Observational Study

Medicine

OPEN

Associations between insomnia and central sensitization in cancer survivors undergoing opioid therapy for chronic cancer pain

A STROBE-compliant prospective cohort study

Chiaki Akui, PharmD[a,b], Takeshi Kimura, PharmD, PhD[b], Munetaka Hirose, MD, PhD[a,*]

Abstract

Several risk factors for insomnia in cancer patients have been recognized, including chronic pain and treatment with opioid. Although associations between insomnia and central sensitization were previously reported in patients with chronic non-cancer pain, those have not been elucidated among cancer survivors undergoing opioid therapy for chronic cancer pain. To investigate the associations between insomnia and central sensitization among cancer survivors undergoing opioid therapy for chronic cancer pain, consecutive patients undergoing chemotherapy with chronic cancer pain under opioid therapy on an outpatient basis were enrolled from September 2019 to August 2020 and answered questions from the Athens Insomnia Scale (AIS) for assessing insomnia. Pain characteristics, including pain intensity, neuropathic pain, central sensitization assessed using the central sensitization inventory (CSI), opioid use disorder, and pain-related psychological symptoms were also examined. Uni- and multivariate regression analyses were performed to elucidate correlations between the AIS score and these pain characteristics. Of 44 enrolled patients, 20 patients completed to answer all questions. Insomnia was identified in 9 patients (45%). Although AIS scores showed no significant associations with pain intensity, neuropathic pain, opioid use disorder, or psychological symptoms, multivariate regression analysis revealed that CSI scores showed a positive relationship with AIS scores (P = .004). Discrimination was assessed using linear regression analysis which confirmed a significant association between the AIS and CSI scores (P = .002). Insomnia appears to be associated with central sensitization in cancer survivors with chronic cancer pain under opioid therapy.

Abbreviations: AIS = Athens Insomnia Scale, BMI = body mass index, CSI = central sensitization inventory, DN4 = Douleur neuropathique 4, DSM-V = diagnostic and statistical manual of mental disorders, ECOG = eastern cooperative oncology group, NRS = numerical rating scale, OME = oral morphine equivalents, PCS = pain catastrophizing scale, PS = performance status, SRQ-D = self-rating questionnaire for depression, STAI-1 = state-trait anxiety inventory 1, VIF = variance inflation factor.

Keywords: chronic pain, opioid use disorder, palliative care, sleep disturbance

1. Introduction

A high prevalence of insomnia is a serious concern among cancer survivors.[1] Several risk factors for insomnia in cancer patients have been recognized, including younger age, chronic pain, and treatment with opioid, delirium, depression, or anxiety.[1,2] On the other hand, in patients with chronic non-cancer pain, sleep disturbance reportedly correlated with central sensitization.[3–7] Although an association between insomnia and central sensitization is strongly expected in cancer survivors having with chronic cancer pain, the association has not been examined well.

Since the prevalence's of both chronic pain[8,9] and high-dose opioid use for chronic pain[10] were reportedly high in cancer survivors compared to the general population, elucidation of the detailed associations between insomnia and central sensitization could contribute to better treatments for insomnia in cancer survivors undergoing opioid therapy for chronic cancer pain. To identify the association, we prospectively examined insomnia with these pain characteristics in cancer survivors in the present study.

2. Methods

2.1. Ethics

This prospective observational study was approved by the Ethics Committee at Hyogo College of Medicine (Ethical Committee number 3296) on 9 September 2019. Written informed consent

This study was supported by the institutional budget.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Anesthesiology and Pain Medicine, Hyogo Medical University (Formerly Hyogo College of Medicine), School of Medicine, Nishinomiya, Hyogo, Japan, [b] Department of Pharmacy, Hyogo Medical University Hospital, Hyogo, Japan.

**Correspondence: Munetaka Hirose, Department of Anesthesiology and Pain Medicine, Hyogo Medical University (Formerly Hyogo College of Medicine), School of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan (e-mail: mhirose@hyo-med.ac.jp).*

How to cite this article: Akui C, Kimura T, Hirose M. Associations between insomnia and central sensitization in cancer survivors undergoing opioid therapy for chronic cancer pain: A STROBE-compliant prospective cohort study. Medicine 2022;101:38(e30845).

