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CASE REPORTS

Transient Central Sleep Apnea Runs Triggered by Disorder of Arousal in a Child

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We report the case of a 5-year-old girl with frequent nocturnal episodes of disorder of arousal (confusional arousals, sleep terrors, and sleep walking), occurring at the end of periods of slow wave sleep, followed by return to sleep accompanied by the occurrence of periodic breathing with a run of approximately 10 to 20 central events. The duration of the central events and oxyhemoglobin desaturation were both maximum at the beginning of each run and became progressively less prominent with the development of the sequences. Night episodes disappeared with bedtime clonazepam but behavioral problems occurred as a paradoxical response; thus, clonazepam was stopped. Sleep extension and melatonin were then started, which were followed by a reduction of night episode frequency and intensity. This observation appears to be the first report of central sleep apnea sequences triggered by parasomnia and, if confirmed by additional reports, it might be considered to be a possible new classification of "complex parasomnia."

Keywords: central apnea, night terrors, parasomnia

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INTRODUCTION

The International Classification of Sleep Disorders, Third Edition (ICSD-3)[1] includes the diagnostic criteria of disorder of arousal (DOA): the episodes are recurrent, there is incomplete awakening from sleep, no dream recall or cognition, amnesia for the episode, inappropriate or absent response to parental intervention, and not associated with other medical disorder or medication effect. In childhood, DOA occurs essentially with three main clinical presentations: confusional arousals, sleep terrors, and sleep walking.[1] Although obstructive sleep apnea fragments sleep and has been reported to favor the occurrence of parasomnia events,[2] to our knowledge the association between central sleep apnea (CSA) and DOA has never been reported before. We describe here the case of a child with CSA runs triggered by the occurrence of DOA events.

REPORT OF CASE

A 5-year-old girl was referred for evaluation of frequent nocturnal events that started more than 1 year earlier with apparent progressive worsening in frequency and intensity. Sleep history showed a bedtime routine that started at approximately 7:00–7:30 PM with brushing teeth, putting on pajamas, and playing with her dolls. She was able to fall asleep without parental intervention, but her sleep latency was often delayed until 11:00 PM. After sleep onset there were an average of 3 episodes per night, approximately every 1 to 2 hours, consisting of a combination of screaming, crying, talking, and suspicious for sleepwalking (she would go to the parents' room and appear confused). The parents did not notice any stereotypic movements or repetitive behaviors; there was no recall and there was return to sleep within a few minutes. The child did not have any symptoms of apnea, gasping, increased work of breathing, restless legs, daytime sleepiness, or hyperactivity. She took a nap during the day from 1:00–2:30 PM.

There was no significant family history, or past medical or surgical history. Review of systems was negative. Brain magnetic resonance imaging was normal.

