DISORDERS OF AROUSAL AND DREAM ENACTMENT: EXPLORING THE WORLD OF NREM AND REM PARASOMNIAS

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ICSD-3 Criteria

Parasomnias classification is determined (primarily) by the state out of which they arise. NREM-Related Parasomnias include the disorders of arousal: confusional arousals, sleepwalking, and, sleep terrors. Sleep related eating disorder (SRED), is another NREM-Related Parsomnia that for all practical purposes is sleepwalking with eating. REM-Related Parasomnias include REM sleep Behavior Disorder (RBD), recurrent isolated sleep paralysis, and nightmare disorder. In addition, there are several abnormal nocturnal behavior disorders that do not consistently stratify into either sleep state. These conditions, the Other Parasomnias include: sleep enuresis, sleep related hallucinations, and the fantastically named exploding head syndrome (AASM 2014).

This syllabus, and lecture will focus upon the disorders of arousal (with SRED) and RBD. Sleep enuresis, exploding head syndrome, sleep related hallucinations, and sleep paralysis will be briefly mentioned.

NREM PARASOMNIAS

Introduction and ICSD-3 Criteria

Disorders of arousal are abnormal nocturnal behaviors with impaired judgment and amnesia. Unlike the ICSD-2, where each individual disorder of arousal had it's own criteria the ICSD-3, published in 2014, has four unifying criteria: recurrent episodes of incomplete awakening from sleep, the patient unable to be redirected during episodes, limited to no dream imagery, as well as partial or complete amnesia. Ambulation out of bed distinguishes sleepwalking from confusional arousals; if the patient eats the parasomnia is SRED. Sleep Terrors, differ from the other disorders of arousal as the patient demonstrates intense fear (episodes typically begin with a scream) and signs of autonomic arousal (mydriasis, tachycardia, tachypnea, diaphoresis) (AASM 2014).

Etiology-The Three P's

Disorders of arousal occur when the cortex incompletely dissociates from deep NREM sleep. Pressman's 3P model suggests that *predisposed* patients are *primed* by conditions that impair normal arousal. Parasomnias are then *precipitated* by events that lead to sudden wakefulness (Pressman 2007). Well known priming factors include sleep deprivation and sedative medications (Dolder 2008). Precipitating factors can be internal pathologies (such as sleep disordered breathing) or external factors (noise) (Espa 2002, Guilleminault 2003 and 2005, Pilon 2008).

While much is known about *priming* and *precipitating* factors we have little insight into which patients are *predisposed* to NREM parasomnias. Some cases are familial but their genetic basis is elusive (Hublin 1997). Further, very little is known about the mechanisms driving behavioral expression. For example, why do some patients sleepwalk and others only have confusional arousals. Why do some sleepwalkers eat (i.e. SRED)?

Predisposed by Ekbom's syndrome

Scrutiny of the medical literature would suggest that many cases of NREM parasomnias, in particular SRED, are driven by underlying restless legs syndrome (RLS). In particular when RLS patients are understandably mistaken, and treated, for psychophysiological insomnia.

RLS affects approximately 8-10% of the adult population and is thus a common causes of sleep initiation and maintenance difficulties (Allen 2005, AASM 2005). RLS sleep failure stems from a different mechanism than the cognitive hypervigilance of psychophysiological insomnia (INS). However, RLS is easily mistaken for INS and treated as such. Further, commonly prescribed alpha-2 delta ligands (gabapentin, pregabalin) and opioid agents,

will partially mask motor restlessness and thus obscure the diagnosis. Of note alpha-2 delta ligands and opioid agents are pervasive amongst patients presenting to a neurology clinic. Thus it is not unexpected that many patients with RLS will be mistakenly treated with therapies developed for INS, such as benzodiazepine receptor agonists (Howell 2012b).

