Sleep and Chronic Pain in an Ethnically Congruent Sample of Adult Patients with Sickle Cell Disease (SCD)

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Resumen

Disturbios del sueño son complicaciones comunes entre pacientes con la enfermedad de Anemia Falciforme (AF). La prevalencia de trastornos del sueño y su impacto en el estado afectivo, estrés y dolor no han sido documentados entre pacientes adultos con AF. Los hallazgos de este estudio sugieren que estos disturbios son comunes y angustiantes para los adultos con AF. Este estudio representa un paso importante en discutir disturbios del sueño en esta población. Se discuten las implicaciones para investigaciones futuras.

Palabras claves: Enfermedad de anemia falciforme, disturbios del sueño, dolor

Abstract

Sleep disturbance is a common complication among patients with sickle cell disease (SCD). The prevalence of sleep disturbances and their impact on affective status, stress and pain has not been well documented among adult patients with SCD. The findings of this study suggested that sleep disturbances are common and distressing among adults with SCD. This study represents an important step in addressing sleep disturbances in this population and implications for future directions in research are discussed.

Key Words: Sickle cell disease, sleep, pain

Sickle Cell Disease (SCD) is a genetic class of blood disorders that are characterized by systemic tissue damage, increased infections, intermittent and recurrent, unpredictable episodes of pain and respiratory difficulties. Sleep disturbance is a common compliant among patients with chronic illnesses and can be associated with declines in cognitive functioning (Jaussent, Bouyer, Ancelin, et al., 2012). Sleep disturbances among patients with sickle cell disease (SCD) are often attributed to sleep-disordered breathing that arises secondary to respiratory complications related to SCD or insomnia secondary to pain or pain medications (Bryson, Edwards, In press). These disturbances have primarily been documented among pediatric populations (Goldstein, Abramowitz, Weedon, Koliskor, Turner, Taioli, 2011; Samuels, Stebbens, Davies, Picton-Jones, Southall, 1992) but adult studies are beginning to emerge. For example, there is increasing evidence for significant heritability of insomnia and familial patterns of adult sleep disturbance (Wing, Zhang, Lam, Tang, Lai, Ki, 2012) that may account for some of the clinical presentations seen in patients with chronic illnesses. Of interest, the prevalence of sleep disorders among adult patients with SCD has received very little research attention. In addition to vasculopathological mechanisms associated with SCD that precipitate systemic painful and debilitating episodes, sleep disturbances can generate a sequelae of biological, psychological and social issues that interfere and disrupt the normal daily functioning and quality of life among adult patients with SCD (Lui, Ng, Lo, 2002; Currie, Wilson, Currain, 2002).

The relationship between pain and biological underpinnings (i.e. oxygen saturation) that govern sleep as well as sleep architecture has been well documented. However, research in this area among patients with SCD has initiated more queries than resolutions. A cardinal biological process of SCD is the physiological manifestation of vaso-occlusive events (VCE). VCE are precipitated by the intracellular sickling and adhesion of immature red blood cells (erythrocytes) to the endothelium of vessels. The distortion of erythrocytes is induced by a desaturation of oxygen in the blood (hypoxemia). A body of literature suggests that upper airway obstruction (UAO) is a reason for hypoxemia

that complicates normal sleep functions in patients with SCD, in that low nocturnal oxygen saturation is significantly related to VCE. It further states that treatment of hypoxemia may reduce the frequency of crisis pain (Roth, Geisser, Theisen-Goodvich, Dixon, 2005). There is also evidence that although nocturnal oxyhemoglobin desaturation is common among SCD patients, it is not considered a precursor to or part of the beginnings of UAO (Wesolowski, Szyber, 2004).

Diurnal and nocturnal respiratory difficulties are significant contributors to impaired sleep and disrupted sleep patterns. Sleep can also be interrupted by apnea in patients with chronic illness (Correia, Souza, Garcia, et al., 2012), and in particularly patients with SCD. This apnea-associated hypoxemia is also a likely contributor to strokes (Kirkham, Hewes, Prengler, Wade, Lane, Evans, 2001). Additionally, it was found that obstructive sleep apnea might also be an important factor in the development of strokes (Manoach, Cain, Vangel, Khurana, Goff, Stickgold, 2004). The relationship between sleep and chronic pain has been primarily investigated in children with SCD; however there is a lack of research in the adult populations. The present study finds the relationship between pain and sleep in adult patients with SCD equally important.

