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Characteristics of REM Sleep Behavior Disorder in Childhood

Robin Lloyd, M.D.; Maja Tippmann-Peikert, M.D.; Nancy Slocumb; Suresh Kotagal, M.D.

Center for Sleep Medicine and the Departments of Pediatrics and Neurology, Mayo Clinic, Rochester, MN

SCIENTIFIC INVESTIGATIONS

Study Objective: To describe our experience regarding the clinical and polysomnographic features of REM sleep behavior disorder (RBD) in childhood.

Methods: This was a retrospective chart review of children and adolescents with RBD and REM sleep without atonia. Demographics, and clinical and polysomnographic information were tabulated. Our findings were compared with those in the existing literature.

Results: The 15 subjects identified (13 RBD and 2 having REM sleep without atonia) had a mean age at diagnosis of 9.5 years (range 3-17 years); 11/15 (73%) were male. Nightmares were reported in 13/15 and excessive daytime sleepiness in 6/15. Two children had caused bodily harm to bedmate siblings. Comorbidities, which were multiple in some subjects, included anxiety (8/15), attention deficit disorder (10/15), nonspecific developmental delay (6/15), Smith-Magenis syndrome (1/15), pervasive developmental disorder (1/15), narcolepsy (1/15), idiopathic hypersomnia (1/15), and Moebius Syndrome (1/15). Abnormal MRI scans were seen in 5/8 evaluated subjects. Treatments consisted of clonazepam (10/15), melatonin (2/15), and discontinuation of a tricyclic agent (1/15), with a favorable response in 11 of 13. Two of 15 patients with REM sleep without atonia did not require pharmacotherapy.

Conclusions: RBD in children may be associated with neurodevelopmental disabilities, narcolepsy, or medication use. It seems to be modestly responsive to benzodiazepines or melatonin. The etiology is distinct from that of common childhood arousal parasomnias and RBD in adults; congenital and neurodevelopmental disorders, medication effect, and narcolepsy coexisted in some, but none had an extrapyramidal neurodegenerative disorder.

Keywords: REM sleep behavior disorder, parasomnia, polysomnography

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REM sleep behavior disorder (RBD) was initially described by Schenck et al. in 1986 as a REM sleep related parasomnia of older men.[1] It is now recognized as a disorder of all ages and both sexes, though still predominately occurring in men.[2,3]

In adults, there is clear association of RBD with synucleinopathic degenerative disorders such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.[4-6] The condition is also a side effect of treatment with medications such as selective serotonin reuptake inhibitors (SSRIs).[6,7]

The hallmark of RBD is preservation of muscle tone during REM sleep, allowing for motor dream enactment that is sometimes aggressive or violent in nature, leading to injury to self, others, or property. The pathophysiologic mechanisms of this disorder have been discussed by Boeve et al.[8,9] There is dysregulation of inhibitory brainstem motor mechanisms. While the exact pathway in humans has not been determined, neuroimaging data from the few published human RBD cases associated with structural lesions have implicated the dorsal midbrain and pons. Studies in cats suggest involvement of the subcoeruleus region, while those in rats point to the sublaterodorsal nucleus as crucial to the development of RBD.[8,9]

Polysomnographic monitoring reveals increased muscle tone in the chin, arm, and leg electromyograms (EMGs). On video surveillance, the patient can be witnessed having activity of the extremities and body, often in an aggressive manner, sometimes associated with yelling. While RBD has important implications in adults from the standpoint of prognosis, the long-term implications in childhood are unknown.

BRIEF SUMMARY

Current Knowledge/Study Rationale: REM sleep behavior disorder was originally described as a parasomnia in older men. It is now recognized as a disorder of all ages and both sexes but most likely occurs more frequently in children than identified. The clinical and polysomnographic characteristics of this disorder during childhood need further characterization.

Study Impact: This study will hopefully increase the awareness of RBD in children. It describes commonly associated conditions with RBD in children including centrally mediated hypersomnia, pharmacologic agents, neurodevelopmental disorders and structural brainstem abnormalities.

