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SCIENTIFIC INVESTIGATIONS

Polysomnographic predictors of abnormal brainstem imaging in children

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Study Objectives: Evaluation of elevated central apnea-hypopnea index (CAHI) or prolonged central apneas in pediatric patients typically includes neuroimaging with a focus on brainstem pathology. There is little evidence guiding thresholds of polysomnographic variables that accurately predict abnormal neuroimaging. We sought to evaluate whether additional polysomnographic variables may help predict brainstem pathology.

Methods: A 10-year retrospective review of patients ages 1–18 years who received a brain magnetic resonance imaging (MRI) for an indication of central sleep apnea diagnosed via polysomnography was performed. Demographics, medical history, polysomnogram variables, and MRI results were compared.

Results: This study included 65 patients (69.2% male). The median age was 5.8 years (interquartile range, 3.0–8.3). Most patients had negative (normal or nonsignificant) MRIs (n = 45, 69.2%); 20 (30.8%) had abnormal MRIs. Of the patients with abnormal MRIs, 13 (20.0%) had abnormalities unrelated to the brainstem. Seven patients (10.8%) were found to have brainstem pathology and had a median CAHI of 10.8 events/h (interquartile range, 6.5–21.9), and three of seven (42.9%) had hypoventilation and were more likely to have developmental delay, abnormal neurological examinations, and reflux. Other patients (n = 58) had a median CAHI of 5.6 events/h (interquartile range, 3.1–9.1), and seven (12.1%) had hypoventilation. Area under the curve and receiver operating characteristic curves showed a CAHI ≥ 9.5 events/h and ≥ 6.4% of total sleep time with end-tidal CO_2 ≥ 50 mm Hg predicted abnormal brainstem imaging. Prolonged central apneas did not predict abnormal brainstem imaging.

Conclusions: Most patients with central sleep apnea do not have MRIs implicating structurally abnormal brainstems. Utilizing a cutoff of CAHI of ≥ 9.5 events/h, ≥ 6.4% total sleep time with end-tidal CO_2 ≥ 50 mm Hg and/or frank hypoventilation, and additional clinical history may optimize MRI utilization in patients with central sleep apnea.

Keywords: polysomnography, central sleep apnea, Chiari malformation, MRI, hypoventilation

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BRIEF SUMMARY

Current Knowledge/Study Rationale: When central sleep apnea is detected in pediatric patients during polysomnography, neuroimaging is typically pursued to evaluate for brainstem abnormalities. Population studies describe ranges of normal indices and durations of central apneas, but there is no study that evaluates at what point such findings predict abnormal imaging related to the brainstem.

Study Impact: This study at a tertiary referral center found that most children with elevated or prolonged central sleep apneas had negative neuroimaging findings, patients with abnormal brainstem findings were more likely to have a central apnea-hypopnea index ≥ 9.5 events/h and an elevated percentage of total sleep time with elevated end-tidal CO_2 levels and/or frank hypoventilation, and central apneas ≥ 20 seconds were not predictive of brainstem abnormalities. The absence of these variables or the presence of developmental delay or abnormal neurological exam may help optimize decisions to perform neuroimaging in these patients.

INTRODUCTION

Pediatric central sleep apnea (CSA) is diagnosed by polysomnographic confirmation of an elevated central apnea-hypopnea index (CAHI). Normative population data regarding central apneas have suggested that a CAHI > 1 event/h is abnormal,[1–4] although some authors have suggested that significant CSA is better defined by a CAHI ≥ 5 events/h. This argument is supported by the fact that young children have an active Hering-Breuer reflex, wherein sighs and large inspirations result in a physiologically normal respiratory pause and may result in a CAHI as high as 3.0 events/h; additional studies have shown that a CAHI ≥ 5.0 events/h in neonates may even be acceptable.[5–7] Beyond elevated CAHI, a central apnea ≥ 20 seconds must also be considered because similar polysomnographic population data suggest that essentially no normal central apnea exceeds such a duration.[1–7] This point is particularly true of longer central apneas or frequent prolonged central apneas because these may indicate central nervous system pathology, particularly a dysfunctional medullary control of respiration.[8–10]

When either prolonged central apnea or an elevated CAHI is encountered, it is generally recommended to perform brain magnetic resonance imaging (MRI) with a focus on the brainstem. Brain MRI may help detect pathologies causing anatomical crowding at or near the foramen magnum, such as

Chiari malformations, or intrinsic abnormalities of the brainstem, such as in neoplasms or developmental disorders.[11,12] Several retrospective cohorts of pediatric CSA have been previously reported, yet these have all included small numbers of patients with variable inclusion criteria and resultant neuroimaging findings.[12–14] No study has sought to determine whether the evaluation of polysomnographic variables could further predict the results of abnormal brainstem imaging, which would prompt a consideration of more urgent changes in clinical care (ie, neurosurgical intervention).

METHODS

A 10-year (2009–2018) retrospective review was performed to include patients ages 1–18 years who received a brain MRI at our tertiary referral children's hospital for an indication of CSA, as diagnosed by polysomnography. Each polysomnogram was performed with an indication for sleep-related breathing concern and may have been ordered by community pediatricians or subspecialists including those in the areas of otolaryngology, pulmonology, sleep medicine, and neurology. We included all available patients, including those with prior polysomnograms and evidence of CSA or obstructive sleep apnea (OSA) and those with prior brain imaging, as long as the latest or subsequent brain imaging order was in direct response to central apneas detected on recent polysomnography. No lower-limit CAHI was utilized because the clinical decision to order brain imaging was contingent on what was determined to be clinically significant or prolonged CSA from the polysomnogram by the clinician. Past medical history was reviewed, and focus was attributed to the following: developmental delay, epilepsy or seizure, attention-deficit hyperactivity disorder, autism spectrum disorder, headache or migraine, heart disease, lung disease (subsumed disorders such as chronic lung disease of prematurity and asthma), gastroesophageal reflux (GERD), obesity, abnormal tone or neurological exam, OSA, and other conditions.