Method

Participants

Of the 178 African American patients who were approached about participation, 143 consented for the current study. Individuals who refused participation generally indicated: (1) time constraints; (2) already participating in a research study; or, (3) not interested in participating in scientific research as their primary reason for refusal. Of patients consented, 67 completed testing, 40 partially completed testing, and 36 had not begun testing by the time of analysis more than 12 months after signing consent. Only participants with complete assessments were used in the current analysis. All subjects were given and signed informed consent and the study was approved by the Duke Institutional Review Board.

Sixty-seven consecutive patients, mean age 36.82 ± 11.47 (range 18-70), were recruited from the Duke Comprehensive Sickle Cell Center during routine clinic appointments. Participants were excluded from participation in the study if they were actively in an acute episode of pain or other urgent medical crisis at the time of clinic visit, had been diagnosed with an eating disorder, or if they were unable to read and comprehend the written instructions for testing. Patients were also excluded from analysis if they had a significant diagnosis other than SCD (Mental Retardation, etc.).

Mean years of education were 13.28 ± 1.84 and ranged from 9 to 18 years. Forty-five percent of patients (30) were male and 67 participants completed assessment during the first year of evaluation. Thirty-two percent of patients were married, 48% were single, 2% were separated, 15% were divorced, and 3% were living with a significant other. Of those participants who reported that they were involved in a relationship, the mean relationship duration in months was 89.92 ± 107.70 months. On a 0-10 scale where 0 represents "Poor quality" and 10 represents "Highest quality", patients in relationships rated their mean relationship quality 7.57 ± 2.35. Sixty-four percent of patients were employed at the time of assessment.

Instruments

Longitudinal Exploration of Medical and Psychosocial Factors in Sickle Cell Disease (LEMPFSCD) The LEMPFSCD is a multidimensional paper and pencil instrument designed specifically for examining this population. The LEMPFSCD is a 700-question tool consisting of pain, demographics, and 8 validated (1- Symptoms Checklist 90-items, Revised, 2- Beck Depression Inventory, 3- Multidimensional Pain Inventory, 4- Short-Form McGill Pain Questionnaire, 5- Menstrual Symptoms Questionnaire, 6- Marlowe Crowne Scale of Social Desirability, 7- Duke Religiosity Scale, 8- John Henryism Scale), content-driven instruments for the assessment of psychiatric, behavioral, and social functioning. As such, it does not yet have its own psychometric properties (validity and reliability) beyond that associated with each individual scale. For the purpose of the current

study the following content areas were examined: demographics, sleep, pain, and healthcare utilization will be evaluated.

Sleep

Participants responded to several questions designed to assess sleep patterns and efficiency. Patients were asked to choose the statement that best described how they felt in the past week regarding sleep on the Beck Depression Inventory (BDI; Beck, 1978) which ranges from 'I can sleep as well as usual' to 'I wake up several hours earlier than I used to and cannot get back to sleep.' Patients were also asked 'How much has your pain interfered with your ability to get enough sleep?' as a part of the Multidimensional Pain Inventory (MPI; Kerns, Turk, Rudy, 1985) which used a 7-point Likert scale.

Beck Depression Inventory

The Beck Depression Inventory (Beck, 1978) was used to measure the severity of depression. It consists of 21 self-report items that are rated on a 0-3 scale. The ratings on the scale are represented with a 0 for the least pathological statement in the group. The sum of the individual items provides an index of depression, with a minimum score of 0 and a maximum of 63. Scores from 0-9 are considered minimal or no depression. Scores from 10-18 represent slight depression, scores from 30-63 are associated with sever depression. The BDI has test-retest reliability (.48-.86), and good construct and concurrent validity (.60-.72).

