REVIEW ARTICLE

Patho-mechanisms of NREM Parasomnias: Explanation of the Experience

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Abstract

Clinical recognition of NREM parasomnias is relatively straightforward but the understanding of the causative factors is equally important in the management of these disorders. Genetic and environmental factors coupled with physiological and psychosocial triggers are the primary mechanism. Electrophysiological studies and functional network analysis has demystified the final common pathway of these events .The presence of hypersynchronous delta slow wave sleep abnormalities and increased cyclic alternating pattern (CAP) instability are widely recognized while the role of excitatory and inhibitory neural pathways and cortical pattern generators are being intensely studied.

Introduction

Parasomnias are arguably the most interesting and intriguing set of sleep disorders. Apart from the fascination of their presentations, the less trodden path of understanding their origins is the quest of this review. By definition, parasomnias are undesirable or unpleasant behavioural or experiential phenomena occurring preferentially or exclusively during sleep[1]. They are broadly classified into NREM and REM parasomnias depending on the stage of sleep in which they emerge. They generally occur in the first half of sleep when slow wave sleep dominates and rarely recur during the night. The cardinal features that help in the recognition of these disorders apart from their semiology are:

a. First decade onset

b. Occurrence in the first one third of sleep

c. Family history of parasomnias/ sleep disorders

d. Factors both predisposing and precipitating like change of life circumstances, fear, anxiety, and poor sleep hygiene

The most well characterized of non REM parasomnias are the disorders of arousal comprising of confusional arousals, sleep walking and sleep terrors.

Confusional arousals, as the name denotes, are episodes of partial or complete awakening from sleep where the patient appears confused and incoherent with decreased responsiveness. They display various abnormal behavioural patterns which are non stereotypical like movements in bed, inconsolable crying, purposeless actions or irrelevant speech. The episodes may last from few seconds to several minutes and the person usually has no recall of them. Frontal lobe epilepsy (FLEP) is the closest differential to distinguish in which the FLEP scale is remarkably useful[2]. Somambulism or sleep walking refers to episodes of wandering out of bed sometimes even to another room. The person may have a calm disposition or a violent one, the latter often provoked by attempts to awaken the patient.Sleep terrors are by far the most disturbing of the lot with the classical manifestation of a blood curdling scream followed by

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extreme panic, agitated and aggressive behaviour which can even lead to bodily harm[1,3].

Considering the rarity of this events in the adult population, it is prudent to investigate for a secondary cause whenever they are encountered beyond the first decade. In any scenario, the jobs of a clinician doesnot end with the identification of a parasomnias or their classification. The challenge remains of identifying the etiopathology of the disease so that the management plan can be tailored for the specific situation. Thepathomechanisms that unlock the alternatereality of the classical NREM parasomnias are examined in this review.

Game of Thrones- Sleep versus Wakefulness

The foundational theory that attempted to explain these instances of paradoxicalwakefulness during sleep centred around the imagery of a dissociated mind - a battle ground where sleep and wakefulness struggle to emerge out of the clutches of each other.This neuropsychological perspective can be clarified better if one were to examine closely the networks that are operational behind the stage.The credibility of this hypothesis is defended by the coexistence of the electrophysiological signatures of wakefulness and sleep. The connectomics,however, of parasomnic as opposed to epileptic phenomenology has not been elucidated clearly. The excitation of some and inhibition of other neural substrates would result in an incoherent and non-coordinated display of cognitive, behavioural, verbal, emotional, autonomic and motor expressions. A favoured and logical postulation based on intracerebral recordings is that the tempero-amygdalo-insular areas are predominantly activated and disengaged from the frontal inhibitory pathways resulting in marked emotional, amnesic and autonomic manifestations [4].Frontal cholinergic arousal system is also implicated in the pathophysiology of complex automatic behaviour observed in disorders of arousal as well as nocturnal frontal lobe epilepsy[5]. Another candidate in this growing debate on the perpetrator of automatic behaviour in sleep is the motor and central cingulate cortex which continues to fire while the dorsolateral frontal and parietal association areas slumber in slow wave sleep[6,7]. A network mechanism akin to ictal propogation is certainly appealing to an open mind; for how often while hearkening to the descriptions of these legends of the night have been reminded of their epileptic counterparts.

