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SCIENTIFIC INVESTIGATIONS

Rethinking bedtime resistance in children with autism: is restless legs syndrome to blame?

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Study Objectives: In this study we investigated the clinical correlates of restless legs syndrome in children with autism and report on our experiences with response to treatment.

Methods: A retrospective chart review of children seen in our sleep center from 2016–2019 was performed to identify children with autism and chronic insomnia. Patients underwent clinical assessments for restless legs symptomatology. Overnight polysomnogram, serum ferritin testing, and response to clinical treatment data were collected.

Results: A total of 103 children with autism and chronic insomnia were identified (age range 2–19 years). Of these, 41 children (39%) were diagnosed with restless legs syndrome. The diagnosis of restless legs syndrome was associated with significantly lower serum ferritin levels (mean 29 ± 18.62 ng/mL vs non–restless legs syndrome 56.7 ± 17.59, $P < .001$) and higher periodic limb movements of sleep on polysomnogram (8.12 ± 6.6 vs non–restless legs syndrome 0.06 ± 0.17). The presence of leg kicking, body rocking, or any symptoms involving the legs was highly correlated with the diagnosis of restless legs syndrome. Positive treatment response was noted in nearly all treated patients, including those treated with oral iron supplementation alone (25 children, 23 responders), gabapentin alone (12 children, all responders), and combination therapy (3 children, all responders).

Conclusions: Our findings suggest restless legs syndrome may represent an under-recognized cause of insomnia in children with autism. Initial assessment should include a thorough query of behaviors related to nocturnal motor complaints, because restless legs syndrome may be a treatable cause of sleep disruption.

Keywords: autism, insomnia, restless legs syndrome, nocturnal leg kicking, periodic leg movements, motor restlessness, iron deficiency, ferritin, pediatric

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disturbances are highly prevalent in children with autism spectrum disorders. The sleep complaint typically includes some combination of bedtime resistance, prolonged sleep latency, and frequent middle-of-the-night awakenings. The etiology of this sleep disturbance is poorly understood. A caregiver report of nocturnal motor complaints, such as leg kicking or body rocking, should prompt a clinical investigation for restless legs syndrome. There currently exists a critical gap in knowledge as to how this disorder may manifest in children with autism.

Study Impact: We characterize clinical presentations of restless legs syndrome in children with autism. Our findings suggest restless legs syndrome may be an under-recognized cause of insomnia in this population. Targeted treatment for restless legs syndrome may provide clinical benefit.

INTRODUCTION

Bedtime resistance and sleep disturbances are highly prevalent in children with autism spectrum disorder (ASD), with many studies reporting prevalence as high as 60% to 80%.[1,2] The sleep phenotype in ASD is as heterogeneous as the condition itself. The range of reported sleep problems includes prolonged sleep onset latency, frequent middle-of-the-night awakenings, and circadian cycle irregularity with no predictable periodicity of sleep.[3–5] Identifying the drivers of sleep disruption can be challenging. The etiology of the sleep problem in ASD is often elusive, multifactorial, and notoriously difficult to treat.

Caregivers describe sleepless nights with bedtime resistance starting well before lights out. Sleep disturbances may feature waves of motor restlessness and unsettled sleep that lingers throughout the night. Bedtime resistance and motor restlessness in these children are frequently considered behavioral manifestations of autism, and rarely prompt concern for a separate medical problem. However, these behaviors may signify a distinct and treatable sleep-related medical condition. Restless legs syndrome (RLS) is a heritable condition with an underlying pathophysiology linked to dopaminergic dysfunction and decreased iron storage,[6] and children with ASD are thought to be more vulnerable to iron deficiency due to their restrictive diet habits.[7] The condition is

hallmarked by an urge to move the legs when at rest and further characterized by its night-time circadian predominance.[8] This urge to move is usually, but not always, accompanied by discomfort or pain, and is relieved by movement. RLS often goes unrecognized in young children and those with language impairment, because the current diagnostic construct relies upon the patient's ability to communicate. As such, detecting RLS in children with neurodevelopmental disabilities can be challenging.

