Predictors of motor outcome after childhood arterial ischemic stroke

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PUBLICATION DATA
Accepted for publication 7th April 2021.
Published online

ABBREVIATIONS

AIS	Arterial ischemic stroke
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
CASCADE	Childhood AIS Standardized Classification and Diagnostic Evaluation
CST	Corticospinal tract
DWI	Diffusion-weighted imaging
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
RRQ	Recurrence and Recovery Questionnaire

AIM To identify clinical and radiological predictors of long-term motor outcome after childhood-onset arterial ischemic stroke (AIS) in the middle cerebral artery (MCA) territory.
METHOD Medical records of 69 children (36 females, 33 males; median age at index AIS 3y 3mo, range: 1mo–16y) who presented to Great Ormond Street Hospital with first AIS in the MCA territory were reviewed retrospectively. Cases were categorized using the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE). Magnetic resonance imaging (MRI) and angiography were evaluated. An Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was calculated on MRI. The Recurrence and Recovery Questionnaire assessed motor outcome and was dichotomized into good/poor.
RESULTS Eventual motor outcome was good in 49 children and poor in 20. There were no acute radiological predictors of eventual motor outcome. At follow-up, CASCADE 3A (i.e. moyamoya) and Wallerian degeneration were significantly associated with poor motor outcome. In the multivariate analysis, younger age and CASCADE 3A predicted poor motor outcome.
INTERPRETATION In the context of recommendations regarding unproven and potentially high-risk hyperacute therapies for childhood AIS, prediction of outcome could usefully contribute to risk/benefit analysis. Unfortunately, paradigms used in adults, such as ASPECTS, are not useful in children in the acute/early subacute phase of AIS.

Childhood arterial ischemic stroke (AIS) has an annual incidence of 1 to 2 out of 100 000 children in Western countries[1] and is a significant cause of morbidity.[2] Motor function is most commonly affected, with hemiparesis reported in up to three-quarters of children.[3,4] The costs of care and dependency arising from an early brain insult has major medical, personal, and societal costs.[5,6]

Hyperacute recanalization therapies (thrombolysis/thrombectomy) have proven efficacy in adult AIS. Current paediatric guidelines provide recommendations regarding paediatric use; however, the pathological substrate of AIS is significantly different in the two groups[7,8] and both approaches likely carry significant risk in children. A trial exploring the safety and efficacy of hyperacute thrombolysis in childhood AIS (Thrombolysis in Paediatric Stroke)[7] closed because of lack of recruitment and it is unlikely that any further trials of recanalization therapies will be conducted.

Imaging enables diagnosis and eligibility for recanalization therapies in adults, and predicts outcome after AIS.[9] Such prognostication in children could usefully inform decision-making about recanalization therapies in this age group.

Here we investigate the relationship between the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on acute magnetic resonance imaging (MRI) and long-term motor outcome in a recent cohort of children with middle cerebral artery (MCA) AIS.

METHOD

Patient selection

AIS was defined as an acute focal neurological deficit which correlated with radiological evidence of cerebral infarction in an arterial territory. Children (29d–18y) with first MCA territory AIS admitted to Great Ormond Street Hospital for Children, London, UK, between 2005 and 2017 were included. Exclusion criteria were those presenting with recurrent clinical AIS; with less than 6 months follow-up data; or missing/non-diagnostic neuroimaging. All children were managed according to Royal College of Paediatrics and Child Health guidelines (https://www.rcpch.ac.uk/resources/stroke-childhood-clinical-guideline-dia

DOI: 10.1111/dmcn.14914

gnosis-management-rehabilitation). This study was approved as a retrospective audit of existing data.

Clinical data

Medical charts were reviewed to extract data on demographics, clinical presentation, recurrence, risk factors, and AIS management. As multiple risk factors may predict poor outcome,[10] risk factors were coded as none/single/multiple. Clinical presentation was coded as global (reduced level of consciousness, generalized seizures, headache), focal (hemiparesis, visual field/speech deficit, focal seizures), or both, as previously described.[11] Patients were categorized using Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE), an AIS classification system based primarily on neuroimaging features.[12] Recurrence was defined as further ischemic event(s) after the index AIS with evidence of further infarction (new infarction/extension of previous infarction) on neuroimaging. Clinically silent infarcts after the index AIS were included as recurrence.

