

Chapter 2

Pathophysiology of Parasomnias

Suresh Kotagal

Introduction

Parasomnias may occur at the transition from wakefulness to non-rapid eye movement (NREM) sleep, e.g., hypnic starts, during NREM sleep, e.g., teeth grinding, head banging, sleep walking, confusional arousals, and sleep terrors, or during rapid eye movement or REM sleep, e.g., nightmares and REM sleep behavior disorder [1, 2]. The occurrence of parasomnias in preschool age children is almost ubiquitous. In a series of approximately 1000 children followed prospectively between the ages of 2 and 6 years, Petit et al. found that 88 % of children in their cohort had manifested at least one parasomnia during the study period [3]. The highest incidence of parasomnias is in preschool age children, with a gradual reduction into later childhood. Adults also experience parasomnias, though to a lesser degree than children. The observations of Mahowald and Schenck underscore the point that one of the key features of parasomnias is the dissociation of behaviors characteristic of one state (wakefulness/REM sleep or NREM sleep) and their superimposition on to another state [1].

No satisfactory theory explains the clustering of NREM parasomnias into early childhood. A valid theory in this regard must explain the relative paucity of NREM parasomnias during the first 12 months of life, their frequent occurrence in preschool age children, and the gradual dissipation during the second decade.

Phylogenic Aspects

The Tendency for Dissociation of Elements Sleep and Wakefulness States Is Ubiquitous

Instead of *sequentially* manifesting wakefulness and sleep, some marine mammals manifest these states *simultaneously*, such as during the process of unihemispheric

S. Kotagal (✉)
Division of Child Neurology, Mayo Clinic, 200 First Street,
SW, Rochester, MN 55905, USA
e-mail: kotagal.suresh@mayo.edu

sleep. This temporal co-occurrence of wakefulness and sleep in marine mammals subserves thermoregulation and the maintenance of vigilance during continuous living in the aquatic environment. Unihemispheric sleep has been documented in bottlenosed dolphins, seals, beluga whales, and killer whales [4, 5]. In the beluga whale and the dolphin, the hemisphere contralateral to the eye that is kept open and out of the water remains awake, while the opposite hemisphere remains asleep [5]. Terrestrial mammals transition to bihemispheric sleep, with presence of high voltage activity on the electroencephalogram (EEG) during NREM sleep [6]. A tendency to retain some electrophysiological properties of wakefulness even during sleep persists in precocial species mammals such as the elephant and the giraffe, which routinely manifest sleep state dissociation in the form of sleeping while standing [7, 8]—a feat that requires the maintenance of balance and tonic lower extremity extensor muscle contraction while still asleep.

Ontogenic Aspects

Sleep State Dissociation Is Highly Prevalent in Human Newborns and Infants

The maturation of human neonatal REM and NREM bihemispheric sleep emerges in utero from a background of undifferentiated, spontaneous fetal activity, [9, 10], which has also been termed “pre-sleep” by Hamburger [9]. With progressive maturation of the prematurely born infant, the independent oscillations of neuronal activity, autonomic function, and overt behavior become cohesively organized into distinct sleep states termed active and quiet sleep (synonymous with REM and NREM sleep respectively) [11]. An overlap between sleep states (sleep–wake dissociation) is fairly common in full-term babies, however, and about 5 % of newborn sleep is characterized as “indeterminate” during which there is intermingling of elements of both active and quiet sleep [12]. With progressive cortical maturation, indeterminate sleep resolves over the ensuing weeks.

An important feature of human newborn sleep is the presence of stereotyped, nonepileptic patterns of behavior such as nonnutritive sucking or bicycling which represent the intrusion of patterns of wakefulness onto sleep (sleep–wake dissociation) [13, 14]. These behaviors remain fragmentary and subtle, however, simply because the synaptically immature cortical neuronal network, cerebellar system, and incomplete myelination of the pyramidal tracts limit outward expression of sustained motor activity. Indeed the period from birth to 12 months may be a “silent period” from the standpoint of paucity of expression of the results of sleep state dissociation in the form of NREM parasomnias.