Collaborative efforts by the pediatric working group of the International Restless Legs Syndrome Study Group established a framework for diagnosing "probable" or "possible" RLS in children with limited communication abilities by relaxing the diagnostic threshold and allowing the clinician to integrate caregiver report and presence of coexisting risk factors in decision making.[9,10]

In this retrospective study, we examined the prevalence of RLS in children with ASD presenting over a 3-year period to our sleep clinic. We describe the clinical correlates of RLS in this population and report on our clinical treatment outcomes.

METHODS

A retrospective chart review of patients seen at the Children's Healthcare of Atlanta Sleep Disorders Clinic, Center for Advanced Pediatrics, and the Marcus Autism Center (Atlanta, Georgia, USA) from 2016–2019 was performed. Children with ASD who were referred for a chief complaint of chronic insomnia were identified. Patients with a history of obstructive sleep apnea or a polysomnogram showing apnea-hypopnea index > 1 event/h were excluded, because obstructive sleep apnea may also cause insomnia symptoms and sleep fragmentation. This study was approved by the Emory University and Children's Healthcare of Atlanta institutional review boards.

Each patient underwent a comprehensive pediatric sleep evaluation by a board-certified sleep medicine physician. Per our clinic protocol, this assessment included a semistructured diagnostic interview of both the child and the caregiver to assess symptoms of RLS and other sleep disorders. Children with ASD who had sufficient language proficiency participated in the interview and questionnaire responses. Sleep questionnaires completed by caregivers at every sleep clinic encounter were reviewed for details about the child's bedtime routine, sleep habits, sleep onset latency, nocturnal awakenings, sleep duration, and typical sleep-wake schedules. Caregiver descriptions of sleep complaints, bedtime behaviors, leg discomfort, kicking during sleep, excessive nocturnal movements, restless sleep, pacing behaviors, and nocturnal wandering were compiled and analyzed. Descriptions of a behavior that included a motor component were classified as "nocturnal motor complaint." The International Restless Legs Syndrome Study Group task force diagnostic pediatric RLS criteria were utilized in clinical decision making and included cases of "probable" or "possible" RLS in situations where language impairment or age prevented direct interview. Additionally, it is standard clinical practice at our sleep center when there is a high clinical suspicion for the disorder to assign a diagnosis of RLS to children who otherwise meet criteria for probable RLS but do not have a first degree relative with definite RLS and cannot tolerate a polysomnogram.

Additional relevant medical data were extracted from the electronic medical record. Patient age, sex, family history, comorbid medical problems, medication exposure to selective serotonin reuptake inhibitors, atypical antipsychotics, and antihistamines were ascertained. Baseline and follow-up laboratory measures of serum ferritin and the results of polysomnogram (PSG) studies were also ascertained. Serum ferritin was defined as low if less than 50 ng/mL.[10]

