Childhood restless legs syndrome: a longitudinal study of prevalence and familial aggregation

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Short title: Childhood and adolescence RLS

Total number of words: 2726; **Number of references:** 31

Conflict of interests: M-H Pennestri, D Petit, J Paquet, E Touchette, S Côté, RE Tremblay and Michel Boivin have no conflict of interest to disclose. J Montplaisir received consultant honorarium during the study period from Takeda Pharmaceuticals, Novartis Pharmaceuticals, Merck Pharmaceuticals, Jazz Pharmaceuticals, UCB Canada, and Valeant Canada. During the study period, Alex Desautels received research grants from Novartis, Pfizer, Jazz Pharma, Flamel Ireland, Biron, Canopy Growth, and has served on advisory boards from UCB, Eisai, and Jazz Pharma and received honorarium for speaking engagement from UCB, Biogen, and Paladin Labs. None of the financial disclosures is relevant to the submitted work.

Author contributorship: *Dr Pennestri* conceptualized the study, carried out the statistical analyses, interpreted the data, drafted the initial manuscript, reviewed and approved the final manuscript as submitted, and agrees to be accountable for all aspects of the work. *Dr Petit, Dr Desautels and Dr Touchette* interpreted the data, critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work. *Dr Paquet* supervised the statistical analyses, participated in the data interpretation, critically reviewed the manuscript for important intellectual content, approved the

final manuscript as submitted, and agrees to be accountable for all aspects of the work.
Dr Côté, Dr Tremblay, Dr Boivin and Dr Montplaisir participated in the study conceptualization and design, designed the data collection instruments, coordinated and supervised the data collection, interpreted the data, critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Summary
Restless legs syndrome is a relatively common neurological disorder in adults. In childhood, however, its prevalence and genetic contribution are still largely unknown. The objectives of this study were to assess the prevalence of RLS during childhood and adolescence in a large population-based cohort and evaluate the degree of association with parental history. Data from a large prospective longitudinal cohort from the Quebec Longitudinal Study of Child Development of 1856 children born in 1997-1998 were studied from 2005 to 2013. The prevalence of RLS was assessed at ages 7, 8, 12, 13, and 15 years through a questionnaire completed by the mother. Parental history of RLS was also queried. Between 7 and 15 years of age, the yearly prevalence of RLS ranged from 2.4 to 3.1%, with a higher prevalence in boys than girls at 12 years old. The prevalence of RLS at any time during this period was 8.6% but only 1.8% of parents answered positively at least twice during the longitudinal study. This low persistent rate could be explained by remissions or the use of parental report. The prevalence was higher when there was at least one parent affected with RLS (13.0%) compared to children without a parental history (6.9%). Findings from this population-based study confirm the high prevalence of RLS in children aged 7 to 15 years and corroborate the strong familial aggregation for RLS. Parents should be encouraged to inform the pediatrician about the presence of RLS in the family to help the diagnostic process.

Keywords: Restless legs syndrome, prevalence, familial aggregation, children, adolescents

Introduction

Restless legs syndrome (RLS) is a neurological condition characterized by an urge to move, usually associated with paresthesia (or pain in severe cases), that occurs or worsens at rest and is relieved by activity (Allen et al., 2014). Symptoms typically worsen in the evening and night (Hening et al., 1999; Michaud, Chabli, Lavigne, & Montplaisir, 2000; Michaud et al., 2004; Trenkwalder et al., 1999). As in adults, RLS and periodic limb movements during sleep (PLMS) are often associated in children (Delrosso et al., 2020). The circadian nature of RLS and its accompanying PLMS contribute to sleep disruption, leading to increased sleep latency, more frequent awakenings, and a reduction in total sleep time (Allen et al., 2005).

In adults, prevalence rates between 5.5% and 11.6% were reported in North American and European populations (for review (Koo, 2015)). However, clinically significant cases account for about 2.7% (Allen et al., 2005). Although about one-third of patients with RLS experienced symptoms in childhood, few studies have looked at the prevalence of RLS in children (Walters et al., 1996). One large epidemiological study conducted online in a random selection of households identified from a large, volunteer market-research panel in the United Kingdom and United States found a prevalence of 2.6% in children aged 8 to 11 years and 2.3% in adolescents aged 12 to 17 years (probable + definite RLS) with an “at least once per month” criterion (Picchietti et al., 2007).