Multidimensional Pain Inventory

The Multidimensional Pain Inventory is a short form of the West Haven- Yale Multidimensional Pain Inventory (WHYMPI; Kerns, Turk, Rudy, 1985). The MPI-2 contains Section I of 28 questions that assesses by self-report, the level of the pain experience and the extent to which it interferes with normal daily activities. These questions are answered using Likert type ratings from 0 to 6. Zero indicates such ratings as "Very intense pain "to questions such as "Rate the level of your pain at the present moment". Section II concerns perceptions of the individual

as to how a spouse or significant other responds to the person when he or she is in pain. Fourteen typical statements include "Ignores me" and "Tries to involve me in some activity." Response ratings are 0-6, that correspond to "Never" to "Very often". Section III the participant is asked to rate the frequency he or she participates in 19 daily activities listed. Typical activities listed. Typical activities include "Wash the dishes" and "Go to a park or beach." Responses are rated from 0-6, or from "Never" to "Very often." The MPI evaluates the impact of diverse chronic pain syndromes on multiple dimensions of one's life. Internal reliability coefficients of the WHYMPI range from .70 to .90 and test-retest reliabilities over a 2-week period interval range from .62 to .91 (Turk, Melzack, 2001).

Coping

Coping was measured using the twelve-item John Henryism Scale of Active Coping (JHAC12), [11] which uses a five-point Likert-type scale to derive a total JH score that ranges from 12-60 (with high scores representing higher levels of JH). The JHAC12 has demonstrated acceptable internal consistency among African-American samples: Black men (a=.67, n=180), and Black women (a=.71, n=242). Adult samples tend to score near the high end of the JHAC12 (James, 1994; Whitfield, Brandon, Robinson, Bennett, Merritt, Edwards, 2006; Edwards, Bennett, 2006; McDougald, Edwards, Wood, et al., 2009).

Healthcare Utilization

Healthcare utilization was calculated as the number of emergency room visits, number of hospitalizations, and the number of days retained in the hospital once hospitalized for the year that the patient participated in the study for the first time.

Procedures

Study procedures are described in more detail in several previous and recent studies (Harrison, Edwards, Koenig, Bosworth, DeCastro, Wood, 2005; Edwards, Whitfield, Sudhakar, et al., 2006; Pells, Presnell, Edwards et al., 2005; Pells, Edwards, McDougald, et al., 2007). All patients were consented and enrolled individually in the current study during routine visits to the hematology clinic. Patients were identified by the study hematologist as suitable for participation based upon the patient's ability to read, and their characteristics matched against inclusion and exclusion criteria. They were then approached by study personnel about participation. All patients were given a brief verbal over of the study which included conducting a re of their historical patterns of healthcare utilization from their medical records, and then allowed to read the consent forms. Each subject was allowed to ask questions and gain clarification before signing consent.

Participants were then provided a copy of the survey, moved to a relatively quiet or isolated portion of the waiting room when possible, and given instructions for completion of the survey by a member of the study team. Additional clarification or instructions were given to patients as requested. Once complete, the survey was collected and an informal debriefing was provided.

Study Design

The current study represents a cross-sectional survey of first-year data collected as part of a five-year, longitudinal evaluation of the relationship of medical and psychosocial factors to pain in patients with SCD. We sought to explore the effects of gender and age on reports of pain and sleep in adult patients with SCD.

Results

Descriptive Statistics

Mean BDI summary score was found to be in the asymptomatic range at 8.31 ± 7.79 with scores ranging from a score of "0" to "39". Twenty-nine percent of patients reported that they had experienced "Anxiety," and 36% indicated that they had experienced "Depression" in the thirty days prior to assessment. Patients who endorsed these psychological symptoms did not differ in their age, education, tendency to report in a socially desirable manner, or reports of pain from patients who did not endorse the presence of these symptoms.

