Extent of collateralization predicting symptomatic cerebral vasospasm among pediatric patients: correlations among angiography, transcranial Doppler ultrasonography, and clinical findings

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OBJECT Although the development and prevalence of cerebral vasospasm (CV) has been extensively investigated in adults, little data exist on the development of CV in children. The authors hypothesized that even though children have highly vasoreactive arteries, because of a robust cerebral collateral blood flow, they rarely develop symptomatic CV.

METHODS The authors retrospectively reviewed their university hospital's neurointerventional database for children (that is, patients ≤ 18 years) who were examined or treated for aneurysmal or traumatic subarachnoid hemorrhage (SAH) during the period 1990–2013. Images from digital subtraction angiography (DSA) were analyzed for the extent of CV and collateralization of the cerebral circulation. Results from transcranial Doppler (TCD) ultrasonography were correlated with those from DSA. Cerebral vasospasm on TCD ultrasonography was defined according to criteria developed for adults. Clinical outcomes of CV were assessed with the pediatric modified Rankin Scale (mRS).

RESULTS Among 37 children (21 boys and 16 girls ranging in age from 8 months to 18 years) showing symptoms of an aneurysmal SAH (comprising 32 aneurysms and 5 traumatic pseudoaneurysms), 17 (46%) had CV confirmed by DSA; CV was mild in 21% of these children, moderate in 50%, and severe in 29%. Only 3 children exhibited symptomatic CV, all of whom had poor collateralization of cerebral vessels. Among the 14 asymptomatic children, 10 (71%) showed some degree of vessel collateralization. Among 16 children for whom TCD data were available that could be correlated with the DSA findings, 13 (81%) had CV according to TCD criteria. The sensitivity and specificity of TCD ultrasonography for diagnosing CV were 95% and 59%, respectively. The time to CV onset detected by TCD ultrasonography was 5 ± 3 days (range 2–10 days). Twenty-five (68%) of the children had good long-term outcomes (that is, had mRS scores of 0–2).

CONCLUSIONS Children have a relatively high incidence of angiographically detectable, moderate-to-severe CV. Children rarely develop symptomatic CV and have good long-term outcomes, perhaps due to robust cerebral collateral blood flow. Criteria developed for detecting CV with TCD ultrasonography in adults overestimate the prevalence of CV in children. Larger studies are needed to define TCD ultrasonography–based CV criteria for children.

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KEY WORDS cerebral vasospasm; subarachnoid hemorrhage; pediatrics; vascular disorders

ABBREVIATIONS ACA = anterior cerebral artery; CV = cerebral vasospasm; DSA = digital subtraction angiography; EC-ICA = extracranial-internal carotid artery; GCS = Glasgow Coma Scale; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale, PCA = posterior cerebral artery; PTA = percutaneous angioplasty; SAH = subarachnoid hemorrhage; TCD = transcranial Doppler.

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CEREBRAL vasospasm (CV) continues to be a leading cause of increased morbidity and mortality rates in the setting of subarachnoid hemorrhage (SAH), especially in the young adult population.²⁰ Our center recently reported that among 546 adult patients admitted with an SAH almost one-half developed symptomatic CV.¹⁹ Although CV has been studied extensively in adults, there is a paucity of literature evaluating the pathophysiology and epidemiology of this condition in children.

The effect of age on CV remains controversial. Some studies have suggested that younger adults have a higher risk for developing CV.^{28,29,49} There is no clear consensus, in part because CV can be diagnosed with different modalities and approaches, including digital subtraction angiography (DSA), CT angiography, transcranial Doppler (TCD) ultrasonography, and evaluation of clinical symptoms. The few published studies on CV in children have concluded that this group has a relatively high rate of CV diagnosed by angiography.^{11,16,33,37,39,40} For example, Ostergaard and Voldby³⁷ reported a 53% rate of CV diagnosed on angiographic images in a pediatric cohort. Our own clinical observations and the results of the aforementioned studies suggest that, despite showing a high rate of CV on angiographic images, children tend not to develop symptoms referable to CV.

