JOGNN

IN FOCUS

Heredity of Restless Legs Syndrome in a Pregnant Population

Mary Dawn Hennessy and Frances Aimee De La Torre

Correspondence
Mary Dawn Hennessy, RN, PhD, CNM
Assistant Professor, Department of Women Children, and Family Health Science, University of Illinois at Chicago
845 S. Damen Ave. MC802, Chicago, IL 60612.
mary.hennessy@ucsf.edu

Keywords
restless legs syndrome
pregnancy
genetics
heredity
family history
gender

ABSTRACT

Objective: To synthesize published research on genetic and heredity findings related to restless legs syndrome (RLS) in a pregnant population.

Data Sources: PubMed, CINAHL, and PsycINFO databases and reference lists from published articles.

Study Selection: Literature searches were conducted for primary research studies published in English on the genetic and heredity findings of RLS in pregnant populations.

Data Extraction: Study characteristics and findings related to genetic and heredity aspects of RLS in a pregnant population.

Data Synthesis: Five data-based articles met the criteria for study inclusion. Study findings comprised Level-2 and Level-3 evidence. Four of the five studies were larger population studies and contained a subset of pregnant participants. Parity and family history were important predictors of RLS proband status. Probands reported symptoms were often initiated during or after pregnancy.

Conclusions: Symptoms of RLS for female probands are often initiated during pregnancy or after childbirth. A history of RLS in a previous pregnancy and family history of RLS were strong predictors of RLS in the current pregnancy. Future research on genetic associations of RLS in pregnancy is warranted.

JOGNN, 42, 737-748; 2013. DOI: 10.1111/1552-6909.12248

Accepted March 2013

Frances Aimee De La Torre, BSN, RN, is a registered nurse in the Department of Pediatrics, Mt. Sinai Hospital, Chicago, IL.

Mary Dawn Hennessy, RN, PhD, CNM, is an assistant professor, In the Department of Women, Children, and Family Health Science, University of Illinois at Chicago, Chicago, IL.

The authors report no conflict of interest or relevant financial relationships.

Restless legs syndrome (RLS) is a neurological movement disorder characterized by a strong urge to move the legs that is worse in the evening and at rest and is relieved with movement (Allen, 2007; Hening, 2007). Restless legs syndrome can be classified as primary or secondary. Primary RLS has no known etiology and appears to be hereditary, whereas secondary RLS can be attributed to underlying medical conditions such as pregnancy, anemia, and kidney failure (Allen).

Restless legs syndrome disrupts the initiation of sleep and subsequently decreases quality of life (Abetz et al., 2004; Allen et al., 2005; Cho et al., 2009). Patients with RLS have increased risk for sleep apnea, insomnia, and drowsy driving. They report daytime fatigue, being late to work, missing work, making errors at work, and missing social events because of sleepiness (Phillips, Hening, Britz, & Mannino, 2006). In one study, researchers found that RLS patients have 20% decreased productivity at work, equating to about one day per 40-hour work week (Allen, Bharmal, & Calloway, 2011). Restless legs syndrome also has negative effects on cognitive ability (Pearson et al., 2006), and depression and anxiety symptoms are common in patients with RLS (Celle et al., 2010; Pantaleo, Hening, Allen, & Earley, 2010). Aside from the health impact, the average annual cost of treatment for RLS patients is about $500 (Allen et al.). Over a lifetime, this financial burden can be as high as $25,000 per patient.

Currently no definitive diagnostic tests are available for RLS, and a lack of provider awareness exists resulting in underdiagnosis and missed opportunities for treatment of this disorder. As a result, diagnosis is based on five criteria determined by the International Restless Leg Syndrome Study Group (IRLSSG): (a) an urge to move legs caused by uncomfortable sensations in the legs, (b) symptoms that worsen during times of inactivity, (c) relief of symptoms with movement, (d) symptoms that worsen at night, and (e) the occurrence of the above features not solely accounted for as symptoms primary to another medical or a behavioral condition (Allen et al., 2003). The fifth criterion was recently added to the original four

Restless legs syndrome disrupts the initiation of sleep and subsequently decreases quality of life, increases symptoms of depression and anxiety, and decreases cognitive function.

diagnostic criteria in 2011. The Hopkins Diagnostic Telephone Interview (HDTI) is a validated diagnostic telephone interview developed using the original four IRLSSG diagnostic criteria; therefore, the same four criteria must be met for RLS diagnosis (see Table 1) (Hening, Allen, Washburn, Lesage, & Earley, 2008; Hening et al., 2003). Despite specific diagnostic criteria, RLS is often underdiagnosed because no diagnostic biomarkers are available, and RLS symptoms can be confused with other disease related symptoms, especially during pregnancy.

