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Original article

Validation of the focal cerebral arteriopathy severity score (FCASS) in a Swiss cohort: Correlation with infarct volume and outcome

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ABSTRACT

Background: Focal cerebral arteriopathy (FCA), a major cause of childhood arterial ischemic stroke (AIS), can progress and lead to increased infarct size and/or recurrent stroke. Evaluating treatment options depends on the ability to quantify reliably the degree of stenosis in FCA.
Aims: We validated the recently introduced FCA severity score (FCASS) in an independent cohort from the Swiss Neuro-Paediatric Stroke Registry (SNPSR).
Materials and methods: We included children with FCA who had MR or CT angiography and a Pediatric Stroke Outcome Measure (PSOM) at 6-months and 2-years post-stroke. A paediatric neuroradiologist applied the FCASS and the modified pediatric Alberta Stroke Program Early Computed Tomography Score (ASPECTS), a measure of infarct volume, to all available imaging. Two senior paediatric stroke neurologists and a neuroradiology fellow independently assigned FCASS scores to test interrater reliability. Pairwise correlations between FCASS, pedASPECTS, and PSOM were examined.
Results: Thirty-two children [median (IQR) age = 5.9 (1.8, 9.6), 19 males] were included. The median maximum FCASS score at any time was 9 (IQR 6, 12; range 3, 16). Larger infarct volume scores correlated with both higher maximum FCASS scores and worse post-stroke outcomes, although we found no direct correlation between FCASS and outcomes. Stroke neurologists tended to assign lower FCASS scores than the neuroradiologist, but interrater reliability was predominantly good.
Conclusions: In this independent validation cohort, higher maximum FCASS correlated with greater infarct volume scores that also correlated with worse neurological outcomes. Scoring by non-imaging specialists seems to be valuable, although differences are present.
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1. Introduction

Arteriopathy is responsible for approximately half of the arterial ischemic strokes (AIS) in childhood [1], with focal cerebral arteriopathy (FCA) found in one third of the cases [2]. FCA is increasingly regarded as an inflammatory arteriopathy; it is a monophasic disease probably triggered by a recent infection in susceptible children [3–5]. Neuroimaging plays a key role in the diagnosis and also follow-up of childhood arteriopathies [6]. FCA involves mainly the anterior circulation (internal carotid artery (ICA) terminus, middle cerebral (MCA) and anterior cerebral (ACA) arteries) and is characterized by irregularity or stenosis of the affected vessel and vessel wall enhancement of the affected segments [7], supporting an inflammatory nature of the disease. FCA is associated with an increased risk of stroke recurrence [5,8,9] and its evolution over time is generally characterized by worsening during the first weeks

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to months, followed by stabilization, improvement or—in a small number of cases—complete resolution [3,10].

Due to its suspected inflammatory background and characteristic progression during the first days to weeks post-stroke [3], FCA is increasingly treated with corticosteroids [1]. Treatment trial protocols under development need a quantitative measurement of FCA severity in order to analyze FCA evolution, treatment effect and correlation with outcome [1,3,11].

Recently, a neuro-imaging based grading score for the evaluation of the FCA severity was developed [3]. The 5-segment score, comprised of an evaluation of the supraclinoid ICA, M1, M2, A1 and A2 segments, can be calculated simply and reliably and correlates well with clinical outcomes. In the derivation cohort, FCASS peaked at 1–4 weeks post-stroke, and maximum FCASS correlated with infarct size and outcome at 1-year, as determined by the Pediatric Stroke Outcome Measure (PSOM) [3]. This study validated the FCASS in an independent (Swiss) cohort, while testing interrater reliability between paediatric neurology professionals with varying levels of neuroradiological experience. Volume was assessed using pedASPECTS and correlated with the FCASS and with 6-month and 2-year PSOM scores.

2. Materials and Methods

2.1. Study design and study population

The Swiss Neuropaediatric Stroke Registry (SNPSR) is a nationwide prospective registry and includes all children living in Switzerland who have been diagnosed with AIS [12]. SNPSR is approved by the cantonal ethics committee and by the Swiss Ministry of Health. We identified those strokes likely due to FCA through searches of the SNPSR database from 2000 until March 2018. For the purposes of our study we used banked neuroimaging (for the FCA cases, available starting 2005) and previously acquired 6-month and 2-year PSOM scores. No Swiss cases were included in the original study [3] and there was no overlap between the cohorts.

