Periodic limb movements in sleep and attention deficit hyperactivity disorder: Are they related?

Charissa Pockett BSc MD, Valerie Kirk MD FRCPC

C Pockett, V Kirk. Periodic limb movements in sleep and attention deficit hyperactivity disorder: Are they related? Paediatr Child Health 2006;11(6):355-358.

BACKGROUND: Periodic limb movements in sleep (PLMS) is an uncommon sleep disorder in the paediatric population. Recently, an association between PLMS and attention deficit hyperactivity disorder (ADHD) in children was identified.
OBJECTIVE: To review the current literature and describe the common clinical presentations and pathophysiology related to both ADHD and PLMS.
METHODS: A comprehensive, electronic medical literature review was performed using search terms related to both PLMS and ADHD, with age limits applied to select for the paediatric population. A manual review of these articles was performed to identify other key reports relating to the topic.
RESULTS: The symptoms of PLMS in children are very similar to those of ADHD. Both disorders are related to dopamine production and metabolism, and both respond to dopaminergic therapy. The coexistence of ADHD and PLMS is reported to occur with some frequency. The potential for misdiagnosis of ADHD in a child with PLMS exists, given the similar clinical presentations. Recommendations regarding the identification of children undergoing evaluation for possible ADHD who may benefit from polysomnography are suggested.
CONCLUSIONS: Both ADHD and PLMS may present with daytime symptoms of hyperactivity, impulsivity, inattentiveness and decreased school performance. Physicians should consider PLMS in the differential diagnosis of a child with ADHD symptoms.

Key Words: *Attention deficit hyperactivity disorder; Children; Periodic limb movement disorder; Restless legs syndrome; Sleep disorders*

Les mouvements involontaires des membres pendant le sommeil et le trouble de déficit de l'attention avec hyperactivité : Sont-ils reliés?

HISTORIQUE : Les mouvements involontaires des membres pendant le sommeil (MIMS) sont un trouble du sommeil peu courant au sein de la population pédiatrique. Récemment, on a remarqué une association entre les MIMS et le trouble de l'attention avec hyperactivité (TDAH) chez les enfants.
OBJECTIF : Analyser les publications à jour et décrire les présentations cliniques courantes et la physiopathologie reliées tant au TDAH qu'aux MIMS.
MÉTHODOLOGIE : Une analyse électronique complète des publications médicales a été exécutée à l'aide de termes de recherche reliés à la fois aux MIMS et au TDAH, des limites d'âge étant appliquées pour sélectionner la population pédiatrique. Un examen manuel de ces articles a permis de repérer d'autres comptes rendus importants sur le sujet.
RÉSULTATS : Les symptômes de MIMS chez les enfants sont très semblables à ceux du TDAH. Ces deux troubles sont reliés à la production et au métabolisme de la dopamine, et tous deux réagissent à un traitement dopaminergique. Le TDAH et les MIMS coexistent à une certaine fréquence. Il existe un potentiel de faux diagnostic de TDAH chez un enfant atteint de MIMS, en raison des présentations cliniques similaires. Des recommandations sont suggérées à l'égard du dépistage des enfants subissant une évaluation en vue d'un TDAH et qui pourraient tirer profit d'une polysomnographie.
CONCLUSIONS : Tant le TDAH que les MIMS peuvent s'associer à des symptômes diurnes d'hyperactivité, d'impulsivité, d'inattention et à de moins bons résultats scolaires. Les médecins devraient envisager la possibilité de MIMS dans leur diagnostic différentiel d'un enfant présentant des symptômes de TDAH.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) affects 5% to 10% of school-aged children in North America and is the most commonly diagnosed behavioural disorder in the world (1-4). Children with ADHD have 150% more primary care visits and roughly 10 times more outpatient mental health visits per year than do children without ADHD (5). It is estimated that two-and-a-half billion dollars per year are spent on the diagnosis and treatment of ADHD in the United States (6). When children go undiagnosed, the costs to the health care system, the educational system, their families and the children themselves have the potential to be immense and long-standing. Children with ADHD have been shown to have a higher school dropout rate, achieve a lower educational level than average, have lower paying jobs and be at an increased risk of living in poverty (6-8). Added to this are the frustration and cost of a potential misdiagnosis. The family physician has an important and critical role in providing a prompt and accurate diagnosis for a child with ADHD.