The date of deficit onset and the first MRI were recorded to identify delays in radiological diagnosis. The follow-up period was defined as the time between deficit onset and most recent clinical assessment. The referring hospital was coded as within/outside the Great Ormond Street Hospital for Children North London catchment area to assess for referral centre bias. Global neurological and motor outcome was scored from notes using the Recurrence and Recovery Questionnaire (RRQ)[13] and dichotomized into 'good' and 'poor', an approach used previously[14] (see Table 1). Although initially developed for use as a parental questionnaire, the RRQ can be scored from medical notes[15] (in contrast to the Paediatric Stroke Outcome Measure which is scored in person).[16] RRQ scoring was completed from the time of index AIS and the last documented follow-up appointment. Unfortunately, it was not possible to score acute stroke severity with the Pediatric National Institutes of Health Stroke Scale retrospectively from records, therefore the initial RRQ score was used as a proxy of acute motor impairment.

Imaging analysis

MRI data were reviewed by two paediatric neuroradiologists. Presence and localization of abnormalities in T2-weighted, T1-weighted, diffusion-weighted imaging (DWI), and magnetic resonance angiography (MRA) were described from the admission scan and most recent follow-up. As previously suggested,[17] the ASPECTS score was calculated on MRI (computed tomography [CT] not being available in most cases) on DWI in the first scan and T2-weighted imaging in the last scan. As in adults, an ASPECTS score of <8 increases the likelihood of poorer functional outcome and intracerebral haemorrhage; this cut-off point was used in the present study. ASPECTS modified for paediatric MRI[17] includes the anterior and posterior cerebral artery territories, as well as the thalamus, and is therefore not appropriate for this MCA territory focussed study. In adults, a normal MCA territory is assigned 10 points with a point deducted for each affected region (M1–M6, the caudate nucleus, lentiform nucleus, insula, and/or the internal capsule), thus lower scores indicate more extensive involvement.

Atrophic evolution of acute abnormalities was defined as presence of lacunae surrounded by gliosis and/or ex vacuo enlargement of the ventricles or sulci in the MCA territory on the follow-up scan.

Secondary degeneration of the corticospinal tract (CST) on the affected side was defined as presence of diffusion restriction along the posterior limb of the internal capsule and/or brainstem on the side of the initial ischaemic lesion (i.e. pre-Wallerian degeneration) and reduction in physiological signal of the posterior limb of the internal capsule and/or reduction in size of the side of the brainstem on the side of the ischaemic lesion (i.e. Wallerian degeneration).[18]

MRA findings were categorized as normal (no reduction of the calibre of the MCA compared with unaffected side), narrowed (reduction of MCA calibre compared with unaffected side), or completely occluded (absent flow signal in the MCA or its branches on the affected side).

Statistical analysis

To investigate acute and longer-term predictors of eventual motor outcome, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate logistic regression. ASPECTS, MRA, pre-Wallerian

What this paper adds

- Adult paradigms, such as the Alberta Stroke Program Early Computed Tomography Score system, are not useful for predicting outcome in children.
- Younger children tend to have a poorer long-term prognosis than older children.
- Moyamoya is associated with poor prognosis.