Similar results were obtained more recently. In a survey conducted in 6437 children and adolescents from the province of Henan, China (Xue, Liu, Ma, Yang, & Li, 2015), the prevalence of definite RLS was estimated at 1.8% in 8-11 year-olds and 2.4% in 12-17 year-olds. The prevalence of definite RLS in 4344 Turkish children and adolescents (10-19 years) was estimated

at 2.7% (Turkdogan, Bekiroglu, & Zaimoglu, 2011). In a group of 5720 adolescents aged 13 to 16 in the province of Kayseri in Turkey, a prevalence of 2.9% was found (Per, Gunay, Ismailogullari, Oztop, & Gunay, 2017). Finally, in a smaller cohort of 383 children and adolescents from Brazil (5-17 years old), the lifetime prevalence of RLS was 6.3% and the presence of symptoms twice a week was 1.9%, as assessed by a neurologist (Sander et al., 2017).

RLS runs in families. It is estimated that more than 50% of idiopathic cases show a positive family history of RLS (Montplaisir et al., 1997; D. L. Picchietti, Rajendran, Wilson, & Picchietti, 2009; Walters et al., 1996; Xiong et al., 2010). A study reported that 10 out of 12 monozygotic twins were concordant for RLS status (Ondo, Vuong, & Wang, 2000), suggesting that genetic factors could explain at least part of the reported familial aggregation. The much higher concordance rate in monozygotic (53.7%) than in dizygotic (15.4%) twins found in another study also supports the genetic susceptibility in RLS (Xiong, Dion, et al., 2007; Xiong, Jang, et al., 2007). Thus far, 8 genetic loci have been identified in familial RLS using linkage studies, while 19 risk loci have been obtained through genome-wide association studies (GWAS), including 6 loci replicated from previous studies (Jimenez-Jimenez, Alonso-Navarro, Garcia-Martin, & Agundez, 2018; Schormair et al., 2017; Winkelmann et al., 2011; Winkelmann et al., 2007).

In summary, there are a few population-based and cross-sectional studies of RLS prevalence in children, but none of the published studies were longitudinal in nature. Moreover, none of these studies evaluated the risk of children to develop RLS as a function of parental history. The aims of the present study were therefore to: 1- assess the prevalence of RLS during childhood and adolescence in a large prospective longitudinal sample of children; 2- assess the degree of association between parental history of RLS and the presence of RLS in children and adolescents.

Methods

Subjects

This study was conducted from March 2005 to March 2013 as part of the Quebec Longitudinal Study of Child Development. All children were recruited from the Quebec Master Birth Registry managed by the Ministry of Health and Social Services. A randomized, 3-level, stratified survey design was used to study a representative sample of infants who were born in 1997 and 1998 in the province of Quebec, Canada. The 3 levels were geographic regions of Quebec, each region subdivided into areas that were representative of the number of births in the region, and the number of children selected per area proportional to the number of births and the sex ratio of this area. Families who lived in the northern part of the province of Quebec, Inuit territories, and First Nations reserves were excluded for technical reasons. Children with known neurological conditions were excluded from the cohort. All families received detailed information by mail about the aims and procedures of the research program and signed a consent form before each assessment. The protocol was approved by the "Institut de la Statistique du Québec" ethics committee.

At the inception of the Quebec Longitudinal Study of Child Development (March 1998), 2223 children aged 5 months were included. Throughout the years, some attrition occurred. In all, 1882 children (84.6% of the initial sample) were included in the present study, but there is attrition at each assessment time point, leaving 1116 children at age 15. However, the number of subjects may vary from one analysis to another because of missing data on specific questions or at certain assessment times or because of the number of missing values allowed in specific analyses. The majority of the sample was Caucasian (93.3%). Black Africans, Native Amerindians, Arabs, and

Asians each represented less than 2% of the sample. More than 80% of the study sample was speaking French at home.

Data collection

The presence of RLS was assessed at 7, 8, 12, 13, and 15 years of age using questions included in the Self-Administered Questionnaire for the Mother. The first question was: "Does your child have unpleasant sensations in his/her legs that force him/her to move?" and the response choices were "Yes" or "No". If the mother answered yes, she had to answer "Yes" or "No" to three supplementary questions: 1- Is it worse in the evening or at night than during the daytime?; 2-Is it worse while resting or during an inactivity period (sitting or lying down)?; 3-Are the unpleasant sensations relieved by activity? A child was considered to be suffering from RLS if all four answers were "Yes".