In addition to the classical symptoms, RLS is characterized by various non-motor nocturnal urges (Provini 2009 and 2010). Wakeful evening and nocturnal (after falling asleep but prior to final morning awakening) eating is common (60%) in RLS and the feeding behavior closely resembles the motor activity. Like the compulsion to move, RLS patients often describe an urge to eat, not driven by hunger, but instead by the perception that eating will allow for sleep initiation (Provini 2009, Howell 2012a). This restless eating is unique to RLS. For example, patients with INS do not frequently eat at night nor do they describe nocturnal eating urges (Howell 2012a). Further, RLS patients who smoke tobacco unlike non-RLS smokers, smoke later into the evening and were far more likely to smoke after a middle of the night awakening. This restless smoking among RLS patients commonly coincides with nocturnal eating and appears to be one reason for failed smoking cessation (Provini 2010).

Incredibly, nocturnal eating and nocturnal smoking were both observed by Ekbom in his original 1960 paper describing RLS (Ekbom 1960).

"They often have to get up and walk, "like a caged bear," to quote one of my patients, or they go into the kitchen and get something to eat. Others sit and smoke…"

Importantly, nocturnal eating and SRED (amnestic binge eating) in RLS is not caused by dopaminergic RLS therapies, treatments that can trigger impulsive behaviors such as gambling (Driver-Dunckley 2007). Nocturnal eating and SRED present prior to or concomitant with, but not after, motor restlessness (Provini 2009, Howell 2012a). Further, when the presence or absence of nocturnal eating behaviors are known prior to treatment, nocturnal eating and SRED do not emerge after the start of dopaminergics (Howell 2012a). Further, impulsive behaviors on dopaminergic agonists are common in Parkinson's disease (PD) but not RLS alone (Ondo 2008). This is likely related either to the higher doses typically needed to treat PD or possibly related to underlying PD pathology. Finally, several studies have noted that dopaminergic agents suppress feeding and successfully resolve both wakeful nocturnal eating and amnestic SRED (Martin-Iverson 1988, Schenck 1991, Provini 2005, Mahowald 2010, Howell 2012b).

Primed with benzodiazepine receptor agonists

As patients with RLS are *predisposed* to ambulation and eating it is not unexpected that parasomnias characterized by walking (sleepwalking) and/or eating (SRED) would emerge when *primed* with a sedative agent (Morgenthaler 2002, Dolder 2008). BRA's impair memory and executive function through central GABAa receptors (Canaday 1996, Tsai 2007, Dolder 2008). In one investigation 80% of RLS patients that had been exposed to sedative-hypnotic agents had subsequent sleepwalking or amnestic SRED (Howell 2012a).

Conversely zolpidem induced NREM parasomnias are rare when prescribed to patients with INS where RLS has been carefully excluded. In the investigation noted above only 2 out of 25 (8%) INS patients treated with sedative hypnotic agents report amnestic behavior and in neither case did the events persist (Howell 2012a). These findings are consistent with previous reports where NREM parasomnias are rare (<1%) in clinical trials where RLS is an exclusion factor (Holm 2000).

In conclusion, BRA induced sleepwalking, in particular SRED, is predominantly mistreatment of RLS as INS. This is not unexpected as RLS is characterized by nocturnal urges to ambulate and eat, often difficult to diagnose, frequently masked by medications, and thus easily mistaken and treated as INS. As BRA's such as zolpidem (39 million prescriptions in the US in 2011) inhibit executive and hippocampal function it is not unexpected that that these agents would unleash inappropriate amnestic walking and eating behaviors.

NREM Parasomnia Management

Management of NREM parasomnias, as with all parasomnia management, should initially focus on environmental safety by modifying the sleeping environment. Removal of bedside firearms and other weapons is of paramount importance. Windows, or other exits that could result in a fall, should not be easily accessible. Automatically

locking doors are to be avoided as sleepwalkers may ambulate outside of their residence without means of reentry. If necessary, a door alarm is often useful to alert other family members that the patient is ambulating through the house.

Attempts should be made to eliminate sedating agents as well as to identify and treat comorbid sleep and circadian disorders. Most cases of sedative-induced sleepwalking behaviors are terminated following discontinuation of offending medications. Further, sleepwalking typically resolves once the underlying sleep deprivation, obstructive sleep apnea, or restless legs syndrome are effectively addressed (Guilleminault et al 2005; Howell 2012; Howell and Schenck 2012).