Approximately 10% of the general population is affected by RLS, with women twice as likely to experience RLS symptoms as men. However, the rates of RLS in nulliparous women are similar to the rates for men. This difference in rates appears to be associated with a previous pregnancy (Berger, Luedemann, Trenkwalder, John, & Kessler, 2004). The prevalence of RLS increases in the pregnant population to 25% to 30% occurrence (Lee, Zaffke, & Baratte-Beebe, 2001; Pantaleo, Hening, Allen, & Earley, 2010).

Whites have been reported as having the highest prevalence of RLS, however, these results may be related to factors related to access to care. In a study among 358 African Americans, 633 Whites, and 33 others, researchers found the rates were similar for African Americans (4.7%) and Whites (3.8%) after adjusting for age, gender, medical comorbidities, and socioeconomic status (Lee et al., 2006). Barriers affecting access to care settings for African American RLS patients may be an important factor to consider.

The pathophysiology of RLS is poorly understood and involves dopamine and iron regulation with patients responding positively to dopaminergic medications (Hening, Allen, Earley, Picchietti, & Silber, 2004). However, objective measures of dopamine function are not clinically available and radionuclide imaging results of dopamine receptors are conflicting (Allen, 2007; Earley et al., 2011). Researchers have identified a central nervous system (CNS) iron deficiency in RLS pathophysiology (Earley et al.), and periodic CNS iron deficiency can occur when peripheral serum iron levels are low, for example, the evening nadir of iron's circadian rhythm (Connor et al., 2011). Additionally, iron is a cofactor in dopamine metabolism (Patrick, 2007), therefore measures of iron status such as lower hemoglobin have been associated with RLS (Lee et al., 2001).

Family history of RLS in 60% to 77% of patients suggests a genetic link (Winkelmann et al., 2002; Xiong et al., 2010). Humans have 22 chromosome pairs plus two sex chromosomes. Each chromosome is identified by a number. Human chromosomes have a long arm and a short arm separated by a centromere. The short arm is designated the *p arm* whereas the long arm is the *q arm*. To date five loci associated with RLS have been identified at regions on chromosomes (chr) 2q, 9p, 12q, 14q, and 20p (RLS 1–5) (Bonati et al., 2003; Desautels et al., 2001; Levchenko et al., 2006). Several genes have been identified that contribute to the development of RLS, including BTBD9, MEIS1, MAP2K5/LBXCOR1, and PTPRD (see Table 2) (Kemlink et al., 2009; Schormair et al., 2011; Stefansson et al., 2007; Winkelmann et al., 2007). Evidence also exists to support the involvement of the neuronal nitric oxide synthase (NOS1) pathway (12q) (Winkelmann et al., 2008).

Nitric oxide (NO) is an important cellular signaling molecule that controls CNS development and is associated with pain perception as well as sleep/wake regulation (Gautier-Sauvigne et al., 2005). The NO-arginine pathway modulates dopaminergic transmission (Kiss, Zsilla, & Vizi, 2004) and opioid regulation (Hervera, Negrete, Leanez, Martin-Campos, & Pol, 2011). Genetic studies of RLS have focused on European cohorts with little racial heterogeneity (Winkelmann et al., 2008).

Because a large percent of RLS cases are familial, occurring or tending to occur among members of a family, and RLS prevalence is highest in the pregnant population, examining genetic aspects of RLS in a pregnant population warrants further study. Therefore, the purpose of this literature review is to examine the existing literature on genetic and heredity studies considering RLS in a pregnant population.

Methods

Data Sources

The studies reported in this review were found using electronic databases CINAHL, PubMed, and