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ABSTRACT

BACKGROUND AND PURPOSE: Hyperintense FLAIR signal in the cerebral sulci of anesthetized children is attributed to supplemental oxygen (fraction of inspired oxygen) but resembles FLAIR hypersignal associated with perfusion abnormalities in Moyamoya disease and carotid stenosis. We investigated whether cerebral perfusion, known to be altered by anesthesia, contributes to diffuse signal intensity in sulci in children and explored the relative contributions of supplemental oxygen, cerebral perfusion, and anesthesia to signal intensity in sulci.

MATERIALS AND METHODS: Supraventricular signal intensity in sulci on pre- and postcontrast T2 FLAIR images of 24 propofol-sedated children (6.20 ± 3.28 years) breathing supplemental oxygen and 18 nonsedated children (14.28 ± 2.08 years) breathing room air was graded from 0 to 3. The Spearman correlation of signal intensity in sulci with the fraction of inspired oxygen and age in 42 subjects, and with dynamic susceptibility contrast measures of cortical CBF, CBV, and MTT available in 25 subjects, were evaluated overall and compared between subgroups. Factors most influential on signal intensity in sulci were identified by stepwise logistic regression.

RESULTS: CBV was more influential on noncontrast FLAIR signal intensity in sulci than the fraction of inspired oxygen or age in propofol-sedated children (CBV: $r = 0.612$, $P = .026$; fraction of inspired oxygen: $r = -0.418$, $P = .042$; age: $r = 0.523$, $P = .009$) and overall (CBV: $r = 0.671$, $P = .0002$; fraction of inspired oxygen: $r = 0.442$, $P = .003$; age: $r = -0.374$, $P = .015$). MTT (CBV/CBF) was influential in the overall cohort ($r = 0.461$, $P = .020$). Signal intensity in sulci increased with contrast in 45% of subjects, decreased in none, and was greater ($P < .0001$) in younger propofol-sedated subjects, in whom the signal intensity in sulci increased with age postcontrast ($r = .600$, $P = .002$).

CONCLUSIONS: Elevated cortical CBV appears to contribute to increased signal intensity in sulci on noncontrast FLAIR in propofol-sedated children. The effects of propofol on age-related cerebral perfusion and vascular permeability may play a role.

ABBREVIATIONS: FiO_2 = fraction of inspired oxygen; SSI = signal intensity in sulci

Accurate detection of leptomeningeal metastatic disease is critical for appropriate risk stratification and treatment of patients with CNS malignancies, particularly childhood posterior fossa tumors such as ependymoma and medulloblastoma, for which the diagnosis of metastasis is critical to staging and treatment.[1] T2-weighted FLAIR imaging is particularly sensitive for detection of intracranial leptomeningeal metastasis due to intrinsic sensitivity to the T1 effects of gadolinium at low concentrations, nonvisualization of intravascular blood, and CSF suppression,[2-4] but it is subject to artifactual increases in CSF signal in sulci, most commonly at the cerebral convexities, which could obscure or mimic leptomeningeal disease.[5]

In 2001, it was reported that children receiving propofol, but not chloral hydrate, showed CSF hyperintensity on FLAIR imaging.[5] Early theories that this artifactual signal might be due to intrinsic T1 hyperintensity of anesthetics crossing the blood-pial barrier were laid to rest by phantom studies.[5-7] Subsequent studies found that patients receiving high concentrations of supplemental oxygen were more likely than those receiving lower concentrations to have increased CSF signal intensity, even without anesthesia.[7,8] However, in the largest such study in anesthetized children, there was considerable overlap between groups, with 67%

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of patients with low fraction of inspired oxygen (FiO_2) having hyperintense CSF compared with 84% in the high-FiO_2 group.[9] A later finding that sulcal signal intensity (SSI) decreased when FiO_2 was reduced from 100% to 30% in intubated children under propofol anesthesia[10] confirmed an influence of hyperoxygenation on SSI, but SSI persisted in 35% of children with FiO_2 of 30%, contrary to a previously established threshold of 50% below which no abnormal SSI was seen.[8] No studies to date have documented a linear relationship between FiO_2 and SSI, to our knowledge.