When serious nocturnal behaviors persist despite these interventions or in situations with a high probability of injury, pharmacotherapy may be considered. A variety of different therapies, typically benzodiazepines, have been reported as effective for sleepwalking. However, at present, there is a paucity of clinical trial data. Instead, a consensus has arisen, based on case series and small clinical trials. Importantly, national and international agencies that regulate drug approval do not recognize these treatments (Harris and Grunstein 2009; Howell 2012).

The most commonly reported pharmacological treatments for sleepwalking are intermediate- or long-acting benzodiazepines. Most commonly reported agent is clonazepam. The efficacy of clonazepam would be paradoxical as other sedative hypnotics, such as benzodiazepine receptor agonists, frequently induce amnestic nocturnal behavior (Dolder and Nelson 2008). Limiting side effects of clonazepam include morning sedation as well as gait impairment and pertain to its prolonged duration of action.

In conclusion, the most effective sleepwalking therapy is to identify and treat comorbid predisposing, priming, and precipitating conditions. Even subtle sleep-disordered breathing or motor restlessness should be considered as a potential target to resolve sleepwalking (Guilleminault et al 2005; Howell 2012, Howell et al 2015). The patient should also attempt to optimize the duration and circadian timing of sleep. Finally, if pharmacological therapy is utilized, patients should be made aware that evidence supporting these treatments is minimal.

REM PARASOMNIAS
REM Sleep Behavior Disorder

Introduction and ICSD-3 Criteria

Under normal physiological conditions REM sleep is characterized active dream mentation combined with skeletal muscle paralysis. In REM sleep behavior disorder (RBD) the skeletal muscle paralysis is lost leading to dream enactment behaviors such as: punching, kicking, jumping, or thrashing about in bed. These behaviors are potentially injurious to the patient and/or bed partner (Howell 2012, Howell and Schenck 2015).

According to the most recent ICSD-3 criteria a patient has RBD if they have: repeated episodes of sleep-related vocalizations and/or complex motor behaviors, PSG demonstrates that these behaviors occur during REM sleep or due to clinical history of dream enactment presumably arise from REM sleep, and PSG demonstrates REM sleep without atonia. Thus RBD is the only parasomnia that requires a sleep study to confirm the diagnosis (AASM 2014).

RBD etiology

Among cases not associated with medications or narcolepsy (see below) RBD is a prodromal syndrome of alpha-synuclein pathology (such as Multiple System Atrophy, or Dementia with Lewy Bodies). Separate case series indicated that between 81-91% of surviving patients ultimately convert to a neurodegenerative disorder (Schenck et al 2013, Iranzo et al 2014). RBD is often combined with other non-motor symptoms such as anosmia and constipation and when present often predicts a more aggressive clinical course (Romenets et al 2012).

Among PD patients approximately 40% have RBD (Boeve 2010, Sixel-Doring et al 2011, Nihei et al 2012, Poryazova et al 2013). PD+RBD patients are more likely to manifest the non-tremor predominant subtype and suffer from freezing of gait (Romenets et al 2012, Videnovic et al 2013). As noted in the case below, James Parkinson reported the combination of both dream enactment and gait freezing in the same 72-year old man in his original 1817 monograph on the disorder that would later bear his name.

Case VI

"His attendants observed, that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm…

"…if whilst walking he felt much apprehension from the difficulty of raising his feet, if he saw a rising pebble in his path? He avowed, in a strong manner, his alarm on such occasions; and it was observed by his wife, that she believed that in walking across the room, he would consider as a difficulty the having to step over a pin."

James Parkinson 1817

Other etiologies of RBD include the orexin deficiency of narcolepsy as well as serotonergic antidepressant medications. A recent investigation suggests that antidepressant medication induced RBD may instead be an early signal of neurodegeneration (Postuma et al 2013) and not necessary just a toxic response from the agent.

Management

The spectrum of dream enactment behavior in Rapid Eye Movement (REM) sleep Behavior Disorder (RBD) ranges from benign hand movements to violent life-threatening actions (thrashing/lunging). The goal of RBD management is to prevent sleep related injury. Thus educating the patient's and bed partner's about the potential dramatic consequences of dream enactment is an important first step as subsequent measures ranging from environmental modification to the treatment of co-morbid sleep disorders will depend upon their adherence and follow through.