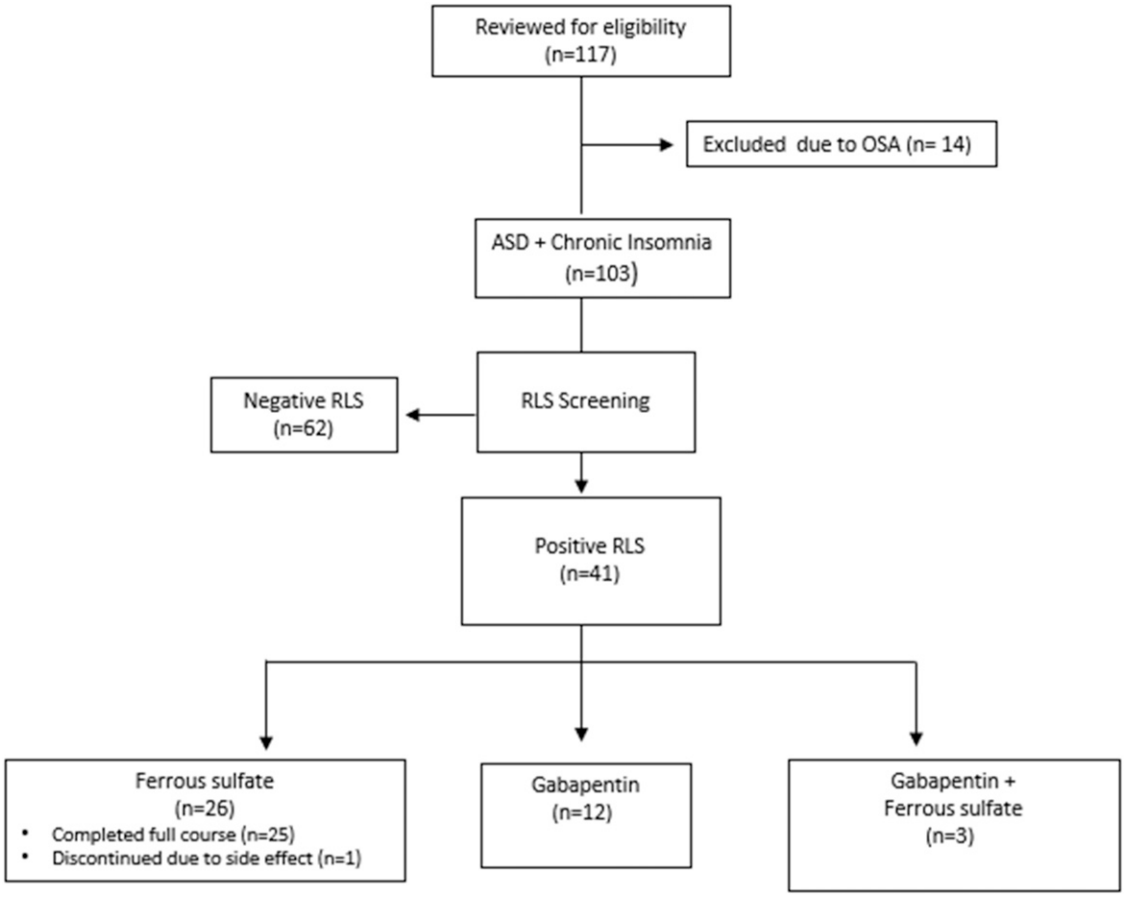
Overnight PSG at our pediatric sleep laboratory was recorded using the Cadwell Easy III PSG system (Cadwell Industries, Kennewick, WA). The standard pediatric montage was utilized in accordance with standards defined by the American Academy of Sleep Medicine (AASM) and included continuous monitoring of electroencephalogram, eye movements, chin electromyogram, bilateral anterior tibialis electromyogram, electrocardiogram, nasal airflow, chest and abdominal wall motion, snore recording, transcutaneous and end-tidal carbon dioxide monitoring, pulse oximetry, and body position. The studies were scored by a certified sleep technologist and interpreted by a board-certified sleep physician according to standard criteria. The PSG report was reviewed for periodic limb movements in sleep (PLMS). Per AASM pediatric scoring criteria, elevated PLMS was defined by an index score of > 5 events/h.

All statistical analysis was performed using IBM SPSS Statistics for Windows (Version 26.0.; IBM Corp, Armonk, NY). Descriptive statistics included means and standard deviations for continuous variables and percentages for categorical variables. For group comparisons, *t* tests were used for continuous variables and Chi-square testing was used for categorical variables, with alpha set to 0.05. Paired *t* tests were used to compare pre- and post-treatment ferritin levels.