Physiologic factors may account for a nonlinear relationship of SSI and FiO_2, apparent differences in SSI between anesthesia protocols, and the overlap in SSI with low-versus-high FiO_2. It has been our observation that the diffuse, symmetric FLAIR SSI in anesthetized children resembles the asymmetric FLAIR signal seen in the sulci of patients with intracranial vascular stenosis, found to correlate with angiographically evident pial collaterals.[11] The appearance is also similar to the leptomeningeal "ivy sign" in patients with Moyamoya disease, found to correlate with cerebral perfusion, dilated pial vessels, and decreased cerebrovascular reserve.[12-14] We hypothesized that cerebral perfusion, known to be altered by anesthesia,[15] may contribute to diffuse FLAIR SSI. The purpose of this study was to investigate whether cerebral perfusion and enhancing pial vessels contribute to diffuse SSI in a relatively homogeneous pediatric neuro-oncology cohort and, if contributory, to explore the relative contributions of supplemental oxygen, cerebral perfusion, and anesthesia to SSI on T2-weighted FLAIR imaging.

MATERIALS AND METHODS

Subjects

A retrospective search of our institutional data base, conducted with institutional review board approval and waiver of consent, yielded 198 children with brain tumors without leptomeningeal metastasis who had pre- and postcontrast FLAIR MR imaging with supratentorial dynamic susceptibility contrast perfusion imaging at our institution between April 2008 and March 2011. MR imaging and anesthesia chart review were conducted in tandem until 50 complete MR imaging examinations without evidence of intracranial tumor or supratentorial resection, ischemia, metallic artifacts, or vascular or other supratentorial brain abnormality, performed with propofol-only anesthesia or no anesthesia, were identified. Patients receiving other anesthetic agents or opioids were ineligible due to potential confounding effects on cerebral perfusion.[15] Two subjects who had intravenous contrast within 48 hours before the graded scan[16] and 6 subjects with remote documented or suspected leptomeningeal disease not captured in our data base search were subsequently excluded. This process yielded 42 total subjects ranging in age from 1.2 to 18 years (mean, 9.66 ± 4.92 years; 48% male). Of these, 25 subjects (1.2–18 years; mean, 10.3 ± 4.60 years; 36% male) had technically adequate supraventricular PWI. To increase statistical power to detect associations between age, FiO_2, and SSI, we included the 17 subjects without perfusion imaging (1.3–16 years; mean, 8.75 ± 5.36 years; 65% male) for those analyses.

Anesthesia

Twenty-four subjects received propofol anesthesia (6.20 ± 3.28 years; range, 1.2–13 years). One hundred percent oxygen was administered by simple face mask, the flow rate in liters per minute (LPM) was recorded, and the FiO_2 was calculated by:

$$FiO_2 = LPM \times 4 + 20.$$

Eighteen subjects received no anesthesia (14.28 ± 2.08 years; range, 12–18 years) and breathed room air (FiO_2 = 21%).

MR Imaging

Dynamic susceptibility contrast PWI was performed at 1.5T (Magnetom Avanto; Siemens, Erlangen, Germany) during injection of 0.1-mmol/kg gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) at 0.8–1 mL/s (standardized to be tolerated by all vascular access devices), with TR, 1910 ms; TE, 50 ms; flip angle, 90°; 15 sections; 4- to 5-mm section thickness (0 gap); 128 × 128 matrix; 1.6 × 1.6 mm in-plane voxel size; and bandwidth of 1346 Hz/pixel (86.144 kHz). T2-weighted fast FLAIR imaging was performed before and ~21 minutes after (mean, 20.90 ± 2.25 minutes) contrast injection, with TR = 7000–9140 ms; $TE_{effective}$ = 106–115 ms; TI = 2500 ms; 4- to 5-mm section thickness (0 gap).