Many disorders have symptoms that overlap with those of ADHD. Historically, the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (9) diagnostic criteria for ADHD included sleep disorders among the differential diagnoses, which needed to be excluded before a diagnosis of ADHD could be made. Despite mounting evidence of the connection between sleep disorders and ADHD, the more recent *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (10) does not include sleep disorders as a cause for ADHD-related symptoms. Nevertheless, the following sleep disorders have been shown to be associated with symptoms of ADHD: sleep-related breathing disorders, such as sleep apnea and upper airway resistance syndrome; restless

Department of Paediatrics, Faculty of Medicine, University of Calgary, Calgary, Alberta
Correspondence: Dr Valerie Kirk, Department of Paediatrics, Faculty of Medicine, University of Calgary, 1820 Richmond Road Southwest, Calgary, Alberta T2T 5C7. Telephone 403-943-2923, fax 403-943-7059, e-mail val.kirk@calgaryhealthregion.ca

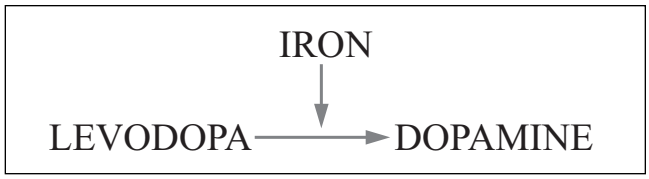

Figure 1) *Conversion of levodopa to dopamine*

legs syndrome (RLS); periodic limb movements in sleep (PLMS); and narcolepsy (11-20). The present review focuses on the relationship among RLS, PLMS and ADHD.

RLS AND PLMS

RLS is a clinical disorder that is commonly associated with ADHD (16). RLS has been loosely defined as an uncomfortable sensation in the legs that is relieved by leg movements, and tends to be worse at night and when sitting or lying. There are no standardized diagnostic criteria for the diagnosis of RLS and, consequently, there are no studies that report the incidence of RLS in children (21). However, 80% of patients with RLS also have characteristic leg movements during sleep that meet the diagnostic criteria for PLMS (22). PLMS is objectively defined as the presence of repetitive movements, typically flexions, of the toes, feet, legs, thighs and, sometimes, arms that last 0.5 s to 5 s and occur at 5 s to 90 s intervals during sleep. These movements are identified and quantitated with an anterior tibialis electromyogram during overnight polysomnography (PSG) testing (sleep study). For the purposes of clarity throughout the present review, the authors use the term PLMS to refer to children with repetitive limb movements that meet the objective diagnostic criteria as outlined above, occurring at least five times or more per hour (8).

The prevalence of PLMS in children diagnosed with ADHD is estimated to be as high as 26% compared with a prevalence of only 1.2% in paediatric populations at risk for sleep disorders (15,16,23). The increased rate of PLMS in children with ADHD may be due to the considerable overlap in symptoms of the two disorders. In children, both disorders produce daytime symptoms of hyperactivity, inattentiveness, distractibility, motor restlessness, moodiness, emotional sensitivity and decreased academic performance (16,17,23-27). These commonalities suggest that there may be a subset of children diagnosed with ADHD who actually have unidentified PLMS rather than a behavioural disorder. Alternatively, the commonalities of symptoms may prove to be a consequence of a shared pathophysiology of the two disorders, leading to their coexistence.

PATHOPHYSIOLOGY OF ADHD AND PLMS

The etiology of ADHD is most certainly complex, and various potential pathways have been hypothesized. Despite great interest and research efforts, the etiology of ADHD remains unknown. Current treatments for ADHD – methylphenidate and dextroamphetamine sulfate – increase dopaminergic activity in the central nervous system (28-30). Attention, therefore, is now being focused on the potential relationship between dopamine deficiency and the symptoms of ADHD. Konofal et al (31) have contributed to this hypothesis: they reported that low serum ferritin levels were commonly identified in a significant number of children with ADHD and PLMS. They noted that serum ferritin levels correlated with the severity of ADHD symptoms (31). Iron is required for the rate-limiting step in the conversion of tyrosine to levodopa, an important precursor to dopamine (Figure 1). Decreased iron availability decreases the production of levodopa and, therefore, of dopamine.

