Sleep Medicine 11 (2010) 897–906

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Development of the Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS)©: A patient-reported outcome measure of pediatric RLS symptoms and impact

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ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form 19 March 2010
Accepted 25 March 2010

Keywords:
Restless legs syndrome
Symptoms
Sleep disorder
Children
Patient-reported outcome
Quality of life
Questionnaire development
Attention-deficit/hyperactivity disorder

ABSTRACT

Objective: To develop a questionnaire to measure Pediatric Restless Legs Syndrome (P-RLS) symptoms and impact for use in clinical research.
Methods: Questionnaire items were developed based on open-ended, qualitative interviews of 33 children and adolescents diagnosed with *definite* RLS (ages 6–17 years) and their parents. The draft questionnaire was then tested through cognitive debriefing interviews with 21 of the same children/adolescents and 15 of their parents. This involved the children and parents answering the draft items and then interviewing them about the child's ability to understand and interpret the questionnaire. Expert clinicians provided clinical guidance throughout.
Results: Draft severity questions were generated to measure the four-symptom and four-impact domains identified from the concept elicitation interviews: RLS sensations, move/rub due to RLS, relief from move/rub, pain, and impact of RLS on sleep, awake activities, emotions, and tiredness. RLS descriptions, symptoms, and impact were compared between those who had comorbid attention-deficit/hyperactivity disorder and those who did not. Revisions to several questions were made based on the cognitive debriefing interviews and expert clinician review, resulting in a severity scale with 17 morning and 24 evening items. Caution regarding self-administration in children ages 6–8 years is recommended. To complement the child/adolescent measures, a separate parent questionnaire was also developed.
Conclusions: The P-RLS-SS was constructed based on detailed input from children and adolescents with RLS, their parents, and clinical experts, thus providing a scale with strong content validity that is intended to be comprehensive, clinically relevant, and important to patients. Validation of this scale is recommended.

1. Introduction

Pediatric restless legs syndrome (P-RLS) is a relatively common neurological disorder that can impact sleep, cognition, and affect. First described in detail in 1994, P-RLS is now characterized by a substantial medical literature that has recently been reviewed [1–3]. Pediatric-specific diagnostic criteria for RLS were developed at a National Institutes of Health (NIH) workshop and published in 2003 [4]. As in adults, the core feature of P-RLS is a prominent urge to move the legs, usually associated with other uncomfortable and unpleasant sensations. These symptoms typically occur when sitting or lying down (e.g., while studying and at bedtime), are relieved by movement, and are most severe at night. Early-onset RLS is highly familial, with recent genome-wide scans having identified five common gene variants associated with RLS [5–10]. In addition, periodic limb movements in sleep (PLMS) are present in the majority of pediatric and adult RLS cases [10–14]. The population prevalence of P-RLS was recently found to be 2.0% of

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doi:10.1016/j.sleep.2010.03.016

8–17-year-olds in the United States and United Kingdom, with one-quarter of the children and one-half of adolescents reporting moderate to severe symptoms [15]. This study also described impact on cognition and other domains of health-related quality of life.

Validated severity measures are an essential component of disease assessment for outcomes in clinical trials, particularly for the assessment of symptoms that are known only to the patient, such as those in P-RLS. In addition, classification of severity can be useful for assessment of disease correlates and pathophysiological mechanisms as well as clinical treatment decisions. Although biometric measures, such as serum glucose in diabetes, are important, patient-reported outcome (PRO) measures are equally important in assessing treatment efficacy. PROs are defined as "a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of any aspect of the patient's responses by a physician or anyone else)" [16] and "any outcome evaluated directly by the patient himself and based on (the) patient's perception of a disease and its treatment" [17]. PROs can be used to measure both single- and multidimensional concepts, such as core symptoms, symptom impact on daily life, ability to function, satisfaction with treatment, and physical/psychological/social well-being, the latter often encapsulated by the term health-related quality of life (HRQoL). Furthermore, Food and Drug Administration (FDA) guidelines indicate that fundamental considerations in the development or use of a PRO instrument are clear identifications of the concepts being measured and assurance that those concepts are appropriate, well defined, and relevant to the target population [16,18,19]. The FDA places particular emphasis on demonstrating content validity through performing open-ended interviews with patients who have the disorder being studied.

Several PRO scales have been used to assess the severity of RLS in adults. These include the disorder-specific International Restless Legs Scale (IRLS) [20], Johns Hopkins Restless Legs Severity Scale [21], and Restless Legs Syndrome Quality of Life Questionnaire (RLSQoL) [22], as well as instruments that are generic instruments, such as the Short-Form Health Survey (SF-36) [23,24] and Medical Outcomes Study Sleep Scale [25]. These have been used to demonstrate that moderate to severe RLS in adults has substantial impact on HRQoL [23,24,26–28].

