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Original Article

L-Dopa improves Restless Legs Syndrome and periodic limb movements in sleep but not Attention-Deficit-Hyperactivity Disorder in a double-blind trial in children

Sandra J. England [a], Daniel L. Picchietti [b], Barbara Vera Couvadelli [c], Barbara C. Fisher [d], Fouzia Siddiqui [c,e], Mary L. Wagner [f], Wayne A. Hening [a,g], Daniel Lewin [h], Glenna Winnie [h], Barry Cohen [i], Arthur S. Walters [c,j,*]

[a] UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA
[b] University of Illinois School of Medicine and Carle Foundation Hospital, Urbana, IL, USA
[c] New Jersey Neuroscience Institute at JFK Medical Center, Seton Hall University School of Graduate Medical Education, Edison, NJ, USA
[d] United Psychological Services, Washington Township, MI, USA
[e] Department of Neurology University of Toledo Medical Center, Toledo, OH, USA
[f] Rutgers College of Pharmacy, Piscataway, NJ, USA
[g] Johns Hopkins University, Baltimore, MA, USA
[h] Children's National Medical Center, Washington, DC, USA
[i] Department of Psychology and Biostatistics New York University Medical Center, New York, NY, USA
[j] Department of Neurology Vanderbilt University School of Medicine, Nashville, TN, USA

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ABSTRACT

Background: In a previous open-label study, dopaminergic agents improved Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS), as well as Attention-Deficit-Hyperactivity Disorder (ADHD) in children with both disorders. We therefore conducted a double-blind placebo-controlled trial of L-DOPA in ADHD children with and without RLS/PLMS.
Methods: Two groups of patients (total $n = 29$), those with ADHD only or those with ADHD and RLS/PLMS, were randomized to L-DOPA or placebo therapy. At baseline and after therapy patients were assessed with Conners' parent and teacher rating scales; polysomnography; RLS rating scale; and neuropsychometric measures of memory, learning, attention, and vigilance.
Results: L-DOPA improved RLS/PLMS symptoms in all patients with those disorders compared with placebo ($p = .007$). When assessed by the Conners' Scales before therapy, ADHD was more severe in children without RLS/PLMS than in children with RLS/PLMS ($p = 0.006$). L-DOPA had no effect on Conners' scales, sleep, or neuropsychometric tests when all patients treated with the drug were compared to those on placebo or when patients with ADHD only were compared to those with ADHD and RLS/PLMS.
Conclusions: In this first double-blind study of a dopaminergic therapy in children with RLS/PLMS, L-Dopa significantly improved RLS/PLMS but not ADHD. These results, however, should be interpreted carefully since they may have been influenced by the relatively small sample size and the baseline differences in severity of ADHD symptoms. Further work needs to be done to elucidate the relationship between dopamine, ADHD and RLS/PLMS.

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1. Introduction

Recent literature has shown a higher prevalence of Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS) in both children and adults with Attention-Deficit-Hyperactivity Disorder (ADHD) [1–6]. Although the relationship of PLMS to ADHD has been less consistently reported than that of RLS to ADHD [7,8], a recent meta-analysis of polysomnographic studies verified that PLMS occur more commonly in children with ADHD than normal controls [9]. The reverse relationship is also true, i.e., there is a higher prevalence of ADHD in children and adults with RLS/PLMS [4–6,10–14].

Links between ADHD and RLS/PLMS have been described elsewhere [4,6]. There are reports [4,6] that children diagnosed with RLS appear hyperactive because they cannot sit at their school desks as a result of leg discomfort and this leads directly to inattention. In addition, the sleep disruption from RLS/PLMS may lead to symptoms consistent with ADHD. Yet another possibility is that ADHD and RLS/PLMS share a dopaminergic deficit. There are abnormalities in the brain dopaminergic system in both disorders as determined by Positron Emission Tomography (PET), although

* Corresponding author at: Vanderbilt University School of Medicine, MCN- A-0118, 1161 21st Ave., South, Nashville, TN 37232-2551, USA. Tel.: +1 615 322 0283; fax: +1 615 936 0223.
E-mail address: Arthur.Walters@Vanderbilt.edu (A.S. Walters).

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the distribution is somewhat different [15,16]. In addition, genetic studies have shown alterations in dopamine transporters and receptors in ADHD patients in comparison with normal controls [17]. An alternative possibility is that RLS/PLMS and ADHD may share a genetic link that is independent of dopaminergic function. Indeed this seems to be the case as the Protein Tyrosine Phosphatase Receptor type Delta (PTPRD) gene and the Nitric Oxide Synthase (NOS1) seem to be related to either condition [18–20]. Lastly, both RLS/PLMS and ADHD have been independently shown to be characterized by iron deficiency [21–23] and an interaction of symptomotology of both disorders has been postulated with iron deficiency as intermediary [24,25].

Because of these observations and the effectiveness of dopaminergic therapy in adults with RLS/PLMS [26], we conducted an open-label study of L-DOPA in RLS children with ADHD [27]. The results indicated not only improvement in RLS/PLMS symptoms, but improvement in ADHD symptoms as well. Based upon the open-label study, we conducted the current double-blind placebo-controlled study of L-DOPA to determine if ADHD symptoms improve differentially in children with and without RLS/PLMS. Our primary hypothesis was that ADHD would improve more in children with RLS/PLMS because of allied improvement in sleep disruption. A secondary hypothesis was that L-DOPA would improve symptoms of RLS/PLMS in children under double-blind conditions. To our knowledge, this is the first double-blind placebo controlled study of a dopaminergic agent for the treatment of RLS/PLMS in children.