Imaging results were reviewed and tabulated as negative (including normal and nonsignificant, incidental and/or benign findings) and abnormal. Abnormal findings were further categorized as "unrelated to brainstem" (ie, likely not causal of CSA) and "related to brainstem" (ie, likely causal of CSA, including disorders intrinsic to or affecting the brainstem). Polysomnography reports were reviewed for the collection of numerous variables. Sleep parameters gathered included total sleep time (TST), sleep latency, proportions and durations of nonrapid eye movement sleep and rapid eye movement (REM) sleep stages, REM sleep latency, sleep efficiency, wake after sleep onset, periodic limb movement index, and total arousal index. Sleep respiratory parameters recorded included CAHI, obstructive apnea-hypopnea index, number of central apneas and hypopneas, oxygen nadir associated with a central apnea, periodic breathing percentage, peak end-tidal CO_2 ($ETCO_2$), percentage of TST with $ETCO_2 \geq 50$ mm Hg, and peak and average transcutaneous CO_2 monitoring (TCOM). Hypoventilation was diagnosed by $\geq 25\%$ TST with $ETCO_2 \geq 50$ mm Hg and/or an average TCOM ≥ 50 mm Hg.[15] Because TCOM has a higher risk for overestimating hypoventilation, its results are generally superseded by reliable $ETCO_2$ signals. However, $ETCO_2$ monitoring can be unreliable in young patients (generally ages < 2 to 3 years) because of rapid respiratory rates.[15,16] When there were conflicting data, patient age and $ETCO_2$ signal quality were reviewed to confirm or refute hypoventilation diagnosis.

Direct review of each scored central apnea was performed to collect specific central apnea data, including durations (typical, maximal, and proportion of central apneas ≥ 20 seconds), association with arousal, ≥ 3% oxygen desaturation, or both arousal and oxygen desaturation, and phase of sleep (non-REM sleep or REM sleep) in which it occurred. Direct review of raw polysomnography data was available in 87.7% of children (n = 57) and was not intended for rescoring purposes, although when 120-second epochs including scored central apneas showed events that were erroneously scored or unscored, according to the 2018 American Academy of Sleep Medicine scoring guide (*The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications,* version 2.5),[15] these were remedied. This process resulted in significant (≥ 20% adjustment) changes to the final CAHI from original clinical reports in just 3 records.

Treatment decisions were further assessed in record review, particularly in the evaluation of whether brain imaging influenced treatment choice. Treatments compared included upper-airway surgery (eg, adenotonsillectomy), continuous or bilevel positive airway pressure modalities, supplemental oxygen, medications, observation, or other treatments.

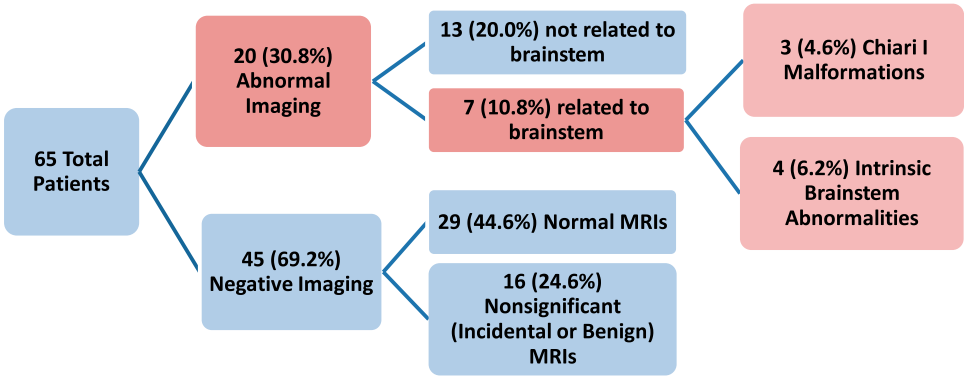
Descriptive statistics were reported in percentages or median and interquartile range (IQR). Comparative statistics between patients with and without abnormal brainstem imaging results were performed using Mann-Whitney *U* tests and standard analysis of variance *F* and *z* scores with the significance set at $P < .05$. Receiver operating characteristic curves and areas under the curve were calculated to find the best predictor within the polysomnographic metrics of abnormal brainstem on MRI. Simple logistic regression was used to evaluate the odds of having an abnormal brainstem in the MRI with different polysomnographic variables. In addition, a best-subsets general discriminant analysis was performed where all possible subsets of predictors (maximum 5 predictors) were fitted. The best model(s) were selected based on the number of predictors and cross-validation prediction accuracy. The best 20 models were investigated to determine which predictors consistently occurred in these models. The 3 most common treatment modalities were compared using the Kruskal-Wallis *H* test with post hoc Mann-Whitney *U* tests. Statistical analyses were performed using the STATA 14 statistical package (StataCorp LP, College Station, TX).

RESULTS

Frequency of abnormal brainstem MRIs in patients with elevated central apneas

A total of 65 patients (69.2% male) underwent brain MRI after polysomnography detected excessive and/or prolonged CSA

Figure 1—Patient grouping according to MRI findings and composition of the abnormal MRI group regarding brainstem pathology.



MRI = magnetic resonance imaging.

between 2009 and 2018. The median age was 5.8 years (IQR, 3.0– 8.3 years), and the median CAHI was 5.6 events/h (IQR, 3.1–10.5 events/h). **Figure 1** shows the division of imaging findings of patients. The largest group of patients (29; 44.6%) had normal MRI scans, followed by nonsignificant incidental or benign findings in 16 patients (24.6%). These negative brainstem MRI results accounted for 69.2% of the cohort. Abnormal imaging results were thus common in this study population, accounting for 30.8% (n = 20) of the cohort. Abnormal findings were unrelated to the brainstem in 13 patients (20.0%). We observed that 7 patients (10.8%) had abnormal findings related to the brainstem—Chiari I malformation was detected in 3 patients (4.6%), and intrinsic brainstem abnormality was detected in 4 (6.2%) patients. No neoplastic or infiltrative processes were identified.

Table 1 compares the polysomnographic variables between patients with abnormal imaging related to the brainstem and the rest of the cohort. Patients with abnormal imaging related to the brainstem had a significantly longer REM sleep latency, a greater percentage of TST with $ETCO_2 \geq 50$ mm Hg, and a higher peak $ETCO_2$. The CAHI did not significantly differ between the groups ($P = .11$).

