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Editorial

EDITORIAL

Sickle cell disease and obstructive sleep apnea—bad news for the brain

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Sickle cell disease (SCD) is a hemoglobinopathy with a prevalence of 17 cases per 10,000 people among African Americans. It is characterized by a wide range of clinical manifestations that include recurrent pain attacks, neurological complications, acute chest syndrome, pulmonary hypertension, and upper and lower airway obstruction [1].

Hypoxemia, especially at night, and obstructive sleep apnea (OSA) are emerging as risk factors for increased morbidity, and even mortality, in SCD. Furthermore, SCD patients are prone to poor sleep not just because of OSA, but due to other factors such as chronic pain and restless legs syndrome [2].

The American Thoracic Society had recently identified two research gaps in relation to sleep-disordered breathing in SCD [3]: (1) How does sleep-disordered breathing impact SCD morbidity and mortality; and (2) How does the treatment of sleep-disordered breathing impact SCD outcomes.

The study by Tsou et al. [4] in the current edition of the Journal, provides compelling evidence to fill the first gap establishing OSA in SCD as an independent risk factor for neurological complications.

Tsou et al. analyzed a US nationwide hospital discharge database of over 200,000 children with SCD, investigating whether the diagnosis of OSA was associated with an increased prevalence of neurological complications, defined as stroke, seizure, or transient ischemic attack. In this inpatient dataset, roughly 2% had neurological complications and 1.4% OSA. The authors found a significant association between the two conditions in children with SCD. They also validated prior findings of an increased risk of acute chest syndrome in children with OSA. Finally, the authors verified previous reports of the increased costs associated with the diagnosis of OSA in children with SCD.

There are several pathophysiological considerations that may explain the increased risk observed here of neurological complications in patients with SCD and OSA, since both conditions activate some common pathogenic cascades that may lead to similar downstream clinical manifestations. Daytime and nighttime hypoxemia have a clear impact on SCD severity. Hypoxemia increases red blood cells' sickling, hemolysis, and adhesion to endothelium, thus propagating vaso-occlusion [5, 6]. Repeated cycles of hypoxia-re-oxygenation, such as those that occur during sleep in OSA, lead to increased production of inflammatory mediators and reactive oxygen species. Finally, in SCD, decreased nitric oxide (NO) bioavailability has been implicated as one of the main drivers of vascular complications [7]—intravascular hemolysis impairs NO bioavailability, leading to oxidative stress and increased inflammation, which in turn further impair endothelial function, promoting regional vasoconstriction and subsequent blood vessel remodeling. Similarly, reduced NO bioavailability is one of the hallmarks of OSA-associated endothelial dysfunction and downstream vascular damage [8].

In addition to the shared pathophysiology, there are clinical observations that support the findings in this study. Increased cerebral blood flow (CBF) velocity as measured by transcranial Doppler is a surrogate marker for the risk of stroke in SCD. Healthy children with OSA have increased CBF [9], and in children with SCD, CBF decreases following adenotonsillectomy [10]. Patients with SCD, with no history of stroke, show signs

of impaired cognitive function as early as infancy, suggesting ongoing microvascular CNS pathology due to constant hypoperfusion to vulnerable brain areas, such as those involved in executive functions. Accordingly, increased CBF is associated with executive dysfunction in children with SCD [11] and healthy children with OSA [12].

It is worth noting that not all neurological complications were increased in children with OSA in this study. The association with OSA was most apparent for increased seizure prevalence, but not for stroke. Stroke is one of the most devastating complications of SCD, with a first-stroke incidence of 1:100 patient-years between 2 and 5 years of age. By the age of 20, 11% of SCD patients have already sustained one stroke episode, and 60% of them will suffer recurrent events. Interestingly, children with OSA and SCD in the current study did not seem to be at increased risk of stroke, contradicting prior evidence. Tripathi et al. [13] found that children with SCD and OSA are at increased risk of stroke, with risk reduction occurring after adenotonsillectomy. The lack of such an association in the current study may be due to an unaccounted confounding variable such as treatment with hydroxyurea, or due to the relative rarity of the condition in children with SCD.

The study also sheds light on the impact of treating OSA on the risk of neurological complications. In this study, treating OSA with non-invasive ventilation rendered the association of OSA with neurological complications insignificant, thereby suggesting a protective role for this treatment. The effect of adenotonsillectomy in this study was less clear. It should be noted that the retrospective nature, and the administrative data used, do not allow for a proper causative analysis. Adenotonsillectomy is the first line of treatment for OSA in children, and as the authors acknowledge, the effect of non-invasive ventilation may have been driven by a small subset of very sick children with recurrent admissions, not apparent in this dataset due to de-identification of the data. Prospective studies, such as the one currently underway [14], are needed to address the role of positive pressure ventilation in SCD.

Some limitations should be kept in mind when reading the study—administrative data used in this study is prone to misdiagnoses and misclassification, leading potentially to a bias. Particularly, the prevalence of OSA in children with SCD in this study was similar to the prevalence of OSA in the general healthy pediatric population—1%–4%, whereas previous studies have suggested a much higher prevalence in children with SCD. For example, in a prospective multi-center study of 243 children with mostly mild-moderate SCD, OSA was present in 41%, and moderate-severe OSA (AHI ≥ 5/hrTST) in 10% of the children [15]. Furthermore, it is well established that OSA-associated neurocognitive complications do not affect children with OSA uniformly, but rather those with the more severe disease manifest the most severe neurocognitive deficits. Even in the latter group, not all children are affected the same. The current study did not, and could not, determine which of the clinical parameters of the OSA-SCD co-morbidity contribute to the increased rate of neurological complications.

In summary, the current study emphasizes the importance of diagnosing OSA in children with SCD, implicating OSA as a potential culprit for neurological complications in these children. Future studies are needed to identify those children with SCD-OSA most prone to suffer from neurological complications, and to clarify the role of treating OSA on neurological complications.

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