There have been several small case reports of children with RBD. In 1975 Barros-Ferreira et al. reported a case of an 8-year-old girl with a brainstem tumor who had clinical signs of RBD with polysomnographic evidence of atonia before RBD was a defined entity.[10] Schenck et al. described a 10-year-old girl who had clinical RBD after removal of a midline cerebellar astrocytoma; interestingly, her healthy 8-year-old brother had similar aperiodic movements in NREM and REM but without clinical sleep disturbance.[11] Turner et al. reported a 16-year-old male with narcolepsy and clinical RBD.[12] Schenck and Mahowald described 17 narcoleptic patients with RBD, of whom 3 were between the ages of 10 and 19 years.[13] Nevsimalova et al. documented 2 girls, ages 7 and 9, with narcolepsy-cataplexy

Table 1—Demographics, presenting complaints, family history of parasomnia

Subject	Gender	Presenting Sleep-Wake Complaint	Age at Onset	Age at RBD Diagnosis	Family History of Parasomnia
1	F	Fatigue	3	5	None
2	F	SIMD, EDS	5	14	None
3	M	Nightmares,	2	6	None
4	F	EDS	2	5	Somnambulism
5	M	Nightmares	4	11	Unknown
6	M	Nocturnal spells	1.5	3	None
7	M	EDS	11	16	None
8	F	Nocturnal awakenings	1	4	None
9	M	Nightmares, awakenings	6.5	7	None
10	M	EDS	6	9	Somnambulism
11	M	Nocturnal awakenings, EDS	15	18	None
12	M	EDS	10	12	None
13	M	SIMD	1	5	None
14	M	Fatigue, EDS	8	10	None
15	F	Fatigue, EDS	14	17	None

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; DD, developmental delay; EDS, excessive daytime sleepiness; FTT, failure to thrive; LD, learning disability; NF-1, neurofibromatosis, type 1; OCD, obsessive compulsive disorder; PDD, pervasive developmental disorder; SIMD, sleep initiation and maintenance difficulties.

in whom RBD was one of the initial symptoms.[14] Sheldon and Jacobsen identified 5 children who met the criteria for RBD and described the clinical and polysomnographic characteristics of these patients, one of whom had narcolepsy.[2] RBD has also been linked to juvenile Parkinson disease[15] and with autism in children.[16]

Based upon the above information, it appears that the pediatric RBD literature is composed of small case series. We wish to report the clinical and polysomnogram findings and our experience in a slightly larger case series of 13 subjects who met diagnostic criteria for RBD and an additional 2 who had REM sleep without atonia.

METHODS

This was a descriptive study of children and adolescents seen at our sleep center between 2000 and 2010 with RBD or REM sleep without atonia on overnight polysomnogram (PSG) and simultaneous video monitoring. The study was approved by the institutional review board.

Patients were identified by cross-matching age at time of initial evaluation with diagnostic codes of RBD or REM without atonia. Diagnosis was based on: (a) polysomnographic evidence of REM sleep without atonia, or (b) clinical history of parasomnia combined with PSG evidence of REM sleep without atonia. Exclusion criteria were: (a) age < 1 year or > 18 years at the time of sleep evaluation; (b) seizure disorder; and (c) sleep disordered breathing. We excluded patients with seizures because there was not a 16-lead EEG (2 patients), or the EEG was abnormal and it was difficult to tell if they were having seizures (2 patients).

The polysomnogram was conducted as an all-night examination in accordance with standards defined by the American Academy of Sleep Medicine, with the addition of a bitemporal and parasagittal 16-lead EEG. Scoring of the PSG was conducted initially by certified PSG technicians, followed by independent review by 2 certified sleep specialists (RL + MTP or SK +MTP), utilizing standard criteria described by Rechtschaffen and Kales[17] or the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.[18] For patients diagnosed since 2007, sustained tonic muscle activity in REM sleep was defined as a 30-sec epoch of REM sleep with ≥ 50% of the epoch having chin EMG amplitude greater than the minimum amplitude seen in NREM. Excessive transient muscle activity (phasic activity) in REM sleep was defined as 50% of an epoch of REM sleep containing bursts of transient muscle activity. These bursts had to be 0.1-5.0 seconds in duration and ≥ 4 times as high in amplitude as the background EMG activity. This is comparable to the criterion utilized by Sheldon et al.,[2] where increased tone was defined as lasting > 3 sec and < 15 sec as per Rechtschaffen and Kales.[17]