Inclusion criteria for the study were: (1) age 1 month to 16 years at time of stroke; (2) available follow-up data by PSOM at 6 months and when possible at 2 years; (3) good quality vascular and structural magnetic resonance imaging (MRI) for measurements of FCASS and pedASPECTS; and (4) diagnosis of focal arteriopathy within the anterior circulation in the acute phase, determined to be transient on follow-up (no long-term progression by clinics and/or imaging data) [12].

2.2. Imaging analysis

Childhood AIS was defined as a new (focal) neurological deficit with evidence of an acute infarct on MRI confined to an arterial territory. FCA was defined as unilateral focal stenosis or irregularity affecting medium to large vessels of the anterior circulation [3,13], assessed on time-of-flight MR angiography (MRA) and/or contrast-enhanced MRA. The recently introduced FCA severity score (FCASS) was used to quantify degree of stenosis. To calculate the FCASS, individual severity scores are first derived for each of five segments–supraclinoid ICA, M1, M2, A1 and A2–as follows: 0 for no involvement, 1 for irregularity, 2 for <50% stenosis, 3 for >50% stenosis, and 4 for occlusion. Because of the smaller diameter of M2 and A2 branches, *any* stenosis of those segments was scored as 3 (with no option to score as 2); these segments were therefore classified into one of 4 categories (scored 0, 1, 3, or 4). The scores for the individual arterial segments are then summed without weighting to provide an initial total FCASS score. If a change occurred over time within a category, (e.g., progression of a stenosis from 60% to 90%, both of which would be coded as "3"), a delta point was applied: a single point that could be added/subtracted to demonstrate worsening (+1) or improvement (−1) [3]. If serial MR imaging in a single case of FCA was available, FCASS was applied to each MRA image (Fig. 1).

The maximum FCASS for each case was defined as the highest total score at any time point. If only a single FCASS score was available, it was considered the maximum. An attending paediatric neuroradiologist (N.S.) applied the FCASS to all available vascular imaging. Attending paediatric stroke neurologists (H.F, M.S.) and a neuroradiology clinical fellow (P.B.) independently applied the FCASS to the same imaging studies in order to test interrater reliability.

PedASPECTS is an ordinal measure of infarct volume in childhood stroke in which every abnormal area is assigned a point. Higher scores represent greater volumes, with a maximum possible score of 30 (15 per hemisphere) [14,15]. Scores were calculated based on diffusion-weighted imaging sequences from the "baseline" MRI study (the first-available post-stroke brain MRI for every patient). Posterior stroke cases were excluded from the analysis since the ASPECT score refers to supratentorial stroke only, and thus does not include all posterior stroke locations. This is consistent with the original study, which also excluded the posterior cerebral artery from the model [3]. All measurements were made by the neuroradiology attending (N.S.).

2.3. Clinical assessment: PSOM

The PSOM is a measure of stroke outcome that summarizes deficit severity after confirmed AIS in five subdomains (right/left sensorimotor, language production/comprehension, cognitive and behavioral). A score of 0–2 is assigned to each subdomain, where 0 = no deficit, 0.5 = mild deficit with normal function, 1 = moderate impairment with decreased function, and ≥2 = severe deficit with missing function [16–18]; these are summed for a maximum total score of 10) [19,20]. Outcome was considered good with a total score <1 or poor with a total score of ≥1. PSOMs at 6-months and 2-years were based on clinical data collected from retrospective chart review of the SNPSR database. Methods for measuring PSOM in the SNPSR have been previously described [12].

2.4. Statistical analysis

Non-parametric Spearman rank-order correlation was used to test for the potential association between the outcome at two-years as defined by the PSOM, and both the baseline FCASS and maximum FCASS. We assessed interrater reliability of the total FCASS score across raters with varying degrees of neuroradiology experience using two-way random effects models to calculate intraclass correlation coefficients (ICC). The evaluation of an attending paediatric neuroradiologist (N.S.) was considered the "gold standard", to which the ratings of two paediatric stroke experts (H.F, M.S.) and a neuroradiology fellow (P.B) were compared. An ICC is considered to indicate moderate agreement if 0.41–0.60, good if 0.61–0.80, and excellent if 0.81–1.00 [21].