The BDI measure of sleep functioning correlated significantly and positively with the measure of disturbance in sleep onset and

awakenings, the average weekly pain rating, and the depression total score (see Table 1). Similarly, the MPI measure of sleep functioning correlated positively and significantly with the measure of disturbance in sleep onset and awakenings, current and weekly pain, pain severity, and the depression total score (see Table 1). Sleep disturbance as was measured by the BDI exerted significant effects on the number of emergency room visits during the first year of evaluation. Neither measure of sleep functioning (e.g., MPI or BDI) correlated with active coping or exerted significant effects on the number of hospitalizations or the number of days hospitalized during the evaluation year (see Table 2).

In response to stressful experiences, 72 % (48) of patients with SCD reported that they experienced at least "a little bit" of difficulty falling or staying asleep in the past 30 days, ($\chi 2(1)12.55$, p=.0004). Eighty-two percent (27/33) of patients with SCD responding to the MPI reported that their pain has interfered with their sleep, while 64% (21) of patients responding to the BDI reported that, at a minimum, they don't sleep as well as they used to ($\chi 2(3)11.73$, p=.008). A simple "yes" to endorse or "no" to deny sleep symptoms revealed that 57.6% (38) of patients with SCD characterized their sleep as falling into the insomnia or hypersomnia range ($\chi 2(1)1.52$, p=.22).

Discussion

Interests in sleep disturbance among patients with SCD has historically focused on children. Studies to explore sleep disturbance in adults with SCD is a much more recent, but very necessary, endeavor. In the current study, we found that greater than 2/3 of patients with SCD reported sleep disturbance often related to their experiences of pain, stress, and depression. Although average depression scores were found to be in the asymptomatic range, approximately 1/3 of patients reported that they experienced depression and/or anxiety in the 30 days prior to evaluation. We further found that sleep disturbance as evaluated as part of the characterization of depression was associated with other measures of sleep dysfunction, average weekly pain ratings, and the number of emergency room visits. Sleep disturbance as evaluated as part of the measurement of the impact of chronic pain was associated with other measures of sleep dysfunction, current and weekly pain intensity ratings, and pain severity. Sleep disturbance, depression, and pain are likely to be highly interrelated in SCD as is the case with other forms of chronic illness. It is, however, noteworthy to consider the episodic nature of depression, stress, and pain associated with SCD. This was suggested by the finding that 1/3 of patients reported some level of depression or anxiety within the 30 days prior to participating in this study. Fluctuating levels of pain characteristics, depression, anxiety, and general stress lend to the notion that sleep disturbance among those with SCD may also fluctuate significantly depending on the specific state of the individual at a given point in time. This would suggest that patients being treated for SCD receive frequent and specific assessments of pain, sleep, and depression as a part of routine care.

Recent evidence has found that almost 90% of patients admitted with affective disturbance and suicide attempts have a definable sleep disturbance (Sjostrom, Waern, Hetta, 2007). Although we did not assess this relationship directly in the present study, it is quite plausible that depression associated with suicidal intentions would be of sufficient intensity to disrupt sleep. Based on existing knowledge of suicide, depression, and pain it is recommended that observable and reported sleep disturbances be considered as a cautionary sign prompting for careful evaluation of suicide potential in those patients.

Utilizing available sleep data from existing measures of pain and depression provided insight into the characteristics of sleep disturbances in the context of pain and depression associated with SCD in adults. The high percentage of sleep disturbances related to these conditions in this population is concerning and highlights the need for further study. At this time, it is suggested that treatments aimed at reducing pain and depression would also be likely to contribute to an amelioration of the sleep disturbances associated with these conditions.

The effects of sleep-disordered breathing were not directly assessed in this study, although believed to be fully present in this population. It would be expected that the underlying pathophysiology of SCD in adults would manifest similar effects on respiration in the sleep period much as it does in children. This is an area that needs

considerable attention given the known consequences of hypoxemia on physiological and psychological functioning.

Exploring sleep disturbances among adults with SCD will require a considerable amount of study in the future. It is clear from this study that sleep disturbance is quite prevalent and distressing to patients. Further, SCD is associated with depression, anxiety, pain, and stress that share a relationship with sleep disturbance. Identifying effective ways to assess and treat SCD in a comprehensive manner is highly desirable and critical for patient care.

