Parasomnia Overlap Disorder

By Regina Patrick, RPSGT, RST

In 1934, French researcher Henri Roger coined the term *parasomnie* (in English, parasomnia; from the Greek *para* meaning "alongside" and Latin *somnum* meaning "sleep") for phenomena that occur in the transition from sleep to wake or vice versa.[1] A parasomnia can occur during the transition between non-rapid eye movement (NREM) sleep and wake (i.e., NREM parasomnias such as sleepwalking, sleep terrors, confusional arousal, sleep-related eating disorder) or during the transition between rapid eye movement (REM) sleep and wake (i.e., REM parasomnias such as REM sleep behavior disorder [RBD], recurrent isolated sleep paralysis, nightmare disorder). A parasomnia has the following features: recurrent episodes of incomplete awakening from sleep, an inappropriate or lack of response to intervention or redirection during an episode, limited or no cognition of dream imagery and partial or complete amnesia for the event. In addition, the nocturnal disturbance is not explained by other sleep, psychiatric or medical disorder or medication/substance use. Some people experience REM parasomnias and NREM parasomnias, a condition called parasomnia overlap disorder (POD). A person with POD has a disorder of arousal (e.g., sleepwalking confusional arousal, sleep terror) and rapid eye movement sleep behavior disorder (RBD; which involves vivid, often unpleasant dreams; vocalization during sleep and sudden, often violent, arm and leg movements during REM sleep [i.e., dream-enacting behavior]).

In 1997, POD was first described by Carlos Schenck et al.,[2] who initially proposed that it was a subtype of RBD. In 2013, Dumitrascu et al.[3] were the first scientists to propose that POD was a distinct parasomnia rather than a subtype of RBD, based on their experience with five patients with POD; they noted that the onset of POD symptoms occurred earlier in life than did the symptoms of someone with RBD only, the NREM parasomnia symptoms were more pronounced than the RBD features and the POD symptoms were not associated with any neuropathy.

Why an overlap between NREM and REM parasomnia occurs in some people is unclear, although genetic factors[4] and impaired neuroactivation in the brain[5] may contribute to it. In addition, recent case reports indicate that it can be secondary to (i.e., caused by) another problem such as obstructive sleep apnea (OSA) or the use of certain drugs and that treating the causative factor may eliminate or reduce symptoms of POD.[6-8]

Investigations of possible genetic factors associated with NREM or REM parasomnias have indicated a higher prevalence of human leukocyte antigen (HLA) genes among people with non-REM parasomnias such as sleepwalking, sleep terrors, and confusional arousals, and among people with REM parasomnias such as RBD.[9-13] For example Anna Heidbreder et al.[9] found a higher prevalence of the HLA DQB1*05:01 allele (an alternate form of a gene) among patients with NREM parasomnias (e.g., sleepwalking, sleep terrors, confusional arousals), regardless of the type of parasomnia, than in patients without NREM parasomnias. Licis et al.[10] reported a higher prevalence of a gene on chromosome 20 (i.e., 20q12-q13.12) among several generations of sleepwalkers in a large family. Some research indicates that the prevalence of DQB1*05 and DQB1*06 alleles is higher among people with RBD than among people without RBD.[11]

With regard to specific genetic factors among people with POD, some research indicates that a mutation in the gene that codes the glycine receptor may contribute to POD. (The inhibitory neurotransmitters glycine

and gamma-aminobutyric acid (GABA) are involved in inhibiting motor function during REM sleep.) Regis Lopez et al.[4] described their experience with two teen-aged sisters who had hereditary hyperekplexia, a genetically transmitted disorder that involves increased muscle tone and an exaggerated startle reaction, after which an affected individual has a brief period of rigidity and inability to move. Individuals with hereditary hyperekplexia have a mutation in the alpha-1 subunit of the glycine receptor gene (GLRA1).