Past medical history

Table 2 details the past medical history data between patients with and without abnormal brainstem imaging; some patients had multiple comorbidities and thus the numbers do not add up to 100%. History of developmental delay, abnormal tone/neurological exam, or GERD were significantly more common in patients with abnormal imaging related to the brainstem (all $P < .05$). Few patients had no notable past medical history preceding polysomnography (n = 17; 26.2%). The most common past medical history within the overall cohort included GERD (n = 14; 21.5%), lung disease (n = 14; 21.5%, including disorders such as asthma, bronchopulmonary dysplasia, and chronic lung disease), developmental delay (n = 13; 20.0%), OSA (n = 13; 20.0%), and abnormal tone or neurological exam (n = 9; 13.8%). A large portion of patients (n = 23; 35.4%) had some "other" or additional notable medical history, including various genetic disorders in 7 patients (including chromosomal abnormalities such as 22q11 microdeletion syndrome in 2 patients and trisomy 21 in 1 patient), known/reported brain abnormalities (eg, hydrocephalus, hypoxic ischemic injury, Chiari malformation) in 7 patients, a history of prematurity in 2 patients, and syndromic craniosynostosis in 2 patients.

Incidence of hypoventilation

Sixty-three patients had $ETCO_2$ monitoring, and 9 (13.8%) showed an $ETCO_2 \geq 50$ mm Hg for ≥ 25% TST. Twenty-five patients had TCOM sensors, and 8 (32.0%) had an average TCOM ≥ 50 mm Hg. In the 14 patients with either sensor suggestive of hypoventilation, formal hypoventilation diagnosis was made in 10 (15.9% of 63 patients with some form of CO_2 monitoring). In those 10 patients, 6 diagnoses were made based on $ETCO_2$ alone, 1 diagnosis was made based on TCOM alone, and 3 diagnoses had concordant elevated $ETCO_2$ and TCOM signals.

MRI details

Of the 65 MRIs performed, 38 (58.5%) were performed without intravenous contrast. Anesthesia or sedation services were required for 43 patients (66.2%). One patient experienced an adverse event from sedation/anesthesia with persistent hypoxemia, requiring a brief inpatient hospitalization.

Abnormal MRIs related to the brainstem

Of the 7 patients with abnormal MRIs related to the brainstem, 3 patients were identified as having Chiari I malformations on MRI; 1 of these patients was known to have a Chiari I malformation secondary to syndromic craniosynostosis and had previously undergone suboccipital decompressive surgery. Four patients were identified as having intrinsically abnormal brainstems; 1 patient had a known prior brainstem stroke and showed expected regions of encephalomalacia and gliosis in the brainstem, and another patient had known Dandy-Walker malformation, hydrocephalus requiring ventriculoperitoneal shunt placement, and ventral displacement of the brainstem with resultant flattening of the ventral pons. Thus, only 4 patients (62%) had novel diagnostic MRI findings (2 with Chiari I malformations and 2 intrinsic to the brainstem) implicating structural brainstem pathology as the source of central apneas. The 7 patients are described in detail in **Table 3.** The median age

Table 1—Comparison of polysomnographic variables between patients with and without abnormal brainstem imaging.

	Abnormal Brainstem MRI (n = 7)	Normal Brainstem MRI (n = 58)	*P*
PSG sleep parameter			
Age (y)	6.0 (2.6–10.6)	5.8 (3.0–8.2)	.89
Sex			
Female	3	17	.47
Male	4	41	.47
Sleep latency (min)	11.5 (9.5–59.3)	28.5 (8.5–54.5)	.81
TST (min)	382.0 (348.0–440.3)	436.0 (389.5–465.5)	.37
Wake after sleep onset (min)	84.5 (40.3–102.5)	45.0 (20.0–82.0)	.23
Sleep efficiency (%)	72.0 (63.7–84.0)	83.5 (78.3–89.8)	.21
N1 duration (min)	11.0 (9.0–22.3)	13.5 (4.5–26.0)	.99
% N1 sleep	3.4 (2.0–6.2)	3.2 (1.1–6.3)	.85
N2 duration (min)	138.5 (123.5–153.0)	169.8 (128.6–195.6)	.07
% N2 sleep	34.5 (29.3–39.7)	40.2 (34.1–45.7)	.16
N3 duration (min)	116.0 (107.8–161.5)	134.0 (109.3–162.5)	.62
% N3 sleep	35.4 (31.3–41.3)	31.5 (26.4–41.8)	.25
REM sleep duration (min)	92.5 (53.3–120.5)	88.8 (66.9–112.3)	.97
% REM sleep	23.6 (15.8–28.0)	20.4 (16.4–24.6)	.83
REM sleep latency (min)	226.5 (139.3–289.0)	110.0 (64.5–145.0)	.04
Total arousal index	15.5 (10.0–21.8)	15.3 (10.7–20.4)	.89
Periodic limb movement index	0 (0–1.5)	0.5 (0–2.2)	.42
Respiratory-related arousal index	2.2 (1.7–3.2)	4.5 (1.9–7.5)	.16
PSG respiratory parameter			
Obstructive AHI (events/h)	2.0 (0.3–2.1)	2.1 (0.6–6.2)	.90
CAHI (events/h)	10.8 (6.3–21.9)	5.6 (3.1–9.1)	.11
Number of CAs	77.0 (25.0–142.5)	32.5 (20.3–57.0)	.19
% NREM sleep CAs	61.8 (59.3–84.9)	78.5 (62.7–89.8)	.43
Median CA duration (s)	12.2 (9.3–14.2)	11.4 (9.8–13.2)	.79
% of CAs associated with SpO_2 desaturation	96.6 (71.8–99.7)	86.7 (70.0–93.4)	.32
% of CAs associated with arousal	40.0 (21.9–52.9)	58.8 (37.5–79.7)	.09
% of CAs associated with arousal and SpO_2 desaturation	15.6 (4.6–32.3)	30.3 (11.9–52.2)	.18
# of CAs ≥ 20 seconds	0 (0–3.5)	0 (0–2)	.66
% of total CAs ≥ 20 seconds	0 (0–16.3)	0 (0–5.9)	.69
Number of central hypopneas	0 (0–0.5)	0 (0–1.0)	.19
SpO_2 nadir associated with CA	84.0 (81.5–85.5)	86.0 (77.0–89.0)	.69
Longest CA (s)	19.0 (17.5–24.6)	19.0 (16.0–24.4)	.80
Periodic breathing %	2.0 (0.8–6.5)	1.6 (0.5–4.3)	.67
Peak $ETCO_2$ (mm Hg)	59.4 (55.5–61.5)	51.5 (50.0–55.9)	.01
% TST with $ETCO_2$ ≥ 50 mm Hg	10.8 (3.8–72.5)	0.1 (0–2.5)	.02
Peak TCOM (mm Hg)*	59.0 (45.0–63.0), n = 5	52.5 (48.0–57.3), n = 20	.54
Average TCOM (mm Hg)*	50.0 (41.0–53.0), n = 5	47.0 (43.5–49.5), n = 19	.67