In this study, we present our experience with CV in a pediatric cohort in the setting of both aneurysmal and traumatic SAHs. We hypothesized that even though children have a high rate of angiographic CV, they rarely develop clinically evident symptoms of CV, partly because individuals in this age group have a robust cerebral collateral blood flow.

Methods

Patients

With a protocol approved by our internal review board, we performed a retrospective review of our tertiary care hospital's neurointerventional radiology database and medical records (University of California San Francisco Medical Center and Benioff Children's Hospital). Among 90 children (age ≤ 18 years) presenting with symptoms of intracranial aneurysms or pseudoaneurysms during the period 1990–2013, we identified 37 children who showed symptoms of SAH confirmed by a nonenhanced head CT or by lumbar puncture and for whom interpretable angiograms were available. The medical records of these children were reviewed and data were retrieved for the following variables: patient age and sex; date of symptom onset; Hunt and Hess grade;¹⁷ Fisher grade;⁷ location, type, and complications of aneurysms; onset, duration, distribution, and severity of CV; and pediatric modified Rankin Scale (mRS) scores³⁸ at the last follow-up.

Initial Patient Management

All patients were admitted to the pediatric neurointensive care unit where they received standard SAH management, modified for a pediatric population, including administration of oral nimodipine. Conventional 4-vessel DSA was performed to confirm the presence of an aneurysm and to serve as a baseline. Ruptured aneurysms were

secured by surgical clipping or endovascular coil embolization.¹³ Frequent neurological examinations were performed, and, when available, serial TCD ultrasonograms were obtained. Patients were prophylactically placed on hypervolemic therapy when they were thought to be at risk for CV. If patients developed new neurological deficits not explained by other causes (such as recurring hemorrhage, hydrocephalus, seizures, infection, or metabolic disturbances) and the aneurysm was secured, they were treated with pressor drugs with a goal of high normotension to mild hypertension adjusted for age; drug doses were titrated to levels resulting in an effect on the neurological deficits. Patients with rising TCD velocities suggesting worsening vasospasm were similarly placed on pressor drugs even if they had not yet developed focal neurological deficits. Those who showed persistent, worsening, or recurrent neurological deficits or increasing TCD velocities and Lindegaard ratios after 12–24 hours of treatment were considered medically refractory and were taken to the neuroangiography suite for further examination.

Endovascular Treatment

Initial DSA was performed to confirm the presence of an angiographic CV and to identify the vessel affected. The supraclinoid internal carotid artery (ICA), M₁ segment of the middle cerebral artery (MCA), A₁ segment of the anterior cerebral artery (ACA), intracranial vertebral artery, basilar artery, and P₁ segment of the posterior cerebral artery (PCA) were considered proximal vessels. Those beyond the above classification (for example, M₂, A₂, and P₂ segments) were considered distal vessels in the sense that catheterization and percutaneous angioplasty (PTA) of these smaller vessels would likely result in an unacceptable risk for vessel rupture, given their small size at baseline. For all arterial segments of the circle of Willis, the DSA images were compared with those of the pre-vasospasm baseline DSA images (if available) to avoid PTA of hypoplastic arterial segments.

The severity of CV was determined by experienced interventional neuroradiology attending physicians (C.F.D., V.V.H., R.T.H., and S.W.H.) who visually assessed the luminal narrowing relative to the widths of adjacent vessels in comparison with the baseline DSA. Mild CV was defined as $< 30\%$ luminal narrowing, moderate CV as between 30% and 50% luminal narrowing, and severe CV as $> 50\%$ luminal narrowing. Patients were treated with PTA, intraarterial verapamil infusion, or both at the discretion of the interventional neuroradiology attending physician according to our institutional standard of practice.¹⁹ Generally, severe proximal CV was treated with PTA, and distal CV was treated with verapamil.