The sisters had experienced frequent night terrors since childhood. One sister had complex sleep behaviors (e.g., gesturing, screaming and laughing), which were associated with dream content (indicative of RBD). They underwent video polysomnography (PSG) studies without clonazepam (a drug that enhances GABA transmission; the sisters had long used it to control motor activity during sleep) and with clonazepam. On the untreated night, they had frequent startles in NREM, microarousals in N1 and N2 sleep and sleep terrors in N3 sleep. However, they did not have startles in REM sleep, although they had motor behavior (e.g., head jerks, flexion or turning of the head, upper limb movement). Muscle tone was increased throughout REM sleep. On the treated night, NREM startles and motor behaviors and REM sleep muscle tone were decreased. Based on these findings, Lopez concluded that the sisters had features of POD secondary to hyperekplexia. However, the extent that genetic factors contribute to POD remains unclear.[3]

The fact that hyperekplexia is associated with a mutation in the GLRA1 gene suggests that impaired glycinergic transmission may be involved in POD. Animal studies support this possibility. In a study in which genetically modified mice had a mutant form of the GLRA1 receptor, Brooks et al.[14] demonstrated that the mutation caused glycine receptors and GABA receptors to be less responsive to their respective neurotransmitters and resulted in RBD symptoms. Based on this finding, Brooks suggested that deficits in glycine- and GABA-mediated inhibition triggers all RBD symptoms.

Other research has focused on neurotransmission factors that are responsible for muscle atonia during REM sleep. Valencia Garcia et al.[5] recently demonstrated in their rat study that glycinergic and GABAergic neurons (i.e., neurons that secrete or transmit glycine and GABA) are localized within the ventromedial medulla (i.e., the front middle portion of the medulla), and that impairing inhibitory neurotransmission from the ventromedial medulla resulted in REM sleep without atonia and abnormal and violent motor activity and reduced REM sleep quantity — symptoms that closely mimic RBD in humans. However, some researchers have had contradictory findings by demonstrating that lesions in the ventral medulla had no effect on atonia in REM sleep[15] or induced intermittent loss of atonia with exaggerated muscle twitches during REM sleep[16], and demonstrating that muscle tone during REM sleep is unaffected by inhibiting the actions of GABA neurons within the ventral medulla or blocking GABA/glycine neurotransmission from the ventral medial medulla.[16, 17] Therefore, the exact role of this brain region in REM sleep atonia continues to be investigated.

In recent years, reports have emerged describing secondary POD.[6-8, 18] Sun et al.[6] described a case of POD secondary to OSA in a middle-aged man who reported experiencing vivid dreams for several years and the recent development of violent complex behavior during sleep (i.e., dream enactment). He had no memory of his sleep behavior. Magnetic resonance imaging and electroencephalography showed no brain abnormalities. He also reported snoring and snoring-related arousals. His video polysomnography (PSG) study revealed severe OSA (40 respiratory events/hour), lack of muscle atonia during REM sleep and dream enactment (i.e., RBD). Based on these findings the patient was diagnosed with severe OSA and POD. He was treated with continuous positive airway pressure, which reduced his apnea-hypopnea index to three respiratory events/hour. After eight weeks of treatment, his distressing dreams and nocturnal behavior had stopped. Thus, the patient's POD was determined to be secondary to OSA. Sun suggests that OSA may have contributed to POD by causing frequent arousals from sleep. Repetitive arousals contribute to sleep instability, which can then contribute to phenomena such as confusional arousals and sleepwalking.

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Mahismita Patro et al.[7] recently described a case of POD induced by the use of mirtazapine, a selective serotonin reuptake inhibitor. The patient, a 70-year-old man, had abnormal sleep behaviors such as shouting, punching, sleepwalking and dream enactment, and he had symptoms of OSA (e.g., snoring and excessive daytime sleepiness). He had been prescribed antidepressants (i.e., mirtazapine, sertraline and olanzapine) for depression. His abnormal sleep behaviors began after he began using mirtazapine. He was treated for OSA, but eliminating mirtazapine eliminated his nocturnal symptoms. In a different case study, Esaki et al.[8] reported a patient who developed

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symptoms of POD after beginning paroxetine (e.g., punching his bed partner, howling like a wolf). Once paroxetine was discontinued, all POD symptoms stopped.

POD was initially classified as an RBD variant.[19] As information has accumulated, its classification has been revised to REM sleep-related parasomnia.[20, 21] The co-occurrence of NREM and REM features in POD continues to perplex scientists with regard to its causes. Most information on POD in the medical literature has been case reports. Therefore, more in-depth research is needed to determine the factors (e.g., genetic, neurological) that distinguish someone with POD from someone with a NREM or REM parasomnia only; the long-term outcome of people with POD (for many people with RBD only, the onset of Parkinson's disease or related disease occurs late in life; the extent that this is true for someone with POD is unclear); and the pathophysiology of secondary POD versus that of primary POD. This information could potentially allow clinicians to recognize and diagnose POD more readily.

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