Image Analysis

Supraventricular SSI was rated from 0 to 3 (Fig 1) on pre- and postcontrast T2- weighted FLAIR images by 2 independent board-certified neuroradiologists with Certificates of Added Qualification (N.D.S. and J.H.H., with 9 and 5 years' experience) blinded to anesthesia and contrast status. Differences were resolved in consensus. Signal intensity was not graded in the basilar cisterns or ventricles due to potentially confounding CSF flow-related artifacts, lack of evidence for significant oxygen effects on ventricular CSF FLAIR signal, and our primary interest in evaluating sulci for factors affecting leptomeningeal metastasis detection.[7-9,17]

Twenty-five subjects (12 awake, 13 propofol-sedated) had technically adequate supraventricular PWI. Time-dependent contrast concentration, $C(t)$, was calculated from T2* signal intensity as described by Østergaard.[18] Following automated arterial input function determination via iterative Kohonen self-organizing map-based pattern recognition,[19] the global arterial input function was used for nonparametric deconvolution by standard-form Tikhonov regularization by using minimized generalized cross-validation for pixel-by-pixel truncation threshold selection.[20]

CBF, CBV, and MTT were calculated relative to the arterial input function as

$$CBF = \frac{k_H}{\rho} \times \frac{C(t)}{\int_0^t C_a(\tau)R(t-\tau)d\tau}$$

$$CBV = \frac{k_H}{\rho} \times \frac{\int C_t(t)dt}{\int C_a(t)dt}$$

$$MTT = \frac{CBV}{CBF}$$

where $C_a(t)$ is the arterial input function, $R(t\text{-}\tau)$ is the tissue residual function, $C_a(\tau)R(t\text{-}\tau)$ represents the fraction of contrast in