Table 1: Recurrence and Recovery Questionnaire (RRQ) scoring

Global RRQ	Each domain is scored 0 (no deficit), 0.5 (mild deficit, no impact on function), 1 (moderate deficit, reduced function), or 2 (severe deficit, profound impact on function). Total/10
Good outcome	
No deficit	0 in all five domains
Mild deficit	0.5 in one domain
Poor outcome	
Moderate deficit	0.5 in >1 domain; or 1 in one domain; or 1 in one domain *and* 0.5 in one domain
Severe deficit	0.5 in all five domains; or 1 in two domains; 1 in one domain *and* 0.5 in two domains; or 2 in one domain
Motor RRQ	Summation of right and left sensorimotor scores. Total/4
Good outcome	Right and left sensorimotor score combined <0.5
Poor outcome	Right and left sensorimotor score combined >0.5

Each patient was given a score for the following domains: right sensorimotor, left sensorimotor, language production, language comprehension, and cognition/behaviour, and a total score. The motor component was calculated by summating right and left sensorimotor scores.

degeneration, and age were examined as acute predictors. Recurrent AIS, Wallerian degeneration, length of follow-up, risk factors, and CASCADE classification were included as long-term factors. Number of risk factors and CASCADE classification were considered long-term factors as these are often not known in the acute setting after first AIS. Significant and clinically relevant variables were entered into multivariate analysis. χ^2 was used to measure the goodness of fit (χ^2 [10, n=65]=35.113, p<0.001). A p-value of <0.05 was used to indicate statistical significance. Statistical analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Eighty-eight children were eligible, of whom 69 were suitable for inclusion (36 females, 33 males). Nineteen were excluded for the following reasons: posterior circulation stroke (n=7), <6 months follow-up data (n=5), bilateral watershed infarcts (n=3), missing neuroimaging (n=3), and one child died during follow-up. Twelve had been referred from hospitals outside the Great Ormond Street Hospital for Children catchment area. Median age at AIS diagnosis was 3 years 3 months (range: 1mo–16y), and patients were followed up for a median of 7 years (range: 1y 8mo–18y). Sixty-seven children presented with an acute lateralized hemiparesis (with seizures in six). At least one risk factor was present in 55 (79.7%) children. Six (8.7%) children experienced a recurrent AIS during follow-up. Data on clinical characteristics are summarized in Table 2.

Initially all children had poor global neurological function (median RRQ=2; interquartile range [IQR]: 2–4) and poor motor function (median RRQ=1; IQR: 1–2). Eventual neurological function was poor in 21 (30.4%) children (median RRQ=1, IQR: 1–2). Thus, global neurological function had improved in 59 children, remained the same in five, and worsened in five children. Eventual motor outcome was good in 49 (71%) children (no deficit, RRQ=0 in 34 children, mild deficit, RRQ=0.5 in 15) and poor in 20 (29%) children (moderate deficit, RRQ=1 in 12 children, severe deficit, RRQ=2 in 8), with a median score of 0.5 (IQR: 1–2). Over time the RRQ motor outcome scores improved in 58 children, stayed the same in nine, and worsened in two children. Notably one child had a follow-up score of 4 (increased from 2) indicating a severe deficit and loss of function on both left and right side. This child did not have a recurrent AIS but did have evidence of mature subclinical infarcts on initial imaging.

Sixty-eight children were commenced on antithrombotic therapy for secondary prevention as per the guidelines (https://www.rcpch.ac.uk/resources/stroke-childhood-clinical-guideline-diagnosis-management-rehabilitation). The remaining child had sickle-cell disease and had a blood transfusion. Nine children had revascularization surgery (six bilateral and three unilateral extracranial–intracranial bypass), four of whom had a poor long-term motor outcome.

The most common CASCADE category was CASCADE 2B (unilateral focal cerebral arteriopathy of the anterior circulation without collaterals, n=24), followed by CASCADE 6A (other, undetermined aetiology, n=17). Poor motor outcome was most common in those with CASCADE 3A, bilateral cerebral arteriopathy with collaterals (i.e. moyamoya). Of the nine children with moyamoya, six had established subclinical infarcts on initial imaging, five of whom had a poor long-term motor outcome.