RESULTS

We identified a total of 117 children with ASD presenting to the sleep clinic for evaluation of insomnia. Fourteen were excluded for having a diagnosis of OSA, resulting in a total 103 children who met our inclusion criteria of insomnia in the absence of OSA (**Figure 1**). Of these 103 patients, 41 (39%) were diagnosed by the treating sleep physician as having RLS (36 males, 5 females) with a mean age of 7.7 years (range 2–17 years) (**Figure 1**). The remaining patients (62/103) also had chronic insomnia but lacked clinical features of RLS, and they served as the comparison group. The prevalence of comorbid attention deficit hyperactivity disorder (ADHD) was comparable in those diagnosed with RLS (17.7%) vs non-RLS (14.6%), $P = .4$. There was no difference in the rate of medication exposure to selective serotonin reuptake inhibitors, 14.6% RLS vs 8% non-RLS ($P = .304$). Similarly, antihistamine medication use was not statistically different between the two groups (RLS 7.3% vs 6.4% non-RLS, $P = 1.0$)

Figure 1—Flow diagram of study patients through treatment approach.



ASD = autism spectrum disorder, OSA = obstructive sleep apnea, RLS = restless legs syndrome.

Sleep complaints reported by individual patients and their caregivers were also analyzed and are represented in **Table 1**. Based on our inclusion criteria, all patients had chronic insomnia. Analysis revealed no difference in the insomnia subtype (ie, onset vs maintenance problem) between the two groups. "Restless sleep" occurred in equal frequency across both groups (34% RLS vs 29% non-RLS, $P = .58$). Caregiver endorsement of a nocturnal motor complaint was higher among RLS patients compared to those without RLS (100% RLS vs 56% non-RLS). Both leg kicking (21.9% RLS vs 3.2% non-RLS) and body rocking (12.2% RLS vs 1.6% non-RLS) were more frequently endorsed in patients with RLS. RLS patients also had higher occurrences of two or more discrete nocturnal motor symptoms (14.6% RLS vs 1.6% non-RLS). Nocturnal pacing was reported in two of the RLS patients, but in none of those in the comparison group (4.8% RLS vs 0% non-RLS).

PSG data was available for 53.6% (22/41) of the RLS patients and 25.8% (16/62) of the non-RLS comparison group. All patients in the comparison group had normal PLMS (range 0–0.6). The majority of RLS patients (17/22, 77%) were found to have elevated PLMS (mean PLMS 8.12 ± 6.59, range 0–26.1, $P < .0001$).

Baseline serum ferritin levels were located in the medical records of 90.2% (37/41) of RLS patients and 17.7% (11/62) of the non-RLS group. Low serum ferritin was found in 89% of RLS patients and in 36% of the non-RLS group. The mean ferritin for the RLS group was significantly lower than that of the non-RLS (RLS 29 ± 18.62 ng/mL vs non-RLS 56.7 ± 17.59, $P < .001$).

The medical records of RLS patients were analyzed for treatment intervention and clinical outcomes. Patients with RLS who had a low serum ferritin were treated with oral iron supplementation at standard dosing of elemental iron (3–6 mg/kg/d) for 3 months and instructed to obtain a repeat serum ferritin.

A flow diagram summarizing the treatment approaches for patients in our study is shown in **Figure 1**. There were 25 patients (61%) who received a full course of oral iron therapy as the sole treatment, 92% of whom (n = 23) reported improvement at clinic follow up and required no further treatment. Oral iron supplementation was well tolerated in all patients, except one, who discontinued treatment early due to complaints of nausea and vomiting. None of the patients receiving iron therapy were found to have a medical condition in their record (eg, history of bowel resection, celiac disease) thought to potentially interfere with response to oral iron therapy. Follow-up ferritin values were located for 26 patients, and showed significant improvement after treatment (absolute mean difference 23.0 ± 21.0, $P < .0001$). One patient's data set was excluded due to an abnormally high follow-up ferritin level (> 500 ng/mL), felt to be related to an acute-phase reactant response.

Table 1—Comparisons of demographics, clinical variables and sleep characteristics in ASD chronic insomnia patients with and without RLS.

