 out of 24 points on Epworth sleepiness scale). The patient reported neither chronic diseases nor chronic medication use. The physical examination revealed a mildly obese patient (BMI-33.7 kg/m^2) with no other apparent abnormalities.

The polysomnography resulted in the diagnosis of OSAS: apnea/hypopnea index (AHI) was 49/h (desaturation index - 46/h); no positional effect, but REM sleep dependence was visible (AHI in REM - 60/h *vs* 45/h in non-REM) *(figure 1A)*. Sleep was fragmented (arousal index - 45/h); with stage N1 dominance, deprived of slow wave sleep. The patient became eligible to undergo a nasal-CPAP treatment trial under polysomnographic monitoring which resulted in significant improvement: AHI along with the desaturation index declined to 6/h; the sleep structure improved (reduction of stage N1 and appearance of slow wave sleep), as well as arousal index (11/h). This was due to the CPAP pressure reaching 11 mbar in REM, supine *(figure 1B)*.

In October of 2003, CPAP treatment was initiated but the patient reported no modification in the frequency of night episodes. In December of 2003 (subsequent to an additional night incident) the standard EEG registered regular and symmetric alfa rhythm with the frequency of 9 Hz and amplitude of 60 μV and scattered slow theta waves (5-6 Hz); furthermore sharp waves (0.5 s duration) with the sharp-slow wave complex occurred in temporal leads with the predominance on the left side. They were augmented by hyperventilation and stroboscopic stimulation. These findings along with the patient's history facilitated a final diagnosis of a rare form of pure sleep epilepsy presenting as isolated tonic seizures.

For the duration of two hospitalizations in 2004 for nocturnal seizures, the patient was initially treated with phenytoin, and then sodium valproate was introduced, without effect on seizure frequency. By July of 2004, the patient endured 22 episodes of seizures exclusively at night, with an average frequency of 1.5 per month, separated at times by 2-3 days, or 2-3 weeks. Disappointed by ineffectiveness of CPAP with regard to the occurrence of nocturnal fits, the patient discontinued this treatment at his own discretion. Concurrently, clonazepam (1 mg at bedtime) was introduced by another neurologist, and was subsequently tapered to 0.5 mg and discontinued after 6 months. Since the induction of this treatment there was no relapse of night seizures hitherto.

In September of 2007 the patient was invited to the follow up visit. His body habitus did not change significantly (BMI - 36.0). He reported no nocturnal seizures since July of 2004. The control polysomnography revealed a similar pattern of disordered sleep breathing with REM sleep dependence, however, a mild improvement in sleep apnea parameters was noted: AHI index dropped to 19/h (desaturation index to 23/h); similarly to the baseline, no positional effect but augmentation in REM sleep was present (AHI in REM - 35/h *vs* 18/h in non-REM).

Discussion

The difficulty in the attainment of a final diagnosis in our patient originated from the coexistence of two separate diseases, symptomatic exclusively at night. Indeed, apnoeic periods are associated with sleep; however in the preponderance of epilepsy presentations, this is usually not the case (eventually with the exception of frontal seizures). At the end of a sleep apnoeic period, there is usually a defensive mechanism of arousal that terminates the event preventing from prolonged asphyxia; in epilepsy such a defensive mechanism is absent. The prolonged, spurious apnea observed in our patient, was rather due to the tonic contracture of respiratory muscles compromising the chest wall compliance and thereby, affecting minute ventilation. Thus, the presentation of a semi-comatose, confusion phase after such an event may have the foremost differential value. Nocturnal frontal lobe epilepsy which should be included in differential diagnosis presents with episodes of dystonia (Provini *et al.*, 2000), thus, it is rather not likely that the tonic contracture of axial musculature observed in our patient may be a form of dystonia; a subsequent confusional state is also not compatible with this diagnosis.

It was reported that OSAS evoked seizures in epileptic patients and its effective treatment decreased the frequency thereof (Hollinger *et al.*, 2006; Miano *et al.*, 2009); alas the patient reported no subjective reduction in seizure frequency on CPAP treatment. Transient respiratory acidosis as a consequence of alveolar hypoventilation related to OSAS may actually protect the CNS from seizures; alternatively, frequent arousals from apneas and related sleep deprivation may facilitate epileptic seizures. Consequently, effective CPAP treatment prevents respiratory acidosis and possibly by induction of relative hyperventilation may enhance neuronal activity promoting seizures, while the reduction of arousals may induce a contrary effect. Clonazepam, a seemingly effective treatment in our patient, is thought to enhance sleep apnea due to its muscle relaxing effect. However, this may not be the case, as demonstrated in a clinical trial showing its ability to reduce AHI in OSAS patients in mono-therapy (Noseda *et al.*, 2002). Thus one can speculate on its possible effectiveness in treating both conditions in our patient.