3. Results

3.1. Descriptive analyses and change in FCASS over time in the Swiss cohort

Of 229 cases of AIS enrolled in the SNPSR, 32 met the inclusion criteria [median (IQR) age of 5.9 (1.8, 9.6) years; 19 males, 59%]. Timing and availability of initial and follow-up imaging are detailed in Fig. 2.

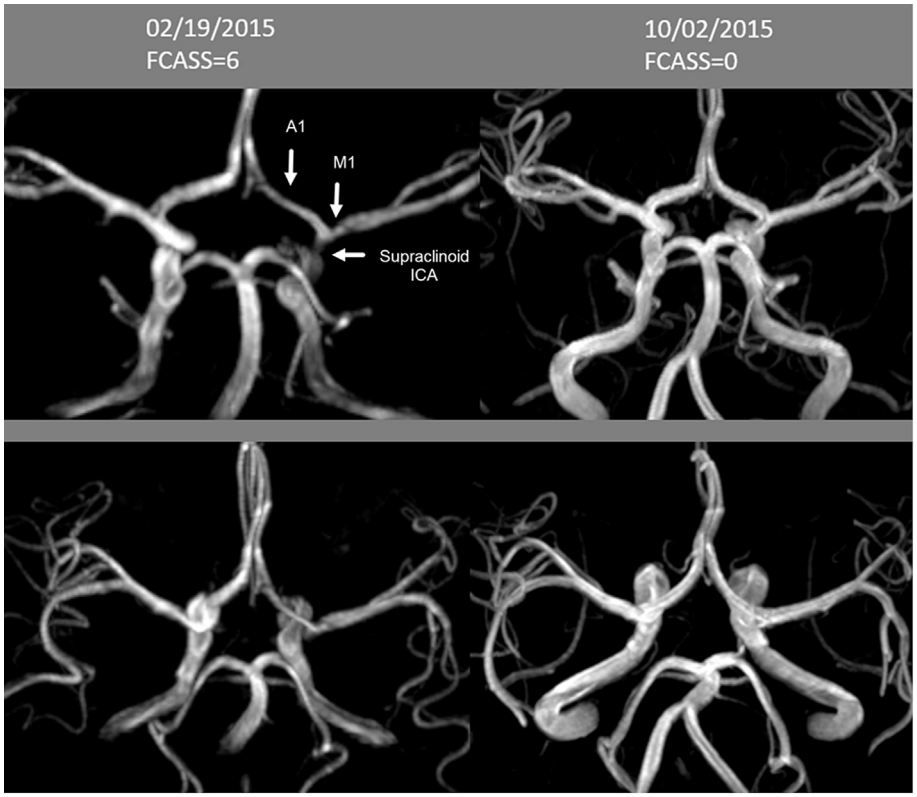

Fig. 1. Example of FCASS applied to repeat MRA imaging in a single case of FCA. At baseline, the child had an FCASS score of 6: the sum of 3 for >50% stenosis of the left supraclinoid internal carotid artery (ICA), plus 2 points for <50% stenosis of the M1 segment of the middle cerebral artery and 1 point for banding of the A1 segment of the anterior cerebral artery (arrows). At follow-up, approximately 7.5 months later, the child's arteriopathy had resolved completely (note also better flow to the A1 and M1 segments due to improvement of the ICA stenosis). Lower row images represent different projection of the same time-of-flight MR angiography maximum intensity projection (MIP) reconstructions from the given examination.