Received: 18 April 2022 / Received in final form: 30 August 2022 / Accepted: 31 August 2022

http://dx.doi.org/10.1097/MD.0000000000030845

for study participation was obtained from all participants. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Patients

Participants were consecutive cancer survivors undergoing chemotherapy on an outpatient basis from September 2019 to August 2020 at the chemotherapy center in Hyogo Medical University Hospital. Eligibility criteria for the present study were chronic cancer pain ≥3 months in duration with opioid treatments in this cohort. We excluded patients <20 years old and those who could not answer questions for the assessment of pain characteristics.

2.3. Data collection

To achieve the purpose of this study, namely the associations between insomnia and central sensitization, we prospectively obtained clinical data of age, sex, body mass index (BMI), and eastern cooperative oncology group (ECOG) - performance status (PS) in addition to information on insomnia, central sensitization, and pain characteristics.

Insomnia in cancer survivors was assessed using the Japanese version of the Athens Insomnia Scale (AIS). Sleep difficulty increases the AIS score, with a final score ranging from 0 to 24.[11,12]

The Central Sensitization Inventory (CSI) was used to assess symptoms associated with central sensitization in chronic pain patients.[13,14] The CSI contains 25 items, one of which directly relates to sleep conditions. Total CSI score ranges from 0 to 100. Higher CSI scores suggest abnormal and intense enhancement of pain by mechanisms in the central nervous system.[13]

Information on pain characteristics, including pain intensity, neuropathic pain, durations of opioid use, opioid doses, opioid use disorder, and pain-related psychiatric symptoms, were obtained from all enrolled participants by completing the following questions. Pain intensity at rest and during movements was assessed using the numerical rating scale (NRS) score, ranging from 0 as "no pain" to 10 as "the worst imaginable pain". Screening for neuropathic pain was performed using the Douleur Neuropathique 4 (DN4) questionnaire.[15,16] DN4 scores (range, 0–10) represent the number of neuropathic pain symptoms. To diagnose opioid use disorder, we used the diagnostic criteria for substance use disorder in the 5th edition of the diagnostic and statistical manual of mental disorders (DSM-V).[17] This criterion contains 11 items, and higher scores correspond to greater severity of opioid use disorder. Pain-related psychiatric conditions of pain catastrophizing, depression, and anxiety were assessed using the Pain Catastrophizing Scale (PCS), Self-Rating Questionnaire for Depression (SRQ-D), and State-Trait Anxiety Inventory 1 (STAI-1), with scores ranging from 0 to 52, from 0 to 36, and from 20 to 80, respectively.[18–20]

2.4. Sample size calculation

The sample size in this study was calculated using software (PS Power and Sample Size Calculations, version 3.0, Dupont WD and Plummer WD). The calculation was performed based on the assumption that a type I error had a probability of 0.05 and power of 0.8. From previous studies,[12,14] the standard deviations were 6 in the AIS score and 14 in the CSI score. The slope of the correlation coefficient between these two scores was assumed to be 0.35. Then, the sample size was estimated to be 14 patients. In consideration of the potential for study dropouts, we enrolled 44 patients in the present study.

2.5. Statistics

Statistical testing was performed using JMS Pro version 14.2.0 (SAS Institute Inc., Cary, NC). Values of $P < .05$ were considered to indicate statistical significance. Normality of data was assessed using the normal quantile plot.

Uni- and multivariate regression analyses were used to identify correlations between AIS scores and central sensitization. To exclude the confounding effects of CSI, we selected duration of opioid therapy, daily dose of opioid using oral morphine equivalents (OME), and each score of opioid use disorder, NRS at rest and during movements, DN4, PCS, SRQ-D, and STAI-1, as candidate variables for univariate analysis. If multicollinearity was present between variables based on a variance inflation factor (VIF) <10, variables were deleted from the analysis.[21] A multivariate logistic regression model was built using those variables showing values of $P < .05$ from univariate analysis. To report the performance of multivariate regression modeling, discrimination was assessed using the linear regression analysis.[21]

3. Results

Of forty-four enrolled patients, 10 patients refused to answer questions and 14 patients did not complete all questionnaires. Thereafter 20 patients completed to answer all questions in the present study. No data were missing in these patients. Table 1 shows the demographic characteristics of patients. Pathological insomnia, based on a cutoff AIS score of 6, was identified in 9 patients (45%). Central sensitization for pain (CSI score ≥ 40)[13,14] was detected in 2 patients (10%), opioid use disorder (opioid use disorder score ≥ 2)[17] in 1 patient (5%), and neuropathic pain (DN4 score ≥ 4)[15,16] in 1 patient (5%). Pain catastrophizing (PCS score ≥ 30),[20] depression (SRQ-D score ≥ 16),[18] and anxiety (STAI-1 score ≥ 40)[19] were identified in 3 (15%), 10 (50%), and 15 (75%) patients, respectively.