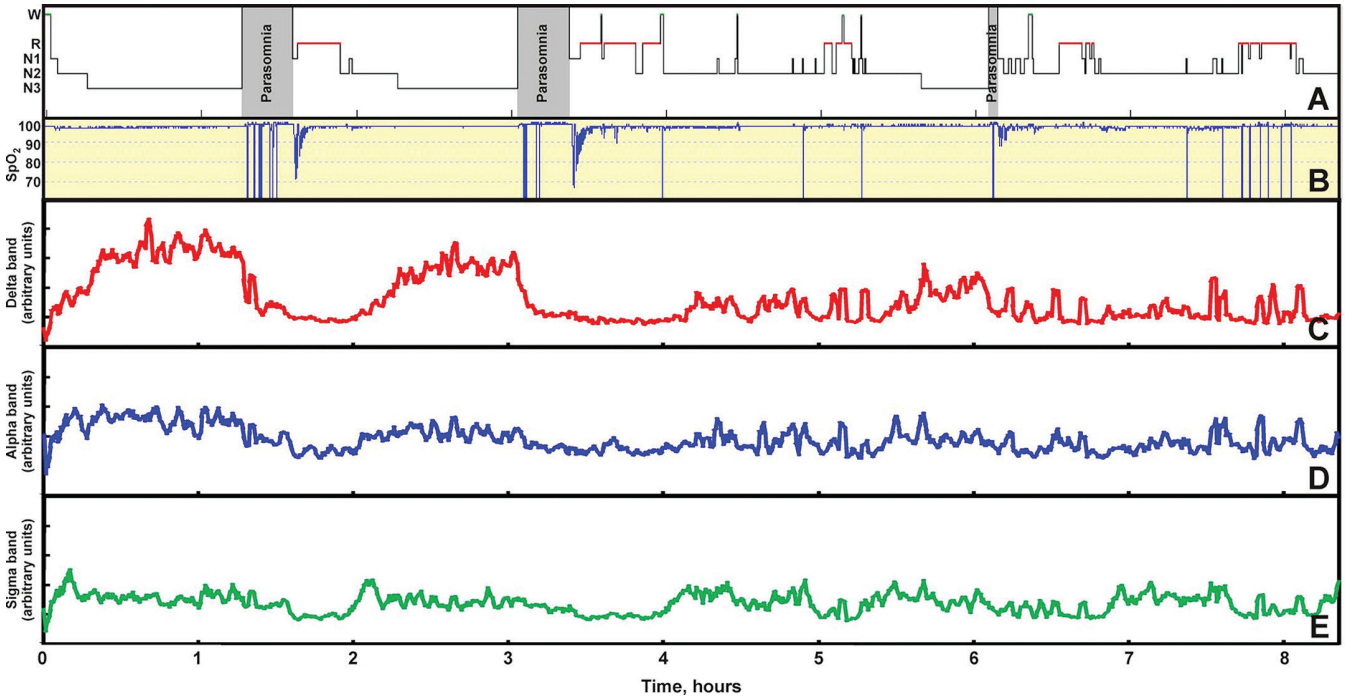
Physical Examination

The child was delightful and cooperative. Her vital signs were: heart rate 93 bpm, blood pressure 98/50 mmHg, temperature: 36.9°C (98.5°F), respiration rate 12, oxyhemoglobin saturation 98%, weight 20.5 kg, height 112.7 cm, and body mass index 16.14 kg/m^2 (75th percentile, Z = 0.68). Her tonsil size was 2+ and her lungs were clear and normal the remainder of the examination.

Electroencephalogram

Twenty-four-hour video electroencephalogram (EEG) showed two marked episodes logged by the family, described as typical events. The first episode occurred at 1:54 AM and aroused the patient from slow wave sleep. The patient clinically had an arousal, sitting up in bed and screaming. The EEG revealed an arousal manifested by large amounts of diffuse delta compatible with delta hypersynchrony. This rhythm and the behavior lasted approximately 30 seconds, at which point the child fell back to sleep with immediate onset of spindles and vertex waves compatible with normal stage N2 sleep. A similar episode of a minor arousal was captured at 3:15 AM, again revealing no associated epileptiform or pathologic electrographic activity.

Figure 1—Hypnogram of the diagnostic night, all-night oxygen saturation, and the outline of the EEG power computed from the channel C3-M2.



Hypnogram of the diagnostic night **(A)** plotted together with the all-night oxygen saturation **(B)** and the outline of the EEG power in the delta (0.5–4 Hz) **(C)**, alpha (8–11 Hz) **(D)**, and sigma (11–16 Hz) **(E)** bands, computed from the channel C3-M2. Demonstrating that events arouse from delta sleep and there was no wakefulness. EEG = electroencephalogram.

Polysomnography

Complete full-night video polysomnography (PSG) recording was obtained on a separate night from EEG. PSG showed a total recording time (TRT) of 500.9 minutes, total sleep time (TST) of 490.9 minutes, and sleep efficiency (TST / TRT) of 98.0%. The sleep latency (SL) was 0.0 minutes and the latency to the first occurrence of stage R was 111.7 minutes. The percentage of TST in each stage was: stage N1 sleep 8.1%, stage N2 sleep 41.3%, stage N3 sleep 33.6%, and stage R sleep 17.0%. Arousal index (AI) was 6 events/h. Periodic leg movement index (PLMI) was zero. Central apnea-hypopnea index (AHI) was 5 events/h and obstructive AHI was 3 events/h. Although within mild abnormal range, all events occurred exclusively after a night terror.

