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CLINICAL REVIEW

Hemoglobinopathies and sleep – The road less traveled

Alex Gileles-Hillel, Leila Kheirandish-Gozal, David Gozal*

Section of Pediatric Sleep Medicine, Department of Pediatrics, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL, USA

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SUMMARY

Sickle cell disease and thalassemia are common hereditary blood disorders associated with increased systemic inflammation, tissue hypoxia, endothelial dysfunction and end-organ damage, the latter accounting for the substantial morbidity and abbreviated lifespan associated with these conditions. Sleep perturbations in general, and sleep-disordered breathing in particular are also highly prevalent conditions and the mechanisms underlying their widespread end-organ morbidities markedly and intriguingly overlap with the very same pathways implicated in the hemoglobinopathies. However, little attention has been given to date to the potential contributing role of sleep disorders to sickle cell disease manifestations. Here, we comprehensively review the pathophysiological mechanisms and clinical manifestations linking disturbed sleep and hemoglobinopathies, with special emphasis on sickle cell disease. In addition to a broad summary of the available evidence, we identify many of the research gaps that require attention and future investigation, and provide the scientific contextual setting that should enable opportunities to investigate the intertwined pathophysiological mechanisms and clinical outcomes of sleep disorders and hemoglobinopathies.

Introduction

Sickle cell disease (SCD) is a common genetic disorder with a wide range of clinical manifestation including recurrent pain attacks, acute chest syndrome, pulmonary hypertension, and upper and lower airway obstruction. Hypoxemia, especially at night, and sleep-disordered breathing (SDB) are emerging as risk factors that confer significant increases to the prevalence and severity of sickle cell disease manifestations, and even to mortality. Here, we will critically review in detail the potential epidemiological links between SCD and SDB and explore the potentially overlapping pathophysiological components of both disorders, and their potential impact on clinical phenotype and course. For the sake of completeness, we will describe the relatively scarce information currently available on the association of thalassemia, the second most common hemoglobinopathy, with sleep disorders. Based on our comprehensive literature searches toward the preparation of this review, we clearly identify a knowledge gap, as there are almost no prospective studies that have been conducted to test the impact of treating sleep disorders on the outcomes of hemoglobinopathies.

Hemoglobinopathies

Hereditary disorders of hemoglobin, also known as hemoglobinopathies, are a group of genetic disorders of hemoglobin structure. They primarily comprise two disease groups – sickle cell disease (SCD) and the thalassemias [1]. These disorders are among the most common hereditary disorders worldwide – the birth rate of people homozygous or compound heterozygotes for symptomatic globin disorders revolves around 2.4 per 1000 births, of which 1.96 have SCD and 0.44 have thalassemias [2,3].

Sickle hemoglobin (HbS) is caused by a mutation in the β-globin gene in which the 17th nucleotide is changed from thymine to adenine causing a change of the 6th amino acid from hydrophilic glutamate for the hydrophobic valine. This mutation produces a hydrophobic motif in the deoxygenated HbS tetramer that results in binding between β1 and β2 chains of two hemoglobin molecules. The hydrophobic binding between the beta chains produces an expanding polymer which fills the red blood cell, disrupting its structure and elasticity (i.e., the process of "sickling") and promotes cellular dehydration, the latter being exacerbated by physical activity and by oxidative cellular stress. The degree of hemoglobin

* Corresponding author. Department of Pediatrics, The University of Chicago, 5721 S. Maryland Avenue, MC 8000, Suite K-160, Chicago, IL 60637, USA. Tel.: +1 773 702 3360; fax: +1 773 926 0756.
E-mail address: dgozal@uchicago.edu (D. Gozal).

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Abbreviations

ACS	acute chest syndrome
AHI	apnea-hypopnea index
ANS	autonomic nervous system
CPAP	continuous positive airway pressure
hs-CRP	high-sensitivity C-reactive protein
LV	left ventricular
NFκB	nuclear factor-κappa B
NO	nitric oxide
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PFTs	pulmonary function tests
PLMS	periodic leg movements
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
REM	rapid eye movement
RBC	red blood cell
SCD	sickle cell disease
SDB	sleep disordered breathing
TRV	tricuspid regurgitation jet velocity
TST	total sleep time

deoxygenation and the intracellular HbS concentration ultimately determine the rate and the extent of HbS polymerization and sickling, the main determinant of disease severity [4]. Clinical manifestations of SCD, both acute and chronic, can be categorized according to their underlying pathophysiological process(es) – i.e., vaso-occlusive or hemolytic [5]. Vaso-occlusive complications include acute pain crises, acute chest syndrome (ACS) and osteonecrosis. Hemolytic complications, on the other hand, comprise of the spectrum of pulmonary hypertension, priapism and leg ulcers. The most common reason for emergency room visits and hospitalization in both children and adults with SCD is the occurrence of acute pain crises, which although not usually and immediately associated with end-organ damage, are severely debilitating and have been associated with increased mortality in adult SCD patients. Acute chest syndrome is the second most common cause of hospitalization in SCD patients, and is defined as a new focal lung infiltrate. The pathophysiology of ACS includes pulmonary vaso-occlusion, infection, and in some cases, fat embolism. However, the exact pathophysiology of many events remains unknown. Other less frequent complications of SCD include increased incidence of stroke, heart disease, pulmonary hypertension, renal disease and hyper-hemolysis [4].