The journey to the understanding of this overlap between sleep and wakefulness is extremely interesting and warrants more elaboration. It all started with simple observations in the sleep EEG like anterior dominant delta preceding the onset of episodes marked by motor activity, which clearly depicted this paradox[8]. Rhythmic,continuous, hyper-synchronous, and high amplitude (> 150 mv) delta waves were also observed un-associated with the events in the sleep EEG of parasomnic patients[9]. Increased instability of the cyclic alternating pattern (CAP)of slow wave sleep(SWS) is another notable feature in dedicated sleep recordings[10]. Further, one needs to assimilate the concept of sleep and wakefulness as a continuum rather than an abrupt switch of states[11].The authors believe that the transition being more gradual and remarkable in children could be one explanation for their more frequent occurrence in this age group. Stereo-EEG observations in patients undergoing pre-surgical evaluation for refractory epilepsy with concurrent NREM parasomnias have thrown new light by showing that there is dissociation between thalamic and cortical activation in these patients[12].

However, not everyone is an advocate of this theory. Inability to sustain slow wave sleep and undulations of delta power is an alternate explanation that has emerged from recent investigations[13,14].

Central pattern generators (CPGs) and brain maturation

Central pattern generator (CPG) is a caucus of neurons orchestrating coordinated motor routines of innate behaviours. Subcortical CPGs act via brainstem and spinal cord connections to produce specific movement patterns like bicycling, circling and walking[15]. Disinhibition of these generators could explain the association of NREM parasomnias with stereotypical movements like rhythmic movement disorder and bruxism[16]. Increased prevalence of parasomnias among those with perinatal risk history and developmental disorders like dyslexia, attention deficit hyperactivity disorder(ADHD), developmental dysphasias,dysgraphia lends support to this hypothesis[17]. Children with autistic spectrum disorders are also more likely to suffer from NREM and rarely REM parasomnias[18].(Fig. 1)

Subcortical inhibitory networks predominantly GABA-ergic are instrumental in suppressing electrical activation of the motor cortex during sleep. A perinatal

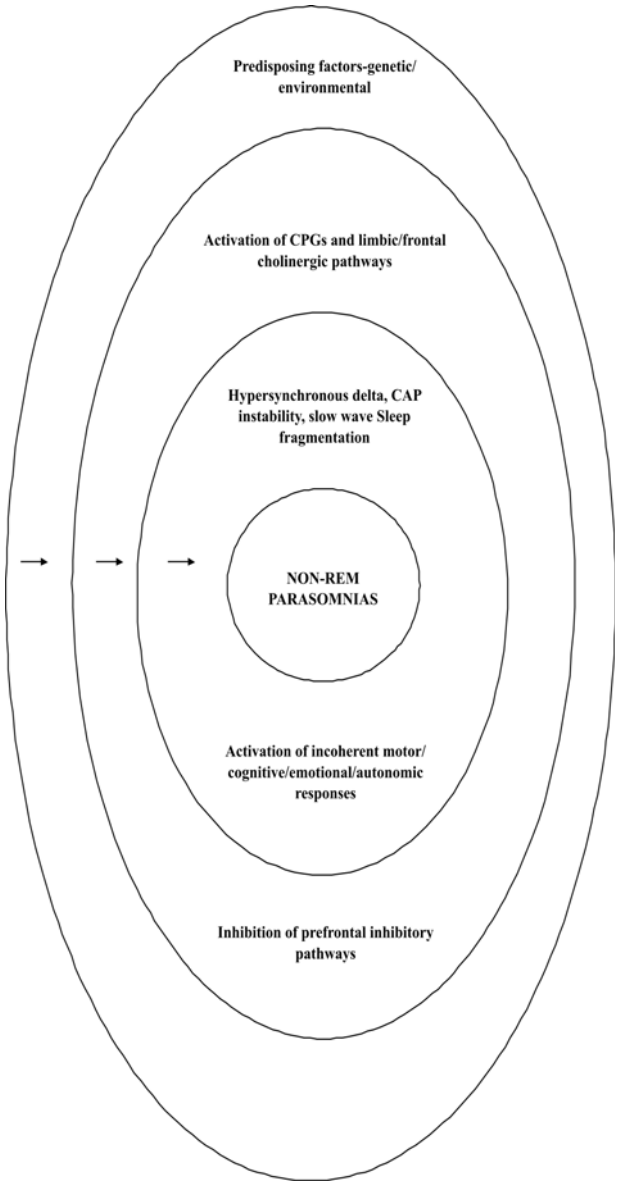

Figure 1: The figure portrays a four step model illustrating the interplay of the factors that ultimately result in a NREM parasomnia. The outer circle shows the predisposing influence of genetic and environmental factors alongside the precipitating factors like stress. The second circle shows the probable pathways recruited by these influences; the third circle shows the impact of these networks on the person's sleep leading to intrusion of wakefulness and incoherent cognitive, behavioural and motor activity; and the innermost circle represents the clinical syndrome that emerges as a result, namely NREM parasomnia.

or developmental insult to the brain can disrupt these networks and produce uninhibited and undesirable motor behaviour like sleep walking[17,19].