Table 2: Clinical AIS characteristics

AIS presentation	Whole cohort (n=69); n (%)
Focal	61 (88.4)
Global	1 (1.5)
Both	7 (10.1)
Risk factors for AIS	
None	14 (20.3)
Single	39 (56.5)
Multiple	16 (23.2)
Recurrent AIS	
Yes	6 (8.7)
No	63 (91.3)
AIS classification (CASCADE)	
2B. Unilateral FCA: anterior circulation without collaterals	24 (34.7)
3A. Bilateral cerebral arteriopathy: with collaterals	9 (13)
4A. Aortic/cervical arteriopathy: dissection	3 (4.3)
4C. Aortic/cervical arteriopathy: other	1 (1.4)
5A. Cardioembolic: definite	3 (4.3)
6A. Other: undetermined aetiology	17 (24.6)
6B. Other: unclassifiable	11 (15.9)
7. Greater than one anatomical site of disease	1 (1.4)

AIS, arterial ischemic stroke; CASCADE, Childhood AIS Standardized Classification and Diagnostic Evaluation; FCA, focal cerebral arteriopathy.

MRI

Median time to first MRI was 1 day (range: 0–20d). Twenty-two children (35.5%) were scanned within 24 hours of deficit onset and 96% within 5 days (i.e. the window for diffusion restriction changes). Total ASPECTS scores ranged from 0 to 9 out of 10 (median=8). Thirty-two (46.4%) children had an ASPECTS score of <8. Nine (13%) children had evidence of mature infarction on acute MRI, six of whom had moyamoya. Despite evidence of established infarcts on imaging, the current AIS was the first clinical presentation, and therefore these children were included in the study. Five of these children had a poor outcome.

The patients with abnormal initial DWI showed abnormal follow-up T2-weighted imaging which is the expected radiological evolution together with evolving atrophy (Figs 1 and 2).

In the two children with radiological signs of haemorrhagic changes in the area of stroke (T1-weighted imaging hyperintensity in the first scan), the changes were located in the basal ganglia. Outcome was good in one of these children and poor in the other who had an *ACTA2* mutation.

