

A Review of Sleep Concerns in Pediatric Sickle Cell Disease

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Abstract

Children with sickle cell disease (SCD) are at an increased risk of sleep disorders as compared with healthy children, possibly because of disease processes, pain, ethnic minority status, and living in an urban environment. Adequate sleep is an essential component of typical child development, mood-and-affect regulation, and health maintenance, but more research is needed to understand the contribution of sleep to health outcomes in children with SCD. SCD is a chronic disease that can be influenced by environmental, health, and behavioral factors. Understanding the impact of the disease on sleep is important to maximise the quality of life in these children. If SCD causes poor sleep quality, then children may be at risk of a host of developmental and psychosocial problems beyond those caused by the disease. Also, poor sleep may affect the disease course, thus exacerbating symptoms. In this article, prevalent sleep disorders in this population are reviewed, including sleep-disordered breathing, periodic limb movement disorder, restless legs syndrome, and nocturnal enuresis. Also, the contribution of the disease symptoms—such as pain, hypoxemia, and daytime tiredness and fatigue—to disrupted sleep are examined. Finally, the effects of sociodemographic factors, such as poverty and ethnic minority status, are described, as these contextual factors significantly impact sleep across several chronic conditions in pediatric patients. Frequent monitoring for sleep disruptions can be essential to improving health outcomes and quality of life in children with SCD.

Keywords

Sickle cell disease, pediatrics, sleep, sleep-disordered breathing, enuresis, pain, socioeconomic status

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The symptoms of sickle cell disease (SCD) as well as underlying disease processes affect sleep across development, which has important implications for academic and behavioral functioning and overall health outcomes in children and adolescents with SCD. High frequencies of arousals and fragmented sleep related to sleep disorders that are more prevalent in SCD coupled with sleep-interfering disease symptoms (i.e., pain, enuresis, hypoxemia) result in chronic sleep disruption that can affect development and health outcomes. Rates of sleep-disordered breathing conditions, including obstructive sleep apnea (OSA),¹⁻³ periodic limb movements during sleep (PLMS),⁴ restless legs syndrome (RLS),⁴ and nocturnal enuresis^{5,6} have been documented in children and adolescents with SCD compared with healthy peers. In children without chronic illness, sleep problems have been linked to behavior problems,⁷ poor academic outcomes,⁸ depression,⁸ and reduced cognitive performance.⁹

A greater understanding of the interplay between SCD, health outcomes, and sociodemographic factors that are known to affect sleep¹⁰ is necessary to target and improve sleep in children with SCD. This article describes highly prevalent sleep disorders in SCD, disease factors associated with disrupted sleep and the sociodemographic contributions to sleep patterns in children and adolescents with SCD.

Sleep Disorders Prevalent in Pediatric Sickle Cell Disease

Sleep-disordered Breathing

Sleep-disordered breathing is one of the most frequently observed sleep disorders in children with SCD and can significantly impact health and behavioral outcomes in child development. Sleep-disordered breathing refers to the category of disorders of abnormal respiration during the night, either based on ventilation patterns or quantity of ventilation throughout the night.¹¹ OSA is the most common of these disorders, caused by a collapse of the upper airway that restricts airflow and causes hypoxia, disruptions in sleep, hypercapnia (increased carbon dioxide), and reduced neurocognitive performance.¹¹ Sleep-disordered breathing contributes to behavioral problems and learning difficulties (for a review see Owens¹²), pulmonary hypertension, arterial hypertension, nocturnal enuresis, and reductions in growth.¹³

A handful of studies have described the occurrence of sleep-disordered breathing and OSA in children and adolescents with SCD using polysomnography (PSG), the gold standard for diagnosing sleep-disordered breathing. Three studies have described rates of sleep-disordered breathing in children and adolescents clinically referred for PSG because of suspected sleep-disordered breathing.¹⁻³ Most recently, 69 % of children with either SCD genotypes HbSS or HbSC