Future Directions

The study presented here, again, highlights the need for further exploration into sleep disturbances among adults with SCD. There are many facets of sleep disturbance in this population that need to be specifically explored. Foremost, studies are needed to explore the cumulative effects of sleep disturbance in patients with SCD with sleep apnea and other sleep disturbances on depression, anxiety, nocturnal cerebral hypoxia, and pain (Gibson, Morgan, Abel, Sewell, Martin, Lowe,… Asnani, 2013). It will also be important to address the dynamic nature of the pathophysiology of SCD, depression, and pain on the respiratory and pain associated sleep disturbances as a function of time. Longitudinal studies utilizing survey, observation, and polysomnographic data are desirable to achieve this goal.

The effects of depression and anxiety, both independently and synergistically, on sleep in adults with SCD is also recommended for future study. Further, the relationship of depression and anxiety, both in contribution and consequence, to pain, sleep-disordered breathing, oxygen obstruction, and VCE should be explored. Techniques to effectively treat depression and anxiety such as pharmacotherapy and psychotherapy should be explored in terms of reducing sleep disturbances in this population.

Nocturnal hypoxemia is certainly of concern in those with SCD. A limited number of studies show that although nocturnal oxyhemoglobin desaturation and OSA is common among children and adolescents with SCD; desaturation and VCE are not necessarily due to UAO (Hargrave, Wade, Evans, Hewes, Kirkham, 2003; Needleman, Franco, Varlotta, et al., 1999). Studies on the role of UAO, nocturnal hypoxemia, and VCE are even less understood among adults with SCD. It is likely that nocturnal oxygen desaturation is related to multiple etiologies and may also exist to some degree in both sleep and wake states (Hargrave, Wade, Evans, Hewes, Kirkham, 2003). Although preliminary evidence downplays the role of UAO and OSA in oxyhemoglobin desaturation and VCE, it is still of critical importance in terms of sleep continuity disruption and the presence of depression (Hargrave, Wade, Evans, Hewes, Kirkham, 2003; Kawahara, Akashiba, Akahoshi, Horie, 2005). OSA has also been associated with an increased risk of myocardial infarctions, hypertension, cardiac arrhythmias, and strokes Sherpard, 1992). Efforts are certainly needed to further attempt to clarify the contributions of these events on nocturnal hypoxemia and to identify specific treatment options that target each of these conditions and improve nocturnal oxygen saturation.

Sickle cell disease pain related to headaches associated with sleep disturbances may subsequently lead to excessive sleepiness during waking hours. This circumstance would likely produce significant and subsequent fatigue, cognitive impairments, heightened stress, and greater pain perception. Gaining a better understanding of the relationship among all of these conditions in the context of sleep disturbances in adults with SCD is also suggested as a topic of future inquiry.

Pain management techniques such as relaxation therapies, biofeedback, hypnosis, prayer, pharmacotherapies, positive thinking, as well as physical, occupation, and kinesthetic therapies should all be explored in terms of reducing not only pain, but the sleep disturbances associated with pain as well. Exercise is generally encouraged for those with both pain and depression, although studies have shown that strenuous exercise is difficult for patients with SCD. An exploration of the effectiveness and impact of various types of exercise, as well as various intensity levels on pain and depression, and subsequent effects on sleep, should also be pursued.

The effects of specific treatments, both pharmacological (Feliu, Wellington, Crawford, Wood, Edwards, Byrd, & Edwards, 2011) and behavioral, on the pathophysiology of SCD, depression, anxiety, and pain should be studied in terms of carryover effects on sleep disturbance. Specific behavioral sleep medicine techniques such as cognitive-behavioral therapy for insomnia, including sleep hygiene education, should also be evaluated as a way to directly target the sleep disturbances associated with SCD. There are many areas to explore in terms of understanding the complexity in which sleep disturbances play in the overall presentation of SCD and also in ways to utilize treatments to directly and indirectly improve sleep quality. The findings of this study highlight the importance of scientists and clinicians across many specialties to actively continue efforts to explore the role of sleep and sleep disturbances among adults with SCD.

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