Values presented are medians with interquartile ranges in parentheses. *TCOM data included a smaller portion of each cohort with the n listed. AHI = apnea-hypopnea index, CA = central apnea, CAHI = central apnea-hypopnea index, $ETCO_2$ = end-tidal CO_2, MRI = magnetic resonance imaging, NREM = non–rapid eye movement, PSG = polysomnography, REM = rapid eye movement, TCOM = transcutaneous CO_2 monitoring, TST = total sleep time.

of these patients was 6.0 years (IQR, 2.6–10.6 years). The median CAHI was 10.8 events/h (IQR, 6.5–21.9 events/h). Three patients (42.9%) had central apneas ≥ 20 seconds and 3 had hypoventilation present.

Abnormal MRI findings unrelated to the brainstem

A total of 13 patients (20.0%) had an abnormal MRI unrelated to the brainstem. Some patients had multiple, multifocal abnormalities detected. A cerebellar abnormality was noted in 6

Table 2—Comparison of features of past medical history between patients with and without abnormal brainstem imaging.

	Abnormal Brainstem MRI (n = 7)	Normal Brainstem MRI (n = 58)	Total (n = 65)	*P*
None	0	17 (29.3%)	17 (26.2%)	.095
Developmental delay	4 (57.1%)	9 (15.5%)	13 (20.0%)	.009
Epilepsy or seizure	1 (14.3%)	2 (3.4%)	3 (4.6%)	.197
ADHD	1 (14.3%)	7 (12.1%)	8 (12.3%)	.865
Headache/migraine	0	1 (1.7%)	1 (1.5%)	.726
Heart disease	0	4 (6.9%)	4 (6.2%)	.472
Lung disease	3 (42.9%)	11 (19.0%)	14 (21.5%)	.147
GERD	4 (57.1%)	10 (17.2%)	14 (27.7%)	.015
Abnormal tone or neurological exam	3 (42.9%)	6 (10.3%)	9 (13.8%)	.019
Obesity	0	7 (12.1%)	7 (10.8%)	.332
OSA	2 (28.6%)	11 (19.0%)	13 (20.0%)	.549
Autism spectrum disorder	0	3 (5.2%)	3 (4.6%)	.535
Other	6 (85.7%)	17 (29.3%)	23 (35.4%)	n/a

Values do not add up to 100% because some patients had multiple components to their past medical history. "Other" represents a subsumed category of multiple distinct disorders. ADHD = attention-deficit hyperactivity disorder, GERD = gastroesophageal reflux disease, MRI = magnetic resonance imaging, OSA = obstructive sleep apnea.

patients (eg, dysplasia, arachnoid cyst causing local mass effect). Other observations included asymmetric, enlarged, or dysmorphic lateral ventricles in 4 patients, an abnormal corpus callosum (dysplastic or absent) in 3 patients, and gray-matter heterotopia in 2 patients. In these patients, the median CAHI was 6.5 events/h (IQR, 3.9–10.5 events/h), 5 (38.5%) had central apneas ≥ 20 seconds in duration, and 2 (15.4%) had hypoventilation.

Negative imaging findings

Twenty-nine patients (44.6%) had normal structural MRIs. The median age was 7.3 years (IQR, 3.7–8.3 years), and the median CAHI was 5.5 events/h (IQR, 2.9–12.0 events/h). Fourteen (48.3%) had central apneas ≥ 20 seconds and three (10.3%) had hypoventilation.

Sixteen patients (24.6%) had brain imaging with nonsignificant (benign or incidental) findings. These included 6 patients with benign cysts (eg, arachnoid cysts not causing local mass effect, pars intermedia cysts, and pineal cysts), enlarged adenoids and/or tonsils in 3 patients, cerebellar tonsillar ectopia not meeting the criteria for Chiari malformation in 2 patients, and mildly delayed myelination in 1 patient (not manifesting as disease on follow-up). The median age of these patients was 3.1 years (IQR, 2.7–9.7 years), and the median CAHI was 3.4 events/h (IQR, 2.9–5.9 events/h). Six patients (30%) had central apneas ≥ 20 seconds and 2 (12.5%) had hypoventilation.

Polysomnographic predictors of abnormal brainstem imaging

Upon reviewing the differences between the small cohort of patients with abnormal imaging related to the brainstem and the remainder of the cohort, we found that elevated $ETCO_2$ (ie, evidence of hypoventilation) became a candidate metric to assess predictive diagnostic attributes. CAHI and the presence of central apneas ≥ 20 seconds were also evaluated as the primary clinical indicators for neuroimaging.

In determining the level of CAHI with optimal sensitivity and specificity, we created a plot (**Figure 2**) with increasing CAHI and found an intersection at 7.0 events/h (sensitivity 62.5% and specificity 62.1%). Sensitivity remained at 62.5% through a CAHI of 9.5 events/h before drastically lowering. Specificity rose to 75.9% with a CAHI of 9.5 events/h.

In predicting an abnormal brainstem finding on MRI, we found that the presence of hypoventilation (n = 63) was associated with a 42.9% sensitivity and 87.5% specificity. The negative predictive value of hypoventilation was 92.5%, and the positive predictive value (PPV) was only 30.0%. The positive and negative likelihood ratios of hypoventilation associated with abnormal brain stem imaging were 3.43 (95% confidence interval [CI], 1.14–10.31) and 0.65 (95% CI, 0.34–1.25), respectively. The Fisher exact probability showed no statistical significance ($P = .07$).