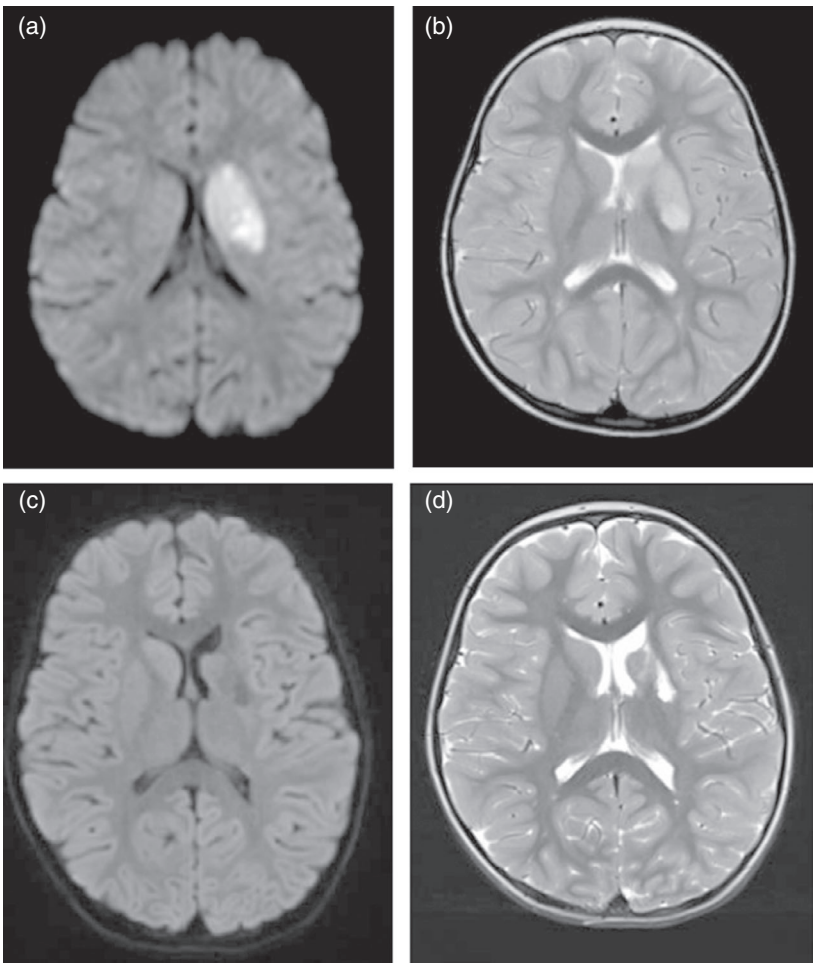

Figure 1: Acute (a,b) and chronic (c,d) brain magnetic resonance imaging after arterial ischemic stroke (AIS) in middle cerebral artery (MCA) territory at 3 years old. Acute changes on axial diffusion-weighted imaging (DWI) (a) and axial T2-weighted imaging (b), involving the left putamen and caudate nuclei (MCA territory). Brain imaging from the same patient at 2-year follow-up depicting the chronic evolution of AIS, with free diffusion on DWI (i.e. absent hyperintense signal [c] and atrophy on T2-weighted imaging [d]).

Follow-up DWI showed free diffusion in 59 out of 62 children, T2-weighted imaging illustrated gliosis in all, and scans showed focal atrophy in 62 out of 63.

The only three children with restricted diffusion on follow-up imaging had had further infarction. The child who did not have detectable atrophic stroke evolution had a very small infarcted area. Of the four children with abnormal T1-weighted imaging at follow-up, indicative of cortical laminar necrosis, one had a poor long-term motor outcome.

Intra- and extracranial MRA data were available for 67 out of 69 children at presentation. This was normal in 20 children and abnormal in 47 (narrowed n=33; completely occluded n=14) (Fig. 3). Three children with arterial occlusion had a thrombus associated with cardio-embolic aetiology. Forty-five out of 47 children with abnormal arterial imaging initially had follow-up MRA imaging. Arteriopathy was stable in 30, had progressed in three, and improved in 12 children. One child with progressive arterial disease experienced a recurrent AIS.

Acute and long-term predictors of eventual motor outcome

Univariate logistic regression showed no acute clinical or imaging predictors of eventual motor outcome (Table 3). With regards to longer-term factors, Wallerian degeneration of the CST (OR 8.14; 95% CI 2.44–27.15; p=0.001) and CASCADE 3A (moyamoya; OR 10.00; 95% CI 1.73–57.72; p=0.010) were significantly associated with poor long-term motor function (Table 4). In contrast to previous studies the presence of multiple risk factors,[19] recurrent AIS,[19] and basal ganglia involvement[20] did not influence outcome. There were no acute predictors of long-term global outcome (using global RRQ score; Table S1, online supporting information). Similarly, our receiver operating characteristic curve/area under the curve