were diagnosed with OSA using PSG, with no difference in diagnosis between the two genotypes.² Kaleyias et al. found that 12 of 19 children and adolescents with SCD, who had parent reports of snoring and irregular night-time breathing, met criteria for OSA, and three additional patients were given the diagnosis of upper airway resistance syndrome (a milder form of sleep-disordered breathing).¹ Similarly, clinical assessment of children with genotypes HbSS and HbS β 0 thalassemia indicated that 29 of 53 children demonstrated sleep-disordered breathing, and further evaluation using multichannel respiratory recording determined that 18 of 50 children demonstrated upper airway obstruction that could contribute to sleep-disordered breathing.³ Salles et al. conducted an observational study of children aged 2–19 years with HbSS and found a lower prevalence of sleep-disordered breathing when compared with samples with more than one genotype.¹⁴ Of 85 children and adolescents who underwent PSG, prevalence rates of OSA were 10 % and snoring occurred in 44 % of the sample.¹⁴ In a descriptive study of 50 children aged 10–18 years and adolescents with the genotype HbSS, oxyhemoglobin desaturation during rapid eye movement sleep (<93 %) was related to higher rates of obstructive apneic events, higher heart rates during sleep and higher waking heart rates.¹⁵ Souza and Viegas suggest that the higher levels of sleep-disordered breathing in patients with oxyhemoglobin desaturation during rapid eye movement sleep is related to diurnal desaturation rather than to pulmonary events,¹⁵ as previously suggested in other studies.¹⁶ Higher rates of sleep-disordered breathing may be caused by enlarged tonsils and adenoids that block airflow as a result of more frequent childhood infections secondary to early spleen damage.¹⁷ Alternatively, adenotonsillar hypertrophy may be related to compensatory lymphoid tissue enlargement.

Successful treatment of OSA in children with SCD using adenotonsillectomy has been described in two small studies.^{3,18} Maddern et al. found that in 13 children who underwent surgery there were fewer subjective sleep complaints (e.g., restlessness, wakings, sleepiness), lower end-tidal CO₂ on PSG, shorter apneas, but no difference in the number of apneic events when compared to baseline PSG.¹⁸ Samuels et al. found a significant reduction in nocturnal hypoxemia or in some cases no hypoxemia on the night studied in 15 patients post-surgery.³ Although not a pre- and/or post-examination of surgical intervention, Rogers et al. described PSG variables in children who underwent adenotonsillectomy and found that 8 of 10 children continued to meet criteria for sleep-disordered breathing, but overall rates of apneic events were lower compared with children with OSA who had not undergone surgery.² The continued occurrence of obstructive events post-surgery may be due to more severe cases of OSA leading to referral to surgery. There are increased risks when using surgical intervention in patients with SCD, including anemia, hypoxia, and higher rates of post-operative complications; however, surgery can produce significant improvement with protocols to reduce sickling and hypoxemia.¹⁸

Periodic Limb Movement Disorder and Restless Legs Syndrome

PLMS and RLS are related but separate neurological conditions that can occur in pediatric SCD. PLMS are short, repetitive movements of the arms and legs that occur during sleep and are sometimes associated with arousal and/or sleep fragmentation.¹⁹ RLS is a

sensorimotor disorder that results in the urge to move one's legs to relieve uncomfortable sensations that occur when resting.¹¹ Subjectively, patients report experiencing tingling or 'creepy-crawly' sensations in their legs that is relieved by moving the legs.²⁰ Although these sensations may occur throughout the day, they are associated with inactivity and thus they are most evident upon lying down to sleep.²⁰ Diagnosis of PLMS occurs during PSG, while RLS is a clinical diagnosis.¹⁹ Both conditions are associated with low iron, thus serum ferritin levels are often important to diagnosis and treatment. Rogers et al.⁴ described the increased occurrence of PLMS and RLS in 64 children and adolescents with the HbSS genotype who were not currently receiving transfusion or hydroxyurea. Almost a quarter of the sample (23.4 %) had PLMS at a rate of at least five events per hour, the cut off for diagnosis of periodic limb movement disorder. PLMS appeared to be unrelated to the occurrence of OSA in this sample. This rate is significantly higher than previous reports in healthy children, which estimated the prevalence to be 2.2 %.²¹ Clinical assessment indicated that 12 % of the sample experienced symptoms of RLS, and these symptoms were more common in children with PLMS. Mechanisms explaining the higher rates of PLMS and RLS among children with SCD are unclear, especially given the relationship to low serum ferritin levels in healthy children, which are not typically low in SCD due to transfusion, and in response to tissue damage related to vaso-occlusive episodes.²² The authors suggest a relationship with central nervous system iron levels, which can remain low despite normal serum levels and have been documented in adults with RLS (but not in SCD)²³ or disease factors that affect iron regulation.²⁴