Furthermore, in predicting an abnormal brainstem finding on MRI, we found that the presence of a central apnea ≥ 20 seconds (n = 64) was associated with a 42.9% sensitivity and 56.1% specificity. The negative predictive value of a central apnea ≥ 20 seconds was 88.9%, and the PPV was only 10.7%. The positive and negative likelihood ratios of a prolonged central apnea associated with abnormal brainstem imaging were 0.98 (95% CI, 0.40–2.41) and 1.02 (95% CI, 0.51–2.01), respectively. The Fisher exact probability showed no statistical significance.

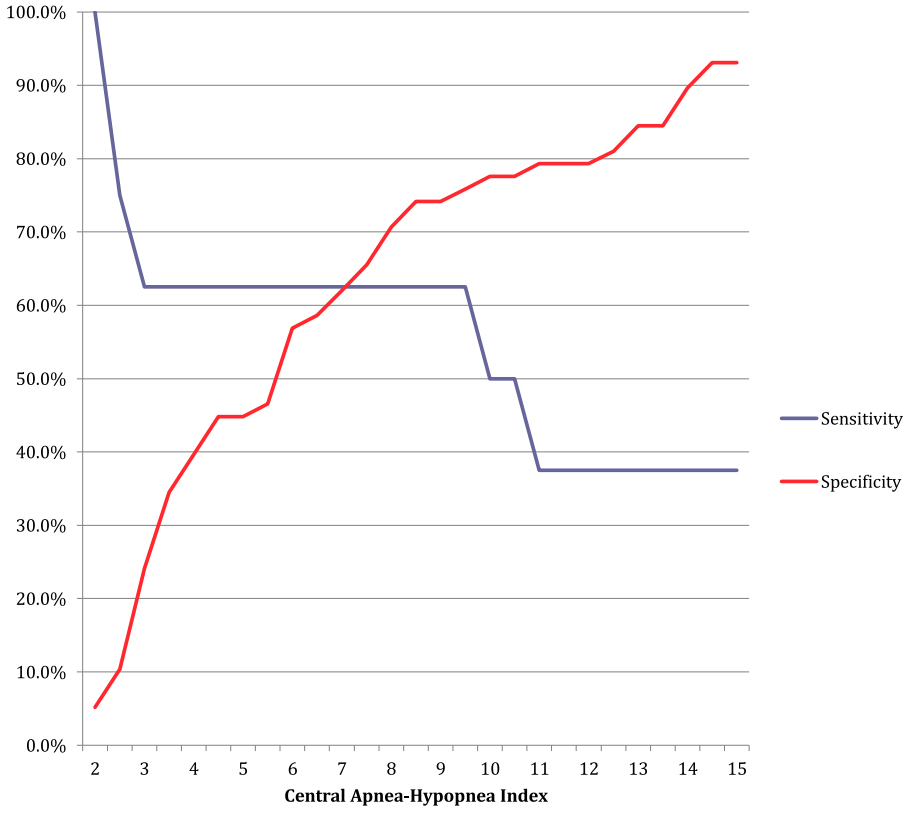
Combining patients with both a CAHI ≥ 9.5 events/h and hypoventilation, the sensitivity and specificity for abnormal brainstem imaging were 42.9% and 100%, respectively. The negative predictive value was 93.6%, and the PPV was 100%. The negative likelihood ratio of these combined metrics with abnormal brainstem imaging was 0.57 (95% CI, 0.30–1.09). The Fisher exact probability showed a significance of $P < .001$.

Table 3—Detailed list of patients with abnormal brainstem imaging.

Age (y)	Sex (M/F)	Past Medical History	Central AHI	Longest CA (s)	% TST $ETCO_2$ ≥ 50 mm Hg	Average TCOM	SpO_2 Nadir	PB %	Obstructive AHI	REM Sleep Latency (min)	MRI Findings	Treatment
2.1	M	Developmental delay, Hirschsprung's disease	9.6	11.4	0.9	56.0	80	2.7	2.0	74.5	Chiari I malformation, no syrinx	Found to have *PHOX2B* mutation, BPAP
12.25	M	Pfeiffer syndrome, tracheostomy dependence, Chiari malformation status post-decompressive surgery	10.8	23.2	96.1	53.0	84	0.4	0.9	328.5	Chiari I malformation with multiseptated syrinx from C2-C3 levels with posterior adhesion to dorsal thecal sac; stable VPS and evidence of prior suboccipital craniotomy	Suboccipital decompression, BPAP
6	F	None	27.8	19.0	53.8	—	85	0	58.4	249.5	Chiari I malformation, no syrinx	T&A
17.5	M	Prior catastrophic brainstem stroke with resultant abnormal tone/neurological examination, ADHD	24.2	26.0	10.8	50.0	86	32.6	0.8	197	Encephalomalacia and gliosis involving medial left cerebellar hemisphere and brainstem from remote brainstem insult	BPAP
8.9	M	Dandy-Walker malformation, hydrocephalus s/p VPS, GERD, OSA, developmental delay, epilepsy, lung disease	2.9	44.0	0	41.0	71	2.0	2.0	226.5	Dandy-Walker malformation with ventral brainstem displacement and flattening of ventral pons	Underwent VPS X-ray series, BPAP
1	F	Prematurity (35 weeks), right neck cystic hygroma	3.3	18.1	0.2	39.0	83	1.2	2.2	81.5	Microcephaly, mid- and hindbrain hypoplasia suggestive of pontocerebellar hypoplasia, dysmorphic CC	BPAP
3	F	Developmental delay, GERD, dysphagia	19.6	16.9	7.4	—	90	10.2	0.9	347	Dysmorphic CC and pons, ventral concavity of medulla, pointed cerebellar tonsils 4 mm below foramen magnum, reduced CSF space at craniocervical junction	Suboccipital decompression

ADHD = attention-deficit hyperactivity disorder, AHI = apnea-hypopnea index, BPAP = bilevel positive airway pressure, CA = central apnea, CAHI = central apnea-hypopnea index, CC = corpus callosum, CSF = cerebrospinal fluid, $ETCO_2$ = end-tidal CO_2, GERD = gastroesophageal reflux disease, MRI = magnetic resonance imaging, PB% = percentage of sleep spent with periodic breathing, REM = rapid eye movement, s/p = status post, T&A = adenotonsillectomy, TCOM = transcutaneous CO_2 monitoring, TST = total sleep time, VPS = ventriculoperitoneal shunt.