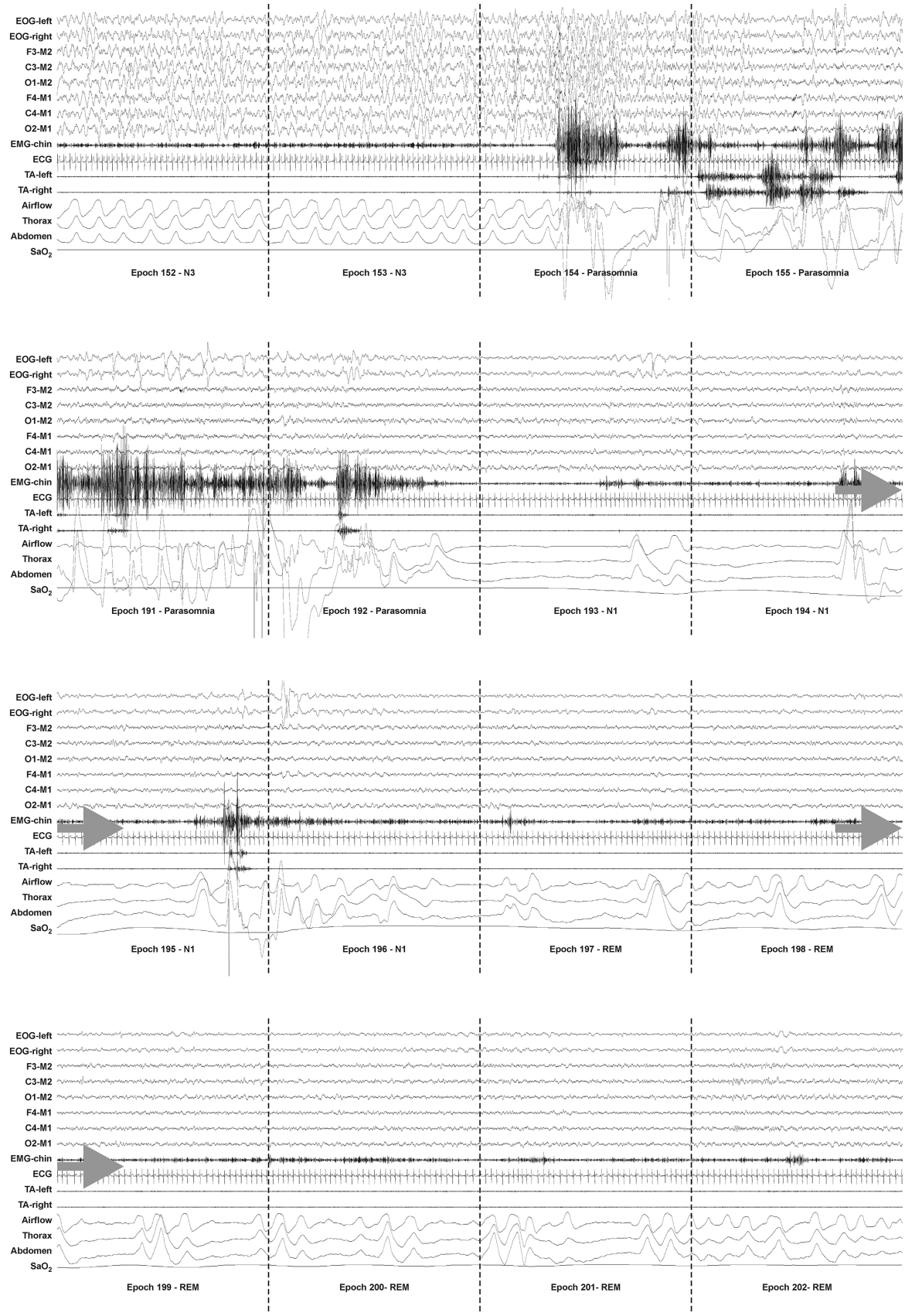
Three episodes occurred, all at the end of stage N3 sleep periods (at 10:29 PM, at 12:15 AM, and at 3:17 AM) of variable duration (19.5, 20, and 3.5 minutes, respectively) starting with arousal activity and continuing with mixed EEG features of sleep, wakefulness, presence of eye movements, and electromyography activity over the chin and limbs. There were no triggers to the events. Behaviorally the child screamed on the first episode, and cried and mumbled on the other episodes. In the first two events, the behavioral episodes were followed by rapid return to non-rapid eye movement (NREM) sleep, soon followed by rapid eye movement (REM) sleep, while NREM sleep remained for long after the third short episode (**Figure 1**). In all cases, after the parasomnia ended, return to sleep was accompanied by the occurrence of periodic breathing with a run of 12, 22, and 10 central events, respectively. The duration of the central events was maximum at the beginning of each run (the first one after the second event lasted for 54 seconds), as well the oxygen desaturation, and both became less prominent with the development of the sequences until their completion (**Figure 2**). The central events were not associated with arousals and the child returned to sustained sleep.

DISCUSSION

Some of the episodes presented by the patient reported here met ICSD-3 criteria for night terrors: fear, autonomic activation, and screaming; some met ICSD-3 criteria for confusional arousals: confused behavior and absence of terror.[1] Although not completely clear, the patient may have also experienced episodes of sleep walking on the nights she went to the parents' room. The child experienced at least three episodes a night and, as seen in **Figure 1**, they were associated with a run of central apneas followed by significant desaturation. How can we explain the breathing pattern after the parasomnia event?