If concerning dream enactment persists once ancillary sleep disorders, in particular sleep related breathing disorders, are treated and RBD inducing medications are minimized then medication therapy is reasonable. The most commonly employed agents include low dose (0.25-1.0mg) clonazepam or high dose (6-18mg) melatonin taking at bedtime. However clinicians should be aware that the evidence supporting these therapies is primarily based upon case series, small clinical trials, and expert consensus (Boeve 2010, Howell and Schenck 2015).

As RBD is a prodromal syndrome of alpha-synuclein pathology management should include monitoring for signs of neuro-degeneration. This includes continued careful clinical follow-up for subtle abnormalities of movement and cognition.

Sleep Enuresis

Sleep enuresis is defined by recurrent (at least twice a week) involuntary urination during sleep that has lasted at least 3 months. By the age of six 90% of children have developed 24 hour a day control of micturition. Sleep enuresis is either primary, in a patient who has never developed nocturnal continence, or secondary, in a patient who had previously been continent but then subsequently lost bladder control at night (AASM 2014).

Primary sleep enuresis is often either a failure of the brain to arouse from sleep in response to bladder expansion or due to inappropriate bladder contraction during sleep. Familial cases are common and boys are more commonly affected than girls. The vast majority of primary sleep enuresis cases spontaneously resolve. The most commonly prescribed medication for primary enuresis is desmopressin, an analog of desmopressin, with anti-diuretic properties. Non-pharmacological treatments include: evening fluid restriction, scheduled awakenings, and enuresis bed alarms (Wills and Garcia 2002)

Secondary sleep enuresis is most commonly due to other sleep disorder such as obstructive sleep apnea (OSA). A collapsing airway in combination with increased respiratory effort decreases intrathoracic pressure and subsequently, atrial naturetic peptide is secreted from the heart leading to increased urinary output. In addition OSA also leads to enuresis by impairing cortical arousal through increased homeostatic sleep drive combined with increase autonomic activity. Other etiologies of secondary sleep enuresis include urinary tract disorders, nocturnal seizures, and disorders that lead to increased urine production (AASM 2014).

Exploding Head Syndrome, Sleep Related Hallucinations, and Sleep Paralysis

The sleep-wake transition is associated with experiences that include the exploding head syndrome, sleep related hallucinations (hypnogogic or hypnopompic hallucinations), and sleep paralysis (AASM 2014, Howell 2012).

The theatrically named exploding head syndrome describes a startling auditory hallucination at the initiation of sleep. Patients claim they are awoken buy the sudden loud noise and may describe the feeling as “an exploding head”. The character of auditory hallucination varies from simple (a church bell) to complex (the sound of someone pounding on several piano keys). Myoclonic jerks often co-occur with the auditory phenomena.

Sleep related hallucinations (either hypnogogic or hypnopompic) are typically visual and in human or other animal form. They are often associated with anxiety and a foreboding sense of terror. This feeling is heightened if hallucinations are combined with sleep paralysis. Of note, sleep paralysis is often perceived as a sense of dyspnea, from the lack of accessory muscle of respiration (it is a persistence of REM atonia into wakefulness), with frightening dream mentation, such as a demonic presence. Various cultures have paranormal or religious interpretations to these experiences, as patients without history of a thought disorder, will describe in vivid detail: alien abduction, sexual assault by animals, or demonic possession. The painting by John Henry Fuseli, “The Nightmare” (1781) illustrates REM sleep-to-wake experiential phenomena. The woman in the painting clearly demonstrates the atonia of sleep paralysis combined with frightening visual hallucinations.

These experiential parasomnias most often occur in the setting of either sleep deprivation or comorbid sleep pathology. Sleep Paralysis and sleep related hallucinations are part of the classical quatrad of narcolepsy along with hypersomnolence and cataplexy. These conditions lead to experiential parasomnias by impairing a sharp transition between sleep and wakefulness. Treating underlying sleep disorders and optimizing the duration and circadian timing of sleep will successfully treat the vast majority of cases. REM suppressing agents, antidepressants, can sometimes be useful for challenging cases of sleep paralysis and sleep related hallucinations (Howell 2012, AASM 2014).

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