When the child was 12 years old, the mother also had to report whether she (if she was the biological mother) or the biological father, or both, had a history of RLS during either childhood or adulthood. The following operational definition of RLS was given to guide the mother: i.e., unpleasant sensations in your legs in the evening or at night that force you to move, which happen during a period of inactivity, are relieved by activity, and are worse in the evening or at night than during the daytime. Response choices were "Yes" or "No".

Prevalence data were adjusted through weighted variables (according to the 3-level survey design described in the Subjects section) at each time point so that results could be generalized to the target population of the Quebec Longitudinal Study of Child Development. The mothers had to respond to at least one time point (from age 7 to age 15) for children to be included. Pearson Chi-

Square tests were used to evaluate the effect of the sex of the children on the prevalence of RLS at each age.

Univariate logistic regressions were used to evaluate the association between "lifetime" RLS (presence of RLS in the period from 7 to 15 years of age) in children and their parents' history of RLS. For these analyses, mothers had to respond to at least 3 time points from 7 to 15 years of age for the data on childhood RLS to be considered valid. All prevalences, unadjusted and adjusted odds ratios are reported with their corresponding 95% confidence intervals. Statistical analyses were conducted using SPSS 22 (IBM, Chicago, IL).

Results

Prevalence of RLS in mid-childhood to adolescence: 7 to 15 years

The prevalence of RLS per year (total and by gender) from age 7 to age 15 is shown in Table 1. The prevalence per year was around 2.3 to 3.1%. The aggregate prevalence for children aged 7 to 15 years was calculated to be 8.6% (95%CI: 7.8-9.4). A significant gender difference was observed (boys=10% vs girls=6.5%; $p<0.02$). Persistence of RLS across this period is very low: 8.6% of the children had RLS at one assessment point (at least), but that percentage decreased to 1.8% for the presence of RLS at 2 assessment points or more, and only 0.33% had RLS at 3 assessment points or more (Table 2). Gender was not found to be associated with the persistence of RLS.

Parental history of RLS

A response on parental history of RLS was obtained for 1168 mothers (mean age: 41.5±5.1 years) and 985 fathers (mean age: 44.3±5.3 years) when the children were 12 years old. The prevalence

of RLS in parents themselves was higher for mothers than for fathers (14.5% versus 6.5%; p <0.001); the overall prevalence was 10.8%. In all, 20.3% of the children (95%CI: 19.1-21.5) had at least one parent who had a history of RLS. There was a greater proportion of parental history in children with RLS (31.6% 95%CI: 21.6-41.6) than in children without RLS (18.8%; 95%CI: 16.2-21.4).

If we look at this the other way around, the prevalence of childhood RLS (at least reported once during the period from age 7 to age 15) was found to be higher when there was a parental history of RLS (p=0.006): 13.0% (95%CI: 8.3-17.7) of children who had at least one parent with RLS developed RLS whereas 6.9% (95%CI: 5.1-8.7) of children without a parental history of RLS developed RLS. Overall, children with parental history of RLS had 2.1 times the odds (adjusted model) of having RLS compared to children with no parental history of RLS. Parental history also seems to influence the odds of having persistent RLS (Table 3). Children with a history of parental RLS were 6.5 times more likely to have persistent RLS (95%CI: 1.8-23.4; defined as reported at least twice during the period studied) compared to children with no parental history of RLS.

Discussion

Prevalence of RLS in mid-childhood to adolescence

The results of the present study show that a large number of children experienced RLS symptoms during mid-childhood or early adolescence. This is consistent with retrospective data showing that 27% (Bassetti, Mauerhofer, Gugger, Mathis, & Hess, 2001) to 38% (Montplaisir et al., 1997) of adults with RLS reported having their first RLS symptoms between the ages of 10 and 20 (Walters et al., 1996).

The prevalence rates observed in the present study vary from 2.6 to 3.1 %. These are similar to those reported in other large epidemiological studies that found prevalence rates of 2.6% in children aged 8 to 11, 2.3% in adolescents aged 12 to 17 from the UK and United States (D. Picchietti et al., 2007), 1.8% in 8-11 year-olds, 2.4% in 12-17 year-olds in China (Xue et al., 2015), 2.7% in Turkish children and adolescents (Turkdogan et al., 2011), and 2.9% in another sample of Turkish adolescents (Per et al., 2017).

