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Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function.

Hill CM, **Hogan AM**, **Onugha N**, **Harrison D**, **Cooper S**, **McGrigor VJ**, **Datta A**, **Kirkham FJ**.

Division of Clinical Neurosciences, University of Southampton, United Kingdom. cmh2@soton.ac.uk

OBJECTIVE: Sleep-disordered breathing describes a spectrum of upper airway obstruction in sleep from simple primary snoring, estimated to affect 10% of preschool children, to the syndrome of obstructive sleep apnea. Emerging evidence has challenged previous assumptions that primary snoring is benign. A recent report identified reduced attention and higher levels of social problems and anxiety/depressive symptoms in snoring children compared with controls. Uncertainty persists regarding clinical thresholds for medical or surgical intervention in sleep-disordered breathing, underlining the need to better understand the pathophysiology of this condition. Adults with sleep-disordered breathing have an increased risk of cerebrovascular disease independent of atherosclerotic risk factors. There has been little focus on cerebrovascular function in children with sleep-disordered breathing, although this would seem an important line of investigation, because studies have identified abnormalities of the systemic vasculature. Raised cerebral blood flow velocities on transcranial Doppler, compatible with raised blood flow and/or vascular narrowing, are associated with neuropsychological deficits in children with sickle cell disease, a condition in which sleep-disordered breathing is common. We hypothesized that there would be cerebral blood flow velocity differences in sleep-disordered breathing children without sickle cell disease that might contribute to the association with neuropsychological deficits. DESIGN: Thirty-one snoring children aged 3 to 7 years were recruited from adenotonsillectomy waiting lists, and 17 control children were identified through a local Sunday school or as siblings of cases. Children with craniofacial abnormalities, neuromuscular disorders, moderate or severe learning disabilities, chronic respiratory/cardiac conditions, or allergic rhinitis were excluded. Severity of sleep-disordered breathing in snoring children was categorized by attended polysomnography. Weight, height, and head circumference were measured in all of the children. BMI and occipitofrontal circumference z scores were computed. Resting systolic and diastolic blood pressure were obtained. Both sleep-disordered breathing children and the age- and BMI-similar controls were assessed using the Behavior Rating Inventory of Executive Function (BRIEF), Neuropsychological Test Battery for Children (NEPSY) visual attention and visuomotor integration, and IQ assessment (Wechsler Preschool and Primary Scale of Intelligence Version III). Transcranial Doppler was performed using a TL2-64b 2-MHz pulsed Doppler device between 2 pm and 7 pm in all of the patients and the majority of controls while awake. Time-averaged mean of the maximal cerebral blood flow velocities was measured in the left and right middle cerebral artery and the higher used for analysis. RESULTS: Twenty-one snoring children had an apnea/hypopnea index <5, consistent with mild sleep-disordered breathing below the conventional threshold for surgical intervention.

Compared with 17 nonsnoring controls, these children had significantly raised middle cerebral artery blood flow velocities. There was no correlation between cerebral blood flow velocities and BMI or systolic or diastolic blood pressure indices. Exploratory analyses did not reveal any significant associations with apnea/hypopnea index, apnea index, hypopnea index, mean pulse oxygen saturation, lowest pulse oxygen saturation, accumulated time at pulse oxygen saturation <90%, or respiratory arousals when examined in separate bivariate correlations or in aggregate when entered simultaneously. Similarly, there was no significant association between cerebral blood flow velocities and parental estimation of child's exposure to sleep-disordered breathing. However, it is important to note that whereas the sleep-disordered breathing group did not exhibit significant hypoxia at the time of study, it was unclear to what extent this may have been a feature of their sleep-disordered breathing in the past. IQ measures were in the average range and comparable between groups. Measures of processing speed and visual attention were significantly lower in sleep-disordered breathing children compared with controls, although within the average range. There were similar group differences in parental-reported executive function behavior. Although there were no direct correlations, adjusting for cerebral blood flow velocities eliminated significant group differences between processing speed and visual attention and decreased the significance of differences in Behavior Rating Inventory of Executive Function scores, suggesting that cerebral hemodynamic factors contribute to the relationship between mild sleep-disordered breathing and these outcome measures. CONCLUSIONS: Cerebral blood flow velocities measured by noninvasive transcranial Doppler provide evidence for increased cerebral blood flow and/or vascular narrowing in childhood sleep-disordered breathing; the relationship with neuropsychological deficits requires further exploration. A number of physiologic changes might alter cerebral blood flow and/or vessel diameter and, therefore, affect cerebral blood flow velocities. We were able to explore potential confounding influences of obesity and hypertension, neither of which explained our findings. Second, although cerebral blood flow velocities increase with increasing partial pressure of carbon dioxide and hypoxia, it is unlikely that the observed differences could be accounted for by arterial blood gas tensions, because all of the children in the study were healthy, with no cardiorespiratory disease, other than sleep-disordered breathing in the snoring group. Although arterial partial pressure of oxygen and partial pressure of carbon dioxide were not monitored during cerebral blood flow velocity measurement, assessment was undertaken during the afternoon/early evening when the child was awake, and all of the sleep-disordered breathing children had normal resting oxyhemoglobin saturation at the outset of their subsequent sleep studies that day. Finally, there is an inverse linear relationship between cerebral blood flow and hematocrit in adults, and it is known that iron-deficient erythropoiesis is associated with chronic infection, such as recurrent tonsillitis, a clinical feature of many of the snoring children in the study. Preoperative full blood counts were not performed routinely in these children, and, therefore, it was not possible to exclude anemia as a cause of increased cerebral blood flow velocity in the sleep-disordered breathing group. However, hemoglobin levels were obtained in 4 children, 2 of whom had borderline low levels (10.9 and 10.2 g/dL). Although there was no apparent relationship with cerebral blood flow velocity in these children (cerebral blood flow velocity values of 131 and 130 cm/second compared with 130 and 137 cm/second in the 2 children with normal hemoglobin levels), this requires verification. It is of particular interest that our data suggest a relationship among snoring, increased cerebral blood flow velocities and indices of cognition (processing speed and visual attention) and perhaps behavioral (Behavior Rating Inventory of Executive Function) function. This finding is preliminary: a causal relationship is not established, and the physiologic mechanisms underlying such a relationship are not clear. Prospective studies that quantify cumulative exposure to the

physiologic consequences of sleep-disordered breathing, such as hypoxia, would be informative.