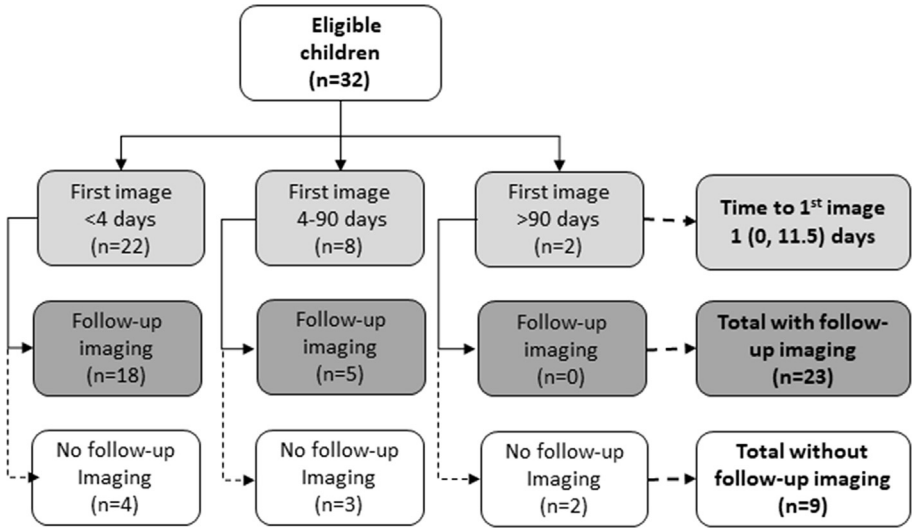

Fig. 2. Representation of imaging available for individual patients, stratified by timing of first imaging (<4 days, 4–90 days, >90 days). Median (IQR) time from stroke to initial imaging is given for all 32 patients.

Twenty-two children had acute imaging (<4 days post-stroke) and follow-up imaging was available for 23 children (72%). The median time from stroke to first vascular imaging was 1 day [IQR (0, 11.5); range 0, 165]. Only two children had a CT as initial imaging modality; a MR examination the following day was considered to be an acute MR imaging. In two children, conventional angiography was also performed.

The median baseline FCASS score (n = 22 with an imaging study <4 days after the stroke) was 7.5 (IQR 5, 9; range 3, 15). Maximum FCASS score at any time (n = 32) was a median of 9 (IQR 6, 12; range 3, 16). Fig. 3 shows the evolution of FCASS over time. The delta point was used by the neuroradiology attending in just one case to illustrate interval improvement within the same stenosis grade.

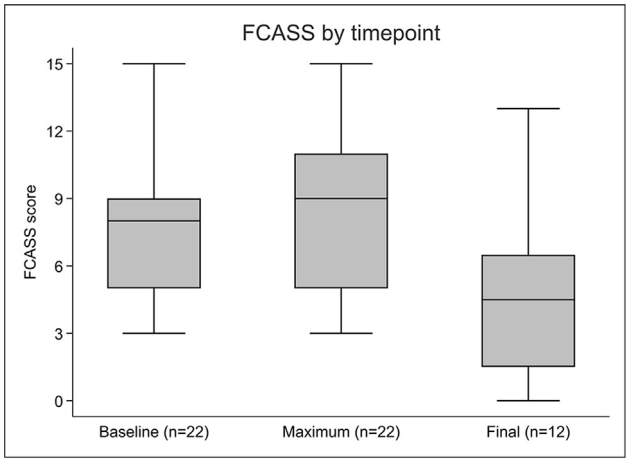

Fig. 3. Box and whisker plots summarizing baseline, maximum, and final focal cerebral arteriopathy severity scores (FCASS). Baseline FCASS includes scores in children with an imaging study <4 days after the stroke (n = 22). Maximum FCASS was defined as the highest total score at any time point (middle box plot) and includes all 32 children. If only a single FCASS score was available, it was considered the maximum. Final FCASS includes 12 cases with follow-up imaging ≥6 months post stroke.

3.2. Correlation between FCASS, infarct volume, and neurological outcome

The median pedASPECTS score (n = 32) on the baseline MRI was 4.5 (IQR 3, 8; range 1, 16). We observed a positive correlation between maximum FCASS at any time and pedASPECTS (n = 32, Spearman's rho = 0.62 p = 0.0002; Fig. 4) suggesting that more severe arteriopathy correlates with greater infarct volume.

All 32 children had a 6-month PSOM available; of these, 29 also had a PSOM recorded at 2 years. For the three children who did not have a 2-year score, 6-month scores were carried forward for the calculation of summary statistics. The median 2-year PSOM was 0.5 (IQR 0, 1.75; range 0, 3). Fourteen children (48.3%) had a 2-year PSOM ≥ 1 and fifteen (51.8%) had a PSOM <1.