Since no multi-collinearity existed between candidate variables, the ten variables of central sensitization, duration of opioid therapy, daily dose of opioid, opioid use disorder, pain intensity at rest, pain intensity during movements, neuropathic pain, pain catastrophizing, depression, and anxiety were selected for univariate analysis. In univariate analyses, scores for CSI and NRS

Table 1

Demographic characteristics of patients.

	Participants, n = 20
Age, years	63 ± 12
Female/Male, n (%)	6/14 (30.0/70.0)
BMI, kg·m^{-2}	21.4 ± 2.9
Cancer type: breast cancer/lung cancer/malignant mesothelioma/ myeloma/ovarian cancer/pancreatic cancer/rectal cancer, n (%)	2/6/7/1/1/2/1 (10.0/30.0/ 35.0/5.0/5.0/10.0/5.0)
ECOG PS: 0/1/2/3/4, n (%)	14/4/1/0/1 (70.0/20.0/5.0/0.0/5.0)

Data represents mean ± SD.

BMI = body mass index, ECOG = eastern cooperative oncology group, PS = performance status, SD = standard deviation.

Table 2

Uni- and multivariate regression analyses of central sensitization with pain characteristics for Athens Insomnia Scale scores.

Pain characteristics		Univariate analysis		Multivariate analysis	
		Standardized Beta	*P*	Standardized Beta	*P*
CSI score	16.0 [14.0–26.8]	0.646	.002**	0.566	.004**
Duration of opioid therapy, months	6.0 [1.9–11.8]	0.064	.790	–	–
Daily doses of opioid, OME (mg)	30 [18–56]	–0.001	.997	–	–
Opioid use disorder score	0 [0–0]	–0.439	.053	–	–
NRS at rest	2.0 [0.3–3.0]	0.472	.036*	0.339	.065
NRS during movement	3.0 [2.0–6.5]	0.353	.127	–	–
DN4 score	1 [1.0–2.0]	0.438	.053	–	–
PCS	13.5 [7.0–26.5]	–0.135	.570	–	–
SRQ-D	15.5 [12.3–19.0]	0.142	.549	–	–
STAI-1	41.0 [37.8–44.43	0.099	.677	–	–

Data represents median [25th–75th percentile].

CSI = central sensitization inventory, DN4 = Douleur neuropathique 4 questionnaire, NRS = numerical rating scale, OME = oral morphine equivalents, PCS = pain catastrophizing scale, SRQ-D = self-rating questionnaire for depression, STAI, state-trait anxiety inventory.

Statistical significances are defined at

*$P < .05$ and

**$P < .01$ using regression analysis.

at rest were significantly associated with AIS scores (Table 2). Multivariate regression analysis was performed using these variables, confirming CSI score as an independent risk factor for insomnia in cancer survivors under opioid treatment for chronic cancer pain (Table 2). Linear regression analysis confirmed a significant correlation between AIS and CSI scores (standardized beta = 0.646, coefficient of determination = 0.417, $P = .002$) (Fig. 1).

4. Discussion

In the present study, we examined AIS scores, revealing that the prevalence of insomnia was 40% in cancer survivors undergoing opioid therapy for chronic cancer pain. The prevalence of insomnia in cancer survivors is also reportedly around 40%.[22,23] Cancer survivors show a higher prevalence of chronic pain than the general population, at around 30% to 50%.[9,10] Since chronic pain is known to be one risk factor for insomnia in palliative care patients,[1,2] high prevalence of insomnia in cancer survivors with chronic cancer pain is reasonable.