Nocturnal Enuresis

Children and adolescents with SCD are more likely to exhibit nocturnal enuresis than age-matched controls.^{5,6} A review of PSG data from healthy children with enuresis found that children with enuresis do not differ markedly from healthy children in sleep architecture (the pattern of sleep stages across the night);²⁵ nonetheless, enuresis can be distressing for both the child and parent. Two studies examined the occurrence of enuresis, finding current clinical enuresis in 20 %⁵ and 25 %⁶ of children with SCD, but not statistically different from rates in sibling controls at 15 %.⁶ Enuresis occurred significantly more often in boys in both studies (28 % of males, 11 % of females;⁵ 30 % of males, 19 % of females⁶). Parents may not associate enuresis with their child's SCD and thus often report withholding fluids as a method of prevention of enuresis, even though fluid intake is important to disease management, which makes screening for and treating enuresis with alternative methods even more important in SCD populations.⁶

Mechanisms of increased rates of enuresis in SCD are unclear. There has been speculation that renal damage caused by dehydration results in increased fluid consumption and urine volume.^{26,27} An alternative explanation is that enuresis is caused by lower levels of antidiuretic hormone.²⁸ Additionally, enuresis is a symptom of sleep-disordered breathing,¹³ which could also contribute to increased occurrence of enuresis in children with SCD. One study that examined enuresis treatments in SCD offered families the option of desmopressin acetate intranasal spray (n=10) or enuretic alarm (n=2).²⁸ Six of 10 patients evidenced an improvement or resolution of enuresis with the nasal spray and four did not respond. Both children using the enuretic alarm

discontinued treatment after three to four months with no improvement. Larger randomized treatment studies are needed to understand whether behavioral methods or combination treatments are efficacious in children with SCD.

Disease Symptoms that Disrupt Sleep Pain

The effects of pain on sleep are a significant concern, with both acute and chronic pain in SCD. In a review of pain literature related to medical conditions, most conditions associated with pain have been shown to reduce sleep efficiency, slow-wave sleep and rapid eye movement sleep.²⁹ Sleep disturbances in children with chronic pain, including those with SCD, have been linked with lower quality of life related to physical health and greater functional disability.³⁰ Using daily diary methodology, frequently used to monitor the occurrence and intensity of pain as well as sleep parameters and subjective reports of sleep quality, nocturnal pain was found to be a frequent occurrence in children and adolescents with SCD, occurring on 12 % of nights.³¹ Shapiro et al. collected pain and sleep diaries twice a day for an average of 10 months in 18 children and adolescents.³² Results indicated that sleep quality was affected by SCD pain (which occurred on 30 % of the days studied), with children rating sleep quality as poor on 43 % of days with pain, as compared with 3 % of days without pain. In this study, sleep duration was also significantly shorter during pain episodes.

Valrie et al.^{33,34} examined the relationship between sleep and pain in 20 children aged eight–12 years by using daily sleep and pain diaries and reports of mood and stress for up to eight weeks. The children reported pain on 21 % of days during the course of the study, and the average pain rating on days with pain was 49.83 (on a 0–100 visual analog scale). Controlling for demographic factors and disease type, the interaction between stress and pain severity created a model that accounted for 72 % of the variance in sleep quality and indicated that younger female patients with the HbSS genotype and greater pain severity were more likely to have poor sleep quality.³³ Further analyses indicated that children experiencing greater stress had a stronger negative relationship between pain intensity and sleep quality. Negative mood was also found to mediate partially the relationship between high pain and poor sleep quality during the night and the following day.³⁴ As participants' moods became more positive, the strength of the pain and sleep quality relationship decreased the following day.