Percutaneous angioplasty was performed as previously described.¹⁴ For systemic anticoagulation, patients undergoing a PTA received intravenous heparin injections delivering a weight-based bolus dose (typically 70 units/kg) with a goal of doubling the baseline-activated clotting time. A guiding catheter was placed on a heparinized saline drip in either the cervical ICA or the cervical vertebral artery. Next, a low-compliance tip-occlusion balloon microcatheter (Sentry-10, Boston Scientific or HyperGlide, Covidien) was navigated over a compatible

0.0254-cm microwire to the most distal aspect of the spastic vessel segment to be treated (that is, the smallest spastic arterial branch farthest from the femoral access site). Brief (< 30 sec) and repeated balloon inflation-deflation cycles (≤ 5) with iodinated contrast material were performed to achieve at least 70% of the expected baseline vascular luminal diameter. The PTA catheter was then withdrawn proximally by 50% of the balloon length (for example, a 5-mm pull back for a 10-mm-long balloon), and this process was repeated as necessary to cover all of the spastic arterial segments. The effect of heparinization was typically not reversed at the conclusion of the procedure.

Intraarterial verapamil infusions were performed by positioning the diagnostic catheter (4F Berenstein III or 5F UCSF2, Codman Neurovascular) in the proximal cervical ICA, the distal common carotid artery (if vascular tortuosity precluded safe ICA catheterization), or in the cervical vertebral artery proximal to the spastic vessel segment (for example, the ipsilateral ICA for treatment of distal vasospasm in the MCA or ACA). Verapamil was diluted in normal saline to a final concentration of 0.5 mg/ml and infused intraarterially at a rate of 0.5 mg/min. For the few cases of isolated or particularly severe ACA or MCA vasospasm, a microcatheter (Prowler-14 LP ES, Codman Neurovascular or Excelsior SL-10, Stryker Neurovascular) over a compatible 0.0356-cm guidewire (Transend EX Platinum, Stryker Neurovascular) was navigated to the A₁, A₂, or M₁ segment. Patients undergoing this microcatheterization were treated with systemic heparinization in a manner similar to that in the patients undergoing PTA, as described above. The dose of verapamil infused into each patient was determined by the catheter position and CV severity. Higher doses of verapamil were used in the less selective catheterizations (for example, common carotid artery catheter position versus ICA catheter position) and in more severe CV. The systemic blood pressure was maintained by titrating intravenous phenylephrine infusion during and after the intraarterial verapamil infusions.

Before 2002, we used intraarterial papaverine to treat CV. In these cases, the microcatheter tip was placed in the supraclinoid ICA above the ophthalmic artery. The dose of intraarterial papaverine infused into each patient was determined by the catheter position and by CV severity.

In all patients, DSA was performed to assess treatment responses and complications immediately after PTA and either immediately or ≤ 30 minutes after the verapamil infusion. Although the vasodilatory effects of PTA are seen immediately, in our experience, corroborated by animal studies,⁴⁶ the full vasodilatory effects of verapamil are not realized for 0.5–1 hour after infusion. We generally

minimized the time of the procedure, and thereby its risk, rather than waiting 30 minutes after the verapamil infusion to confirm the full vasodilatory effect of verapamil by angiography. In very severe cases of CV, however, control angiograms were obtained after a 30-minute delay. Any complications were recorded.

Collateralization Scoring

To assess the extent of collateralization of the cerebral vasculature in our CV patients, we adapted a scoring system that has been established for ischemic stroke (Table 1).⁵

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography was performed at the bedside by experienced sonographers using a 2-MHz pulsed probe and a commercially available TCD ultrasonography unit (Neuroguard Ultrasonographic System, Medasonics). Vessels were insonated using the method previously described by Aaslid and colleagues^{1,2} and included the ICA bifurcations, ACA, MCA, PCA, and vertebral and basilar arteries, as well as the external carotid arteries. Mean flow velocities were recorded in 2-mm increments along the length of each vessel. The maximum mean flow velocity was also recorded. If CV was identified, children underwent daily TCD from the day of onset until the CV had resolved.

