PAIN® 153 (2012) 666–673

PAIN®

www.elsevier.com/locate/pain

Insomnia, sleep quality, pain, and somatic symptoms: Sex differences and shared genetic components

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 26 April 2011
Received in revised form 5 November 2011
Accepted 6 December 2011

Keywords:
Insomnia
Sleep quality
Pain
Somatic symptoms
Sex differences
Heritability

ABSTRACT

This study investigated the sex differences, and the shared genetic and environmental factors underlying the associations of sleep disturbances (insomnia and sleep quality) with pain and somatic symptoms in both adolescents and middle-aged adults. We recruited 259 adolescents (69 with current insomnia) and their parents (256 middle-aged adults, 78 with current insomnia). Insomnia severity and sleep quality were measured by the Insomnia Severity Inventory (ISI) and Pittsburgh Sleep Quality Index (PSQI), respectively. Pain and somatic symptoms were measured by the Somatic Symptom Inventory and Visual Analogue Scale for overall pain. Subjects with insomnia scored higher on all measures of pain and somatic symptoms than non-insomnia patients, in both adolescents and adults ($P < .001$). Both pain and somatic measures were associated with ISI and PSQI scores after controlling for age, sex, depressive and anxiety symptoms. There was an interaction effect between insomnia and female sex on pain and somatic symptoms ($P < .05$), especially in adults. Pain and somatic symptoms ran in family with moderate heritability (range $h^2 = 0.15–0.42$). The phenotypic associations of ISI and PSQI with pain and somatic measures were both contributed by genetic (range $p_G = 0.41–0.96$) and environmental (range $p_E = 0.27–0.40$) factors with a major genetic contribution. In summary, insomnia and poor sleep quality are closely associated with pain and somatic symptoms. Insomnia seems to modulate the sex differences in pain and somatic symptoms, especially in the adult population. A shared genetic predisposition might underlie the associations of insomnia and sleep quality with pain and somatic symptoms.

1. Introduction

Insomnia, which is commonly found in the general population across different age groups and countries [10,24,27,46], is associated with increased health care burden [12,29] and with medical and psychiatric morbidities [27,39]. In particular, insomnia is often associated with somatic and pain symptoms [11]. For example, insomnia has been found to predict pain symptoms or aggravation of pain symptoms in depression [11], burn injury [37], and temporomandibular joint disorders [30]. Our study similarly showed that insomnia was associated with chronic pain in the adult general population at 5-year follow-up [45]. The association between sleep quality and pain is complex, as reflected by their day-to-day symptomatic covaried fluctuations in elderly subjects with insomnia [15]. On the other hand, insomnia is a common complaint in patients with pain symptoms related to their underlying medical disorders, such as rheumatoid arthritis and cancer [36]. Pain was also found to predict new incidence of insomnia [18,21]. Janson et al. found that joint/low back pain at baseline predicted the incidence of insomnia after 10 years in men with an Odds Ratio of 2.95 [18]. More recently, LeBlanc et al. reported that a higher level of body pain was an important predictor for incidence of insomnia [21]. In brief, there is a close and bidirectional relationship between insomnia and pain [36].

However, the mechanism underlying the relationship of insomnia with pain and somatic symptoms is far from clear. Several pathways may account for this relationship. First, sleep loss may play a critical role in the effect of insomnia by sensitizing pain perception [28,33,34]. Second, as a common comorbidity, depression may mediate the relationship of insomnia with pain and somatic symptoms [3]. Third, sex difference may account for the relationship because female predominance is a common phenomenon in insomnia [43], pain, and somatic appraisal [4]. In addition, several aspects remain unclear in the relationship of insomnia with pain

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0304-3959/$36.00
doi:10.1016/j.pain.2011.12.003

and somatic symptoms. First, most previous studies only focused on the intercorrelation among insomnia, pain, and somatic symptoms in adults, and there was a dearth of study on child and adolescent groups. Second, although sex differences in insomnia [43], pain, and somatic symptoms [4] have been consistently found, no study has reported on how sex could modulate the effects of insomnia on pain and somatic symptoms. Third, the genetic basis for these relationships has not been investigated. Given the high heritability estimate of insomnia symptoms [41], it would be worth exploring the heritability or genetic basis of the relationship among insomnia, pain, and somatic symptoms. In this general population-based cross-sectional family study, we aimed to investigate: (1) the associations of insomnia and sleep quality with pain and somatic symptoms in both adolescents and middle-age adults, (2) sex differences in the relationship of insomnia and sleep quality with pain and somatic symptoms, and (3) potential genetic components underlying this relationship.