RESULTS

In all, 22 patients were identified with REM without atonia. Four were excluded because of seizures (2 with no 16-lead EEG and 2 with very abnormal EEGs throughout), and 3 because of sleep disordered breathing, leaving 15 subjects (12 Caucasian, 2 half-African American, and 1 Hispanic). In these 15 patients, the mean age at diagnosis was 9.5 years (range 3.7 to 17.9 years), with 11 of 15 (73%) being male. Demographic information is listed in **Table 1**. Two patients presented with excessive daytime sleepiness only and were found to have REM without atonia. Nightmares were either reported or suspected in 13 of 15 patients. Parents of this group described sleep disruption with crying out and flailing of the arms and legs that was suspicious for dream enactment behavior. Ten of 13 had recollection of vivid frightening dreams involving violence or

Table 2—Comorbidities, neuroimaging, medication and treatment information

	Comorbidities, MRI results, Medication				Treatment and results	
Subject	Comorbid Sleep Diagnoses	Neurologic Diagnoses	MRI	Medications at Time of Evaluation	RBD Treatment	Outcome
1	NM, crying, restlessness, fatigue	None	Chiari 1	None	Clonazepam	Lost to FU
2	NM, hit sister, crying, EDS restlessness, nocturnal enuresis,	ADHD, Delayed secondary sexual maturation	None	DDAVP Imipramine	Iron sup discontinued Imipramine	Improved sleep, 5 month FU, exacerbated by SSRI
3	NM, restlessness, nocturnal enuresis, SIMD	Anxiety, Headaches, FTT, ADHD	Normal	Oxybutynin	Iron sup, Clonazepam	Improved sleep, 6 month FU
4	NM, crying, restlessness	Anxiety, PDD, autonomic dysregulation, FTT/G-tube	Pituitary cyst	Guanfacine, dextro-amphetamine/ amphetamine, sertraline, risperidone	Clonazepam	Improved sleep, 6 month FU
5	NM, EDS, hit brother, crying, restlessness,	ADHD, skull fracture, anxiety, PTSD with abuse	None	Guanfacine,	Clonazepam	Lost to FU
6	Suspected NM, crying, SIMD, restlessness,	Speech apraxia, overactive impulsive, DD	Normal	None	Iron sup, Clonazepam	Improved sleep & development at 3 & 6 mo. FU
7	NM, crying, SIMD, restlessness,	Depression, ADD/LD, Moebius syndrome	Normal	None	SSRI, Clonazepam	Lost to FU
8	Suspected NM, restlessness, crying, EDS	ADHD, DD, Smith-Magenis syndrome	Venous anomaly	None	Clonazepam	Poor response
9	NM, crying, restlessness	ADHD, anxiety	None	Methylphenidate, Quetiapine	Clonazepam,	Improvement w/Tx of anxiety, resolved on PSG at 18 mo
10	NM, crying, EDS, restlessness,	LD, Partial tumor resection Chemo/ radiation, VP shunt,	Pilocytic astrocytoma	None	Clonazepam	Improved sleep, 6 month FU
11	NM, snoring, erratic sleep schedule, EDS	Depression, anxiety, ADD	None	Fluoxetine	Melatonin	Improved sleep, 6 month FU
12	NM, restlessness, EDS/ narcolepsy	Obesity, difficulty concentrating	None	None	Ropinirole, Melatonin, Modafinil	Improved sleep, 3 month FU
13	NM, crying, restlessness	OCD, LD, ADHD anxiety, NF-1,	None	None	Clonazepam	FU pending
14	Nocturnal enuresis, EDS	Tourette, migraines, anxiety, NF-1,	Pilocytic Astro-cytoma	Gabapentin, Sumatriptan	None	Lost to FU
15	Mild snore, EDS/IH	Migraines, OCD	Normal	Fluvoxamine maleate, topiramate	None	Lost to FU

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; DD, developmental delay; EDS, excessive daytime sleepiness; FTT, failure to thrive; FU, follow up; IH, idiopathic hypersomnia; LD, learning disability; NF-1, neurofibromatosis, type 1; OCD, obsessive compulsive disorder; PDD, pervasive developmental disorder; PLMD, periodic leg movement disorder; SIMD, sleep initiation and maintenance difficulties; sup, supplement; TX, treatment.

chasing; 2 had caused bodily harm to bedmate siblings. The 2 youngest (3 and 4 years) had speech apraxia and were unable to describe dream content.

