SUPPLEMENTAL MATERIAL

Title: Focal Cerebral Arteriopathy of Childhood: Novel Severity Score and Natural History

Supplemental Methods:

A. Iterative Process for Simplifying the FCASS Model

Removing Arterial Segments: Our goal was to remove, in a step-wise fashion, any arterial segments that did not add value to the score. We began with nine unilateral arterial segments: cervical, petrous, cavernous, and supraclinoid segments of the ICA; M1 and M2 segments; A1 and A2 segments; and the PCA. The order in which these were removed was determined on the basis of clinical knowledge: arterial segments less commonly involved in FCA (PCA and cervical/petrous/cavernous ICA), segments that have a high-degree of variability in normal size (the A1 that is often congenitally hypoplastic), and segments that are difficult to classify because of their small size (A2, M2). The following order was observed: 1) PCA, 2) cervical/petrous/cavernous ICA, 3) A1, 4) A2, 5) M2. For each step, if the removal of the segment from the score did not make a difference in or improve our metrics (correlation with outcomes or reliability ratings), we left the segment out in order to enhance the simplicity of the scoring procedure.

Collapsing the Numeric Score: In the final refinement step, we tested the effect of collapsing the numeric scoring system (0 to 4, for each arterial segment) into fewer categories. We considered it clinically important (and feasible) for the scoring system to always distinguish a normal arterial segment from a diseased arterial segment. Hence, we never collapsed the score of "0" for "no involvement" with other scores. We tested three collapsed models (**Table II**, below): (1) any abnormality (score 1 through 4) collapsed into a single category; (2) scores 1 and 2 collapsed into a single category, and scores 3 and 4 collapsed into another category; and (3) scores 1 and 2 and 3 collapsed into a single category.

B. Final FCASS Scoring Instructions

The Focal Cerebral Arteriopathy Severity Score (FCASS) has been designed for scoring the severity of focal cerebral arteriopathy (FCA), a presumed inflammatory, monophasic, and unilateral disease of the anterior circulation and a common cause of arterial ischemic stroke in previously healthy children. The FCASS score is generated by individually scoring the appearance of five arterial segments on MRA, CTA, or conventional angiography and then summing the five individual scores (without weighting). The additional "delta point" is applied only to follow-up imaging.

- Individually score each of five arterial segments: supraclinoid internal carotid artery (ICA); M1 and M2 segments of the middle cerebral artery (MCA); A1 and A2 segments of the anterior cerebral artery (ACA)
- Score only unilateral disease
- For any vessel or vessel segment, score the most severe involvement (if only partially involved)
- If a vessel narrowing *could* be hypoplastic, score as 0 (no involvement)

- Score **supraclinoid ICA, M1, A1**:
  - 0=no involvement
  - 1=irregularity or banding with no stenosis
  - 2=stenosis, <50% reduction in diameter
  - 3=stenosis, >50% reduction in diameter
  - 4=occlusion

- Score **M2, A2:**
  - 0=no involvement
  - 1=irregularity or banding with no stenosis
  - (*2 is not an option*)
  - 3=stenosis
  - 4=occlusion

- Delta point: this is intended to capture apparent progression or improvement that has been *not been captured* by the score itself. (For example, isolated M1 stenosis that progressed from ≈60% to ≈95%.) Can apply a "delta bonus point" to indicate this change.

- Score **Delta Point**:
  - +1 if interval worsening (progression) not otherwise captured by the follow-up FCASS
  - -1 if interval improvement not otherwise captured by the follow-up FCASS
  - Only a single delta point is applied, regardless of whether there is change in a single versus multiple arterial segments

- **Final FCASS**: sum the five individual scores (without weighting); the maximum baseline score is 20 (maximum individual segment score of 4 multiplied by 5 arterial segments). For follow-up imaging, apply the delta point if applicable; the maximum follow-up score is 21 (20 plus the delta point).

Supplemental Results:

Table I. Inter- and intra-rater reliability of iterative models of the FCA Severity Score (FCASS). Model A includes: petrous, cavernous, and supraclinoid segments of the ICA; M1 and M2 segments of the middle cerebral artery (MCA); A1 and A2 segments of the anterior cerebral artery (ACA).* Subsequent models exclude arterial segments in an iterative fashion. Final (optimal) model shown in bold.