We observed a positive correlation between modified pedASPECTS scores with 2-year PSOM (N = 32, Spearman's rho = 0.66, p=<0.001 Fig. 5), suggesting that greater infarct volume correlates with poorer outcome.

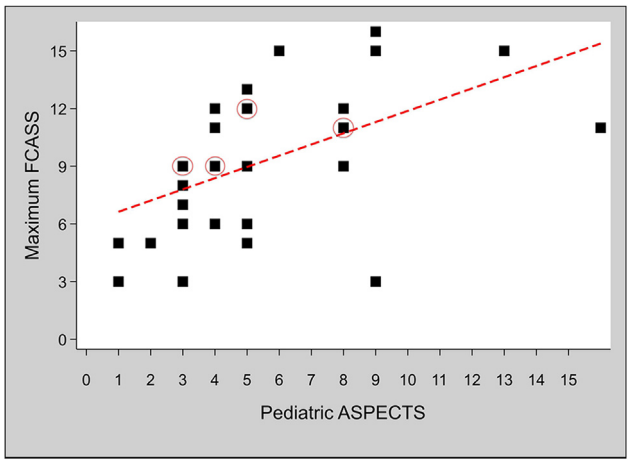

Fig. 4. Correlation between maximum FCASS and pedASPECTS (N = 32). Scatter plot demonstrating that more severe arteriopathy (higher maximum focal cerebral arteriopathy severity score (FCASS)) correlates with greater relative infarct volume (as measured by pedASPECTS) (p < 0.0002). Circled points demonstrate two or more patients with identical scores.

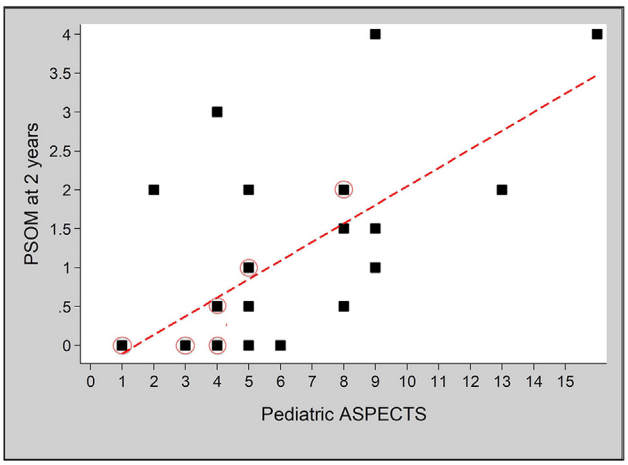

Fig. 5. Correlation between pedASPECTS and PSOM (N = 32). Scatter plot demonstrating that greater relative infarct volume (as measured by pedASPECTS) correlates with poorer neurological outcome (higher PSOM scores) (p < 0.001). Circled plots represent two or more children with identical results.

Among the children from our study, there was only one case with stroke recurrence.

The median pedASPECTS for patients with poor (n = 13) compared to good (n = 19) outcomes were 8 (IQR 5, 9; range 2, 16) and 4 (IQR 3, 5; range 1, 8), respectively (p = 0.002). At 2 years post-stroke (n = 32, with 6-month scores carried forward in three cases lacking 2-year follow up), 13 children had no deficits (PSOM = 0). Their median pedASPECT score was 3 (IQR 3, 4; range 1, 6). Expanding this group to include those with PSOM = 0.5 (considered a "good outcome"), the median pedASPECT score was slightly higher, with a median of 4 (IQR 3, 4; range 1, 8). In those patients with PSOM ≥1 (considered a poor outcome, n = 14) the median pedASPECT score was 8 (IQR 5, 9; range 2,16) (p = 0.0006 comparing PSOM<1 vs. PSOM≥1).

The maximum FCASS did not directly correlate with PSOM (N = 32, rho = 0.29; p = 0.11; Fig. 6).