Central Pattern Generators As Mediators of Stereotyped NREM Sleep Behaviors

Sleep state dissociation may lead to stereotypic motor activity during NREM sleep in the form such as sleep walking [1]. The generation of stereotyped movements at the spinal cord level is due to activation of networks of interneurons and motor neurons that are also referred to as central pattern generators (CPGs) [15–17]. The spinal CPGs must however be activated by rostral, evolutionarily conserved command centers that are located in mesopontine and diencephalic regions [16]. Stimulation of these regions gives rise to walking, trotting, or galloping in cats, depending upon stimulation strengths [16]. Rhythmic suckling in newborn animals can be generated by activation of rhombomeres containing the VII and XII cranial nerve nuclei [18]. The CPG for fictive mastication, which may be relevant to bruxism (teeth grinding), is located in the pons and medulla, with projections to the motor nucleus of the cranial nerve V, and cranial nerves VII and XII [19]. Based upon the entire genome analysis, it has now been established that expression of the CPG for another stereotypic motor sleep pattern, i.e., periodic limb movements in sleep, which is most likely localized to the spinal cord, is mediated by an intronic variant on the *BTBD9* (*broad complex, tramtrack, and bric-a-brac*) gene complex that is located on chromosome 6p21.2 [20]. It has been established that stereotyped patterns of movement such as walking can be generated in segments of the mammalian sacral spinal cord even after it has been deafferented—these spinal generators might be relevant to the phenomenon of sleep walking [21]. *Based upon the type of CPG that has been activated, one may therefore observe clinical sleep phenomena such as periodic limb movements, sleep walking, rhythmic movement disorder, head banging, or bruxism.*

The input received by CPGs is both glutaminergic and serotonergic [16, 21, 22]. The application of NMDA receptor antagonists to regions of the spinal cord leads to suppression of the activity of spinal CPGs [23]. Descending serotonergic projections from the raphe nucleus to the spinal cord also play a role in inhibiting spontaneous and synchronous rhythmic activities of the spinal level [24, 25]. Genetic factors [20] and sleep disorders such as sleep disordered breathing may also activate spinal or brainstem CPGs.

Does Synaptic Pruning Trigger Childhood NREM Parasomnias?

Why NREM parasomnias abruptly start becoming manifested by 2–3 years of age is unclear. It has been established however that around 8 months in the human visual cortex and by 24 months in the frontal cortex, there is commencement of a process of synaptic pruning which removes redundant excitatory and inhibitory synapses. Approximately 40 % of synapses in the cerebral cortex are eliminated through this process, which is complete by age of 11 years [26–28]. This synaptic pruning process occurs in the cerebrum, cerebellum, as well as in the brainstem. The elimination of

unwanted synapses is an important facet of plasticity of the developing nervous system. At least in the cerebellum, activation of the NMDA type of glutamate receptors is involved in synapse elimination [25]. Concurrently, a process of programmed cell death is also initiated in the cerebrum. Both programmed cell death and synaptic pruning are physiologic and adaptive processes that limit competition for trophic factors and eliminate aberrantly developed connections [25].

Starting around 2 years of age, therefore, a genetic predisposition to sleep state dissociation and activation in sleep of subcortical CPGs, especially when combined with activation of these CPGs (e.g., from sleep apnea, gastroesophageal reflux, or periodic limb movement activity), may trigger patterns of abnormal motor behavior that are characterized as confusional arousals, sleep terrors, or sleep walking. Downregulation of descending cortical to subcortical inhibitory projections that have GABAergic properties or a relative deficiency of serotonergic inhibition at the level of the spinal cord may play a key role in disinhibiting brainstem or spinal cord CPGs, the consequence of which is NREM parasomnias.