Increases in AIS score were significantly associated with increases in CSI scores, which represent central sensitization in the present study. Central sensitization is one of the mechanisms underlying the development and maintenance of chronic cancer pain in cancer survivors.[24] Central sensitization is defined as increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent inputs,[25] and the consensus is that hyperexcitability of the central nervous system is the key mechanism in central sensitization.[26] Given that sleep disturbance reportedly correlated with central sensitization in patients with chronic non-cancer pain,[3–7] it would be plausible that the present study showed a significant association between AIS and CSI scores, suggesting that central sensitization might correlate with insomnia in cancer survivors.

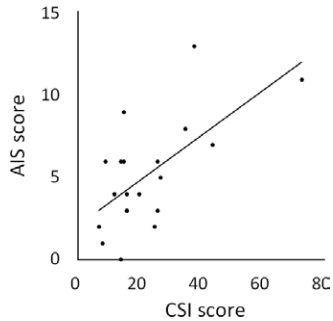

Figure 1. Association between insomnia and central sensitization in chronic cancer pain among cancer survivors. AIS = Athens Insomnia Scale, CSI = central sensitization inventory.

The prevalence of opioid use disorder among participants in the present study was 5%, almost the same as the prevalence of opioid misuse among cancer survivors (3.0%–3.5%) in the United States.[27] Although opioid use disorder was previously suggested to correlate with sleep disturbance,[28] the present study showed no clear associations between these factors.

There are several limitations that need to be considered in this study. First, the study cohort in this investigation comprised only a small number of patients. Although insomnia reportedly correlated with pain intensity, neuropathic pain, and psychiatric states in patients with chronic non-cancer pain,[29–32] insomnia showed no significant associations with these pain characteristics among cancer survivors in this study. Further study is needed to clarify these associations in larger cohorts in future. A secondary limitation was that all participants were receiving different chemotherapies for different types of cancer. Since both chemotherapy and breast or lung cancer are prone to cause insomnia,[1,6] eligibility criteria for study participants need to be more carefully restricted in future research.

5. Conclusion

A significant association likely exists between insomnia and central sensitization among cancer survivors undergoing opioid therapy for chronic cancer pain.

Author contributions

Conceptualization: Chiaki Akui.
Data curation: Chiaki Akui.
Formal analysis: Chiaki Akui, Munetaka Hirose.
Methodology: Chiaki Akui, Munetaka Hirose.
Supervision: Takeshi Kimura.
Validation: Takeshi Kimura.
Writing—original draft: Chiaki Akui.
Writing—review & editing: Munetaka Hirose, Takeshi Kimura.

References

[1] Mystakidou K, Panagiotou I, Parpa E, et al. Sleep disorders. In: Cherny NI, Fallon MT, Kaasa S, et al. eds. Oxford Textbook of Palliative Medicine. 5th ed. Oxford, UK: Oxford University Press; 2015:457-66.

[2] Nzwalo I, Aboim MA, Joaquim N, et al. Systemic review of the prevalance, predictors, and treatment of insomnia in palliative care. Am J Hosp Palliat Care. 2020;37:957–69.

[3] Campbell CM, Buenaver LF, Finan P, et al. Sleep, pain catastrophizing, and central sensitization in knee osteoarthritis patients with and without insomnia. Arthritis Care Res (Hoboken). 2015;67:1387–96.

[4] Nijs J, Mairesse O, Neu D, et al. Sleep disturbances in chronic pain: neurobiology, assessment, and treatment in physical therapist practice. Phys Ther. 2018;98:325–35.

[5] Andias R, Silva AG. Cross-cultural adaptation and psychometric properties of the European Portuguese version of the central sensitization inventory in adolescents with musculoskeletal chronic pain. Pain Pract. 2020;20:480–90.

[6] Liu J, Liu X, Dong M, et al. Symptom trajectories during chemotherapy in patients with non-small cell lung cancer (NSCLC) and the function of prolonging low dose dexamethasone in promoting enhanced recovery after chemotherapy. Thorac Cancer. 2021;12:783–95.

[7] Lerman SF, Mun CJ, Hunt CA, et al. Insomnia with objective short sleep duration in women with temporomandibular joint disorder: quantitative sensory testing, inflammation and clinical pain profiles. Sleep Med. 2022;90:26–35.

[8] Fredheim OM, Skurtveit S, Handal M, et al. A complete national cohort study of prescriptions of analgesics and benzodiazepines to cancer survivors in Norway 10 years after diagnosis. Pain. 2019;160:852–9.