Figure 2—Plot of sensitivity and specificity with increasing CAHI.



CAHI = central apnea-hypopnea index.

Table 4—AUC results for the 3 polysomnographic variables that were statistically different between patients with and without abnormal brainstems and CAHI.

Variable	AUC	AUC (Lower 95%)	AUC (Upper 95%)	AUC *P* Value	Optimal Cutoff	Sensitivity	Specificity
REM sleep latency	0.74	0.50	0.98	.02	195.25	71.4%	84.3%
CAHI	0.68	0.41	0.98	.05	9.55	71.4%	78.4%
Peak $ETCO_2$	0.78	0.53	1	.01	57.5	71.4%	82.4%
% TST with $ETCO_2 \geq 50$ mm Hg	0.76	0.55	0.98	.01	6.40	71.4%	82.4%

AUC = area under the curve, CAHI = central apnea-hypopnea index, $ETCO_2$ = end-tidal CO_2, REM = rapid eye movement, TST = total sleep time.

Area under the curve and general discriminant analyses

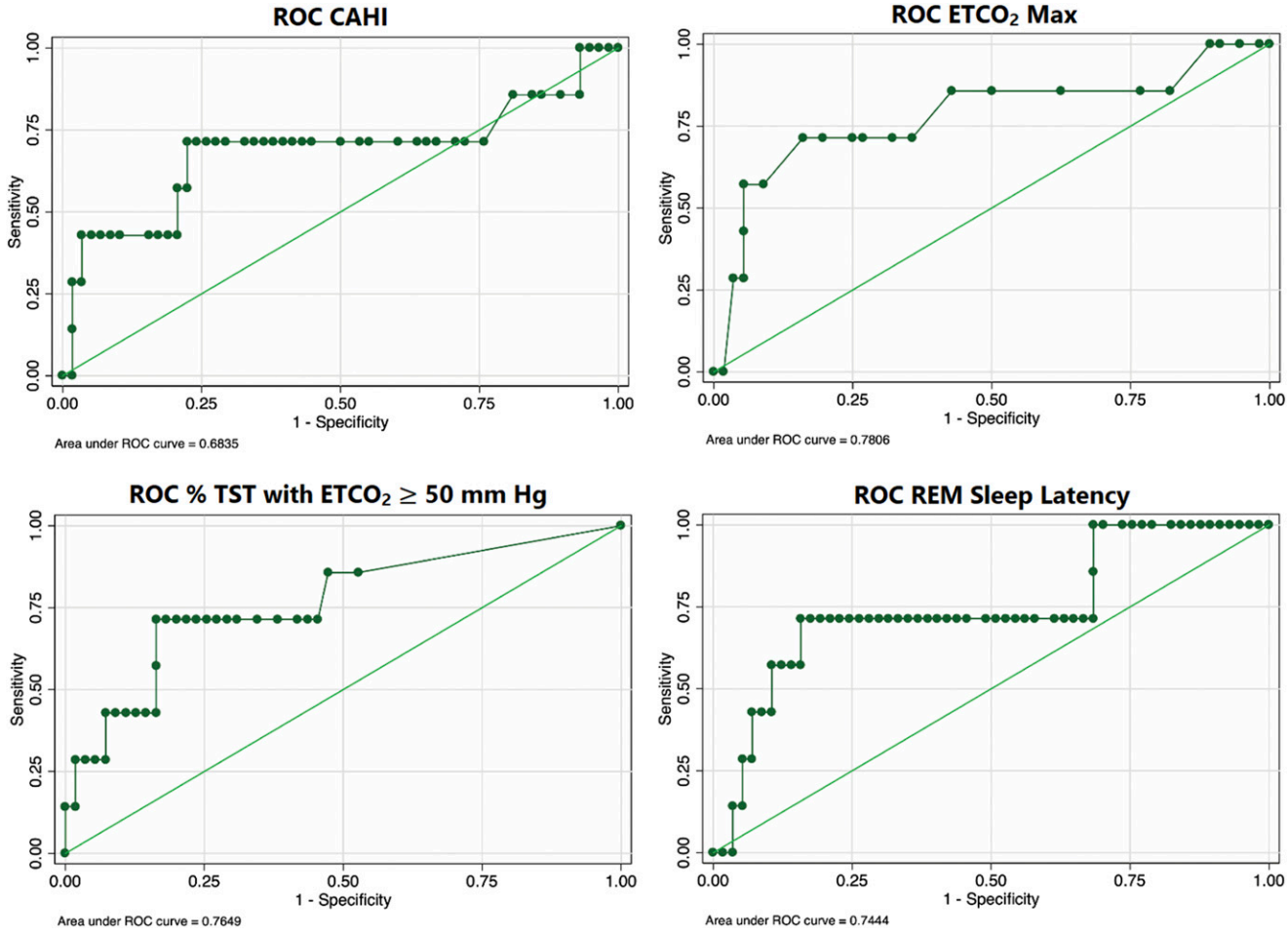
The area under the curve, along with the optimal cutoff value with corresponding sensitivity and specificity, was calculated for 4 different polysomnographic variables: REM sleep latency, CAHI, peak $ETCO_2$, and percentage TST with $ETCO_2 \geq 50$ mm Hg (**Table 4** and **Figure 3**).

The variable for best prediction of an abnormal brainstem in the MRI was percentage TST with $ETCO_2 \geq 50$ mm Hg, with an optimal cutoff point of 6.4% of TST. This metric had a sensitivity of 71.4% and a specificity of 82.4%. The odds of having an abnormal brainstem on MRI were predicted to be significantly larger for a 1% increase in percentage TST with $ETCO_2 \geq 50$ mm Hg (odds ratio, 1.03; $P = .012$; 95% CI, 1.0066–1.0561). The relevance in considering which percentage TST with $ETCO_2 \geq 50$ mm Hg was a valuable predictor for abnormal brainstem was further confirmed by the general discriminant analysis. Overall, percentage TST with $ETCO_2 \geq 50$ mm Hg was the variable that showed up most in the best predictor models, appearing 15 times in the best 20 models ($F = 11.48$; $P \leq .01$). The 2 other variables that appeared significantly in the best 20 models were CAHI, 8 times ($F = 7.39$; $P \leq .01$), and N2 sleep percentage, 6 times ($F = 5.9$; $P = .02$).