Cerebral vasospasm was diagnosed according to criteria used in adults. Specifically, Aaslid and colleagues found that adult patients with vasospasm visible on DSA images had blood flow velocities in the MCA greater than 120 cm/sec and blood flow velocities in the basilar artery of greater than 90 cm/sec on TCD.^{1,2} Subsequently, Lindegaard et al. developed a ratio of flow velocity in the MCA to the flow velocity in the extracranial internal carotid artery (EC-ICA) to help differentiate hyperemia from CV.²⁵ Under the assumption that increased flow velocity in the EC-ICA is due to increased blood flow rather than CV, an MCA/EC-ICA ratio < 3 represents hyperemia. An MCA/EC-ICA ratio > 3 is diagnostic of CV. In our study, the criteria for the presence of CV included flow velocity in the MCA > 120 cm/sec, a Lindegaard ratio > 3, and a flow velocity in the basilar artery > 90 cm/sec. Cerebral vasospasm in the other vascular territories was defined as a flow velocity > 120 cm/sec. We chose this cutoff point because it is commonly used in the literature when examining the association with angiographic vasospasm.⁸

Patient Outcome

The outcomes in patients were retrospectively deter-

TABLE 1. A DSA-based scale for scoring cerebral vascular collateralization in pediatric patients*

Score	Description
1	Collaterals reconstitute distal portion of the narrowed arterial segment
2	Collaterals reconstitute proximal portion of segment adjacent to narrowed segment
3	Collaterals reconstitute distal portion of segment adjacent to narrowed segment
4	Collaterals reconstitute 2 segments distal to narrowed segment
5	Little/no significant reconstitution of the territory served by the narrowed vessel segment

* Based on the classification described in Christoforidis et al.

mined by reviewing the last follow-up examination completed by a stroke neurologist, neurosurgeon, or interventional neuroradiologist and by assigning a pediatric mRS score.^{12,13,42} A functional outcome was considered good when the patient could perform the activities of daily living independently (assessed as an mRS score ≤ 2), while the outcome was considered poor when the patient required assistance (mRS Score 3–5) or had died (mRS Score 6). Any causes of death were recorded.

Statistical Analysis

Means, medians, and standard deviations of ordinal variables were calculated using Excel for Mac 2008. Sensitivity and specificity were calculated using Medcalc version 13.0.2. (Microsoft Partner).

Results

Demographics

The 37 children (21 boys and 16 girls) identified by the survey in the present study ranged in age from 8 months to 18 years (mean 11.8 ± 5 years, median 13 years) and showed signs and symptoms of an SAH (32 aneurysmal SAHs and 5 traumatic pseudoaneurysms). The most common symptom was a sudden onset of severe headache, reported by 26 patients (70.2%) (Table 2). The most common sign was meningismus, which was present in 7 children (18.9%). Among those with an aneurysmal SAH, 28 children (87.5%) had a good preoperative clinical grade (that is, a Hunt and Hess grade of I–III), and 4 (12.5%) had a poor preoperative clinical grade (Hunt and Hess Grade V). All but 1 child with a traumatic SAH were in moderate to severe condition at presentation (2 patients with Glasgow Coma Scale [GCS] scores of 3–8, 2 with GCS scores of 9–13, and 1 with GCS scores of 14–15).

Fifteen (41%) of the children in this cohort had comorbidities that could have predisposed them to vascular diseases such as aneurysms. There were 51 aneurysms in 32 children, with 6 of these children having multiple aneurysms. Aneurysms of the ICA bifurcation were the most common (19.6%) followed by M₁ segment aneurysms (15.7%) (Table 3). Time to treatment (with surgical clipping, coil embolization, or both) was 2.3 ± 1 days.