In the present study, the higher prevalence of RLS in boys (although significant for one time point only) was unexpected considering that a higher prevalence in women is usually reported in adult RLS studies. However, the prevalence of RLS in parents was higher for mothers than for fathers. Other studies on childhood/adolescence RLS found either a trend for a higher prevalence rate in boys (Picchietti et al., 2007), a higher prevalence of RLS in girls (Turkdogan et al., 2011; Xue et al., 2015), or no sex difference (Per et al., 2017). Age and presence or absence of puberty could partly explain these discrepancies. There was no gender difference for persistent cases of RLS in the present study.

This cohort was studied longitudinally and an aggregate prevalence of 8.6 % was found.
This shows a high prevalence of RLS in children between the ages of 7 and 15. However, a large proportion (79%) of children scored positively for RLS at only one assessment point; very few children reported persistent RLS (mostly familial cases). This is congruent with clinical observations made in adults, in whom spontaneous remissions lasting months or years are often seen (Walters et al., 1996), especially during the early stages of disease. These observations have significant clinical implications for the management and treatment of RLS in children and

adolescents. Other studies in adults have also shown that the persistence of RLS symptoms over time was low (Szentkiralyi, Fendrich, Hoffmann, Happe, & Berger, 2011; Walters et al., 1996). Alternatively, the limitations associated with parental reports could also contribute to this low prevalence of persistent RLS.

Considering the large number of children who experience spontaneous remission, the duration of illness should be taken into consideration in the management of RLS in this age group. Parents should also be informed of the possibility of spontaneous remission. Duration of symptoms, in addition to severity, should be taken into consideration before initiating a pharmacological treatment of RLS in children.

Familial aggregation of RLS

The present study corroborates the strong familial aggregation for RLS. It reveals for the first time that children from parents with RLS (at least one of the two parents) have twice the odds of having RLS at one point during childhood and 6.5 times the odds of having persistent RLS starting between the ages of 7 to 15 years. In previous studies of RLS in adults, an earlier age of onset was shown to be associated with a family history of RLS (Allen & Earley, 2000; Allen, La Buda, Becker, & Earley, 2002; Whittom et al., 2007; Winkelmann et al., 2002).

Considering the high prevalence of RLS in the adult population, the increased risk for children of RLS sufferers to develop RLS, and the difficulty to diagnose RLS in childhood, it is important for pediatricians examining children for sleep and behavioral problems to systematically question parents about the presence of RLS in first-degree relatives as they do for other familial diseases.

Limitations

This study has some limitations. The assessment of RLS was not derived from clinicians' diagnoses or supported by objective sleep laboratory assessments. Our data were obtained from parental reports, which could have contributed to the low persistent rate. In addition, as in most other epidemiological studies, we do not have a description of the sensations by the children in their own words to make a more accurate diagnosis. Moreover, we did not enquire about, or exclude, mimics of RLS, i.e. disorders of restlessness or those involving leg pains or discomforts. Although many conditions masquerading as RLS are infrequent in children, some are quite common. For example, some parents may have mistaken growing pains or attention-deficit/hyperactivity disorder for RLS, or vice versa. On the other hand, our questionnaire did contain an operational definition for RLS, and most of the mimics of pediatric RLS are not necessarily worse at night or relieved by activity. An additional fifth diagnostic criterion (i.e., differential diagnosis) has been included to improve specificity(Allen et al., 2014) but this criterion had not yet been published when the questionnaires were designed and distributed to the families. Moreover, parents having RLS symptoms themselves are probably more likely to interpret their children's unpleasant sensations as RLS symptoms, potentially contributing to the higher prevalence of RLS in children of parents with RLS. However, they might also be able to better distinguish between true RLS and mimics. Finally, it should be noted that since 15.7% of answers from fathers were missing, this study probably provides an underestimate of the familial aggregation. Future longitudinal studies should investigate family history more thoroughly, including both parents.

Conclusions

These findings confirm the high prevalence of RLS in mid-childhood to early adolescence and the heritability of RLS. The longitudinal study showed that only a small proportion of children with RLS have persistent RLS. Therefore, non-pharmacological therapies should be used first. For persistent and severe cases, pharmacological treatments, including iron, might be necessary (if non-pharmacological options were found to be ineffective). For the secure management of specific medications and dosages for maximal therapeutic benefit and with minimal side effects, consultation of a sleep medicine specialist is recommended.