[9] Sanford NN, Sher DJ, Butler SS, et al. Prevalence of chronic pain among cancer survivors in the United States, 2010–2017. Cancer. 2019;125:4310–8.

[10] Jiang C, Wang H, Wang Q, et al. Prevalence of chronic pain and high-impact chronic pain in cancer survivors in the United States. JAMA Oncol. 2019;5:1224–6.

[11] Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens insomnia scale: validation of an instrument based on ICD-10 criteria. J Psychosom Res. 2000;48:555–60.

[12] Okajima I, Nakajima S, Kobayashi M, et al. Development and validation of the Japanese version of the Athens Insomnia Scale. Psychiatry Clin Neurosci. 2013;67:420–5.

[13] Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract. 2012;12:276–85.

[14] Tanaka K, Nishigami T, Mibu A, et al. Validation of the Japanese version of the central sensitization inventory in patients with musculoskeletal disorders. PLoS One. 2017;12:e0188719.

[15] Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114:29–36.

[16] Matsuki Y, Sukenaga N, Miyagi K, et al. Reliability and validity of the Japanese translation of the DN4 diagnostic questionnaire in patients with neuropathic pain. J Anesth. 2018;32:403–8.

[17] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th eds. DSM-5. Washington DC, USA: American Psychiatric Pub; 2013:992.

[18] Rockliff B. A brief self-rating questionnaire for depression (SRQ-D). Psychosomatics. 1969;10:236–43.

[19] Spielberger CD, Gorsuch RL, Lushene RE. Manual for State–Trait Anxiety Inventory (STAI). Palo Alto, CA: Consulting Psychologists Press; 1970.

[20] Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess. 1995;7:524–32.

[21] Guglielminotti J, Dechartres A, Mentré F, et al. Reporting and methodology of multivariable analyses in prognostic observational studies published in 4 anesthesiology journals: a methodological descriptive review. Anesth Analg. 2015;121:1011–29.

[22] Taylor TR, Huntley ED, Makambi K, et al. Understanding sleep disturbances in African-American breast cancer survivors: a pilot study. Psychooncology. 2012;21:896–902.

[23] Leysen L, Lahousse A, Nijs J, et al. Prevalence and risk factors of sleep disturbances in breast cancer survivors: systematic review and meta-analyses. Support Care Cancer. 2019;27:4401–33.

[24] Manfuku M, Nishigami T, Mibu A, et al. Comparison of central sensitization-related symptoms and health-related quality of life between breast cancer survivors with and without chronic pain and healthy controls. Breast Cancer. 2019;26:758–65.

[25] International Association for the Study of Pain. Terminology. 1994. Available at: https://www.iasp-pain.org/resources/terminology/ [access date April 16, 2022].

[26] den Boer C, Dries L, Terluin B, et al. Central sensitization in chronic pain and medically unexplained symptom research: a systematic review of definitions, operationalizations and measurement instruments. J Psychosom Res. 2019;117:32–40.

[27] Jairam V, Yang DX, Verma V, et al. National patterns in prescription opioid use and misuse among cancer survivors in the United States. JAMA Netw Open. 2020;3:e2013605.

[28] Wilkerson AK, McRae-Clark AL. A review of sleep disturbance in adults prescribed medications for opioid use disorder: potential treatment targets for a highly prevalent, chronic problem. Sleep Med. 2021;84:142–53.

[29] Kim SH, Lee DH, Yoon KB, et al. Factors associated with increased risk for clinical insomnia in patients with chronic neck pain. Pain Phys. 2015;18:593–8.

[30] Kim SH, Sun JM, Yoon KB, et al. Risk factors associated with clinical insomnia in chronic low back pain: a retrospective analysis in a university hospital in Korea. Korean J Pain. 2015;28:137–43.

[31] Mun CJ, Finan PH, Smith MT, et al. A preliminary investigation of the underlying mechanism associating daily sleep continuity disturbance and prescription opioid use among individuals with sickle cell disease. Ann Behav Med. 2021;55:580–91.

[32] Sun Y, Laksono I, Selvanathan J, et al. Prevalence of sleep disturbances in patients with chronic non-cancer pain: a systematic review and meta-analysis. Sleep Med Rev. 2021;57:101467.