For P-RLS, a literature search did not identify any severity assessment scales, but one study did look at severity based on patient-reported responses to frequency and intensity questions, which was found to correlate with perceived impact [15]. Thus, there is a need for a validated, disorder-specific P-RLS severity scale. The use of adult measures in children or adolescents is generally inappropriate as wording must be adjusted to age and developmental level, and domains of impact that are relevant to adults are not always the same ones that are important to children (e.g., impact on work vs. impact on school) [16]. Child PROs must be developed with consideration of age and developmental limitations in children's vocabulary, memory, attention span, reading ability, and the concepts they are able to understand [29,30]. For HRQoL assessment that is not disorder specific, validated pediatric instruments are available [31,32].

Of interest, there is significant comorbidity of P-RLS with attention-deficit/hyperactivity disorder (ADHD) in approximately 13–25% of P-RLS cases [10,11,15], and it is estimated that one-quarter of children with ADHD meet diagnostic criteria for RLS [33–35]. While the diagnostic criteria for RLS and ADHD are distinct and there are no shared criteria, four of the DSM-IV criteria for the hyperactive–impulsive subtype of ADHD (items a, b, c, e [36]) relate to motor activity while seated or to excessive motor movement, and could be influenced by the presence of comorbid RLS. In addition, there may be overlap in the respective impact ADHD and RLS have on cognition, affect, and sleep (e.g., RLS sensations might produce inattentiveness, and ADHD-related hyperactivity might affect sleep onset) [37,38]. Thus, it seems important to investigate whether RLS symptom experience or impact is different for those who have comorbid ADHD, compared to those who do not.

The specific aim of this study was to develop a multidimensional, self-administered, patient-reported outcome questionnaire to assess pediatric RLS symptom severity and impact—the Pediatric RLS Severity Scale (P-RLS-SS). Rather than modify an adult RLS severity scale we sought to develop a new severity measure based on qualitative interviews with children and adolescents affected by RLS, as well as through input from their parents and guidance by P-RLS clinical experts. Additional objectives were to assess the potential influence of ADHD on P-RLS symptomatology and to assess the feasibility of a parent version of the P-RLS-SS.

2. Methods

2.1. Severity scale development

The development process followed recommendations from regulatory agencies and PRO experts [16,17,39]. As outlined in Fig. 1, the study involved four main steps: (1) qualitative concept elicitation interviews of children/adolescents with RLS and their parents; (2) development of questionnaire items, response options, and instructions based on the concept elicitation findings, with review by an expert panel; (3) cognitive debriefing interviews of the children/adolescents with RLS and their parents to evaluate face and content validity of the draft items; and (4) revisions based on cognitive debriefing findings.

2.2. Participants

Participants in both the concept elicitation and cognitive debriefing interviews were children and adolescents with P-RLS (age range 6–17 years) who were being evaluated at the clinics of four pediatric sleep disorders specialists in the US (authors DLP, JSD, AI, JAO). A purposive sampling strategy ensured inclusion of enough participants to achieve "conceptual saturation" within each of three age ranges (6–8, 9–11, and 12–17 years). This was of primary importance, given that children of different ages vary in their ability to self-report using PRO measures [40,41]. Approximately equal numbers of children with and without comorbid ADHD were included within each age range, to allow comparisons between these groups. The ADHD subgroup had to meet DSM-IV criteria [36] on clinical assessment and had to have a symptom severity score 1.5 standard deviations above age and gender norms on the ADHD Rating Scale-IV: Home Version, indicating the presence of ongoing ADHD symptoms [42].

In order to participate, the children/adolescents had to fulfill NIH diagnostic criteria for *definite* RLS (subtype 1 or 2) [4]; have experienced RLS symptoms at least once in the two weeks preceding the interview; have undergone a physical examination of the lower extremities and demonstrated normal strength, tone, sensation, and reflexes; and be willing to participate. Exclusion was based on mental retardation; significant English-language delay or impairment; secondary RLS due to other health conditions such as renal failure or neuropathy; treatment with stimulant or non-stimulant ADHD medication in the 7 days prior to interview; and treatment within 14 days prior to interview with medication known to significantly influence RLS symptoms (e.g., dopaminergics, dopamine blockers, antiemetics, antidepressants, sedating antihistamines, hypnotics, benzodiazepines, anticonvulsants, clonidine, and opioids). Females were excluded if pregnant.