Treatments

Several patients underwent concomitant treatment plans (eg, upper-airway surgery and positive airway pressure). The most common treatment decision for an elevated CAHI was observation, occurring in 29 patients (44.6%). Seventeen patients (26.2%) received positive airway pressure modalities (3 continuous positive airway pressure and 14 bilevel positive airway pressure). Twelve (18.5%) patients underwent upper-airway

Figure 3—ROC curves with respective AUC for the most predictive polysomnographic variables.



AUC = area under the curve, $ETCO_2$ = end-tidal CO_2, REM = rapid eye movement, ROC = receiver operating characteristic, TST = total sleep time.

surgery, most commonly adenotonsillectomy. There was no difference in ages between the treatment groups. There was a significantly higher degree of OSA syndrome in the upper-airway surgery group. Both the positive airway pressure and surgery groups had a higher proportion of hypoventilation than the observation group, and the positive airway pressure group had a higher proportion of central apneas ≥ 20 seconds compared to the observation group (data not shown).

Less-common treatment modalities included supplemental oxygen in 6 patients (9.2%), medications in 4 patients (6.2%), and decompressive neurosurgery in 2 (3.1%) patients. Medications utilized included antireflux medication (ranitidine) in 1 patient and theophylline in 3 patients. Several patients had other treatments or evaluations pursued, including craniofacial surgery for craniosynostosis, genetic testing for *PHOX2B* defects (2 patients), 1 ventriculoperitoneal shunt X-ray series, and 1 nuclear medicine milk scan to evaluate for GERD.

DISCUSSION

This retrospective cohort of 65 patients who underwent brain MRI after polysomnography showed elevated or prolonged CSA found negative or nonsignificant imaging results in 69.2% of the patients. Most MRIs were normal and, in contrast to a prior study,[13] we did not include findings typically considered benign and incidental such as arachnoid cysts as significant abnormal MRI findings unless there were discrete features suggestive of local mass effect. Abnormal neuroimaging was a frequent finding, at 30.8% of all patients in this mixed population within a tertiary children's hospital. There was a high incidence of various abnormal MRI findings such as cerebellar and corpus callosum abnormalities; however, these would not necessarily be considered contributory or have clear additional diagnostic value in the context of CSA. Reports of vermian hypoplasia and Joubert syndrome have implicated midline cerebellar abnormalities in the genesis of some patients with CSA.[17] The manner by which cerebellar abnormalities contribute to CSA is unclear and warrants further evaluation. Seven patients (10.8%) had evidence of structural pathology related to the brainstem; 3 of these patients had known prior brainstem pathology and thus only 4 patients (6.2%) had novel abnormal structural findings related to the brainstem.

The number of clearly defined changes in clinical CSA care because of neuroimaging results occurred in only 2 patients (3.1%), who underwent decompressive neurosurgical procedures.

Interestingly, in the patient with the most extensive Chiari I malformation found on imaging, decompressive surgery was not pursued after a *PHOX2B* gene mutation was discovered and a diagnosis of congenital central hypoventilation syndrome was made. It is important to note that some of the neuroimaging findings, such as abnormal corpus callosum and even findings included in the nonsignificant category such as mildly delayed myelination, may warrant clinical follow-up, adjustments to clinical care including genetic evaluations, and even repeating neuroimaging on an interval basis. These neuroimaging findings are, however, less likely to influence the direct management of CSA (ie, neurosurgical decompression).

We found that from past medical history alone, our cohort of patients with abnormal imaging related to the brainstem was more likely to have developmental delay, GERD, and the presence of abnormal neurological examination or tone. The presence of known neurological disorder or examination has been echoed in prior studies evaluating CSA.[13,14] We recapitulated the finding by Woughter et al[13] that GERD is more prevalent in such patients, although isolated GERD is probably not an accurate predictor of abnormal brainstem pathology because it is highly prevalent in children with normal brainstem pathology and in children with neurological impairments sich as cerebral palsy.[18]

It is worthwhile to further note that of the 13 patients who had abnormal neuroimaging unrelated to the brainstem, 7 had known genetic abnormalities and all but 1 had either clinical indications for neuroimaging (eg, developmental delay) or prior neuroimaging studies. The only patient without a clear prior indication for neuroimaging had a history of night terrors; polysomnogram showed a mildly elevated CAHI of 3.9 events/h and a single prolonged central apnea of 27 seconds. This child was found to have a focus of supratentorial gray-matter heterotopia unrelated to his mild CSA. Thus, the additive value of CSA in predicting any non-brainstem MRI abnormality is complicated by these pre-existing factors.

There were 3 polysomnographic variables that were statistically different in patients with abnormal imaging related to the brainstem. The prolonged REM sleep latency in patients with abnormal brainstem imaging may have been the result of frequent respiratory events provoking arousals and disturbing the normal progression of sleep stages rather than an intrinsic disturbance of REM sleep onset or generation, especially with no difference in total REM sleep. This variable may be clinically challenging to use further as a differentiator because of the multitude of factors that may result in prolonged REM sleep latency, including medication effect and other sources of frequent arousals. This study does support careful evaluation of the $ETCO_2$ signal to a much more granular perspective than focusing on the current hypoventilation diagnostic cutoff of $\geq 25\%$ of TST with a value ≥ 50 mm Hg. Frank hypoventilation was more common in patients with abnormal brainstems, but by using the $ETCO_2$ signal as a continuous variable, patients with just $\geq 6.4\%$ of TST with $ETCO_2 \geq 50$ mm Hg were significantly more likely to have an abnormal brainstem on imaging. The peak $ETCO_2$ was also significantly higher in patients with abnormal brainstem imaging results. This signal in clinical practice may be a corollary to more prolonged and consistent elevations in CO_2 levels, but it can be challenging to interpret in isolation because drastic fluctuations in this peak $ETCO_2$ may be seen with large body movements and sighs. Although it did not reach significance, it was interesting to note a trend of fewer central apneas associated with arousals in patients with abnormal imaging related to the brainstem. This finding may reach significance in a larger cohort and may support a hypothesis that a dysfunctional system of arousal and/or brainstem ventilatory response to rising CO_2 levels may play a role in the production of frequent or prolonged central apneas.