Variable	RLS Negative	RLS Positive	P-value
Total n (%)	62 (60.2)	41 (39.8)	
Sex, male	46 (74.2)	36 (87.8)	.09
Age, in years[a]	8.2 ± 4.3	7.7 ± 3.6	.58
Clinical sleep disturbance			
Onset problem	16 (25.8)	17 (41.4)	.095
Maintenance problem	15 (24.2)	7 (17.0)	.388
Both	31 (50.0)	17 (41.4)	.395
Nocturnal motor complaint**			
Presence of a motor complaint	35 (56.4)	41 (100)	**
Presence of >2 motor complaints[b]	1 (1.6)	6 (14.6)	**
Absence of motor symptoms	27 (43.5)	0	**
Restless sleeper	18 (29.0)	14 (34.1)	**
Leg complaint (any)	2 (3.2)	22 (53.6)	**
Leg kicking	2 (3.2)	9 (21.9)	**
Nocturnal pacing	0	2 (4.8)	**
Nocturnal walking	1 (1.6)	1 (2.4)	**
Body rocking	1 (1.6)	5 (12.2)	**
Head banging	2 (3.2)	1 (2.4)	**
Need to rub legs/feet	0	1 (2.4)	**
Comorbid ADHD	11 (17.7)	6 (14.6)	.4
Family history of RLS	6 (9.6)	7 (17.0)	.34
Medication exposure			
SSRI	5 (8.06)	6 (14.6)	.304
Atypical Antipsychotic	9 (14.5)	4 (9.75)	.476
Antihistamine	4 (6.45)	3 (7.31)	1.0
Mean Baseline Ferritin[a]	56.7 ± 17.59	29 ± 18.62	<.0001*
PSG Data Available	16 (25.8)	22 (53.6)	
PLMS >5 on PSG	0	17 (77)	
Mean PLMS on PSG[a]	0.06 ± 0.174	8.12 ± 6.59	<.0001*

Although not shown in this table, ferritins significantly improved in the RLS group after treatment; paired t test: mean difference 23 ± 21.0, P < .0001. **P* value < .05 level of significance. **Motor symptoms used by clinician to establish the diagnosis of RLS were excluded from statistical analysis. [a]Continuous variable expressed as mean ± standard deviation. [b]Excludes caregiver report of "restless sleep." ADHD = attention deficit hyperactivity disorder, n = number of study patients, % = percentage, PLMS = periodic limb movements of sleep, PSG = polysomnogram, RLS = restless legs syndrome, SSRI = selective serotonin reuptake inhibitor.

A total of 15 patients (36%) were prescribed gabapentin at bedtime for their RLS symptoms. Two of these patients failed a course of iron supplementation (symptoms persisted), and one patient who had been treated with gabapentin initially but then received iron supplementation due to a later finding of low ferritin. A positive clinical response, as noted by a caregiver report of improvement or resolution in the initial sleep complaint, was documented in the follow-up visit of each patient treated with gabapentin.

DISCUSSION

In this retrospective study of children with ASD and chronic insomnia, we identified a significant number of patients who had clinical features suggestive of RLS. These patients responded positively to treatment, as noted by self-reported improvement or full resolution of their chronic insomnia.

The overall prevalence of RLS in the general pediatric population is estimated to be 1% to 2%.[11–13] Prior studies have shown higher rates in children who have celiac disease (25%),[14] chronic kidney disease (22%),[15–17] and attention deficit hyperactivity disorder (44%).[18] Yet surprisingly, no studies have examined the prevalence of RLS in children with ASD. In our sample the RLS frequency was 39%. We believe this finding strongly argues for a need to conduct extensive research to understand more fully the epidemiology of RLS in ASD.