In children with poor outcome (2-year PSOM ≥ 1), the maximum FCASS was a median (IQR) of 11 (6, 13; range, 3–16). In children with good outcome (2-year PSOM < 1), the maximum

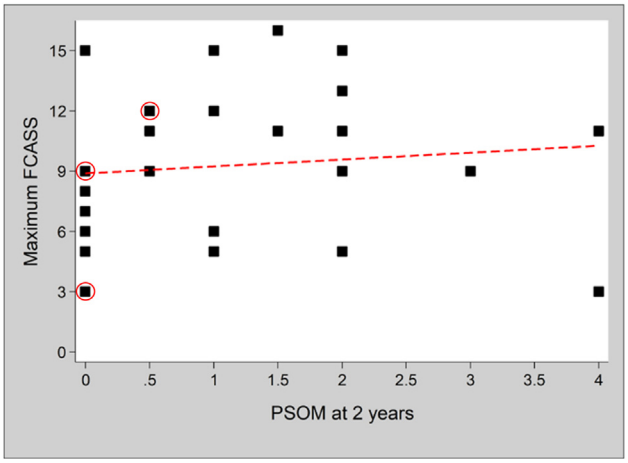

Fig. 6. Correlation between maximum FCASS and PSOM. Scatterplot demonstrating no direct correlation between maximum FCASS and PSOM (N = 32; p = 0.11). Circled points demonstrate two or more patients with identical scores.

FCASS was a median (IQR) of 9 (6, 11; range, 3–15). In children with PSOM of 0 at 2-years (n = 13), eight had improvement evidenced by a decline in FCASS, one had a mixed course with improvement and worsening of FCASS on follow-up imaging, and four had no available follow-up imaging.

3.3. Comparison of FCASS scoring across raters

The median absolute difference in FCASS between the paediatric neuroradiologist (gold standard) and each of the paediatric neurologists and the neuroradiology fellow was 2 (IQR 1, 4). Intraclass correlation coefficients comparing the total FCASS assigned by each paediatric neurologist and the neuroradiology fellow to the neuroradiology attending showed good agreement, The neuroradiology attending tended to give a higher (more severe) score than the neurology attendings (Table 1, Supplemental Fig. 1). In scoring the individual arterial segments, agreement with the gold standard was highest for the supraclinoid ICA (ICC 0.67) and lowest for the A2 (ICC 0.00).

4. Discussion

A better understanding of FCA is considered by international experts to be crucial to the research of paediatric stroke, and is one of the top priorities for study in clinical trials [11]. During the phase of FCA progression, children have an increased risk for recurrent ischemic events in comparison with those who have stable findings on vascular imaging [5,9,10]; therefore, identifying a surrogate marker to characterize accurately the course of stenosis of the affected vessel(s) would be invaluable. Two previous studies used severity scores for childhood arteriopathies [9,22] but did not specifically address FCA. The FCASS [3] was developed to fill this gap, and the primary aim of the current study was to validate this score in an independent cohort, by analyzing its correlation with infarct volume and neurological outcome. We also tested its applicability by professionals at different levels of neuroimaging expertise by comparing their scores to those assigned by a paediatric neuroradiologist—our gold standard. In our validation cohort, the maximum FCASS at any time among all 32 cases (including those with only a single imaging study) was a median (IQR) of 9 (6–12; range, 3–16), similar to the original derivation study cohort (with a median (IQR) of 7 [4–9; range, 1–16]). We also observed similar temporal evolution of FCASS in a majority of our patients, with an increase of stenosis observed within a short time after stroke, with an end-point improvement as expressed by a score drop on the last available image [3].

Worsening arteriopathy has been shown to be related to stroke recurrence [5,9,10], but as in the derivation cohort study, we could not demonstrate a correlation between FCASS and stroke recurrence [3]. This was likely due to insufficient power, given that we observed only one patient with recurrence. Anecdotally, FCA progression can result in worsening neurological deficits (typically a contralateral hemiparesis) without a distinct recurrent stroke event. Additionally, all of our patients were treated with aspirin immediately after diagnosis, with some also receiving corticosteroids. These data have been discussed in a previous paper [1] with significant overlap of study cases.