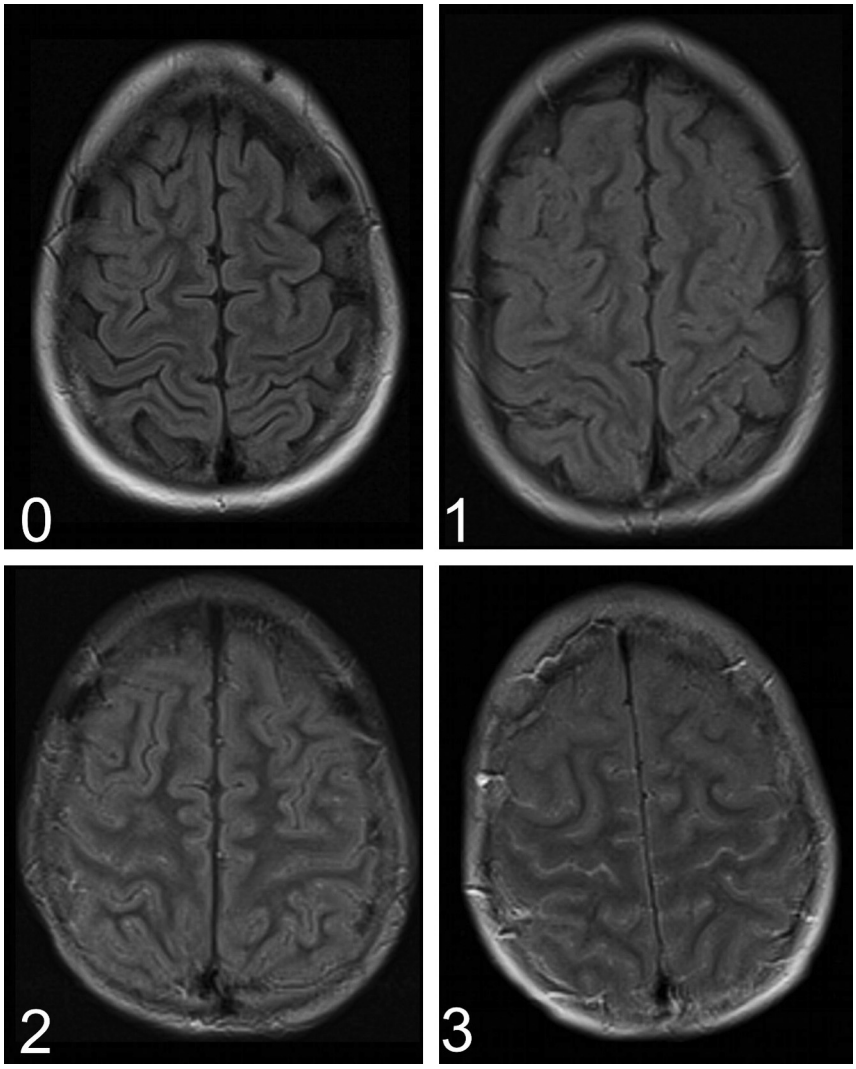

FIG 1. Visual scale for grading SSI in supraventricular sulci: 0 = complete nulling, 1 = stippled hyperintensity, 2 = stippled with areas of confluent hyperintensity, 3 = confluent hyperintensity in sulci. The same grading scale was applied to precontrast and postcontrast FLAIR images.

the tissue at time t after contrast injection at time τ, $C_t(t)$ is the total concentration, and k_H/ρ corrects for the attenuation of brain tissue and the difference between large- and small-vessel hematocrit.[21] GM, WM, and CSF were segmented by an automated hybrid neural network method by using axial T1WI, T2WI, proton density, and FLAIR images.[22,23] CBV, CBF, and MTT were evaluated for cortical GM volumes.

Statistical Analysis

Descriptive statistics include mean and SD (unless otherwise noted) for continuous variables and frequencies and proportions for categoric variables. Wilcoxon rank sum tests were used to examine differences for continuous and ordinal variables between propofol-sedated and awake groups. Univariate analysis based on Spearman rank correlation coefficients was performed to assess the relationships among age, FiO_2, CBF, CBV, MTT, and pre-/postcontrast SSI. Multivariate analysis was performed by backward stepwise ordinal logistic regression modeling to identify the most significant variables influencing SSI from the above potential covariates. The Mantel-Haenszel χ^2 test was used to examine the difference in the proportion of subjects with changes from pre- to postcontrast SSI between propofol-sedated and awake groups. Statistical analyses were performed by using SAS 9.2 software (SAS Institute, Cary, North Carolina). Values of $P < .05$ were statistically significant.

RESULTS

FiO_2 and Age

There was a moderate positive correlation of SSI and FiO_2 before and after contrast in the overall cohort, and SSI appeared to decrease with age (Table 1). However, subgroup analysis demonstrated these correlations to be driven by differences between propofol-sedated and nonsedated children.

Patients under propofol anesthesia were younger, had higher FiO_2, and had significantly greater SSI before and after contrast than awake subjects (Table 2). Contrary to the overall trend, SSI increased with age before and after contrast in anesthetized subjects, and SSI decreased with increasing FiO_2 before, but not after, contrast (Table 1). In awake subjects, FiO_2 was constant at 21%, and there was no correlation of SSI with age.

Age was not a significant influence once the other factors, including CBV, were accounted for in multivariate analysis by stepwise ordinal logistic regression (Table 1).

CBV, CBF, and MTT

Like SSI, cortical CBV and MTT were significantly greater in anesthetized than in awake subjects, though CBF did not differ between groups (Tables 2 and 3). There was a strong positive correlation of SSI with CBV in anesthetized subjects before, but not after, contrast (Table 1). On multivariate analysis, only CBV significantly influenced precontrast SSI in propofol-sedated children once the other factors, including age, were accounted for (Table 1 and Fig 2). CBF, CBV, and MTT had no significant correlation with SSI before or after contrast in awake subjects.

Overall, SSI increased with CBV before and after contrast. These relationships and a positive relationship of MTT with precontrast SSI remained significant by multivariate analysis (Table 1).

Contrast

SSI increased with contrast in 45% (19/42) of all subjects. In propofol-sedated subjects, SSI grade ranged from 0 to 3 before contrast and increased in 9/24 (37%) after contrast. In awake subjects, SSI was nonexistent-to-minimal (grades 0–1) before and after contrast, and it increased with contrast in 10/18 (56%) subjects. The increase in SSI did not exceed 1 grade in any subject.