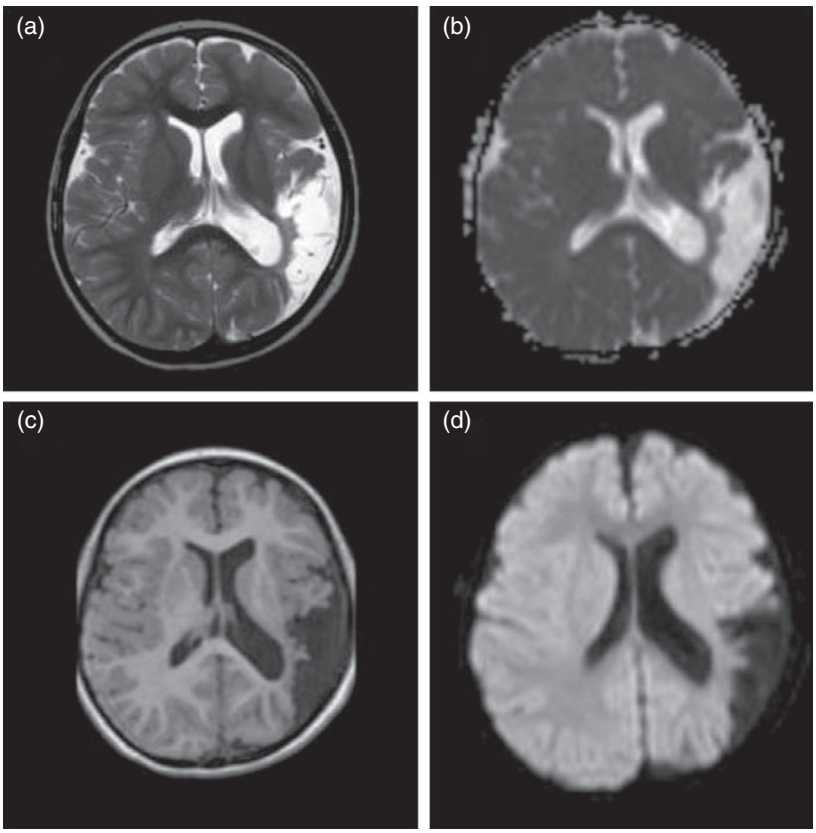

Figure 2: Follow-up imaging 3 years after arterial ischemic stroke (AIS) of a male who presented at 13 months with right sided hemiparesis. Axial T2-weighted imaging (a), apparent diffusion coefficient maps (b), T1-weighted imaging (c), and diffusion-weighted imaging (d) demonstrate the absence of diffusion restriction (i.e. absence of acute cytotoxic oedema) and the longstanding encephalomalacic changes typical of the chronic phase of the infarction.

analysis did not identify an alternative cut-off ASPECTS score to predict long-term motor outcome in children (area under the curve=0.446; *p*-value and 95% CIs are reported in Fig. S1, online supporting information).

There was no significant difference in motor outcome between children referred to Great Ormond Street Hospital for Children from hospitals outside of the North London catchment area and those referred from within (OR 1.72; 95% CI 0.47–6.29; p=0.41).

Despite not reaching significance in the univariate model, age at diagnosis and length of follow-up were included in the multivariate analysis alongside CASCADE classification and CST Wallerian degeneration, as we believe these variables are clinically relevant. CASCADE 3A (OR 11.71; 95% CI 1.44–95.24; p=0.02) remained significant; however, the strength of the association was weak. Age became a significant predictor of poor motor outcome (OR 0.67; 95% CI 0.49–0.93; p=0.018), with younger children being more likely to have poor outcome. Wallerian degeneration (OR 4.74; 95% CI 0.99–22.62; p=0.051) was no longer a significant predictor in the multivariate model.

Royal College of Paediatrics and Child Health guidelines suggest that thrombolysis could be considered for off label use in children ≥8 years. ASPECTS was tested for an association with eventual motor outcome for those <8 years and ≥8 years. No significant relationship was found for either age group (<8y OR 1.29; 95% CI 0.42–3.97; p=0.652; ≥8y OR 1; 95% CI 0.05–20.83; p=1.00).

DISCUSSION

In this uniformly managed cohort of children with MCA AIS, acute imaging assessed using ASPECTS was not predictive of long-term motor outcome. Our results confirm that children with bilateral arterial disease have a more malignant disease course than those with unilateral disease, and that the presence of Wallerian degeneration on follow-up imaging is generally predictive of poorer motor outcome. Unlike previous tertiary care centre studies,[15] there was no suggestion of referral centre bias in our cohort. Limitations include the use of retrospective data, non-availability of advanced magnetic resonance techniques such as perfusion weighted images and diffusion tensor images, missing data, and low statistical power due to a small sample – the latter likely explaining the relatively low rate of recurrent AIS compared to previous cohorts (although this may be due to our eligibility criteria being