Comorbid conditions and medications are listed in **Table 2**. They included anxiety (8/15), ADHD or inattentiveness (10/15), nonspecific developmental delay and learning disabilities (6/15), Smith-Magenis syndrome (1/15), pervasive developmental delay (1/15), non-accidental trauma with skull fracture in infancy (1/15), narcolepsy (1/15), idiopathic hypersomnia (1/15) and Moebius Syndrome (1/15). Magnetic resonance imaging of the brain was abnormal in 5/9 subjects who had undergone imaging, one with Chiari I malformation, 2 with midbrain pilocytic astrocytoma, one with a nonspecific vascular malformation in the right frontal region, and one with a pituitary cyst. Three patients were taking SSRIs. EEG monitoring was normal

in all patients, with the exception of 2 who had the nonspecific finding of alpha intrusion.

Ten of the 15 patients were treated with clonazepam, with resolution of nightmares and abnormal motor behaviors in 8/10. Of the two who did not respond, one had Smith-Magenis syndrome with significant circadian rhythm disturbances; the other had severe anxiety with both day and night symptoms. Two of the 15 were treated with melatonin before bedtime and had resolution of nocturnal symptoms. One patient was treated with discontinuation of a concurrently administered tricyclic antidepressant, which initially improved her sleep symptoms. However, on follow-up 6 years later, she has been diagnosed with depression and ADHD and has had exacerbation of RBD symptoms on SSRI therapy. Two of the 15 patients did not require pharmacotherapy for REM without atonia on PSG in the absence of dream enactment behaviors.

DISCUSSION

Two children who presented with EDS only had REM without atonia and no history or demonstration of dream enactment. The remaining 13 children diagnosed with RBD, had unusual nocturnal motor behaviors described in various ways from restless sleep to frankly aggressive behaviors. Vocalization was common and consisted of yelling rather than the more common talking, crying, or mumbling observed in NREM parasomnias other than sleep terrors. Trying to distinguish NREM versus REM related parasomnias can be difficult based on history alone, but RBD was suspected in three of the patients who had a history consistent with dream enactment or injurious behaviors. In retrospect RBD could be considered in the differential diagnoses of all 13 affected patients, but other sleep disorders were considered initially, given the relatively low incidence of RBD.

Motor activity and recollection of vivid scary dreams can occur independently but together could be clues for consideration of RBD especially when motor activity is of a more aggressive nature. It is important to pay careful attention to the chin and leg electromyogram during review of the pediatric polysomnogram. Other PSG parameters were within normal limits with the exception of an elevated periodic limb movement index (> 5) in 6 of 15 patients. There are technical difficulties in diagnosing RBD in childhood, as seizures and obstructive sleep apnea can also lead to augmentation of muscle tone during sleep. While nocturnal seizures typically present in NREM sleep, they may occur rarely in REM sleep as well. The motor activity associated with seizures may be difficult to differentiate from RBD.[19,20] Children with sleep disordered breathing may also display excessive motor activity after an obstructive respiratory event, especially in REM sleep, making differentiation from RBD difficult.[21]

Further, as pointed out by Thirumalai, et al.,[16] RBD may be prevalent in children with autism and other neurodevelopmental disorders. Unfortunately, these mentally handicapped children are frequently anxious and uncooperative; thus the diagnostic tool of nocturnal polysomnography is difficult to apply to the population that would likely benefit greatly from it. There was no correlation between onset of symptoms of neurodevelopmental disorders and age at diagnosis of RBD.

Fatigue and sleepiness were the most common presenting complaints and occurred in 9 of 15 patients. Two patients were diagnosed with a centrally mediated hypersomnia, one with narcolepsy and one with idiopathic hypersomnia. Long-term follow up is needed to see if any other patients develop an organic hypersomnia with RBD or REM without atonia being the earliest manifestation.