Table 1: Univariate and multivariate analyses for the effects of selected factors on pre-/postcontrast SSI, overall and for propofol subjects

	Overall				Propofol			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	R^b	*P*	OR (95% CI)	*P*	R^b	*P*	OR (95% CI)	*P*
Precontrast SSI								
FiO_2	0.442	.003			−0.418	.042		
Age	−0.372	.015			0.523	.009	1.661 (0.954–2.893)	.073
GM CBF	0.036	.864			0.274	.364		
GM CBV	0.671	.0002	4.127 (1.688–10.089)	.002	0.612	.026	3.964 (1.118–14.054)	.033
GM MTT	0.461	.020	3.769 (1.231–11.537)	.020	0.331	.269		
Postcontrast SSI								
FiO_2	0.453	.003	–	.022	−0.357	.087		
Age	−0.374	.015			0.600	.002	1.658 (0.982–2.8)	.058
GM CBF	0.062	.770			0.180	.557		
GM CBV	0.625	.0008	2.613 (1.225–5.575)	.013	0.376	.205		
GM MTT	0.368	.071			0.199	.516		

[a] Multivariate analysis by stepwise ordinal logistic regression.
[b] Spearman correlation coefficient.

Table 2: SSI, Age, and FiO_2 overall and by anesthesia status[a]

	Overall (*n* = 42)	Propofol (*n* = 24)	Awake (*n* = 18)	P^b
Pre-SSI				
0	21 (50%)	6 (25%)	15 (83%)	.0001
1	12 (29%)	9 (38%)	3 (17%)	
2	8 (19%)	8 (33%)	0 (0%)	
3	1 (2%)	1 (4%)	0 (0%)	
Post-SSI				
0	5 (12%)	0 (0%)	5 (28%)	.0001
1	26 (62%)	13 (54%)	13 (72%)	
2	9 (21%)	9 (38%)	0 (0%)	
3	2 (5%)	2 (8%)	0 (0%)	
Age (yr)	9.66 (4.92)	6.2 (3.3)	14.3 (2.1)	<.0001
FiO_2	0.35 (0.14)	0.5 (0.1)	0.2 (0)	<.0001

[a] Age, FiO_2, given as means (SDs).
[b] *P* value for testing differences between propofol vs awake groups.

Table 3: Perfusion measures overall and by anesthesia status[a]

	Overall (*n* = 25)	Propofol (*n* = 13)	Awake (*n* = 12)	P^b
CBF (mL/min/100 g)	66.86 (15.45)	67.2 (17.7)	66.5 (13.4)	.765
CBV (mL/100 g)	7.45 (1.46)	8.2 (1.5)	6.6 (0.8)	.008
MTT (s^{-1})	6.69 (1.12)	7.2 (1)	6.2 (1)	.013

[a] CBF, CBV, and MTT given as means (SDs).
[b] *P* value for testing differences between propofol vs awake groups.

DISCUSSION

Hyperintense FLAIR signal in the cerebral sulci of anesthetized children has been attributed to T1 shortening effects of supplemental oxygen but resembles the leptomeningeal FLAIR hyperintensity associated with dilated pial vessels in Moyamoya disease and carotid stenosis.[11,12,14,24] In our study, diffuse SSI on noncontrast T2 FLAIR was more strongly correlated with CBV than FiO_2, both in propofol-sedated children and overall, with MTT (CBV/CBF) significantly influential in the overall cohort.