There currently exists a paucity of research examining the frequency, clinical presentation, and treatment course of

pediatric RLS in the setting of autism. In our review of the literature, we found a few prior studies that served as important precursors of our work. Dosman et al showed a link between iron deficiency and restless sleep in a small cohort of children with autism.[19] Similar to our findings, they found significant improvement in restless sleep following an 8-week course of oral iron supplementation. In light of these findings, the authors postulated a correlation between sleep disturbance in autism and RLS. However, in contrast, a more recent randomized placebo-controlled trial of oral iron to treat insomnia in children with ASD failed to show significant clinical benefit in the primary outcome measure of insomnia compared to placebo.[20] However, this lack of difference may be related to the small sample size studied, with only 9 patients in the treatment arm. Kothare et al studied the prevalence of PLMS in a retrospective cohort of 53 children with ASD while comparing ferritins and PSG findings to a control group of children without ASD.[21] The ASD group had significantly lower ferritin levels, increased sleep fragmentation, and a substantially higher rate of PLMS (47% vs 8%) than their typically developing peers. Finally, Ipsiroglu et al compiled child/parent narratives suggestive for "urge-to-move" in a small sample of 26 children with neurodevelopmental conditions with evidence of familial RLS.[22] Those with adequate language underwent a "Suggested Clinical Immobilization Test." Recorded symptomatology associated with RLS included sensory processing abnormalities and tactile sensitivity. Children with language impairment, it was noted, display nonverbal expressions of their physical discomfort through behaviors characterized as "relieving movements." Consistent with our findings, the authors reported an association with chronic insomnia and nocturnal leg kicking.

The use of PSG can be quite helpful in the evaluation of RLS in difficult or atypical cases. Elevated PLMS is a commonly found diagnostic feature, occurring in about 85% to 90% of those with the condition.[23] In our study, PSG data was available for just over half of the patients diagnosed with RLS, which speaks to the difficulty that children with autism may have in tolerating PSG. A majority of the RLS patients demonstrated elevated PLMS on PSG, while all of those negative for RLS had PLMS within the lower limits of normal. We did find several RLS patients who also had normal PLMS. We believe this likely reflects the inherent limitations associated with single-night testing, as there can be a night-to-night variability in PLMS in patients with RLS.[24,25] This lack of consecutive night testing of PLMS is perhaps another limitation of our study. However, in our sample, the preponderance of patients who received a clinical diagnosis of RLS were later found to have elevated PLMS. We believe this positive correlation bolsters our study's conclusions regarding what we have identified as clinical predictors of RLS in the setting of ASD.

Since RLS is a heritable condition, and because childhood presentations are thought to be highly familial, we collected data relative to family history.[26–28] As expected, many children in our sample had a positive family history of RLS. A recent study by Russell et al looked at this genetic dyad relationship from a different angle. These authors conducted a survey of adult biological caregivers of children with autism and found a 22% prevalence of RLS symptomatology.[29] This report immediately caught our attention because the prevalence reported here is much higher than what is typically reported in the United States for community-based adult survey estimates of RLS symptomatology, which are in the range of 9.4% to 15%.[30] We assert that this study provides indirect support for our findings of a high frequency of RLS in children with ASD.

Since children with ASD often have language or cognitive delays that create barriers to RLS assessment, we wanted to examine the nocturnal symptomatology reported by caregivers that may lend clues to its diagnosis. In review of patients' medical records, we found that a caregiver endorsement of a nocturnal motor complaint was a key factor, heavily weighted by the clinician in establishing a diagnosis of RLS. This reflects the appropriate operationalization of the International Restless Legs Syndrome Study Group diagnostic criteria for probable RLS in pediatric patients with cognitive impairment or limited language.[9] Further analysis of the data revealed that a caregiver who endorsed of nocturnal leg kicking or body rocking represented 2 specific motor complaints commonly endorsed in cases of RLS. We also encountered a fair number of caregivers who endorsed a complaint of restless sleep. We speculated this might be a potential red flag for RLS, but on the contrary, we found this sleep complaint occurred in equal frequency across both groups.

As we have pointed out, the clinical evaluation of RLS can be quite challenging in a child with a neurodevelopmental disability. The manifestations of repetitive motor behaviors at bedtime in a child who is typically developing would likely cause their parent to suspect a problem. However, what muddies the water in children with ASD is that they may display repetitive motor mannerisms during the daytime When these behaviors are displayed at night they are likely misconstrued as being related to the autism. This may account for a lot of missed diagnostic opportunities. Evaluation of children with ASD requires a more thorough teasing apart of bedtime behaviors, with specific probing for the presence of motor behaviors that cluster in an evening *circadian* pattern, as this is classic signaling for RLS.