Angiographic Results

Twenty-eight angiograms taken in 17 (46%) of the children (8 boys and 9 girls) showed CV. Of these 28 instances of CV, 6 (21%) were mild, 14 (50%) were moderate, and 8 (29%) were severe. A combined total of 79 vessels were affected by CV; 30 vessels (38%) had mild CV, 30 (38%) moderate CV, and 19 (24%) severe CV. Most cases of CV involved proximal vessels, with the supraclinoid ICA being most commonly affected (32%). Two-thirds of CV events were observed in the anterior circulation and one-third in the posterior circulation (Table 4). All 5 cases of traumatic SAH showed CV on angiograms.

Symptomatic CV was identified in only 3 (17.6%) of the 17 children, 2 of whom had a traumatic SAH. All 3 symptomatic cases showed poor collateralization of their vessels (that is, a collateral score of 5). Of the 14 asymptomatic children, 10 (71%) had CV involving some degree

TABLE 2. Clinical characteristics of the patients in this study

Score/Symptom	No. of Patients (%)
H & H grade for aSAH patients	
I	12 (37.5)
II	10 (31.2)
III	6 (18.8)
IV	0 (0)
V	4 (12.5)
GCS score for tSAH patients	
3–8	2 (40)
9–13	2 (40)
14–15	1 (20)
Fisher grade	
1	6 (16.2)
2	2 (5.5)
3	15 (40.5)
4	14 (37.8)
Presenting signs/symptoms*	
Headache	26 (70.2)
Loss of consciousness	8 (21.6)
Seizures	3 (8.1)
Photophobia	2 (5.4)
Meningismus	7 (18.9)
Cranial nerve deficits	3 (8.1)
Limb weakness	4 (10.8)
Visual field defects	3 (8.1)
Fever	4 (10.8)
Developed hydrocephalus	17 (46.0)
Comorbidities	
Down syndrome	3 (8.1)
Growth hormone deficiency	2 (5.4)
Dwarfism	2 (5.4)
Marfan syndrome	1 (2.7)
Fibromuscular dysplasia	1 (2.7)
Moyamoya disease	1 (2.7)
HIV infection	1 (2.7)
Polycystic kidney disease	1 (2.7)
Sickle cell disease	1 (2.7)
Goldenhar syndrome	1 (2.7)
Nonsyndromic developmental delay	1 (2.7)

aSAH = aneurysmal SAH; H & H = Hunt and Hess; tSAH = traumatic SAH.

* The total percentage exceeds 100% in this category because some patients reported or showed more than 1 symptom.

of collateralization (indicated by collateralization scores of 1–4) (Table 5) (Figs. 1–3).

Of the 17 children with CV, 9 (53%) underwent endovascular therapies; 5 were treated with intraarterial verapamil, 1 with PTA, 2 with both intraarterial verapamil and PTA, and 1 with both intraarterial papaverine and balloon angioplasty.

Of the 37 children with SAH, 14 (38%) showed evidence of brain infarctions on head CT scans or MRI scans obtained during their inpatient stay. Three of these cases

TABLE 3. Number and location of aneurysms

Aneurysm Site	No. of Aneurysms (%)
ICA	
Supraclinoid segment	3 (5.9)
Anterior choroidal	2 (3.9)
Ophthalmic	1 (2.0)
Bifurcation	10 (19.6)
MCA	
M ₁	8 (15.7)
M ₂	1 (2.0)
M ₁ /M ₂	3 (5.9)
ACA	
A ₁	1 (2.0)
A ₂	1 (2.0)
A ₁ /A ₂	3 (5.9)
Pericallosal	1 (2.0)
Basilar	4 (7.8)
PCA	
P ₁	3 (5.9)
P ₂	1 (2.0)
P ₁ /P ₂	2 (3.9)
PCoA	4 (7.8)
SCA	3 (5.9)

PCoA = posterior communicating artery; SCA = superior cerebellar artery.

were potentially related to procedural complications (2 clipping-related infarctions and 1 coil embolization-related infarction), and the remaining 11 were related to CV. Eight of these 11 cases showed small infarctions with no clinical consequence. The remaining 3 patients with infarctions were those who showed symptoms of CV and whose intracranial vasculature had a collateralization score of 5. Nine patients had complications due to infection (3 mycotic aneurysms, 2 ventriculitis, 3 respiratory infections, and 1 sepsis).