We found that maximum FCASS at any time correlated with larger infarct size. Similar findings were observed in the derivation cohort study, even though different volumetric measurements were used. Unlike the derivation study where higher maximum FCASS correlated with higher PSOM at 1-year, in our study infarct volume was positively correlated with both FCASS and 1-year PSOM, while the FCASS and PSOM were not correlated with one another. In light of our limited sample size, this lack of a significant direct correlation likely represented insufficient power, as well as the inconsistent timing of, and indication bias for, follow-up imaging. Overall, however, our results support the use of the FCASS as a quantitative marker for FCA severity and a tool for tracking its course over time, in order to help predict infarct extension and long-term neurological outcome. Furthermore, the use of pedASPECTS allows paediatric neuroradiologists and neurologists to rapidly assess infarct extent, as compared to more time-consuming volumetric measurement techniques.

Our current study supports the use of the FCASS for quantifying the severity and extent of disease in children with FCA. Results were found to have good interrater reliability when applied by different specialists. The attending neurologists tended to assign lower scores than the paediatric neuroradiologist, probably because they were less confident in scoring small-caliber vessels.

The method can be easily performed in a few minutes, does not require software for post-processing and provides valuable information for clinicians in the treatment selection decision. Clinical trials for corticosteroid treatment of FCA that are currently under development in Europe, Australia, and North America plan to use FCASS as an imaging metric; this will also improve consistency of measurement across trials, thus enhancing comparability and generalizability.

The interrater reliability reported in the original study compared two experienced neuroradiologists [3]. We chose to compare between disciplines (an experienced neuroradiologist versus an experienced pediatric neurologist) and between levels of experience (neuroradiology attending versus fellow). The interrater reliability was lower in our study than in the original study. This should be considered in the planning of future studies. A limitation of our study was that we did not measure intrarater variability; each image was only rated one time by individual raters.

Other limitations of our study include small sample size, variable timing of repeat imaging with indication bias, as well as missing imaging during the peak FCASS window for 8 of 32 cases. We hypothesize that the temporal evolution of FCASS may better predict the neurological outcome than the absolute FCASS value. We could not test this hypothesis in our cohort, but did observe good outcomes in some cases where the FCASS score was highest at

Table 1
Correlation between paediatric neuroradiologist and neurology fellow and paediatric neurologists. ICC = intraclass correlation coefficient.

Pediatric Neuroradiologist (Gold standard)	Pediatric Neurologist 1		Pediatric Neurologist 2		Neuroradiology Fellow	
	ICC	95% CI	ICC	95% CI	ICC	95% CI
Total FCASS	0.61	(0.39, 0.75)	0.65	(0.25, 0.82)	0.71	(0.37, 0.85)
By arterial segment						
ICA	0.67	(0.52, 0.78)	0.61	(0.43, 0.74)	0.73	(0.61, 0.81)
M1	0.58	(0.42, 0.70)	0.58	(0.33, 0.74)	0.63	(0.39, 0.77)
M2	0.47	(0.19, 0.66)	0.45	(0.26, 0.61)	0.67	(0.52, 0.77)
A1	0.47	(0.25, 0.63)	0.59	(0.37, 0.74)	0.54	(0.32, 0.69)
A2	0.00	(-0.20, 0.20)	0.22	(0.01, 0.42)	−0.025	(-0.23, 0.19)

baseline and followed by continuous decline. Further prospective cohort studies with larger sample sizes and consistent timing of imaging are needed.

5. Conclusion

The FCASS, which correlates with infarct volume and demonstrates good inter-professional interrater reliability, represents a promising and previously unavailable tool for measuring and tracking stenosis in FCA. Because infarct volume has also been correlated with outcome, it is likely that FCASS measured at peak severity, or trends in FCASS measured consistently within an accurate window of time, would provide a valuable aid in predicting eventual outcome of paediatric stroke.

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Informed consent

Not applicable.

Ethical approval

The SNPSR is approved by the Ethics Committee of the Canton of Bern (Kantonale Ethikkommission für die Forschung) and the Ministry of Health Switzerland.

Guarantor

Prof. Dr. Maja Steinlin.

Contributorship

NS, HF, NH, MM and MS made a substantial contribution to the concept and design of the work. MS was involved in protocol development, gaining ethical approval, patient recruitment and data analysis. NS, PB, NH and MS analyzed and interpreted the data. NS, HF, NH and MS wrote the first draft of the manuscript. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors substantially contributed on to the design of the work; acquisition, interpretation of data, revised manuscript critically for important intellectual content, and approved the version to be published.Disclosures

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2020.07.015.

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