Changes in Transcranial Ultrasound Velocities in Children with Sickle Cell Disease Undergoing Adenotonsillectomy

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Abstract
Objectives. (1) To assess for changes in cerebral blood flow velocity in children with sickle cell disease and obstructive sleep apnea (OSA) following adenotonsillectomy. (2) To determine if clinical factors such as OSA severity affect cerebral blood flow velocity values.

Study Design. Case series with chart review over 10 years.

Settings. Two tertiary children's hospitals.

Subjects and Methods. Children aged 2 to 18 years with a history of sickle cell disease and OSA, as defined by an apnea hypopnea index (AHI) >1 on polysomnography, were eligible for inclusion. Transcranial Doppler ultrasonography was used to assess cerebral blood flow velocity before and after adenotonsillectomy.

Results. Fifteen patients met inclusion criteria; 73% (n = 11) were female. The mean preoperative AHI was 8.9 (range, 1.2-22.2). Six (40%) patients had severe OSA (AHI >10). Following adenotonsillectomy, there was a significant reduction in mean (95% CI) cerebral blood flow velocities of the left terminal internal cerebral artery, 91.2 (79.4-103.1) to 75.7 (61.7-89.8; P = .018), and the right middle cerebral artery, 134.3 (119.2-149.3) to 116.5 (106.5-126.5; P = .003). There was not a significant correlation between baseline AHI and change in cerebral blood flow velocities.

Conclusion. Adenotonsillectomy may result in a reduction in some cerebral blood flow velocities. Further research is needed to determine if changes in cerebral velocities as assessed by transcranial Doppler ultrasonography translate into a reduced risk of stroke for children with sickle cell disease and OSA.

Keywords
pediatrics, obstructive sleep apnea, adenotonsillectomy, sickle cell disease, cerebral blood flow velocity, stroke

Sickle cell disease (SCD) is an inherited hemoglobinopathy affecting red blood cell morphology.1 It affects 1 in 350 African American newborns each year. The sickle cell genetic mutation leads to an amino acid substitution of valine to glutamic acid that causes red blood cells to polymerize in low-oxygen environments.2 The resultant sickling of red blood cell leads to premature cell breakdown, occlusion of blood vessels, and inefficient oxygen delivery. Clinical manifestations of SCD include vasoocclusive complications, such as pain crises and acute chest syndrome, as well as hemolytic complications, such as priapism and pulmonary hypertension. Other complications of SCD include heart disease, stroke, and osteonecrosis.

Stroke can be a devastating neurologic complication for children and adolescents with SCD.3 By 20 years of age, 11% of patients with SCD have experienced at least 1 stroke.4 The increased risk of stroke among children with SCD is likely related to exacerbating disease factors, such as hypoxemia, decreased nitric oxide bioavailability, anemia, and hemolysis. Stroke in these patients typically involves vasculopathy of the internal carotid and middle cerebral arteries. Recent research identified increased cerebral blood flow velocity as a marker for stroke risk among children with SCD.5 Transcranial Doppler (TCD) ultrasonography is now being used to assess cerebral blood flow velocity to predict stroke risk and guide transfusion therapy.5 Thus, clinicians are incorporating TCD surveillance into their management protocols for children with SCD.

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This abstract was presented at the 2017 American Society of Pediatric Otolaryngology Annual Meeting; May 2017; Austin, Texas.

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Received August 20, 2017; revised November 9, 2017; accepted January 10, 2018.
The incidence of obstructive sleep apnea (OSA) increases for children with SCD. Studies showed that up to 70% of children with SCD have OSA, with 10% to 25% of children having moderate to severe OSA. While the link between OSA and SCD is still being investigated, authors postulated that splenic infarction may cause reactive enlargement of adenotonsillar tissue. Increased extramedullary hematopoiesis attributed to hemolytic anemia may also contribute to hypertrophy of upper airway lymphoid tissue and result in obstruction. Nocturnal hypoxemia has also been associated with increased morbidity among sickle cell patients. Adenotonsillectomy is the primary treatment for OSA and was shown to result in improvement in nocturnal hypoxemia. Patients with SCD and comorbid OSA may be at increased risk for vaso-occlusive events, including stroke. Thus, it is recommended that providers who treat children with SCD ask about symptoms of obstruction, such as snoring and poor sleep, to identify those who may require further evaluation and treatment for OSA.

The aim of this pilot study was to examine the association between OSA and SCD among children. Our primary objective was to evaluate changes in cerebral blood flow velocities among children with SCD who were undergoing tonsillectomy and adenoidectomy for OSA. We hypothesized that there would be a decrease in cerebral blood flow velocity, as assessed by TCD, as compared with normative pediatric data. We also sought to determine whether clinical factors, such as severity of OSA, affected changes in TCD velocities.