A necessary caveat is that this patient cohort was selected by the presence of elevated or prolonged central apneas, typically resulting in an elevated CAHI. It is the concomitant presence of an elevated CAHI in conjunction with an elevated percentage TST with $ETCO_2 \geq 50$ mm Hg that should prompt consideration of performing neuroimaging, because significant OSA may produce similar hypoventilation findings. Studies with larger sample sizes and prospective designs could consider exploring and validating these 4 variables further to achieve potentially more accurate predictions.

A CAHI ≥ 9.5 events/h or frank hypoventilation showed poor PPVs, but the combination of these metrics indicated a 100% PPV in this small cohort. Technically, the optimal sensitivity and specificity of the CAHI was determined to be 9.55 events/h by statistically significant area under the curve calculations, but typical polysomnographic scoring software does not calculate beyond the tenths decimal and thus 9.5 events/h is a reasonable benchmark for the prediction of abnormal brainstem findings.

Note that predictive values vary with the frequency of the disease in the patient population being studied; this referral population likely had a *higher* likelihood of abnormal brain imaging than a population of children with normal brain imaging or in a community population with pediatric sleep-disordered breathing. Indeed, the high negative predictive values would likely further increase in such populations. An important distinction from this study is that the presence of central apneas ≥ 20 seconds was not supportive of abnormal brainstem imaging findings. Although population studies support that essentially no "normal central apnea" is > 20 seconds,[1–7] our present study is not powered to assess what duration beyond the 20-second central apnea cutoff would accurately predict abnormal brainstem findings. To highlight this clinical challenge of imperfect predictive values, 1 patient (**Table 3,** patient 5) in our study with an abnormal brainstem imaging had an overall low CAHI of 2.9 events/h, but central apneas were significantly prolonged, as much as 44 seconds.

Limitations include the retrospective nature of the study with a relatively small population, which did not allow for estimation with multivariate predictors. This cohort was defined by the presence of 2 specific tests, polysomnography and MRI, occurring in a particular order. This cohort did not account for patients with elevated or prolonged CAHI who did not undergo neuroimaging, nor did it evaluate patients who were found to have possible brainstem abnormalities or Chiari malformations and then underwent polysomnography. We also did not include computed tomography head scans, which may have limited the neuroimaging cohort, particularly in patients who may not tolerate nonsedated MRI or are prevented from undergoing a

brain MRI (eg, because of cochlear implants). This cohort was chosen based on the clinical bias of practitioners to obtain neuroimaging in the context of what was perceived to be excessive central apnea (in frequency and/or duration), because there is no clearly defined literature to suggest an upper limit of normal that is both developmentally abnormal and clinically significant to predict abnormal imaging findings related to the brainstem.

This study also only utilized clinical MRI reports, which are interpretations of self-reported structural assessments by trained neuroradiologists without explicit volumetric measurements of brain anatomy. There were no attempts at advanced neuroimaging analyses beyond structural assessment, such as spectroscopy or diffusion tensor imaging, to evaluate for specific microstructural abnormalities of tracts involved in the brainstem breathing apparati.[19] It is possible that evaluation of these MRIs with the aforementioned tools may show abnormalities in patients with structurally normal-appearing brainstems.

If we had utilized strict *International Classification of Sleep Disorders* (third edition) criteria for CSA diagnosis (CAHI ≥ 5 events/h; > 50% of total events central in nature), which do not include CSA duration in the definition, the cohort would have been constrained to just 30 patients (28 patients had a CAHI < 5 events/h).[20] That reduced cohort comprised 19 patients with negative neuroimaging and 11 patients with abnormal neuroimaging, including just 4 patients with abnormal brainstem imaging. When comparing between the negative and abnormal neuroimaging groups, we found no significant differences between CAHI, incidence of hypoventilation, or presence of prolonged CSA (data not shown). This constrained cohort would not evaluate an additional 16 patients who had a central apnea ≥ 20 seconds with a total CAHI < 5.0 events/h or < 50% total events central in nature. Seven of those 16 patients had a CAHI < 3.0 events/h but still had a prolonged central apnea that prompted neuroimaging. This consideration permits greater confidence in showing that isolated prolonged central apneas ≥ 20 seconds, particularly in the context of low CAHI or absence of hypoventilation, have poor prognostic significance for brainstem pathology. These patients may benefit from observation rather than obtaining an MRI (possibly requiring sedation/anesthesia for the procedure—nearly two-thirds of our population), unless other clinical indicators warrant more prompt neuroimaging.

CONCLUSIONS

Most patients with CSA have negative neuroimaging findings, and only 6.2% of our study population had MRI-detectable structural abnormalities affecting the brainstem that were not previously known. This study supports using a CAHI ≥ 9.5 events/h as a more accurate predictor of an abnormal imaging related to the brainstem. When an elevated CAHI was observed in conjunction with a percentage TST with $ETCO_2$ ≥ 50 mm Hg beyond the optimal cutoff point of 6.4% of TST, or if frank hypoventilation was present, abnormal imaging related to the brainstem was further predicted. The presence of a prolonged central apnea ≥ 20 seconds in the absence of hypoventilation or an elevated CAHI is not predictive of abnormal brainstem imaging; however, it is possible that a longer central apnea duration threshold would be more suggestive of a dysfunctional brainstem and prompt neuroimaging. Clinical history may further support neuroimaging decisions, such as the presence of developmental delay and abnormal neurological exam or tone. Clinical equipoise is essential in determining the patients in whom neuroimaging may be deferred, such as in patients without significant medical history found to have only an isolated central apnea ≥ 20 seconds or a CAHI < 9.5 events/h, particularly if there is an absence of prolonged elevations in $ETCO_2$.

ABBREVIATIONS

CAHI, central apnea-hypopnea index
CI, confidence interval
CSA, central sleep apnea
ETCO2, end-tidal CO2
GERD, gastroesophageal reflux disease
IQR, interquartile range
MRI, magnetic resonance imaging
OSA, obstructive sleep apnea
PPV, positive predictive value
REM, rapid eye movement
TCOM, transcutaneous CO2 monitoring
TST, total sleep time

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