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Brief communication

Modeling the causal relationships between symptoms associated with restless legs syndrome and the patient-reported impact of RLS

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Abstract

The objective of this study is to examine the causal relationships between the symptoms of restless legs syndrome (RLS) and specific clinical and subjective health-related, quality of life consequences. Structural equation modeling was applied to data from a questionnaire-based observational study. The RLS morbidities of decreased functional alertness and emotional distress in our sample of patients appear to be mostly secondary to the sleep disturbance associated with RLS. There was no clear indication of any other feature of RLS affecting these two aspects of RLS morbidity. A primary treatment goal should be the reduction of the sleep disturbance of RLS, both to decrease the RLS-related nocturnal distress and to improve daytime functioning.

Keywords: Restless legs syndrome; RLS; Structural equation modeling

1. Introduction

Restless legs syndrome (RLS) is a condition characterized by disagreeable leg sensations that are temporarily relieved by leg movement. RLS affects approximately 9–15% of the general population, and the pathophysiology of the disorder is not well characterized. It is estimated that 94% of these patients report sleep-onset insomnia or sleep disturbance due to RLS symptoms [1]. As would be expected given their disturbed sleep, alertness and daytime function are impaired in RLS patients; paradoxically, these patients do not report significant daytime sleepiness or have abnormal Epworth sleepiness scale scores [2]. Failure to observe the profound sleepiness expected from sleep disruption suggests some mechanism among RLS individuals that compensates for daytime sleepiness. Such a compensatory mechanism might be more effective against some of the morbidities associated with sleep loss, such as sleepiness, and less effective in reducing others, such as irritability, mood lability, or problems with alertness.

Our aim was to assess the causal relationships between RLS symptoms, sleep quality, and daytime functioning involving alertness and emotional distress (irritability and moodiness). These relationships were evaluated using key items from the RLS-Quality of Life Instrument (RLS-QLI), a questionnaire specifically developed to assess the impact of RLS on the quality of life among patients with this disorder [3], as well as items taken from the International Restless Legs Study Group's Severity Rating Scale (IRLS) [4]. We used structural equation modeling to explore whether the impaired daytime alertness and emotional distress among these patients are moderated by the sleep disturbance or by some other factor associated with RLS.

Structural equation modeling combines the well-known statistical methods of factor analysis and path analysis, allowing researchers to model complex relationships between observed variables and hypothetical constructs. Path coefficients describe directional causal pathways (e.g. $X \rightarrow Y \rightarrow Z$) [5] and the factor analytic component describes the loadings of observed variables on unobserved factors

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(i.e. latent variables). For example, general intelligence, a latent variable, is measured by an individual's performance on a series of observable educational assessment tasks. In turn, general intelligence can be shown to predict later socioeconomic achievement (a second latent variable) that is measured using observable indicators of educational and financial attainment. Such modeling techniques have a wide variety of applications; of specific interest to us is their use in the causal modeling of disease states [6]. Structural modeling can also be used to examine the directionality of relationships by comparison of the relative fit of two alternate models with observed data.

2. Methods

The data were collected as part of the RLS-QLI Psychometric Development Study, in which 575 members of the RLS Foundation mailing list (5700 total) reported their RLS symptoms and completed the IRLS symptom severity measure, the RLS-QLI (before item reduction), and specific questions regarding sleep-related experiences. The sample had a male:female ratio of 1:1.4, a mean age of 54.5±12.3 years, a mean age of first symptoms of 32.0±16.5 years, and a mean age at first diagnosis of 47.6±12.9 years. The mean self-reported IRLS score was 24.0±6.8 and 67% of the sample were on prescription medications for RLS.

Structural equation modeling was used to explore the relationships between RLS symptoms and specific aspects of sleep experience and subjective, health-related quality of life (HR-QoL) consequences. This statistical methodology uses a hypothesis-testing or confirmatory approach to multivariate analysis of a structural theory bearing on an observable phenomenon [7].

A hypothetical model was designed that specified both a direct and sleep-moderated causal pathway between RLS symptoms and emotional distress and impaired daytime alertness. The causal path coefficients in the model were allowed to float and computed by the statistical software, based on the observed relationships between the variables. A comparison of the relative strengths of the direct and sleep-moderated pathways between RLS symptoms and emotional distress or impaired daytime alertness permitted inferences about the role of sleep disturbance in the impact of RLS on patients' daily lives.