A low serum ferritin level is not identified in all children with ADHD and PLMS, which raises the possibility of additional or alternative problems related to iron metabolism or transport. Children with normal levels of ferritin and transferrin in the serum can have low levels of ferritin and high levels of transferrin in the cerebrospinal fluid, indicating a decreased availability of iron to the brain for essential functions, such as the production of dopamine (32).

Iron deficiency in the brain results in decreased dopamine production, contributing to motor restlessness, particularly in the form of PLMS. The limb movements experienced by these patients during sleep produce sleep fragmentation and can lead to sleep deprivation. Sleep deprivation manifests itself clinically through daytime symptoms of hyperactivity, inattentiveness, distractibility, motor restlessness, moodiness, emotional sensitivity and decreased academic performance, all symptoms supporting a diagnosis of ADHD (11-14,16,17).

Both PLMS and ADHD have been shown to be related to dopamine production and metabolism (33). Walters et al (33) conducted a small, nonrandomized, nonblinded trial to study the effect of dopaminergic therapy in patients with ADHD and PLMS. Their study included eight children: five children had diagnoses of both PLMS and ADHD, two children had only PLMS and one child had RLS. The children were given trials of levodopa and pergolide (dopaminergic agents), and then were retested six months later to determine whether they still met the diagnostic criteria for their disorders. Of the seven children who completed the trial, Walters et al (33) reported that treatment with dopaminergic agents reduced the number of periodic limb movements per hour of sleep ($P=0.018$) and improved daytime symptoms in all participants ($P<0.05$). Daytime symptoms were so dramatically improved that three of the children no longer met the criteria for a diagnosis of ADHD (33). Follow-up three years later revealed that five of the seven children had remained on dopaminergic therapy and continued to show "good response". As a result of this study, Walters et al (33) postulated that "the improvement in ADHD may be the result of the amelioration of RLS/PLMS and its associated sleep disturbance. Alternatively, ADHD and RLS/PLMS may share a common dopaminergic deficit". This study is the foundation for potential larger, randomized, double-blind studies, none of which have been undertaken to date.

IDENTIFICATION OF PLMS IN CHILDREN

Given the similar presentations of ADHD and PLMS, physicians should be familiar with the relationship between them and the potential for misdiagnosis. Chervin and Hedger (22)

recently published a short, validated screening questionnaire that can be quickly and easily incorporated into the workup of a child in whom a diagnosis of ADHD is suspected (34) (Table 1). Positive responses to these questions may help to identify patients with 79% sensitivity and 56% specificity. The positive predictive value of this screening tool is 0.38 and the negative predictive value is 0.89. While not an ideal predictive tool, this questionnaire can be easily and quickly implemented to identify children for whom a referral for further investigation for sleep disorders may be indicated.

PSG is the current gold standard diagnostic test for the diagnosis of PLMS and is available in many paediatric tertiary centres. Complete PSG includes monitoring of the following physiological parameters: electroencephalography for sleep architecture and efficiency, electrooculography to record eye movements, electrocardiography, measures of oral and nasal airflow, ventilation, leg and respiratory accessory muscle electromyography, and pulse oximetry. A PSG technician continuously observes the child during sleep to provide behavioural data. The study itself is noninvasive and performed by staff trained in dealing with the special needs and fears of children. A detailed interpretation and report is forwarded to the referring physician with recommendations for follow-up or treatment, when appropriate. When evidence of PLMS is present on PSG, specific investigation and treatment recommendations are often included with the report.

TABLE 1
Questions shown to indicate possible periodic limb movements in sleep

Does your child describe restlessness of the legs when in bed?
Does your child have 'growing pains' that are worst in bed?
At night, does your child usually get out of bed (for any reason)?
Does your child wake up more than twice a night on average?
Does your child wake up feeling unrefreshed in the morning?
Does your child wake up with headaches in the morning?