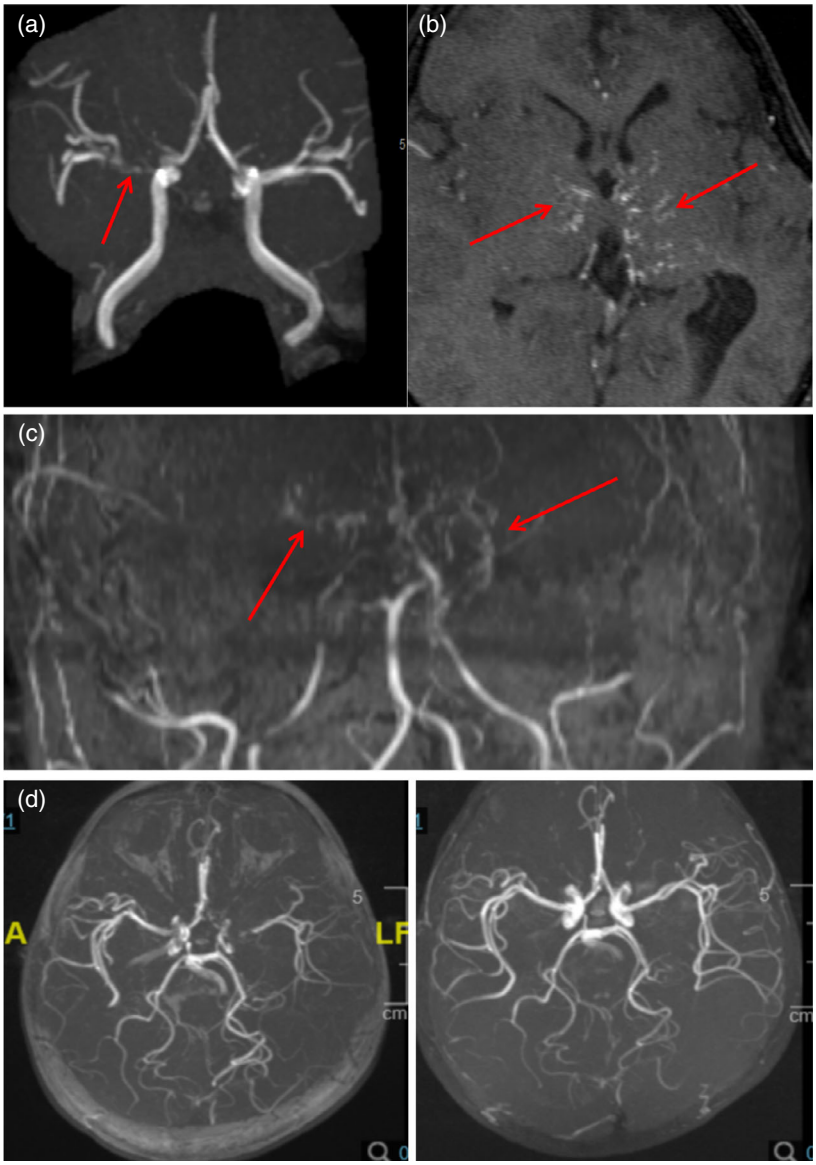

Figure 3: Magnetic resonance angiography images illustrating examples of childhood cerebral arteriopathies. Coronal maximum intensity projection (MIP) images (a) showing signal dropout in the right M1 segment (arrow) in a child with a unilateral focal cerebral arteriopathy (FCA). Axial 3D time of flight images (b) and coronal MIP images (c) in another patient depict typical moyamoya disease: complete occlusion of the middle cerebral artery and anterior cerebral artery, as well as marked narrowing of the distal internal carotid arteries with collaterals (red arrows). Moyamoya, meaning 'puff of smoke' in Japanese, describes the appearance of the collateral vessels which form to compensate for the narrowing of the arteries. MRA axial MIP (d) demonstrating improvement in arteriopathy between acute imaging (left) and 2-year follow-up imaging (right). This child, who presented with recurrent transient ischemic attacks (right sided hemiparesis and dysarthria) has a unilateral focal cerebral arteriopathy without collaterals. [Colour figure can be viewed at wileyonlinelibrary.com]

restricted to those with anterior circulation stroke). Furthermore, the RRQ is a relatively crude measure of outcome, broadly distinguishing between unimpaired and impaired patients. A small proportion of our cohort (13%) had evidence of mature infarction on neuroimaging, despite patients being excluded if they presented with recurrent AIS. We believe it is important to include such patients in the study as this reflects realistic clinical practice.