Correlation of DSA Data With TCD Data

For 16 children—only 1 of whom had symptomatic

TABLE 4. Location and severity of CV*

Vessel/Segment	Degree of Vasospasm			Total
	Mild	Moderate	Severe	
ICA	11	6	8	25
VA	1	1	2	4
A ₁	5	3	2	10
A ₂	2	1	0	3
M ₁	6	7	6	19
M ₂	0	1	1	2
BA	2	7	0	9
P ₁	3	4	0	7
Total	30	30	19	79

BA = basilar artery; VA = vertebral artery.

* The values in this table indicate the number of vessel segments with CV.

TABLE 5. Association between the extent of collateralization and CV

Collateral Score	No. of Patients (%)		
	Total	Symptomatic for CV	Asymptomatic for CV
1	5 (29.4)	0 (0)	5 (35.7)
2	1 (5.9)	0 (0)	1 (7.1)
3	2 (11.8)	0 (0)	2 (14.3)
4	2 (11.8)	0 (0)	2 (14.3)
5	7 (41.2)	3 (100)	4 (28.6)

CV—TCD data were available that could be correlated with data from DSA performed on the same day. Thirteen (81%) of these children showed symptoms of CV according to the criteria used for analysis of TCD data from adults. Among these 13 children, a total of 33 vessels showed CV according to these TCD criteria. However, for 12 children, the results of the TCD and DSA examinations disagreed. Specifically, in 18 (55%) of the vessels, CV was diagnosed by TCD ultrasonography, but no evidence of CV was observed with DSA (Table 6). The average maximum mean flow velocity in these patients was 142.6 cm/sec (range 124–166 cm/sec). The overall sensitivity and specificity of TCD ultrasonography for CV detection were 95% and 59%, respectively (Table 6).

The time to CV onset after an SAH was 5 ± 3 days (range 2–10 days, median 4 days) as measured by TCD ultrasonography; the time to CV onset as determined by DSA was 7 ± 5 days (range 2–23 days, median 5 days). CV persisted for an average of 7.5 ± 3 days (range 3–17 days, median 7 days).

Outcomes

Twenty-five children (68%) had good outcomes (that is, had mRS scores of 0–2) over an average follow-up period of 19.7 months (median 12.0 months). All 3 children who experienced symptomatic CV also had good long-term outcomes over an average follow-up period of 19.7 months.

Discussion

To our knowledge, this is the first study demonstrating a relationship between cerebral arterial collateralization and tolerance to CV in children. Furthermore, this is the first study to attempt to correlate TCD findings with those from DSA in children with CV. Given the paucity of information in the literature on CV in children, we believe our findings will help elucidate the pathophysiology of this disease process in this age group and aid in developing strategies for managing CV in children and young adults.

Although the incidence of symptomatic CV is low in children, the observations in our study indicate that the prevalence of CV determined by angiography is relatively high (that is, 46%). Our findings are consistent with those from a few other studies.^{11,16,33,37,39,40} Saraf et al.⁴³ recently reported a 57% rate of angiographic CV in 14 children with ruptured brain aneurysms. This relatively high rate of angiographic CV is likely due to the high vasoreactivity of

FIG. 1. Shifting watershed pial collateral vessels. **Left:** ICA angiogram in a 16-year-old patient with a ruptured mycotic MCA bifurcation aneurysm (dotted arrow) with adjacent CV of the MCA and collateral vessels from the distal ACA to the distal MCA (arrows). **Right:** ICA angiogram in the same patient with watershed collaterals from the ACA (arrows).

the vessels in young individuals. In contrast, as explained by Magge et al.,²⁹ the increased stiffness of the cerebral vasculature associated with advanced age may explain the lower prevalence of angiographic CV in the population of older adults. Postmortem studies in humans have indicated that aging leads to an increased accumulation of collagen in the vessel wall, along with intimal thickening and fibrosis.^{10,15} These changes and the accumulation of atherosclerotic plaque decrease vessel distensibility. Vessel reactivity to mediators of vasoconstriction (such as serotonin and prostaglandins) may also decrease with age.^{9,18}