Data from reference 22

SUMMARY

Sleep disorders such as PLMS should be considered in the differential diagnosis of a child in whom a diagnosis of ADHD is suspected. Simple screening questions can help identify children who may benefit from PSG study and a referral to a paediatric sleep specialist.

Children with PLMS who are symptomatic but have no identifiable cause of their symptoms should be given a trial of dopaminergic medication. A trial of iron supplementation may also be considered, either before treatment with dopaminergic agents or as adjunctive therapy. Dopaminergic therapies reported for the treatment of PLMS in children include levodopa/carbidopa (75/300 mg to 150/600 mg daily) and pergolide (0.4 mg to 1 mg daily), with a typical dosing of four times daily (30). Collaboration with the sleep specialist and a follow-up PSG study is encouraged to confirm treatment effects.

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CPSP HIGHLIGHTS

International adoption evaluation challenges and survey results

One week after arriving from Asia, parents bring their newly adopted 11-month-old daughter to you for a routine assessment. Her immunization record indicates that she received diphtheria-pertussis-tetanus-poliomyelitis, measles, hepatitis B and bacille Calmette-Guérin (BCG) vaccines. Blood tests performed in Asia at six months of age showed the following results: hepatitis B surface (HBs) antigen negative, HBs antibody positive, HIV ELISA negative and Venereal Disease Research Laboratory negative. Physical examination is normal except for a BCG scar. Her immunization record, positive HBs antibody result and otherwise normal blood results reassure you. Four months later, you learn that another child in the travel group is being treated for tuberculosis (TB). You perform a purified protein derivative of tuberculin, which is positive at 14 mm. The infectious disease specialist recommends a chest x-ray and nine months of isoniazid. Six months later, the father is diagnosed with acute hepatitis B. You test the child and find the following results: HBs antigen positive, HBs antibody negative and hepatitis B core antibody positive indicating active hepatitis B, and was the likely source of the father's infection.

In September 2005, a one-time survey was sent to 2500 CPSP participants to determine their experience and knowledge about screening for infectious diseases in children adopted internationally. Within the past two years, 60% of the 672 respondents had cared for such children.

LEARNING POINTS

- The CPSP survey showed the following results:
  - Respondents confirmed 30 cases of hepatitis B, four cases of hepatitis C, four cases of syphilis, three cases of HIV and 111 cases of TB over the previous two years.
  - Knowledge about screening methods varied significantly, with important gaps, especially for hepatitis B and TB.
  - Screening frequency was suboptimal at 67% and 79% for syphilis and hepatitis B, respectively.
  - Most would consider repeating vaccinations given in the birth country, but many had incomplete knowledge about which serological tests could be used to determine immunity.
- Children adopted internationally are at risk of chronic infections and, in most cases, have no symptoms or signs.
- All children adopted internationally should be tested for syphilis, TB, HIV, and hepatitis B and C on arrival into Canada, regardless of serology results or immunization records in their birth country. In general,
  - repeat testing should be considered for TB, HIV and hepatitis B;
  - positive HBs antibody or hepatitis C virus antibody in children younger than 18 months may indicate transient maternal antibody, and needs further testing; and
  - BCG vaccine is not a contraindication to TB skin testing, which should be interpreted as if no BCG was given (1).
- Depending on the birth country, children have not received all immunizations offered in Canada, and 20% to 40% of them lack immunity on serological testing to diseases against which they were reportedly immunized.
- Immunization can be repeated, or serological testing can be performed to determine immunity for hepatitis B, measles, mumps, rubella, diphtheria, tetanus and varicella. The *Canadian Immunization Guide, 6th edition* (2) provides advice on immunization of children with inadequate records.
- All immediate family members and caregivers should be updated on their immunizations and receive hepatitis B vaccine before the child arrives in Canada.
- In addition, children adopted internationally should have screening tests for infectious and noninfectious conditions, and be monitored for nutrition, growth and development, attachment and behavioural concerns.

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The Canadian Paediatric Surveillance Program (CPSP) is a project of the Canadian Paediatric Society that undertakes the surveillance of rare diseases and conditions in children. For more information, visit our Web site at <www.cps.ca/cpsp> or <www.cps.ca/pcsp>.