		Inter-rater reliability (n=112)†			Intra-rater reliability (n=112)†		
Model	Arterial segments excluded[a]	ICC	(95% CI)	p-value	ICC	(95% CI)	p-value
A	None	0.92	(0.89, 0.94)	<0.0001	0.94	(0.91, 0.96)	<0.0001
B	**Proximal ICA (petrous/cavernous)**	**0.86**	**(0.81, 0.90)**	**<0.0001**	**0.95**	**(0.92, 0.96)**	**<0.0001**
C	Proximal ICA, A1	0.88	(0.83, 0.92)	<0.0001	0.94	(0.91, 0.96)	<0.0001
D	Proximal ICA, A1, A2	0.88	(0.83, 0.92)	<0.0001	0.94	(0.91, 0.96)	<0.0001
E	Proximal ICA, A1, A2, M2	0.85	(0.79, 0.90)	<0.0001	0.93	(0.90, 0.95)	<0.0001

*PCA not included in any model because normal in all cases

†Multiple images were collected on the 41 individual patients over time; each image was considered as independent for purposes of assessing rater agreement

ICC=intraclass correlation coefficients

Table II. Performance of iterative models of Model B of the FCA Severity Score (FCASS), attempting to reduce the number of categories for scoring the indivudal arterial segments.

Model[a]	Categories for scoring individual arterial segments[b]	1-year PSOM p-value[c] (n=39)	1-year PSOM p-value[c, d] (n=32)
B (original)	**5 categories: 0, 1, 2, 3, and 4**	**0.037**	**0.037**
B1	2 categories: 0 and [1&2&3&4]	0.40	0.47
B2	3 categories: 0 and [1&2] and [3&4]	0.10	0.10
B3	3 categories: 0 and [1&2&3] and 4	0.16	0.24

[a]For these models, individual severity scores for the arterial segments were collapsed as shown, then summed to create the total score.

[b]The brackets enclose the individual severity scores that were collapsed into a single score. The score "0" (no involvement) is never collapsed into other groups.

[c]Non-parametric trend test for correlation between maximum FCASS and 1-year PSOM (pediatric stroke outcome measure; categorical variable)

[d] Excludes those with no follow-up vascular imaging studies

Table III. Characteristics and outcomes of FCA cases with versus without follow-up vascular imaging.

Characteristic	With Follow-up (n=33) Median	(IQR)	Without Follow-up (n=8) Median	(IQR)	p-value*
Baseline FCASS	4	(2, 6)	4	(2, 11.5)	0.65
Absolute infarct volume, ml	16.7	(5.8, 43.0)	21	(11.7, 40.2)	0.60
Relative infarct volume, %	1.3	(0.5, 2.3)	1.1	(0.9, 4.5)	0.62
PSOM, one year	1	(0, 1.5)	1	(0, 2)	0.79
Outcome	n	(%)	n	(%)	p-value**
Recurrence	8	(24.2)	0	(0.0)	0.32
Death	0	(0.0)	0	(0.0)	-

* Wilcoxon rank sum test
**Fisher's exact test

Appendix: VIPS Enrolling Site Investigators

Dowling MM(University of Texas Southwestern Medical Center, Dallas), Benedict SL (Primary Children's Medical Center, Salt Lake City), Bernard TJ (Denver Children's Hospital), Fox CK (UCSF), DeVeber G (The Hospital for Sick Children, Toronto), Friedman NR (Cleveland Clinic Children's Hospital), Lo WD (The Ohio State University and Nationwide Children's Hospital, Columbus OH), Ichord RN (Children's Hospital of Philadelphia), Tan MA (University of the Philippines-Philippine General Hospital, Manila), Mackay MT (Royal Children's Hospital Melbourne), Kirton A (Alberta Children's Hospital), Hernandez Chavez MI (Pontificia Universidad Catolica de Chile), Humphreys P (Children's Hospital of Eastern Ontario), Jordan LC (Vanderbilt University Medical Center, Nashville), Sultan S (Columbia University Medical Center, New York), Rivkin MJ (Boston Children's Hospital), Rafay MF (Children's Hospital, Winnipeg, University of Manitoba), Titomanlio (L Hôpital Robert Debré-Paris), Kovacevic GS (Mother and Child Health Care Institute, Serbia), Yager JY (Stollery Children's Hospital), Amlie-Lefond C (Seattle Children's Hospital), Dlamini N (Evelina London Children's Hospital), Condie J (Phoenix Children's Hospital), Yeh A (Women and Children's Hospital of Buffalo), Kneen R (Alder Hey Children's Hospital), Bjornson B (British Columbia Children's Hospital), Pergami P (West Virginia University), Zou LP (Chinese PLA General Hospital, Beijing), Elbers J (Stanford Children’s Health, Palo Alto), Abdalla A (Akron Children's Hospital), Chan AK (McMaster University, Hamilton), Farooq O (Women & Children's Hospital of Buffalo), Lim MJ (Evelina London Children's Hospital), Carpenter JL(Children's National Medical Center, Washington, D.C.), Pavlakis S (Maimonides Medical Center, Brooklyn), Wong VC (Queen Mary Hospital, Hong Kong), Forsyth R (Institute of Neuroscience, Newcastle University, UK)