Learning difficulties, hyperactivity, and mood changes can be a manifestation of sleep disruption in children and were the most common comorbidities found in our study population. Neurobehavioral comorbidities have been described in adults with early onset RBD by Teman et al.[7] who found a high incidence of past and present psychiatric diagnoses. It is difficult to determine the causal relationship, i.e., does the sleep disruption of RBD cause neurobehavioral problems, or do the neurobehavioral substrates predispose to RBD. Children with PTSD and abuse may have similar pathophysiologic mechanisms, though there would be increased risk of traumatic brainstem changes with physical abuse.

Medications which have previously been implicated in RBD (SSRIs and tricyclic antidepressants) were also identified in our patient population. Whether these are causative or trigger RBD in neurologically predisposed individuals warrants further investigation. RBD is associated with progressive, synucleinopathic extrapyramidal disorders in adults. In children, there seems to be no such association as congenital and neurodevelopmental disorders, medication effect, and narcolepsy predominate.

Some children (5 of 9 who had abnormal brain MRI scans) with structural lesions or risk for brainstem dysfunction were identified in our review. This was not unexpected in light of the described pathophysiologic mechanisms for RBD. While MRI imaging of the brain was performed for other reasons in our patients, it would be reasonable to consider obtaining an MRI if RBD is diagnosed.

Regarding treatment, most children were responded to a low dose (0.125 mg) of clonazepam, which was titrated upwards as needed, with only one child requiring a dose as high as 0.75 mg. Melatonin dosing ranged from 3 to 5 mg SR. The appropriate duration of therapy is unclear at this time. One child did demonstrate resolution on a follow-up PSG 18 months later, so periodic trials off medication would appear to be warranted, with monitoring for worsening upon discontinuation of medication.

Our study will hopefully increase the awareness of RBD in children and also advance the understanding of pathophysiology of the condition. As has been recently been proposed by Luppi et al.,[22] RBD may be the end result of dysfunction in different pathways originating from the hypothalamus or brainstem. Three independent subgroups of patients with RBD/REM sleep without atonia can be seen in our study—those with narcolepsy or idiopathic hypersomnia (subjects #12, 15) likely had impaired hypocretin mediated activation of the ventral gigantocellular nucleus in the medulla, which in turn normally inhibits ventral spinal motor neurons. The second group was composed of subjects with autism and neurodevelopmental disorders, such as attention deficit disorder, Smith-Magenis syndrome, Moebius syndrome, neurofibromatosis type 1, and Tourette syndrome (subjects #2, 3, 5, 6, 7, 8, 9, 13, 14). Decreased activation of γ-hydroxybutyrate (GABA) mediated pathways is

common in children with autism.[23] GABA is a key neurotransmitter in the ventral gigantocellular nucleus, and its deficiency might predispose to decreased ability to keep spinal motor neurons hyperpolarized during REM sleep. The third subgroup was composed of those receiving a selective serotonin reuptake inhibitor (subjects #2, 4, 11, 15). Serotonin suppresses REM sleep, but the exact nuclear locus and mechanism of this inhibition are unclear; nevertheless, the quality of REM sleep may be altered, with appearance of features of wakefulness/NREM sleep such as electromyographic tonus and motor behavior. It will be interesting to see if these pathophysiologic concepts can be applied to, and verified in, adults subjects with RBD as well.

CONCLUSION

RBD was previously believed to affect only older men. It is now known to be a disorder of both sexes and all ages, though more prevalent in older men. It most likely occurs more frequently in children and adolescents than previously recognized. Our study will hopefully increase the awareness of this parasomnia in childhood. Childhood RBD seems to fall into one of three categories:

1. Those with narcolepsy or idiopathic hypersomnia
2. Those who have received pharmacological agents that augment muscle tone during REM sleep, such as SSRI agents
3. Those with neurodevelopmental disorders or structural brainstem abnormalities such as autism, Smith-Magenis syndrome, Moebius syndrome, Chiari malformations, and midline tumors.

RBD may be consequent inadequate inhibitory motor mechanisms in the brainstem during sleep. Some pathophysiologic mechanisms are proposed. The long-term implications of childhood RBD remain unknown. In the short term, it seems to be modestly responsive to benzodiazepines or melatonin.

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Address correspondence to: Robin Lloyd, M.D., Center for Sleep Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905; Tel: (507) 266-7456; Fax: (507) 266-7772; E-mail: lloyd.robin @mayo.edu

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