Another study using pain and sleep diaries in 20 adolescents found a cyclical relationship between pain and sleep quality, with poor sleep preceding days with pain and days with pain being followed by poor sleep.³⁵ Analgesic use moderated the relationship between pain intensity and sleep quality such that, when adolescents used analgesics, the relationship between pain and sleep quality was no longer significant. This sample also reported pain on 22 % of study days, indicating marked and frequent disturbances of sleep. A study using retrospective self-reports to examine sleep in 86 adolescents with chronic pain conditions (i.e., headache, juvenile idiopathic arthritis, and SCD) demonstrated a small but significant correlation between pain frequency and daytime sleepiness; also, adolescents with longer pain episodes had later bedtimes.³⁶

There are several proposed mechanisms for increased sleep disruption in the context of pain. Changes in sleep architecture may be due to effects of medications taken for pain, disease processes, pain-related discomfort, lowered pain threshold,²⁹ or a heightened arousal to bodily sensations that keeps the individual from deeper stages of sleep (for a review of pain and sleep in children, see Lewin and Dahl³⁷). Insufficient overnight sleep could, in turn, interfere with pain-coping skills and alter the perception of pain the following day.³⁷ Poor sleep before the onset of a pain episode may also be indicative of biological changes occurring that eventually cause the pain episode.³⁵

Hypoxemia

Nocturnal oxyhemoglobin desaturation is common among children with SCD³⁸ and appears to be unrelated to upper airway obstructive events.¹⁶ Oxyhemoglobin levels can decrease substantially in children with SCD as compared with healthy controls³ and the amount of desaturation is related to the severity of SCD,³⁹ occurring more frequently in children with HbSS and HbS β 0 thalassemia subtypes compared with HbSC and HbS β + thalassemia subtypes.³⁸

Nocturnal desaturation may result in increased occurrences of vaso-occlusive episodes⁴⁰ and/or stroke.⁴¹ Dips in oxyhemoglobin saturation of 4 % below baseline have been associated with an average of 2.97 more days of pain per year.⁴⁰ Decreased nocturnal oxyhemoglobin saturation may instigate pain because of the effects of desaturation on bone marrow leading to vaso-occlusive episodes⁴⁰ or because of an increased tendency for the adhesion of red blood cells to the endothelial cells in children with greater oxyhemoglobin desaturation.³⁹ Nocturnal hemoglobin saturation together with arterial velocity has also been found to predict time until central nervous system events.⁴¹ Cerebrovascular disease caused by hypoxemia, a reduction in the threshold for infarction, or a combination of the two may be mechanisms between sleep-disordered breathing and stroke.⁴¹ Not all research, however, supports the relationship between hypoxemia and SCD severity, as some studies have described similar sleep architecture and nocturnal desaturation in patients with more severe SCD (as indicated by two or more hospitalizations in the previous year) compared with patients with no SCD-related hospitalizations.⁴²

Daytime Tiredness and Fatigue

Given disruptions in overnight sleep that can occur in children with SCD, children may experience more daytime sleepiness than peers;⁴³ however, little research exists describing sleepiness and fatigue in children with SCD. In studies that have described sleepiness in children and adolescents with SCD,^{30,36,44} there are somewhat mixed results regarding the level of sleepiness children experience, depending on the peer-group comparison. When compared with normative values, parents report significantly higher daytime sleepiness in children with SCD—similar to values found in children from a clinical sleep disorders sample.^{30,44} Levels of daytime sleepiness were, however, similar to demographically matched controls.⁴⁴ Adolescents with SCD report similar levels of daytime sleepiness to teens with juvenile rheumatoid arthritis and less sleepiness than adolescents with chronic headaches.³⁶ Increased occurrence of sleep-disordered breathing in children with SCD may also contribute to higher levels of daytime sleepiness, as shown in other populations.^{45,46}

Additionally, fatigue is a known side effect of anemia in SCD.^{47–49} No studies have examined the co-occurrence of sleepiness and fatigue in children with chronic pain, thus it is unclear whether higher levels of daytime sleepiness actually reflect fatigue.³⁰ Describing fatigue from a bio-behavioral framework, Ameringer and Smith describe hypoxemia and inflammation as disease variables that result in fatigue, which is further exacerbated by pain, stress, and depression/anxiety experienced by children with SCD.⁵⁰ The relationship between fatigue, sleep, and quality of life in children and adolescents with SCD has not been studied to date; thus further research is necessary to understand the effects of fatigue on the cognitive functioning and academic performance in these children.