Changes in respiratory patterns are seen in different sleep stages. For example, stage N3 sleep is characterized by a longer duration of inspiration and regular breathing whereas stage R sleep is characterized by irregular respirations with short inspiratory cycles. The timing and characteristics of breathing during various sleep stages and sleep-wake transitions are carefully orchestrated by the interactions between the central

Figure 2—PSG recording of the first parasomnia episode.



The top panel shows the beginning of the episode with the passage from stage N3 sleep to the parasomnia while the remaining panels show 16 consecutive epochs containing the end of the behavioral episode and the run of central breathing events until return to a normal breathing pattern. PSG = polysomnography.

nervous system respiratory nuclei and the peripheral receptors. One theory is that breathing patterns are disrupted simply by changes in sleep stages and sleep-wake transition. Periodic breathing and central apnea are known to occur after arousals and studies have shown NREM sleep instability in children with night terrors[3] and sleepwalking[4,5]; however, NREM sleep instability has been reported to precede parasomnia episodes and probably is a triggering factor. In our patient, the runs of central apnea strictly follow the end of the parasomnia episodes, the events were not associated with arousals nor with sleep instability, and the child returned to sustained sleep.

Breathing is initiated and controlled by respiratory nuclei in the brainstem. These nuclei receive many afferents from various places both peripherally and centrally.[6] Peripheral afferents include vagal signals from the lungs and chemoreceptors in the carotid and aortic bodies. The central afferents include projections from the central nucleus of the amygdala (ACE). The ACE also projects to the nucleus of the tractus solitarius. The ACE receives input from the cortical and subcortical forebrain. Stimulation of the ACE results in long and sustained inspiratory effort.[7] The amygdala plays a role in fear and anxiety response and blood pressure and respiration. A second postulated theory can explain this phenomenon by activation of the ACE with disruption in the breathing signals to the pons. Dlouhy et al. showed that stimulation of the amygdala produced apnea.[8] This may be secondary to connections with the pons. Lacuey et al. also confirmed the role of the amygdala and hippocampus in central apnea and seizures.[9]

A third postulated theory includes autonomic dysregulation. Vagal sensory neurons constitute the major afferent supply to the airways and lungs. The central projections of all vagal afferents end in the brainstem where they connect to second-order neurons that project to other brain stem nuclei, ascend to higher brain regions, or descend to the spinal cord. When there are increased sensory inputs, a "synaptic gain" can occur, rendering the central nervous system hypersensitive so that reflexes are amplified, in this case, affecting respiration. When this altering coupling of sensory stimuli occurs, innocuous stimuli evoke responses characteristic of noxious stimuli. For example, bronchopulmonary C fibers transmit signals to the nucleus of the tractus solitarius via vagal afferents, which in turn are transmitted to the pre-Bötzinger nuclei in the ventral respiratory group of the pons, potentially generating central apnea.[10]

The differential diagnosis includes frontal lobe seizures and nocturnal panic attacks. Frontal lobe seizures usually occur more than three times a night, occur at various times, arise from stage N1 or N2 sleep, last 1 to 2 minutes, and exhibit stereotypic movements.[11] Panic attacks usually occur in the early morning hours, have associated anxiety symptoms, and start in adolescence and younger adulthood.[12]

In our patient, clonazepam 0.125 mg was initiated in the laboratory during a second PSG to monitor breathing and titrated to 0.250 mg to stop the night episodes. On the second PSG, clonazepam 0.125 mg was given at bedtime. SL was 16 minutes, TST was 430 minutes, sleep efficiency was 88%, AI was 3.5 events/h, and PLMI was zero. Central AHI was 2 events/h and obstructive AHI was 0.6 events/h. The central apneas only occurred after a single night terror (at 11:45 PM) followed by a similar breathing pattern as the events described in the first PSG. A second dose of clonazepam 0.125 mg was given at 12:10 AM without further nocturnal episodes of night terror or sleep-disordered breathing. After a couple of days, the parents reported the disappearance of night episodes and increased behavioral problems during the day, including aggression and agitation. A paradoxical response to clonazepam was considered, and the medicine was stopped. Sleep extension was recommended and melatonin 3 mg at bedtime was given to help her sleep earlier. The night episode frequency was reduced to one episode every 2 to 3 days and it was very mild in intensity.

To our knowledge, this is the first report of CSA sequences triggered by parasomnia and we suggest to carefully assess respiration in children with DOA.

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DISCLOSURE STATEMENT

Work for this study was performed at the UCSF Children's Hospital Oakland. All authors have seen and approved the manuscript. The authors report no conflicts of interest.