Materials and Methods

Study Group

Institutional review board approval was obtained from Eastern Virginia Medical School, the Children’s Hospital of The King’s Daughters, and the Cincinnati Children’s Hospital Medical Center. This study featured a retrospective review of data from a 10-year period (2006-2016) from 2 tertiary care children’s hospitals. Inclusion criteria were as follows: (1) 2 to 18 years of age with a history of SCD, (2) history of overnight polysomnogram (PSG), and (3) pre- and postadenotonsillectomy TCD assessment. The incidence of obstructive sleep apnea (OSA) increases for children with SCD. Studies showed that up to 70% of children with SCD have OSA, with 10% to 25% of children having moderate to severe OSA. While the link between OSA and SCD is still being investigated, authors postulated that splenic infarction may cause reactive enlargement of adenotonsillar tissue. Increased extramedullary hematopoiesis attributed to hemolytic anemia may also contribute to hypertrophy of upper airway lymphoid tissue and result in obstruction. Nocturnal hypoxemia has also been associated with increased morbidity among sickle cell patients.

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Results

Patient Demographics

Fifteen children were included in the study. Table 1 shows demographic and baseline PSG data. The mean age of the patients was 7.5 years (SD, 3.2), and 11 (73%) children were female. The mean preoperative AHI was 8.9 (range, 1.2-22.2). Six (40%) patients had severe disease (AHI >10) on baseline PSG. The mean nadir oxygen saturation was 84% (range, 72%-93%). The mean maximum end-tidal carbon dioxide value at baseline was 46 mm Hg (range, 36-57 mm Hg). None of the caregivers reported a history of stroke on the otolaryngology intake form.

Changes in TCD following Adenotonsillectomy

The mean elapsed time between preadenotonsillectomy TCD assessment and surgery was 5.2 months, while the mean time from surgery to postadenotonsillectomy TCD assessment was 11.1 months. Table 2 lists the pre- and postadenotonsillectomy TCD velocities, with the results stratified by laterality and a combined mean value for left and right cerebral blood flow velocities. The majority of children had decreases (improvements) in the MCA velocities (Figure 1) as assessed by TCD. There were significant decreases in the following TCD measurements after adenotonsillectomy: left TICA velocity ($P = .018$), right MCA ($P = .003$), and combined mean MCA ($P = .016$).
Children with severe OSA did not have higher baseline TICA and MCA velocities. There was no correlation between baseline TCD measurements and age or PSG parameters such as AHI, nadir oxygen, and end-tidal carbon dioxide. Similarly, changes in TICA and MCA following adenotonsillectomy did not correlate with PSG parameters. Children with more severe OSA at baseline did not experience improvements in TCD measurements that were greater in magnitude than those with more mild disease.

Discussion

The association between OSA and SCD in children merits further investigation. While the pathophysiology linking these 2 disease entities is still being studied, there is concern that comorbid OSA may increase complications of SCD, such as stroke. Few studies have examined whether treatment of OSA in children with SCD improves morbidity. One recent review of a statewide Medicaid database did examine the cost-effectiveness of performing adenotonsillectomy in children with SCD and OSA. The authors reported a decrease in health care encounters for cerebrovascular ischemia following surgery. There was not a significant change in visits for acute pain crisis.

Due to its noninvasive nature and increasing portability, TCD is more regularly being used to measure cerebral perfusion for clinical and research purposes. According to findings from the STOP trial (Stroke Prevention Trial in Sickle Cell Anemia), elevated cerebral blood flow velocities in patients with SCD predicted increased stroke risk. Researchers also demonstrated that adults and children with OSA but without a diagnosis of SCD have increased cerebral blood flow velocity with TCD. In a recent study published in *Pediatrics*, children with mild sleep disordered breathing had significantly higher MCA velocities when compared with nonsnoring controls. For MCA velocity, children with sleep-disordered breathing had a mean value of 120 cm/s, as opposed to 84 cm/s for healthy nonsnoring controls and 170 cm/s for children with SCD who were at moderate stroke risk. In our study, we also noted a high preoperative MCA value, 131.8 cm/s. While the cause of this increased velocity is unknown, researchers have hypothesized that it may be related to hypoxemia and carbon dioxide retention, elevated blood pressure or increased systemic intravascular resistance, and/or aberrations in cerebral vasoactivity.

Treatment of OSA can result in improvements in cerebral blood flow velocities as measured by TCD. Utilization of continuous positive airway pressure among adults with OSA reduced elevated cerebral blood flow velocities. In otherwise healthy children with mild sleep-disordered breathing, significant improvement in MCA velocities were reported following adenotonsillectomy. Similarly, our study showed improvements in cerebral blood flow velocities among children with OSA and SCD following treatment with adenotonsillectomy. We were not able to identify any PSG parameters, including AHI or nadir oxygen saturation, that correlated with changes in TCD measurements in our subject population.