Psychosocial factors

The first decade of life, especially its early part, is when most of the parasominias run amok and then as age advances they bury themselves in the sands of time. So it is tempting to speculate that factors unique to this age group could definitely hold the key to their origin.

One such factor is separation anxiety which has been discovered to have a consistent association with persistent night waking, somnambulism, bruxism, sleep terrors, and somnoliqy[20]. Adults with somnambulism had anxiety and mood disturbances in upto 25% cases in some reports[22]. In a population based telephonic survey of more than 13,000 subjects, bipolar mood disorder and anxiety were unequivocally linked to confusional arousal[23]. In addition, psychiatric diseases and medications can kindle parasomnic events[24]. Psychopathology is not a consistent accompaniment in adults with parasomnias.

Through structured interview in a cohort of school age children from the Avon Longitudinal Study of Parents and Children (ALSPAC), Wolke and Lereya exposed the role of bullying in the genesis of parasomnias. The regression analysis established bullying as a significant and independent predictor of any parasomnia especially nightmares and night terrors in the 8-10 year age group[25].

Genetic factors

Family history is positive in a very high proportion of patients with NREM parasomnias. 80% of patients with somnambulism haveat least one family member affected; and the risk of a first degree relative developing the disorder is 10-fold more compared to the general population[26]. A possible genetic locus for sleep walking has been detected on chromosome 20[27]. The evidence of genetic contribution for confusional arousals and sleep terrors, although less robust, is derived from twin studies and observations of familial clustering[28]. A definite association with nocturnal frontal lobe epilepsy also supports the genetic backdrop of these disorders[29]. Further, HLA DQB1*05 and DQB1*04 alleles are found to be associated with sleep-walking[30].

Autoimmune hypothesis

With the advent of this millennium, the understanding of the spectrum of autoimmune disorders targeting the nervous system has expanded exponentially. Parasomnias may be seen as part of any of the central nervous system autoimmune disorders but an independent pathogenetic role is not proven although association with certain HLA alleles suggest a putative link.

Among the auto-immune encephalitides, RBD is more commonly observed with anti-voltage gated calcium channel complex (VGKC) associated syndromes while NREM parasomnias are a feature of NMDA-receptor encephalitis[31,32].

Agrypnia excitata is a rare and distinctive parasomnia which has its roots firmly secured in the autoimmune terrain. Antibodies directed against gamma-amino butyric acid-B receptors (GABA-B), VGKC and IgLON5 are the chief culprits causing this extreme sleep disorder where the patient gradually loses all the composition and architecture of sleep[33,34]. The electroencephalogram would show virtual absence of NREMsleep stages and REM sleep associated atonia. The patient would experience heightened autonomic reactivity, dream like wakefulness and continuous muscle fibre activity.

Precipitating factors

A change in sleep habits, life circumstances and various stressors can impose a burden on sustained slow wave sleep leading to fragmentation and increased demand for SWS which in turn facilitates the emergence of parasomnias. Stimulants and other sleep disorders may also have a similar effect in predisposed individuals[35]. Sleep disordered breathing and restless leg syndrome can manifest as parasomnias in children as well as adults[22,36]. Trauma, fever,shift–work and irregular sleep are the other established precipitants[22]. Sleep deprivation and forced arousals from SWS can even be used as a diagnostic tool to provoke episodes of NREM parasomnias[37,38].

Summary

The concern that is generated in the mind of the parents of a child suffering from parasomnia truly justifies the importance of recognizing it clinically and distinguishing it from other paroxysmal events like epilepsy. In this review, the cause for these events could shape the management strategy to eliminate them. The pathomechanisms underlying NREM parasomnias can be envisioned in a sequential manner. The genetic, developmental, and psychosocial predisposition to the disease awaits a trigger which can be stress or fatigue or poor sleep to enter the state of the dissociated mind where motor/cognitive/emotional and autonomic responses emerge through windows of partial wakefulness. This implicit state of unstable slow wave sleep can be further explored electro physiologically as well as through functional and invasive studies of the neuronal networks. The result of such a search will be a wider and NREM parasomnias can be managed. Multiple factors may be operational in the same patient at several times,which underscores the importance of a careful history and diagnostic evaluation. A rational approach would be to address all the responsible elements rather than impetuously attempting to pharmacologically abort the episodes.

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