The thalassemias are an inherited group of disorders resulting from absent or reduced synthesis of normal hemoglobin. The human hemoglobin, during all phases of development, is composed of two beta-like and two alpha-like chains of globin. During the embryonic period, the embryonic genes are active producing the embryonic hemoglobin (eta2, delta2). Between 6 and 8 wk of gestation there is a switch leading to expression of the alpha and the gamma globin genes, that produces the fetal hemoglobin – HbF (alpha-2, gamma-2). Finally, around the birth, the gamma gene is changed to the beta gene, thus producing the adult hemoglobin – HbA (alpha-2, beta-2). The type of thalassemia is defined by the defective globin gene involved – in α-thalassemia the α-globin genes are affected; and in β-thalassemia the β-globin ones. Patients with thalassemia have widely variable clinical presentations, depending on the amount of residual normal hemoglobin, ranging from nearly asymptomatic to severe anemia requiring lifelong blood transfusions with complications in multiple organ systems [1,6].

Pathophysiological considerations

SCD and SDB share some common molecular pathways that can lead to similar downstream clinical manifestations (Fig. 1). In the following several paragraphs, we will describe the similarities between these two conditions, and the available data linking those pathways between SCD and SDB.

Nocturnal hypoxemia

One of the major characteristics of SDB in general, and obstructive sleep apnea in particular, is the oscillating changes in blood gas levels. The most pronounced and well-studied phenomenon is intermittent hypoxia. Repeated cycles of hypoxia and re-oxygenation are thought to play a key role in the maladaptive responses to OSA, leading to the generation of increased oxidative stress, induction of inflammatory signaling cascades and sympathetic hyperactivation [7–13].

Hypoxia in sickle cell disease is one of the major modifiers of disease severity. At the cellular level, low oxygen levels promote HbS polymerization, which leads to red blood cell (RBC) sickling, which in turn leads to impaired blood flow through the microvasculature, thereby causing a vicious cycle of hypoxia, sickling, hemolysis, and further vaso-occlusive episodes, a set of properties that has been recently proposed as a diagnostic method to anticipate the risk of vaso-occlusive phenomena in SCD patients [14,15]. Sickling of cells under hypoxia also promotes red blood cell adhesion to endothelial cells. In addition, hypoxia results in increased reticulocyte egress from the bone marrow, and these reticulocytes exhibit greater adhesive properties to the endothelium when compared to mature erythrocytes, and thus, may further aggravate vaso-occlusion [16,17]. Tissue ischemia is the net result of all these pathological cascades, resulting in pain episodes, vaso-occlusive attacks and acute chest syndrome [18,19]. As most SCD patients are not constantly hypoxemic, the blood hypoxemia and the tissue hypoxia they experience are presumably of intermittent nature, a phenomenon that has been well documented in murine models of SCD [20]. However, as evidenced from near-infrared spectroscopy studies assessing cerebral hypoxia in SCD [21], hypoxia may be present at all times in some tissues. Consequently, the unstable nature of the magnitude of the tissue hypoxemia may be a frequent phenomenon in SCD, even when pulse oximetry appears to be in the normal range [16,22,23].

Several studies have shown that nocturnal hypoxemia is associated with higher morbidity in SCD manifesting as higher degree of anemia and lower cumulative annual average hemoglobin levels [24,25], increased pulmonary artery pressures [26], worse pulmonary function tests [25], increased left ventricular (LV) hypertrophy and LV diastolic dysfunction [27], increased incidence of priapism [28], and nocturnal enuresis [29], more frequent painful [30] and vaso-occlusive crises in general, increased incidence of CNS events [31], worse executive cognitive function [32] and even vitamin C deficiency, suggestive of reduced anti-oxidant capacity [33].

In spite of the detrimental effects of nocturnal hypoxemia described above, one should keep in mind that due to the nature of SCD, pulse oximetry, the most frequently used tool to assess nocturnal oxygen levels, may not be accurate in this population, and potentially lead to underestimates of the frequency of tissue hypoxemic events. Indeed, traditional pulse oximeters will measure carboxyhemoglobin as being oxyhemoglobin, thus overestimating the true oxygen saturation by 3–7% in patients with SCD [34,35]. Nonetheless, when detected, nocturnal oxygen desaturation should be viewed as a surrogate marker for a more severe disease, and those patients should be referred for more comprehensive evaluation. Nocturnal SpO_2 values also correlate with