Interestingly, in our study, both the prevalence and severity of angiographic CV were high in children (79% of our cases exhibited moderate-to-severe CV). Our findings are similar to those of other studies. For example, Yoshimoto and Kwak⁴⁹ and Macdonald et al.,²⁸ who used DSA to diagnose CV, observed that a younger age is associated with a greater frequency of severe angiographic CV. Magge et al.²⁹ also reported that the likelihood of severe vasospasm was greater with a younger age; patients with severe angiographic CV were on average 9 years younger than those with no CV. Again, this is likely attributable to the relatively increased vasoreactivity at younger ages. Thus, the risk for vasospasm detected by angiography can be described as varying linearly with age, with younger individuals being more prone to developing CV than older ones.

Despite the high rate of angiographic CV in our study, only 3 children had symptomatic CV. It appears that children tolerate CV better than adults. Ostergaard and Voldby,³⁷ reported a 53% rate of angiographic CV in children without an associated neurological deterioration. Proust et al.,⁴⁰ in a series of pediatric patients, observed that CV was always asymptomatic. Krishna et al.,²¹ reported that the incidence of angiographic CV was 37% in adults and 41% in children. Clinically symptomatic CV, which was treated with “triple-H” therapy (that is, with interventions inducing hypertension, hemodilution, and hypervolemia), was observed in 28.4% of adults and only in 9.5% of children. Thus, appearance of symptomatic CV may follow an inverted U-shaped curve, with a lower prevalence at both

FIG. 2. Collateralization of vessels pre- and postangioplasty. **A:** Preangioplasty ICA midarterial angiogram in an 18-year-old patient who has a clipped ACA aneurysm exhibiting CV of the ACA (dotted arrows) with distal collateralization from the right MCA (arrows) (that is, the MCA is reaching the vertex more quickly than the ACA does on the anteroposterior view). After pharmacological (with intraarterial papaverine) and mechanical angioplasty, early arterial (**B**) and midarterial (**C**) right ICA angiograms show equalization in flow between the right ACA and right MCA (that is, the MCA and ACA are reaching the same vertical height on the anteroposterior angiogram).

very young and older ages and the highest prevalence in early adulthood.

That children are rarely symptomatic for CV may be due at least in part to their robust collateralization of cerebral vessels. All 3 children who showed CV symptoms had poor collateralization scores (that is, a score of 5), while 71% of the children who showed no symptoms had some degree of collateralization. That not all symptom-free children had a robust collateral flow indicates that the development of symptomatic CV is most likely multifactorial. Other biological features, such as the robustness of the nitric oxide synthase pathway in children may play a role in preventing symptomatic CV.⁴⁵ Furthermore, incipient development of

FIG. 3. Poor collateralization of circulation. **A–D:** Angiograms of a 12-year-old girl with a ruptured basilar tip aneurysm exhibiting diffuse, severe CV with poor collateralization (indicated by a collateral score of 5); the patient showed symptoms consistent with CV. **E–H:** Postangioplasty angiograms after intraarterial verapamil infusions indicate marked improvement of CV in this patient.

collateral vessels does not guarantee that these vessels will persist. Hemodynamic fluctuations may influence the endurance of such collateral circulation.²⁴

The good long-term outcomes among the children in our study may be due to several factors. First, children tend to have better clinical grades than adults. In the present study, 87.5% of the children had a good preoperative grade (that is, Hunt and Hess grades of I–III). The reason for the better clinical grades at presentation is unclear but may be attributable to several factors, such as few comorbidities and a greater tendency among physicians to refer cerebrovascular cases to tertiary care centers.³¹ Second, good long-term outcomes may be partially attributable to the low prevalence of symptomatic CV due to the robustness

of the cerebral collateral circulation in children. However, the 3 children who experienced symptomatic CV also had relatively good long-term outcomes. These outcomes may be due in part to the high brain plasticity and relative lack of atherosclerosis seen in children compared with adults. Velocity of cerebral blood flow declines with age, and this decline may be associated with certain changes in cerebrovascular hemodynamics such as 1) a decreased cerebral blood flow or metabolic demands, 2) vessel-size changes, and 3) lower cardiac output.^{22,26,32,34,41}

