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RLS in middle aged women and attention deficit/hyperactivity disorder in their offspring

Xiang Gao^{*}, Kristen Lyall, Natalia Palacios, Arthur S. Walters, and Alberto Ascherio

Department of Nutrition (XG, NP, and AA), and Department of Epidemiology (KL, AA), Harvard University School of Public Health, Boston, MA; Department of Neurology (ASW), Vanderbilt University School of Medicine, Nashville, Tennessee; and Channing Laboratory (XG and AA), Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA

Abstract

Background—Previous studies have suggested that attention deficit/hyperactivity disorder (ADHD) and restless legs syndrome (RLS) could share some common genetic backgrounds, but the effect of these genetic components could be modest. To test this hypothesis, we conducted a large-scaled cross-sectional study to examine whether women with a child with ADHD had a higher risk of having RLS than women of unaffected children.

Methods—We included 65,554 women free of diabetes, arthritis, and pregnancy in the current analyses. Information on RLS was assessed using a set of standardized questions. Participants were considered to have RLS if they met four RLS diagnostic criteria recommended by the International RLS Study Group and had restless legs ≥ 5 times/month. Information on ADHD in offspring was collected via questionnaire.

Results—We observed a significant association between presence of ADHD in the offspring and risk of having RLS; the multivariate-adjusted OR for RLS was 1.27 (95% CI: 1.15, 1.41; $P < 0.0001$), after adjusting for age, body mass index, number of deliveries during life time and other covariates.

Conclusion—We found that mothers of children with ADHD had an increased risk of having RLS. Further studies are warranted to explore biological mechanisms underling this association.

Keywords

Attention deficit/hyperactivity disorder; Restless legs syndrome; BTBD9; PTPRD; Iron deficiency; Dopamine

Individuals with Restless legs syndrome (RLS) have been shown to have a higher prevalence of attention deficit/hyperactivity disorder (ADHD) relative to those without the syndrome and vice versa (1–4). RLS and ADHD have both been associated with dopamine

^{*}Correspondence and reprint requests to: Dr. Xiang Gao, Department of Nutrition, Harvard School of Public Health; 655 Huntington Ave, Boston, MA 02115, USA; Phone: 1-617-432-5080; Fax: 1-617-432-2435; xiang.gao@channing.harvard.edu.

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deficit and iron deficiency, suggesting these factors may be involved in underlying mechanisms (1,2). In a recent genetic study including 386 children (5), the authors observed a significant association ($P=0.009$) between risk of ADHD and a haplotype consisting of three single nucleotide polymorphisms (SNPs) of the BTBD9 gene, which has previously been identified by genome-wide association studies (GWASs) as a susceptibility gene for RLS and decreased iron store (6,7). However, after correcting for multiple testing, the association between the haplotype and ADHD risk was not significant (5). This study suggests that ADHD and RLS could share some common genetic components but the effect of these genetic factors could be rather modest. Based on this study, we hypothesized that the association between RLS and ADHD may exist across generations. We, therefore, conducted a large-scaled study to examine whether mothers with a child with ADHD had a higher risk of having RLS than women of unaffected children.

Methods

Study Population

The Nurses' Health Study II (NHS II) cohort comprises 116,678 female registered nurses who were 25–42 years of age and resided in one of 14 U.S. states at the time of enrollment in 1989 (8).

Assessment of RLS

In 2005, we asked participants ($n=97,642$, mean age 50.4 ± 5 y) who were still alive and actively participating in the study to self-report their status of RLS (9). These RLS questions were based on the International RLS Study Group criteria in 2005. The following question was asked: "Do you have unpleasant leg sensations (like crawling, paresthesias, or pain) combined with motor restlessness and an urge to move?" Possible responses were "no," "<1 time/month," "2–4 times/month," "5–14 times/month," and "15+ times/month." Those who answered that they had these feelings were asked the following two questions: 1) "Do these symptoms occur only at rest and does moving improve them?" 2) "Are these symptoms worse in the evening/night compared with the morning?" We considered an individual a probable RLS case if the participant answered "yes" for all three of the above questions, and reported a frequency of ≥ 5 times/month.

The questions on RLS were completed by 79,992 (82%) women. Participants who did not complete the RLS questions had similar age (mean age 50.4 years for both) as those with RLS information. To reduce a possible misclassification of RLS, we excluded participants with diabetes, arthritis, and those who were pregnant at the time of completing the questionnaire, leaving 65,544 women in the primary analyses.

Assessment of ADHD in offspring

In the 2005 questionnaire, we asked all women in the cohort whether any of their children had been diagnosed as ADHD. In a validation study including 92 NHS II participants who reported having a child with ADHD (unpublished data), we found that children reported as having ADHD scored high on the ADHD IV rating scale; all girls scored above 90%, whereas 81.1% of boys had a score above 80%, and 63.8% above 90% (10).

Assessment of covariates

Information on age, smoking status, weight, height, reproductive history, use of medicines, phobic anxiety scale (as assessed by the Crown-Crisp phobia index), and history of major chronic diseases was collected via biennial questionnaires throughout the follow-up.

Statistical analyses

Statistical analyses were completed with SAS version 9.1 (SAS Institute, Inc, Cary, NC). Logistic regression was used to test differences in prevalence across categories and to calculate odds ratios (ORs) and 95% confidence intervals (CIs). We examined potential interactions of having ADHD in offspring with age, obesity, and smoking status (never versus ever) by including multiplicative terms in the logistic regression models, with adjustment for other potential confounders.