These findings are consistent with studies demonstrating a positive correlation of CBV and a negative correlation of cerebrovascular reserve (an index of cerebral perfusion pressure represented by CBF/CBV, the inverse of MTT[25]) with the severity of the leptomeningeal ivy sign on noncontrast T2-FLAIR in Moyamoya disease.[12-14,24] Asymmetric FLAIR SSI has also been associated with altered cerebral hemodynamics in patients undergoing internal carotid artery balloon occlusion testing.[26] In such cases, autoregulatory mechanisms triggered by decreased CBF lead to compensatory precapillary vasodilation, increased CBV, prolonged MTT, and decreased cerebrovascular reserve.[27] Indeed, in Moyamoya disease, the ivy sign has been associated with ischemic symptoms and dilated pial vessels at surgery[14] and resolves after revascularization.[24]

We found moderate positive correlations of FiO_2 with SSI before and after contrast in the overall cohort, in keeping with prior studies reporting increased CSF signal intensity with high FiO_2,[5,7-10] but these were driven by significantly higher FiO_2 and SSI in propofol subjects, in whom SSI actually decreased with increasing FiO_2. To our knowledge, no prior study has demonstrated a direct correlation of SSI with FiO_2 under anesthesia-specific conditions, which could account for this apparent discordance. Although no subjects received more than the 60% FiO_2 threshold for increased CSF signal described by Frigon et al[9] and most received less than the "all or none" threshold of 50% FiO_2 described by Braga et al,[8] SSI was sometimes significant. Because nonsedated children did not receive supplemental oxygen, this study does not exclude a direct influence of FiO_2 on SSI. However, we found no FiO_2 threshold below which SSI was nonexistent because even some subjects breathing room air had increased SSI.

Typical of clinical practice, propofol-sedated children were younger and had greater SSI than nonsedated children in this study, raising the question of whether younger children are more likely to have increased SSI due to age alone. If this were the case, one would expect SSI to decrease with age, even in propofol-sedated children. We found the opposite (Table 1), consistent with prior reports,[9] though CBV had a stronger influence. Age-related changes in SSI were not detected in older nonsedated children but cannot be excluded in young nonsedated children because young children generally require anesthesia for MR imaging.

On the other hand, the overall trend of increasing SSI with CBV is consistent with, and apparently driven by, CBV-related increases in SSI in the propofol group before contrast. SSI was uniformly low in nonsedated subjects, even in the range of CBV overlapping that of sedated children.

Differences between propofol-sedated and nonsedated children unexplained by age, FiO_2, or perfusion alone, suggest propofol as a common thread. Indeed, age-related increases in CBV in propofol-sedated children have been previously described[28] and could account for the positive associations of SSI with both age and CBV in our propofol-sedated subjects.

Like SSI, CBV was greater in the younger, propofol-sedated subjects, as previously described (Tables 2 and 3).[28] Although CBF is expected to be greater in younger children,[29,30] there was no significant difference in CBF between (younger) sedated and (older) awake subjects, likely because propofol reduces CBF.[15,31] As a result, MTT (CBV/CBF) was also greater in younger sedated subjects, though MTT is expected to be greater in older children.[32] We speculate that