3. Results

The structural equation model is depicted in Fig. 1. *Latent variables* can be thought of as factors that represent theoretical constructs that underlie the observed clinical

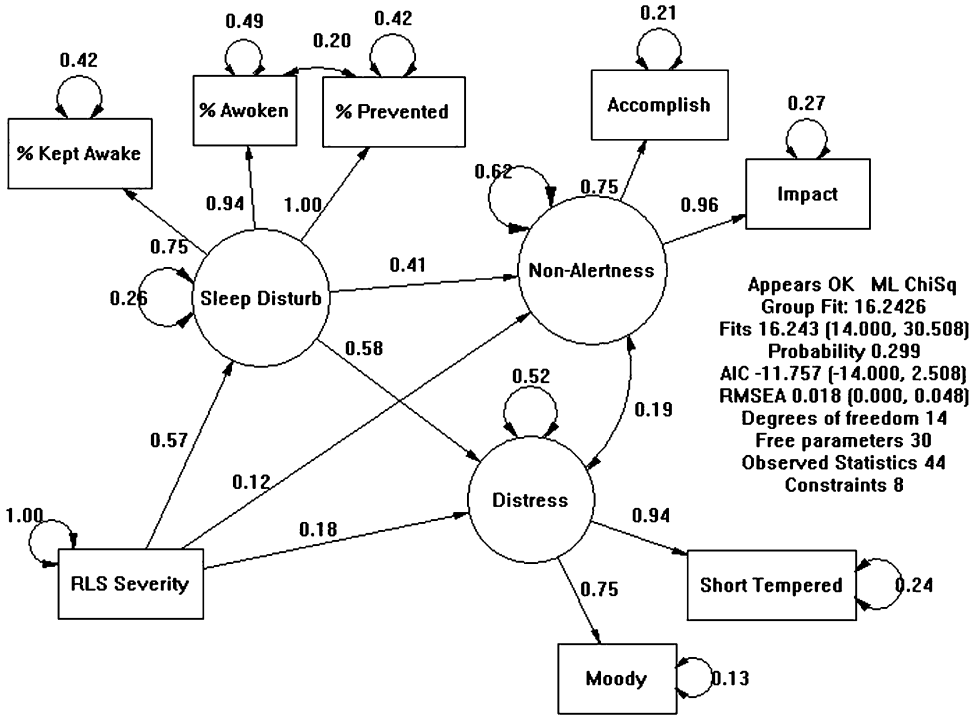

Fig. 1. Structural equation model of the inter-relationships between RLS symptoms, sleep disturbance and symptom impact on patients' lives (HR-QoL). Max Likelihood Chi Square Group Fit (df 14)=16.2. Probability of misfit between model and observed=0.30. Root Mean Squared Error=0.018. Note: There is a slight interpretive difficulty with the path coefficient between the Sleep Disturbance to %Prevented. These kind of anomalous findings are called Heywood cases (highly improbable or impossible results such as negative variances or correlations >1.0) and are likely due to the artifact of the overall fit rather than a 'real' parameter estimate [10,11]. Another path coefficient to %Awoken is very high (0.94). The covariance and complete dependence of the proportion of nights prevented from returning to sleep between two of the sleep disturbance variables are probably responsible for the observed Heywood effect.

Table 1
Observed variables for the causal model

RLS symptoms[a]	Item 1: Overall, how would you rate the RLS discomfort in your legs or arms?
	Item 2: Overall, how would you rate the need to move around because of your RLS symptoms?
	Item 6: Overall, how severe is your RLS as a whole?
	Item 7: How often do you get RLS symptoms?
	Item 8: When you have RLS symptoms how severe are they on an average day?
Sleep disturbance	Please indicate the percentage of nights over the last month that RLS symptoms keep you from falling asleep when you first go to bed
	Please indicate the percentage of nights over the last month that RLS symptoms have awoken you from sleep
	Please indicate the percentage of time that RLS symptoms have kept you from returning to sleep when you have been awakened
Emotional distress[b]	How often are you irritable or short-tempered because of RLS?
	How often are you moody because of RLS?
Lack of daytime alertness[b]	Over the course of a day, how much are your daily activities affected by a lack of alertness?
	How often do you lack the alertness to get things done?

[a] From the IRLS [4], using the six-item scale [9], omitting item 4 (pertaining to sleep disturbance).
[b] Taken from the RLS-QLI [3].

and illness-impact measures [7]. The latent variables (enclosed in circles in Fig. 1) for our study were the subjects' ratings of: (1) Sleep Disturbance--proportion of nights per month they were kept awake, awakened from sleep, and prevented from returning to sleep; (2) Non-Alertness--impact of RLS on their alertness and the impact of their alertness levels on their daily functioning; and, (3) Distress--contribution of RLS to their emotional states of moodiness and temper.

These latent variables are indirectly measured by *observed variables* (Table 1), which are enclosed in boxes (Fig. 1). Directional arrows specify causal pathways, while bi-directional arrows depict non-causal co-variation (e.g. between Non-Alertness and Distress). Residual terms associated with the prediction of each latent hypothetical variable are referred to as *disturbance*; they are depicted as circular arrows next to the circles.