Results

Women who reported having a child with ADHD were more likely to be past smokers, to use antidepressants, and to have more deliveries during their life time, as compared to those who did not report this condition (Appendix).

We observed a significant association between presence of ADHD in the offspring and risk of having RLS; the age- and BMI-adjusted OR for RLS was 1.42 (95% CI: 1.29, 1.57; $P<0.0001$) (Table 1). After further adjustment for smoking, use of antidepressant, and number of deliveries during life time the association remained significant (OR=1.27; 95% CI: 1.15, 1.41; $P<0.0001$). Results did not change after additional adjustment for presence of hypertension, stroke, MI, and phobic anxiety index (RR=1.27; $P<0.0001$). Further, results did not materially change when we excluded women who did not have a delivery during life time (RR=1.26; $P<0.0001$), excluded women who reported use of antidepressant (RR=1.30; $P<0.0001$), and who had coronary heart disease, stroke, hypertension, or a high anxiety score (RR=1.27; $P=0.001$). We did not find any significant interactions between presence of ADHD in offspring and age, smoking, and obesity ($P_{\text{interaction}}>0.4$ for all) in relation to RLS risk.

Discussion

In this cross-sectional study, we found that mothers who reported having a child with ADHD had a modestly increased risk of having RLS, relative to those who did not report this condition. Our results are consistent with previous studies which reported co-occurrence of RLS and ADHD (1,2). For example, in a study including adult patients ($n=171$, mean age 61–63 y) with RLS, insomnia and healthy controls, ADHD, as assessed by DSM-IV ADHD scores, were found in 26% of RLS patients, relative to 6% of insomnia patients, and 5% of controls (3). In a large-scaled cross-sectional study including 10523 children and adolescents high prevalence of ADHD/ADD was found among 206 children or adolescents who met the diagnostic criteria for definite RLS (14.8% among 8 to 11-year-olds and 17.6% among 12 to 17-year-olds) (11). In a study including 18 children and adolescents with RLS, 13 of them were found to have ADHD and 10 with both ADHD and a family history of RLS (12). However, the high proportion of ADHD found in this study could be partly due to the investigators' initial interest in researching RLS patients who were referred for ADHD (12). It is worth noting that, unlike previous published studies, the current study is the first to examine the connections between RLS and ADHD across generations.

A possible interpretation for the observed association between having a child with ADHD and risk of RLS is that these two conditions share common genetic determinants. BTBD9, which has been identified by two recent GWASs to be associated with risk of RLS (6,7), could be a potential candidate (5). Interestingly, the RLS risk allele of BTBD9 is associated with decreased serum ferritin concentration (7). Iron deficiency has been suggested as a risk factor of RLS (13) and ADHD (14,15). Other potential candidate genes include the protein tyrosine phosphatase gene (16) (17) and nitric oxide synthase 1 (18), which have also been found to be associated with risk of both ADHD and RLS. Also of interest is the observation

that both ADHD and RLS have been reported in patients with Tourette's syndrome.(1–4,19,20). In a recent case-control study of three RLS-related BTBD9 single-nucleotide polymorphisms were found to be significantly associated with Tourettes's syndrome risk. (20)

It is also possible that as sleep deprivation or depression is caused by RLS, women with RLS may exaggerate the ADHD-like behaviors in their child. However, we adjusted for use of antidepressants in our main analyses. Further adjustment for anxiety score, as well as exclusion of women reporting use of antidepressants also did not materially change the significance of the observed association.

A limitation of the current study is that we did not collect ADHD status among nurses. Because the heritability of ADHD has been suggested to be high (~60–80%) (5), it is likely that nurses who reported having a child with ADHD were also at high risk of having ADHD. Similar concerns are raised because we did not assess for the presence or absence of RLS in the ADHD children and other family members. Some misclassification in RLS due to some RLS-like symptoms is also likely. Another limitation is that assessment of ADHD in offspring relied on self-reports, and some degree of misdiagnosis is thus inevitable. However, the validation study suggests that the accuracy is rather high; further, this is a sample of medically trained nurses who have been shown to provide reliable and valid information on diseases. Limitations of the current study also include that lack of information on subtype of ADHD, date of ADHD onset, other clinical information (e.g., iron deficiency), and birth order among offspring, as well as the number of affected children in each family.

In conclusion, in this large investigation we found that mothers of children with ADHD have an increased risk of RLS. Because of potential limitations as described above, our study should be considered preliminary. Nevertheless, these results confirm and extend previous observations and are consistent with the existence of a shared genetic susceptibility between RLS and ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Odds ratios (ORs) and 95% confidence interval (CI) of restless legs syndrome according to status of ADHD in their offspring in the Nurses' Health Study II.

	ADHD in offspring		P-value
	No (n= 59,270)	Yes (n= 6,274)	
Mean age, y	50.2	49.1	
# RLS cases	3687	536	
Age- and BMI- adjusted OR	1(ref.)	1.42 (1.29, 1.57)	<0.0001
Multivariate adjusted OR ¹	1(ref.)	1.27 (1.15, 1.41)	<0.0001
Excluding women without delivery during life time	1(ref.)	1.26(1.14, 1.40)	<0.0001

Logistic regression models were used to calculate ORs, adjusted for age (in years), smoking status (never smoker, former smoker, or current smoker: cigarettes/d, 1–14 or ≥ 15), BMI (<23, 23–24.9, 25–26.9, 27–29.9, or ≥ 30 kg/m²), use of antidepressant drugs (yes/no), and the number of delivery