2. Methods

2.1. Subject selection

The current study was part of an ongoing epidemiologic study about sleep problems among Hong Kong Chinese school children and their parents that started in 2003–2004 (baseline) [23,25,42,46]. The follow-up study (wave 2) was conducted with a 2-phase design to investigate the familial aggregation of insomnia during 2008–2011. Phase 1 involved an epidemiological follow-up study with a questionnaire assessment of sleep problems. Phase 2 was a cross-sectional family study with a face-to-face structured diagnostic interview for insomnia and mental disorders and psychometric assessments on sleep quality, mood, quality of life, pain, and somatic symptoms [44,45]. The major aim of this phase 2 family study was to investigate familial aggregation and heritability of insomnia. The protocol of this study was approved by the Institutional Ethics Review Committee. All participants younger than 18 years old gave their written assents and parental consents. All participants age 18 years or older gave their written consents by themselves. In brief, all adolescents with insomniac complaints (classified as high-risk subjects) including difficulty in initiating sleep (DIS), difficulty in maintaining sleep (DMS), and/or early morning awakening (EMA) of at least 3 times per week and/or usual sleep onset latency $\geqslant$30 minutes in the past 12 months at phase 1 questionnaire study were invited to attend the phase 2 clinical interview study. In addition, a group of adolescents without any insomniac complaints were also invited for further clinical interview at Phase 2 (low-risk subjects). The subject recruitment is presented in Fig. 1. All of their biological parents and full siblings over 6 years old were also invited to attend the phase 2 study. Each subject was assessed by a face-to-face structured clinical interview, a set of detailed psychometric questionnaires, and a clinical examination. The determination of insomnia was based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision criteria for insomnia disorder [2], which includes: (1) a predominant complaint of difficulty initiating or maintaining sleep or early morning awakening for at least 1 month; (2) causes significant distress or impairment in social, occupational (or academic in adolescents), and/or other important areas of functioning. Another subtype of insomnia [3], nonrestorative sleep, was not recruited into the analysis because nonrestorative sleep has an overlapping association with other sleep disorders, such as sleep deprivation and sleep apnea syndrome, and in our opinion might be better considered as a distinct sleep problem [31,38].

A total of 285 adolescents were contacted, and 236 of them finally participated, with a response rate of 82.8%. All adolescents were living with their parents and had similar school schedules. Overall, 95 adolescents were initially classified as high-risk subjects and 141 as low-risk. The clinical interviews ascertained a total of 75 adolescents as insomniacs, whereas the rest of the subjects (n = 161) were identified as non-insomniac controls (Fig. 1). In addition, a total of 224 mothers, 196 fathers, and 142 full siblings were recruited into the phase 2 study. The fathers and mothers were grouped as adult samples, whereas probands and their siblings were grouped as adolescent samples for analysis. The current analysis was based on 259 adolescents (68.5%) and 256 middle-age adults (61.0%) who completed the assessment of both pain and somatic inventories. There were no differences in age (46.0 ± 4.2 vs 45.7 ± 5.0) and sex (female 53.1% vs 54.0%) between the adults who did and did not complete the inventories. More female adolescents completed the inventories (54.8% vs 39.3%, P = .011), but adolescents who completed the inventories were of similar age to those who did not complete them.

2.2. Measures of insomnia severity and sleep quality

The severity of insomnia and sleep quality was assessed by the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI), respectively. The ISI is a 7-item questionnaire assessing the subtype, severity, and impact of sleep difficulties in the past 2 weeks with satisfactory psychometric properties [6]. The PSQI is a 19-item questionnaire evaluating sleep quality and sleep disturbances over a 1-month interval [8]. Higher scores in ISI and PSQI indicate more severe insomniac symptoms and poorer sleep quality, respectively.

2.3. Measures of overall pain severity by Visual Analogue Scales

Visual Analogue Scales (VAS) were used to assess the severity of overall pain in the past week [13]. This question was asked as: "The following are questions that describe all the pain you experienced during the previous week. Experiences of discomfort are generally described as 'numbness', 'exhausted', 'heaviness', etc., whereas experiences of pain are generally described as 'tingling', 'dull pain', 'burrowing pain', etc." The pain severity of VAS was anchored by "no pain" on one end and "as severe as I can imagine" on the other in a 100-mm scale.

2.4. Measures of somatic and pain symptoms

Somatic symptoms (including both pain-related and non-pain-related items) were measured by the 28-item Somatic Symptom Inventory (SSI-28), in which each somatic symptom was rated on a Likert scale from 1 (not at all) to 5 (a great deal), according to how much it bothered the participants over the last week [5]. The pain subscore (SSI-pain) was derived by calculating the average score over 7 pain-related items, whereas the somatic subscore (SSI-somatic) constituted the remaining 21 items [5].

2.5. Measures of depressive and anxiety symptoms

Depressive and anxiety symptoms were assessed by the locally validated Chinese version of the Hospital Anxiety and Depression Scale (HADS) for both adolescents and adults [9,22]. The HADS is a 14-item self-reporting questionnaire with two 7-item subscales for anxiety and depression. The items are rated on a 4-point Likert scale from 0 to 3. The anxiety and depression subscores are summed separately in the current study.

2.6. Statistical methods

Descriptive statistics were presented as percentages for discrete variables and as means (standard deviations) for continuous variables. To compare the independent differences for each pain