Based on our findings, specific probing for the presence of nocturnal motor behaviors, such as leg kicking and body rocking, may aid in the detection of RLS, even in children with ASD. But more studies are needed to determine what other nocturnal behaviors may be relevant to elicit, and the sensitivity and specificity of individual features.

Certain medications (eg, selective serotonin reuptake inhibitors, antipsychotic medications, antihistamines) are known to exacerbate RLS symptoms.[31–34] Children with ASD often have psychiatric comorbidities and are often prescribed these medications. Among our sample, 32% were prescribed a medication that fell into one of these categories. Though no significant difference was found between groups, the high rates of medication exposure in children with autism may speak to a potential vulnerability for developing RLS symptomatology.

The initial treatment of RLS begins with the assessment of iron status. This should include a full iron panel with ferritin, followed by a course of oral iron supplementation to achieve a treatment goal of ferritin $\geq$ 50 ng/mL (some experts recommend correction to 75 ng/mL).[35,36] In our study sample, RLS patients

were found to have significantly lower serum ferritin levels. Treatment with iron supplementation resulted in clinical improvement for the majority of these patients. This finding is consistent with previous research showing the clinical benefits of iron therapy and is compatible with current treatment algorithms for the management of RLS.[35,37,38]

In our study, patients who did not improve after iron supplementation were offered a trial of gabapentin. Also, children who had normal ferritin levels and those with ferritin levels within 5 ng/mL range of the lower threshold of normal (ie, at or above 45 ng/mL) were offered a trial of gabapentin. We identified a total of 15 patients that were treated with gabapentin. Although not U.S. Food and Drug Administration–approved for RLS in either adults or children, gabapentin is commonly prescribed off-label for the treatment of RLS in children.[6] Medical treatment with gabapentin represented a total of 36% of patients in our study. Gabapentin was generally well tolerated, and there were no serious adverse side effects reported. At follow up, all reported a positive response to therapy, noted by reports of improved sleep quality or the resolution of insomnia.

We believe our study findings of positive treatment outcomes highlight the importance of screening for RLS symptoms when evaluating sleep disturbances in ASD. Historically the treatment focus for insomnia in ASD has been centered primarily on the role of melatonin or behavioral interventions, as is reflected in the guideline recommendations from the American Academy of Pediatrics and the American Academy of Neurology.[39,40] However, we feel these guidelines may not sufficiently ring the alarm about the possibility of unrecognized RLS as a potential cause of chronic insomnia in children with ASD.

Given the retrospective nature of this study, there were, however, several limitations. One limitation was the lack of utilization of formal screening questionnaires at both intake and follow up. However, this highlights the unique challenge of diagnosing RLS in this population, as no standardized assessment tools exist. Instead, clinicians must rely heavily on the caregiver interview. Another limitation of this study is that we did not have PSG data or ferritin values for a fair number of patients in our sample. Many caregivers declined testing outright because they did not think their child would tolerate the procedure, and a few studies were aborted because the child became overly agitated. Limited tolerance for procedures is a common issue and a real barrier in the assessment of RLS in children with ASD. Based on our study's findings, we advocate having a low diagnostic threshold for RLS, even in situations with limited supporting (objective) evidence. Finally, we found a high frequency of RLS in our sample, and acknowledge this may be an overestimate. Yet, even if RLS represents a small subpopulation, its early recognition and proper treatment are critical.

We hope this work will foster future studies, so that we may better understand the prevalence, unique clinical variables, and most effective treatment for RLS in this special population.

ABBREVIATIONS

ASD, autism spectrum disorder
PLMS, periodic limb movements of sleep
PSG, polysomnogram
RLS, restless legs syndrome

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. The authors report no conflicts of interest. The authors report the off-label use of gabapentin for the treatment of restless legs syndrome.