Acknowledgements

We thank the children and families whose ongoing participation made this study possible. We also acknowledge the considerable contribution of the coordinators of the Quebec Longitudinal Study of Child Development and the Quebec Institute of Statistics, as well as the tireless work of the interviewers who assessed the mothers and children in this study. We thank Rebecca Burdayron for linguistic revision. Jacques Montplaisir has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

Funding was obtained from Quebec's Department of Health and Social Services (Quebec City, Quebec, Canada), the Canadian Institutes of Health Research (Ottawa, Ontario, Canada), the Social Sciences and Humanities Research Council of Canada (Ottawa, Ontario, Canada), the Quebec Fund for Research on Society and Culture (Quebec City, Quebec, Canada), the Quebec Fund for Research on Nature and Technology (Quebec City, Quebec, Canada), the Health Research Fund of Quebec (Quebec City, Quebec), Quebec's Ministry of Research,

Science and Technology (Quebec City, Quebec, Canada), Human Resources Development Canada (Ottawa, Ontario, Canada), Health Canada (Ottawa, Ontario, Canada), the University of Montreal (Montreal, Quebec, Canada), Laval University (Quebec City, Quebec, Canada), and McGill University (Montreal, Quebec, Canada). This funding was obtained throughout the years for the Quebec Longitudinal Study of Child Development as a whole (design and data collection), but not for the specific purpose of the present study.

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Table 1. Prevalence[1] (percentage with 95% confidence intervals) of RLS in a longitudinal and prospective sample of 1430 children from age 7 to 15: boys, girls and total (weighted data).

		Prevalence of RLS (%)		
Age	**N**	**Boys**	**Girls**	**Total**
7	1306	3.6 (2.2-5.1)	2.7 (1.5-3.9)	3.1 (2.2-4.1)
8	1252	2.4 (1.1-3.6)	2.3 (1.1-3.4)	2.3 (1.5-3.2)
12	1197	3.6* (2.1-5.1)	1.6 (0.6-2.6)	2.6 (1.7-3.5)
13	1003	3.9 (2.2-5.6)	2.2 (0.9-3.5)	3.1 (2.0-4.2)
15	1116	2.8 (1.4-4.1)	2.0 (0.8-3.2)	2.4 (1.5-3.3)

Data are courtesy of the Québec Institute of Statistics. [1]The questions asked to the mother were: "Does your child have unpleasant sensations in his/her legs that force him/her to move?"; "Is it worse in the evening or at night than in the day?"; "Is it worse while resting or during a period of inactivity (sitting or lying down)?"; "Are the unpleasant sensations relieved by activity?"; For the child to be considered as having RLS, the mother had to respond yes to the four questions. * $p<0.05$ between boys and girls using Pearson Chi-square tests

Table 2. Prevalence (percentage with 95% confidence intervals) of RLS across childhood.

Lifetime RLS (between 7 and 15)†	**N (1229)**	**% (95%CI)**
Have RLS at least once	106	8.6 (7.8-9.4)
Have RLS at least twice	22	1.8 (1.7-1.9)
Have RLS at least three times	4	0.33 (0.32-0.34)

Data are courtesy of the Québec Institute of Statistics. †Lifetime prevalence of RLS is calculated based on the total number of mothers who responded to at least 3 time points (when their child was 7 to 15 years of age (N=1229)).

Table 3. Results of univariate and multivariate logistic regression to predict RLS in 7- to 15-year-olds.

	Odds ratio (95%CI)	
Predictor	Unadjusted	Adjusted
Have RLS at least once during 7-15 period		
Sex (Male)	**1.59 (1.06-2.39)**	**1.91 (1.05-3.48)**
History of RLS in parents	**2.00 (1.21-3.30)**	**2.11 (1.16-3.84)**
Have RLS at least twice during 7-15 period		
Sex (Male)	0.75 (0.32-1.76)	0.74 (0.18-3.13)
History of RLS in parents	**5.39 (1.98-14.66)**	**6.49 (1.80-23.39)**

Data are courtesy of the Québec Institute of Statistics. Odds ratio in bold are significant at $p<0.05$