By TCD criteria, the children showed a high rate of CV (81%), but the prevalence of symptomatic CV was low (1 child). However, in our study, the findings obtained with TCD ultrasonography differed from those obtained with

TABLE 6. Sensitivity and specificity of TCD findings in diagnosing CV in comparison with DSA findings (used as the gold standard)

Vessel	True Positive (DSA+/TCD+)	False Positive (DSA-/TCD+)	True Negative (DSA-/TCD-)	False Negative (DSA+/TCD-)	Sensitivity (%)	Specificity (%)
MCA	6	5	3	1	85	40
ICA	2	5	3	0	100	40
ACA	1	4	4	0	100	50
PCA	1	0	4	0	100	100
BA	4	4	2	1	80	33
VA	1	0	2	0	100	100
Overall	15	18	18	2	95	59

DSA (the gold standard for CV detection) in 12 of the 13 children who had shown CV by TCD criteria. Therefore, the diagnosis of CV based on TCD criteria developed for adults appears to overestimate the true prevalence of CV in children. Of concern is that baseline flow velocities in children are higher than in adults.^{3,4,44,48} O'Brien et al.,³⁵ examining CV in children after traumatic brain injuries, reported an overall 63.7% incidence of CV by adult TCD criteria. The authors also noted that since normal flow velocities are higher in children than in adults, the adult diagnostic criteria used in their study may have overestimated the true incidence of CV in their pediatric head trauma patients. Our study demonstrates that TCD ultrasonography has high sensitivity but low specificity in diagnosing CV. This is in contrast to what has been described in adults. Lysakowski et al.,²⁷ in a meta-analysis of 26 reports, concluded that for the MCA territory in adults, TCD ultrasonography has high specificity, but low sensitivity in the detection of CV after an aneurysmal SAH. Currently, no case-controlled studies have compared TCD flow velocity data with DSA data in pediatric patients suspected of having CV.

In the present study, the time to onset of CV as determined by TCD ultrasonography was 5 ± 3 days, and CV persisted for an average of 7.5 ± 3 days. These results were comparable to those observed for adults with CV after an SAH.⁴⁷

All 5 children with a traumatic SAH had CV diagnosed with angiography. Although our sample size was small, the prevalence of CV observed in the present study was similar to that reported from several studies in adult patients with traumatic brain injury.^{6,23,30,36}

Our study is limited by its retrospective nature. Not every child underwent a TCD examination, and not every DSA finding could be compared with one from a TCD examination. Although we present one of the largest studies to date on CV in children, a prospective study comparing TCD flow velocity to angiographic data would be helpful in developing more robust TCD criteria for diagnosing CV in children. Such prospective studies could improve the understanding of the true prevalence of this pathological condition and how often CV leads to clinically significant ischemia in children.

Conclusions

Based on DSA findings, children show a relatively high prevalence of moderate-to-severe CV. However, children rarely develop symptomatic CV and have good long-term outcomes, perhaps due in part to their robust cerebral collateral blood flow. Diagnosis of CV with TCD ultrasonography and use of diagnostic criteria developed for adults tend to overestimate the prevalence of CV in the pediatric population.

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Conception and design: Hetts, Moftakhar. Acquisition of data: Moftakhar. Analysis and interpretation of data: Hetts, Moftakhar. Drafting the article: Moftakhar. Critically revising the article: Hetts, Cooke, Fullerton, Ko, Dowd, Higashida, Halbach. Reviewed submitted version of manuscript: Hetts, Amans, Narvid. Study supervision: Hetts, Dowd, Higashida, Halbach.

Supplemental Information

Proceedings

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