This sequence of events, though very plausible, may be difficult to confirm. It is well recognized however that synaptic reorganization during early childhood plays a role in triggering another episodic phenomenon—epilepsy [29]. The hypothesis suggested in this chapter is further supported by the prompt resolution of NREM parasomnias upon treatment with GABA agonists such as clonazepam. Over the first decade and a half, concurrent with progressive maturation of these GABAergic inhibitory projection systems, parasomnias gradually subside. In adults with neurodegenerative processes of the brainstem, there may however be reactivation of brainstem CPGs during sleep and their clinical expression as parasomnias.

The *BTBD9* gene complex that has been established on the basis of whole genome analysis as being involved in the pathogenesis of periodic limb movement disorder is evolutionarily conserved from the *Drosophila*. It is involved in repression of transcription, cytoskeleton regulation, gating of ion channels and ubiquitin dependent protein degradation [30]. It is possible that hitherto undiscovered genes that are involved in the expression of other stereotypic patterns of human behavior in sleep characteristic of NREM parasomnias are also of the same lineage. The search for the genetic basis of NREM parasomnias might need to focus on evolutionarily conserved, homeobox genes that mediate the activity of central pattern generators. From marine mammals to humans, the dictum that ontogeny recapitulates phylogeny may once again hold true!

REM Parasomnias

The pathophysiology of nightmares or “bad dreams” and REM sleep behavior disorder is less clear than that of the NREM parasomnias. Anxiety has been implicated as a risk factor for nightmares. Pagel has characterized dreaming as a complex cognitive state that is affected by a variety of social, medical, or psychological variables [31]. He also indicates that evidence of dream content and its effect on

wakefulness is hard to obtain in children [31]. This has likely impeded our understanding of childhood nightmares. Nightmare focused cognitive behavioral therapy (with exposure and image rehearsal therapy) have better outcome indirect therapies such as relaxation [32].

With regard to REM sleep behavior disorder (RBD) in childhood, what we do know is that in contrast to adults, there is no association with synucleinopathies such as dementia with Lewy body disease or Parkinson disease. RBD may however appear in the early stages of childhood narcolepsy–cataplexy, or with structural brainstem disease, such as neoplasms and Chiari malformations. RBD has also been reported in children with neurodevelopmental disabilities such as autism and Smith Magenis syndrome [33]. Drugs like risperidone and selective serotonin reuptake inhibitors might also predispose to RBD. The repertoire of motor behavior in childhood RBD seems less violent and complex as compared to that of adults (author's opinion). Typically, yelling, thrashing about in sleep, and in some rare occasions, violence directed at a co-sleeping sibling are encountered. Some patients may not show clinical RBD symptoms, but may possess only the polysomnographic correlate, i.e., REM sleep without atonia. It is therefore important to routinely pay close attention to the chin and leg electromyogram during the scoring of children's polysomnograms for evidence of increased muscle tone. The pathophysiology of childhood RBD, though not confirmed, is likely similar to that of adults, with dysfunction of the "REM-off" neurons that are located in the dorsolateral pontine tegmentum. This could lead to uninhibited transmission of descending motor impulses through the brainstem to the spinal cord and activation of motor behaviors.

Practical Points

- The sleep–wake history is key to making a specific parasomnia diagnosis. It can be supplemented by video clips of the events recorded by the parents in the home environment.
- In the case of recurrent and problematic arousal parasomnias, it is helpful to determine if an increased tendency for arousals has developed as a consequence of obstructive or central sleep apnea, gastroesophageal reflux, or periodic limb movement disorder. Treating these underlying triggers may lead to resolution of the arousal parasomnia.
- Since nocturnal seizures can mimic parasomnias, a 16-channel EEG montage should be utilized during polysomnography whenever possible.

Conclusion

The pathophysiology of parasomnias is multifactorial, related to an interplay of genetic and environmental factors. Both phylogenic and ontogenic aspects need also to be considered in arriving at a comprehensive understanding of these sleep-related phenomena.

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