Contributing Sociodemographic Factors

In the US, children with SCD are typically African-American, and an estimated 36 % of African-American children live in low-income families nationally,⁵¹ making low socioeconomic status (SES) a significant concern in this population. One study estimates that 59 % of families with a child with SCD have incomes that qualify them for some type of government assistance.⁵² In addition to lower SES, children with SCD are faced with many other stressors, such as living in urban environments, ethnic minority status, and living in single-parent families.⁵³ These are all important factors to take into account when considering both health and sleep in children. Lower SES has been associated with parent reports of more bedtime problems,⁵⁴ more daytime sleepiness,^{54,55} shorter night-time sleep durations,^{55,56} and a higher occurrence of sleep-disordered breathing.^{45,57} Additionally, children of ethnic minority background have been found to nap more frequently,⁵⁸ report more daytime tiredness,⁵⁵ sleep for shorter periods at night, go to bed later,⁵⁶ and exhibit higher rates of sleep-disordered breathing⁵⁷ compared with Caucasian children.

Differences in sleep habits between majority and minority ethnic groups emphasize the importance of developing more diverse groups when establishing normative sleep habits in children. Given the minority status of most children with SCD, it is important to examine sleep habits in comparison to African-American children without SCD to understand the contribution of disease status to sleep. In our prior research, we found that children with SCD demonstrate significantly more sleep problems than middle-class Caucasian children.⁴⁴ The differences between children with SCD and the demographically matched control group were less pronounced, which suggests that many problematic sleep patterns and behaviors are exacerbated by lower SES, living in an urban environment, and ethnic minority status. Comparing children with SCD to SES-matched controls indicated that children with SCD experience more night waking, sleep-disordered breathing, and enuresis, but similar elevated levels of bedtime behavior problems and daytime sleepiness. This pattern of

results suggests that sociodemographic factors are important determinants of sleep behaviors and quality in children. Within the SCD sample, SES was more highly related to sleep problems than most disease factors (i.e., disease complications, healthcare use, and genotype). It is possible that disease factors are better used as outcome measures than predictors of sleep problems, possibly refuting the assertion by previous research that there is a bidirectional relationship between sleep and disease processes in children with SCD.

Conclusions

Children with SCD are at an increased risk of sleep-disordered breathing,^{1–3} PLMS,⁴ and nocturnal enuresis,^{5,6} as well as of several disease factors—including pain,³⁴ hypoxemia,³⁹ and sleepiness⁴⁴—that may affect sleep patterns and sleep quality. Additionally, contextual and demographic risk factors such as neighbourhood stress, poverty, and ethnic minority status may also contribute to disrupted and insufficient sleep in children with SCD.⁴⁴ Sleep problems may contribute to disease complications, reduce the child's ability to cope with disease complications, and affect overall health status; thus it is imperative that healthcare providers routinely screen children and adolescents for medical and behavioral sleep problems during regular healthcare appointments. Referrals should be made for children with SCD to see sleep specialists when warranted, especially in cases with sleep-disordered breathing, which may result in further disease complications. During hospital follow-up visits, healthcare providers should ask parents and older children with SCD about sleep quality before pain episodes to assess patterns that precede pain episodes and help parents intervene earlier with palliative methods. Lastly, it is important to work with care-givers to modify the sleeping environment (e.g., removing the television from the bedroom, using a white noise maker to drown out ambient noise) and use good sleep hygiene by keeping consistent bedtime routines and schedules, so as to maximise sleep efficiency and sleep quality for children.

Future research should address sleep in children with SCD using objective (e.g., actigraphy, PSG) and subjective (e.g., perceptions of sleep quality, daytime sleepiness) reports in concert to describe sleep habits and behaviors in these children. Other predictors of sleep problems should also be examined within this population to better understand the causes of sleep disruptions. Further examination of the pain and sleep connection using prospective measures, diaries, and objective measurement is important to understand the relationships between these factors. Research that addresses the long-term effects of sleep on disease outcomes and general health are essential next steps. Finally, intervention studies are important for children with SCD, with a specific focus on modifying sleep behaviors and sleep problems in relation to their effects on disease outcome. ■

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