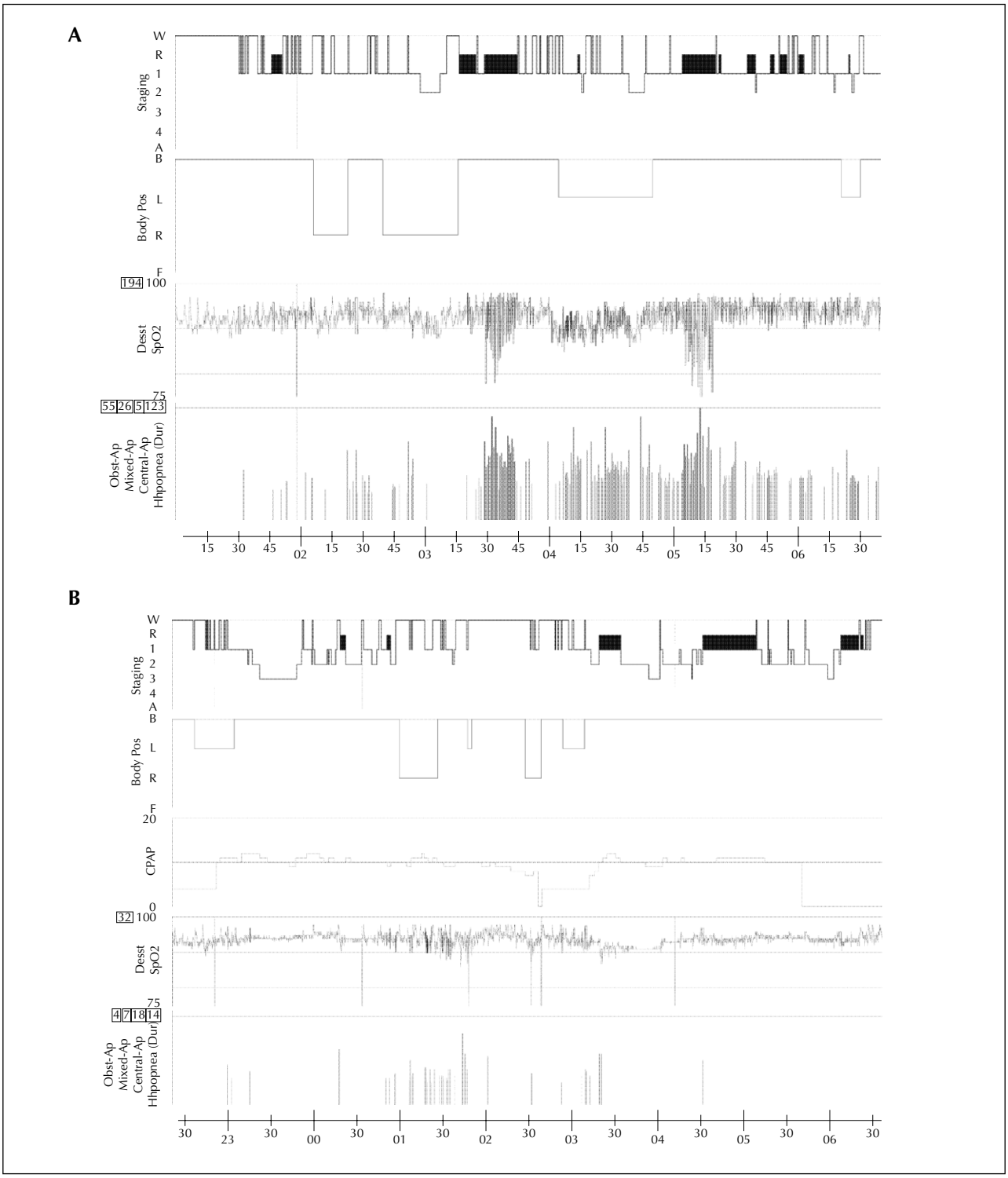

Figure 1. A) Diagnostic polysomnography. **B**) Polysomnography with CPAP treatment.
W: wakefulness; R: REM; 1, 2, 3 and 4: sleep stages; Body pos: body position; B: supine; L: left lateral; R: right lateral; F: front; Desat: desaturations; the horizontal lines represent the levels of saturation: 100, 90 and 80%, respectively; Obst-Ap: obstructive apnea; Mixed-Ap: mixed apnea; Central-Ap: central apnea; Hypopnea (Dur): hypopneas; the height of the vertical lines represents the relative duration of respiratory events; the numbers within the squares represent the amount of desaturations and respiratory events; CPAP: the horizontal line represents the pressure of 10 mbar; horizontal axis: time in hours.

Nevertheless, both diseases seemed to be causally dissociated because effective CPAP treatment of OSAS had no effect on seizure frequency, so the putative effect of clonazepam on OSAS is negligible. Apart from the speculative efficacy of clonazepam, the spontaneous, coincidental remission of seizures cannot be excluded.

The prevalence of epilepsy in different populations lies between 0.5 and 1%; while pure sleep epilepsy is rare and constitutes about 6% (95% CI: 4.1-7.7%) of all epilepsy cases (Gibberd and Bateson, 1974). From these data the prevalence of pure sleep epilepsy in a population may be estimated as 0.03 to 0.06%. OSAS with prevalence in adult population around 5%, may be considered as an independent phenomenon. Thus the coexistence of pure sleep epilepsy and OSAS may be calculated as up to 3 per 10^5, but 85% of all cases with pure sleep epilepsy present as generalized tonic-clonic seizures making the combination of both disorders with described phenomenology even rarer – *i.e.* ca 5 per million (D'Alessandro *et al.*, 2004).

Conclusion

We present a case of pure sleep epilepsy that necessitated discrimination from a coexisting sleep apnea syndrome. To the best of our knowledge this is the first case reporting the coexistence of these two diseases, with tonic seizures mimicking apneas. Any clinical presentation, reminiscent of our case with prolonged asphyxia due to tonic muscle contracture along with a semi-comatose state requires a wider diagnostic panel including a full neurological workup. □

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Disclosure.

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