2. Methods

2.1. General study design, subject recruitment, and initial screening

In this double-blind study, children with ADHD who were on no ADHD medications were divided into two groups: ADHD only or ADHD with comorbid RLS/PLMS. After baseline measurements, they were randomized to receive either Carbidopa/L-DOPA or placebo for 8–13 weeks. Polysomnography, Conners' rating scales and neuropsychometric testing were performed at baseline and endpoint. For most children with RLS, rating of severity of symptoms was also performed at baseline and endpoint.

This study was carried out between 2003 and 2006 at 4 academic medical centers (The New Jersey Neuroscience Institute, Edison, NJ; Robert Wood Johnson Medical School, New Brunswick, NJ; The University of Illinois/Carle Foundation Hospital, Urbana, IL; and the Children's National Medical Center, Washington, DC). Institutional Review Board approval was obtained at each site. Written parental consent and verbal assent from the child were obtained for each participant. Any patients who had received central nervous system-active pharmacologic therapies in the three months before entering the study were excluded. The initial patients who met first level screening criteria consisted of 53 children ages 7–12 years diagnosed with Attention-Deficit-Hyperactivity Disorder (ADHD) using DSM-IV criteria with the onset of ADHD symptoms before the age of 7 years and persistence of symptoms for at least 6 months prior to recruitment [28]. No child was on treatment for RLS/PLMS at the time of the study and none were permitted to take iron supplements during the study. Children with attention problems, hyperactivity, or both were included. Ten parents refused to have their children participate because of either the desire to begin standard therapy for ADHD immediately, objection to the use of drug in this study, or logistics of traveling to the center for multiple visits.

The remaining 43 children were screened for intellectual dysfunction using the parts of the Weschler Intelligence Scale for Children-Third Edition (WISC-III) [29], severe learning problems with the Wide Range Achievement Test-Third Edition (WRAT III) [29], and psychiatric disorders with the NIMH Diagnostic Interview Schedule for Children Version 4.0 (DISC-4.0) [30]. Four children failed these screening procedures.

2.2. Polysomnographic measures

The remaining 39 children underwent two nights of baseline polysomnography in the hospital-based sleep laboratory at their respective site. Trained technicians conducted the polysomnographic studies. Studies were performed and scored prior to the introduction of the new criteria for polysomnography and the scoring of sleep related events [31,32]. During the polysomnographic study, wakefulness and sleep stages were measured by electroencephalography (EEG), electrooculography (EOG) and chin electromyography (EMG). Time in bed, total sleep time, sleep latency, REM latency, and wakefulness after sleep onset were recorded in addition to the percentage of the various stages of sleep (Stage N1, N2, N3, and REM) in relation to total sleep time.

Respiratory parameters were assessed by monitoring abdominal and thoracic movements, airflow by both pressure transducer and thermal sensors, arterial oxygen saturation by oximetry, and snoring by microphone. EKG, infrared video monitoring, and a sensitive intercom were also used to monitor patients. An obstructive apnea was defined as a decrease of $\geqslant$75% in airflow from the baseline value for at least two breaths with continuing respiratory effort. A hypopnea was defined as a discernible decrease in airflow as measured by nasal pressure transducer accompanied by either a decrease in oxygen saturation of $\geqslant$3% or followed by an arousal. Central apnea was defined as cessation in airflow accompanied by absence of effort either lasting 20 s or more or of shorter duration but accompanied by oxygen desaturation >3% or >25% decrease in heart rate. Any child with more than one respiratory event per hour of sleep was excluded from further analysis. This resulted in the exclusion of two subjects who had obstructive events.

Bilateral anterior tibialis electromyography (EMG) was recorded to assess Periodic Limb Movements in Sleep (PLMS). The criteria used were those extant at the time of this study [33]. PLMS were defined as a sequence of four or more limb movements of 0.5–5.0 s in duration, separated by more than 5 and less than 90 s, and amplitude greater than or equal to 25% of toe dorsiflexion during calibration. The PLMS index was calculated by dividing the PLMS by the total number of hours of sleep. Leg movements associated with respiratory events were not scored [33]. Two nights of polysomnography were repeated at the conclusion of therapy (see below). The data from the two baseline studies were averaged for analysis, as were the data from the final studies. All polysomnograms were scored by experienced sleep technicians and over read on an epoch-by-epoch basis by a sleep specialist (SJE or DLP).

2.3. RLS diagnosis

Definite or probable RLS was diagnosed by the obligate criteria established by the International Restless Legs Syndrome Study Group (IRLSSG) [34] as modified for children at the NIH consensus conference on RLS [21]. When possible, the biological parents also were interviewed to establish the RLS diagnosis. For most of those children with an RLS diagnosis, the severity of RLS was assessed at baseline and at the conclusion of therapy using the RLS rating scale, which has been validated in adults with RLS by the International Restless Legs Syndrome Study Group [35]. On this rating scale, there are 10 questions each scored from 0 to 4 with 0 indicating the absence of symptoms and 4 the most severe symptoms. In some cases, when it was deemed necessary, the parents helped the child complete the rating scale.

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