An overall measure of the goodness of fit was used to examine the degree to which the model fit the data; the Maximum Likelihood Chi Square fit for the model was calculated, producing a value of 16.24 ($df=14$, $P=0.30$). The Residual Mean Square was 0.018, indicating that the standardized residual variances and covariances were very near zero, demonstrating a good fit between the proposed model covariance matrix and the input covariance matrix. The Comparative Fit Index was 0.98, indicating that the model accounted for 98% of the variance and covariance in the observed data matrix. The primary comparison of interest in Fig. 1 is the relative strength of the path coefficients between observed RLS Symptoms and Non-Alertness and Distress. Two paths are specified directly from RLS Symptoms to Non-Alertness and Distress; the other paths are moderated through the latent construct of Sleep Disturbance. Using study results, relatively low path coefficients were estimated directly between (observed) severity of RLS symptoms and symptom impact on functional and emotional dimensions of life quality ($r=0.12$ and 0.18). This contrasts with the stronger sleep-moderated pathway between RLS Symptom Severity and Sleep Disturbance (0.57), and from Sleep Disturbance to Emotional Distress (0.58) or Non-Alertness (0.41). While the reasons for the impact of RLS Symptoms on Sleep Disturbance are currently being investigated, the impact of the sensory–motor manifestations of RLS on emotional and alertness functioning appear moderated primarily through the effects of Sleep Disturbance.

4. Discussion

The Chi Square test indicated a very good fit between the proposed causal model and the observed data structure. Moreover, the goodness of fit of this model argues for the plausibility of the proposed relationship among the variables in this sample. While the underlying causal mechanism of RLS is unknown, it appears that the daytime morbidities of decreased alertness and distressed mood are less likely to result from direct and pronounced disruption of daytime neurological mechanisms regulating wakefulness or attention but more likely from an indirect effect of sleep disruption during the prior nights. Further, the hypothetical latent variable 'Sleep Disturbance' is described by the proportion of time kept awake, awakened from sleep, and prevented from falling back to sleep, and thus the primary determinant of sleep disturbance may be the actual loss of sleep time. One cannot rule out the possibility that other factors not taken into account by this model (e.g. cognitive disturbance) might covary with sleep disturbance and prove to be stronger moderators than sleep disturbance.

Intriguingly, given the degree of sleep disruption reported by these patients, one would expect more severe daytime sleepiness; RLS patients may report no significant sleepiness, but rather a subtle breakthrough of decreased daytime alertness proportional to the degree of sleep disruption. As previously noted, RLS patients do not have the expected increased sleep drive, despite significant sleep loss. However, our study indicates that they nonetheless suffer from other physiological and psychological problems resulting from such deprivation. They appear to have the sleep loss but lack the drive to obtain the sleep that would

help reduce these problems; thus some type of compensatory mechanism for the daytime sleepiness typically associated with sleep loss is suspected. An alternative hypothesis is that the RLS-associated discomfort experienced by these patients results in a dissociation in their desire to fall asleep during the day and their reported or objective ability to fall asleep. However, one would expect that the chronic inability to fall asleep would eventually lead to excessive daytime sleepiness by accumulated sleep debt.

Further, the emotional distress observed in RLS patients does not appear to be directly caused by the primary RLS symptoms. In our model, the strength of the causal pathway between RLS severity and distress was moderate, and the relationship appeared to be moderated by the effects of RLS symptoms on sleep. This finding may not be specific to RLS, but rather a more generalized effect of sleep disturbance on an individual's neurocognitive function and resulting subjective life experiences. Mood disturbances, particularly irritability and short-temper, were reported to occur with sleep deprivation in normal subjects [8].

There is a slight interpretive difficulty with the path coefficient between the Sleep Disturbance (latent variable) to %Prevented (observed variable) (Fig. 1). In addition, the morbidity variables measured were primarily those known to be related to sleep disruption; there is little attention to effects on social or cognitive functioning that may result from daytime RLS symptoms. Lastly, this study's self-identified convenience sample may not adequately address concerns about clinical validity of the findings, especially the applicability for extremely symptomatic patient samples. Nonetheless, given the strength of the model for patients within the mid-severity range, it seems likely that it also applies to more extreme cases.

In conclusion, this study reports the first clear evidence regarding the dominant role of sleep disruption in moderating the impact of the important daytime morbidities of RLS. In particular, the current model describes RLS as a source of sleep disturbance, which in turn moderates decreased alertness and emotional distress reported by RLS patients. These results could be extended in future studies by evaluating the relation of the sleep disturbance to other daytime morbidities of RLS, such as social or cognitive functioning, or the relationship of sleep loss to the intensity of the sensorimotor RLS symptoms. Lastly, the findings from this study suggest that treatment of RLS-associated sleep disturbance may improve the daytime symptoms of RLS; conversely, treatment that does not specifically address sleep disturbance may have little effect on the daytime consequences of RLS.

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