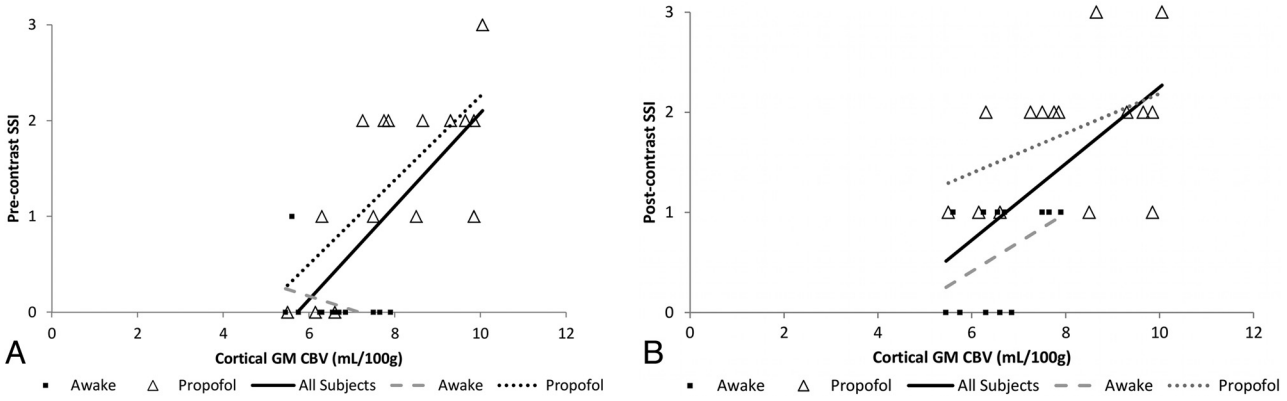

FIG 2. Relationship of CBV with pre-contrast (*A*) and post-contrast (*B*) FLAIR SSI. Significant correlations ($P < .05$) are in black.

propofol-induced decreases in CBF could lead to compensatory dilation of precapillary pial vessels, increasing CBV and prolonging MTT and resulting in diffusely increased SSI, as occurs asymmetrically in patients with Moyamoya disease and temporary ICA balloon occlusion.[24,26] Diffuse SSI may thereby serve as a visual "marker" for general cerebral hemodynamic status in propofol-sedated children without cerebrovascular disease.

SSI increased with intravascular contrast, supporting a vascular contribution to SSI. Greater "stasis" of blood as evidenced by prolonged MTT in sedated children may promote increased diffusion of oxygen to CSF.[33] Additionally, propofol has been found to facilitate disruption of the BBB.[34] Propofol-related increases in vascular permeability to proteins or oxygen,[34] with resultant T1 shortening of CSF,[35] may account for the finding of Filippi et al[5] that children sedated with propofol, but not chloral hydrate, exhibited SSI. Differences in perfusion effects may also contribute; unlike propofol, chloral hydrate increases CBF, potentially precluding a compensatory CBV response.[31,36] Vascular enhancement and leakage of gadolinium across vessel walls rendered more permeable by propofol could obscure more subtle changes related to perfusion or FiO_2, accounting for the loss of a significant relationship of SSI with CBV after contrast in propofol-sedated children. Age-related changes in vessel wall permeability to gadolinium may also influence postcontrast FLAIR SSI.[28,37] Thus, as with CBV,[28] there may be an interactive effect of propofol and age on vascular permeability and SSI.

This study has limitations. The small sample size may have contributed to the lack of a significant association of age with SSI on logistic ordinal regression, for which we could not include subjects without perfusion imaging. However, univariate correlations of age with SSI (by using all subjects) were lower than those for CBV for all but propofol postcontrast, consistent with the multivariate results (Table 1). Dynamic susceptibility contrast measures of CBV are less quantitative than PET, and our low contrast injection rate may have increased variability via a decreased contrast-to-noise ratio,[20] potentially decreasing the strength of linear relationships of CBF, CBV, and MTT with SSI. Future study with PET-MR imaging may better evaluate these relationships. We calculated FiO_2 from the administration rate of oxygen via face mask, an imprecise relationship. Our findings suggest that decreasing the oxygen-administration rate in nonintubated children under propofol anesthesia will not reliably ameliorate artifactual SSI, perhaps due to this imprecision. Similar to authors of other studies, we did not perform concurrent CSF analysis and did not address the potential contribution of CSF protein levels to SSI, which could contribute to variability not captured by our models. We did exclude patients with known, suspected, or remote CSF abnormalities to minimize potential disruption of relationships of SSI with perfusion and FiO_2. Because the threshold for CSF protein detection at our $TE_{effective}$ of 106–110 ms is ~250 mg/dL,[35] far greater than the upper range of normal (60 mg/dL at our institution) and indicative of significant leptomeningeal CNS disease, the contribution of CSF protein to SSI would not be expected to be significant in this study.

CONCLUSIONS

Elevated cortical CBV appears to contribute to increased SSI on noncontrast T2 FLAIR brain images in propofol-sedated children. SSI increased with intravascular contrast regardless of anesthesia, supporting a vascular contribution to SSI. Further investigations into the potential of increased FLAIR SSI as a marker for elevated CBV in propofol-sedated children should consider the potentially interactive effects of age and propofol on cerebral perfusion and vascular permeability.

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