More data are emerging regarding the link between cerebral perfusion and neurocognition. New research demonstrated that cerebral perfusion may correlate with neurocognitive dysfunction in children with SCD; these studies demonstrated that increased cerebral blood flow velocities were associated with

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### Table 1. Demographic and Baseline Polysomnographic Data for Children with Obstructive Sleep Apnea and Sickle Cell Disease Undergoing Transcranial Doppler Ultrasound (N = 15).

<table>
<thead>
<tr>
<th>Mean (Range) or n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>7.5 (2-11)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Obesity (BMI &gt;95th percentile)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Obstructive AHI</td>
<td>8.9 (1.2-22)</td>
</tr>
<tr>
<td>OSA</td>
<td></td>
</tr>
<tr>
<td>Mild (AHI, 1-5)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Severe (AHI &gt;10)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Mean nadir oxygen saturation, %</td>
<td>84 (72-93)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; OSA, obstructive sleep apnea.

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### Table 2. Cerebral Blood Flow Velocities before and after Adenotonsillectomy for Children with Obstructive Sleep Apnea and Sickle Cell Disease Undergoing Transcranial Doppler Ultrasound.

<table>
<thead>
<tr>
<th>Velocity, cm/s, Mean (95% CI)</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal internal carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>91.2 (79.4-103.1)</td>
<td>75.7 (61.7-89.8)</td>
<td>.018</td>
</tr>
<tr>
<td>Right</td>
<td>78.1 (58.8-97.5)</td>
<td>85.7 (60.7-110.8)</td>
<td>.696</td>
</tr>
<tr>
<td>Average</td>
<td>80.3 (69.7-90.9)</td>
<td>77.7 (61.8-93.5)</td>
<td>.361</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>129.4 (120.6-138.2)</td>
<td>120.8 (105.1-136.5)</td>
<td>.126</td>
</tr>
<tr>
<td>Right</td>
<td>134.3 (119.2-149.3)</td>
<td>116.5 (106.5-126.5)</td>
<td>.003</td>
</tr>
<tr>
<td>Average</td>
<td>131.8 (122.2-141.5)</td>
<td>118.7 (107.5-129.8)</td>
<td>.016</td>
</tr>
</tbody>
</table>
deficits in intelligence\textsuperscript{16} and attention.\textsuperscript{17} Furthermore, studies\textsuperscript{13,15} of otherwise healthy children with mild sleep-disordered breathing showed that cerebral hemodynamics may play a role in the link between sleep-disordered breathing and neuropsychological impairment. In the work by Hill et al,\textsuperscript{13} increased cerebral blood flow was associated with poor performance on assessments of visual attention and processing for children with sleep-disordered breathing. After adjusting for other clinical factors, improvements in cognition (including attention and processing) were associated with a reduction in MCA velocities among children with mild sleep-disordered breathing that occurred following adenotonsillectomy.\textsuperscript{15}

To our knowledge, this study is the first to examine changes in cerebral blood flow velocities following adenotonsillectomy among children with SCD. Strengths of the study are objective assessments, including PSG to diagnose OSA and TCD to assess cerebral perfusion. Limitations of this pilot study are the small sample size, the lack of a control group, and the retrospective nature of the review. Thus, we were unable to control for additional factors, such as transfusions, medications (eg, hydroxyurea), and timing of TCD measurements, which may also have affected cerebral blood flow velocities. We suspect that the small sample size is the likely explanation for unilateral improvements in the MCA and TICA TCD measurements. In addition, the majority of studies that reported on normative data for cerebral blood flow velocities focused on MCA. Fewer data are available regarding TICA velocities; further study is required to examine this topic.

Future research is necessary to definitively determine whether adenotonsillectomy results in improvement in cerebral blood flow velocities. A multi-institutional prospective study is needed to assess TCD measurements before and after adenotonsillectomy among children with OSA and SCD. With recent studies showing a correlation between cerebral perfusion and neurocognitive dysfunction, we also plan to include objective neurocognitive assessments in our future protocols. Further studies are also needed to determine whether improvements in TCD measurements following surgery translate into a decreased risk of stroke for children with SCD.

**Conclusion**

When compared with normative pediatric data, children with SCD and OSA have elevated cerebral blood flow velocities as assessed by TCD. Improvements in TCD velocities may occur following adenotonsillectomy. Further research is needed to determine if a decrease in TCD velocities following surgery results in reduced stroke risk for this population of at risk children.

**Author Contributions**

Griffin Santarelli, study design, data collection, drafting of manuscript; Sarah C. De Shields, study design, data analysis, critical review of manuscript; Stacey L. Ishman, study design, patient recruitment, drafting of manuscript; Michael Randall, study design, data collection, critical review of manuscript; Tina D. Cunningham, study design, data analysis, critical review of manuscript; Cristina M. Baldassari, study design, patient recruitment, drafting of manuscript.

**Disclosures**

**Competing interests:** None.

**Sponsorships:** None.

**Funding source:** None.
References