Our results highlight that although all children have poor global and motor function acutely, most (70% and 71% respectively) have a good outcome in the longer term. Initial stroke severity evaluated with standard MRI is therefore not a robust predictor of long-term outcome in children. In adults it is suggested that an ASPECTS score of <8 increases the likelihood of poorer functional outcome and intracerebral haemorrhage after AIS.[21] With regards to children, having an early imaging predictor of motor

Table 3: Univariate analysis for acute predictors of eventual motor outcome

Factor	Good motor outcome (*n*=49); *n* (%)	Poor motor outcome (*n*=20); *n* (%)	OR (95% CI)	*p*[a]
ASPECTS <8 (vs ≥8)	22 (44.90)	10 (50)	1.23 (0.43–3.48)	0.70
Abnormal MRA	17 (34.60)	3 (15)	2.93 (0.74–11.48)	0.12
Pre-Wallerian degeneration	1 (2)	1 (5)	3.21 (0.19–54.80)	0.43[b]
Age at diagnosis, y: mo, median (IQR)	4:2 (15:7)	2:11 (14:5)	0.87 (0.74–1.03)	0.12

[a]*p*-value calculated using logistic regression unless otherwise stated. [b]*p*-value calculated using Fischer's exact test. OR, odds ratio; CI, confidence interval; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; MRA, magnetic resonance angiography; IQR, interquartile range.

outcome that can be implemented easily and quickly in the acute setting could be very useful; however the current study does not suggest that this is possible, at least using adult paradigms such as ASPECTS.

Contrary to current findings, previous tertiary care centre studies have found an association between extent of infarction and outcome.[22,23] Despite no effect of lesion size or location on outcome as a whole, Ganesan et al.[24] found that children had a poorer outcome when infarction was >10% intracranial volume, a finding that was later confirmed by Zecavati et al.[25] However, the latter study looked at outcome at 30 days, and included all brain territories. Similarly, another study noted that executive functioning was demonstrably worse when lesions were >25% brain volume.[26] In a recent prospective study including 288 children with first time AIS, larger infarct volume was associated with worse neurological outcome at 1-year post stroke; however the strength of the relationship was modest. Furthermore, infarcts involving the uncinate fasciculus and angular gyrus, two highly connected regions, were also associated with worse outcome, however only in the univariate analysis.[27] Comparisons between studies are difficult because of heterogeneity among risk-factors, underlying stroke mechanisms, laterality of the insult, and involved arterial territories. For instance, Beslow et al. retrospectively analysed death during hospitalization and identified congenital heart disease and anterior and posterior circulation strokes as the most important risk factors.[22] Anterior and posterior circulation strokes were also associated with reduced survival in other studies,[23] meaning different considerations in terms of pros and cons of treatment and outcome may be needed in cases of isolated MCA stroke, the territory where lesions are most likely to be considered for thrombectomy.

Because of the lack of recognition of childhood stroke, high frequency of stroke mimics, and lack of access to neuroimaging, especially MRI, children are often not scanned in a timely manner. Only a third of children underwent MRI within 24 hours of AIS onset, posing a problem for the proposed 3- to 8-hour time window for initiation of recanalization therapies in adults. Delays in diagnosis have been identified previously, with children often not being referred to tertiary care centres or facilities with MRI and specialized skills until >24 hours after deficit onset.[8,28] This highlights the need for increased education and awareness about childhood stroke amongst physicians and the public.

The paradigm of recanalization therapy is predicated on the majority of adult patients with atherosclerotic disease, and interestingly some studies have shown that the window for intervention can be prolonged up to 24 hours in

Table 4: Univariate analysis for long term predictors of eventual motor outcome

Factor	Good motor outcome (*n*=49); *n* (%)	Poor motor outcome (*n*=20); *n* (%)	OR (95% CI)	*p*[a]
Recurrence (vs no recurrence)	4 (8.2)	2 (10)	1.25 (0.21–7.44)	0.81
No. of AIS risk factors				
None	9 (18.4)	5 (25)	Reference	Reference
Single	30 (61.2)	9 (45)	0.54 (0.14–2.02)	0.36
Multiple	10 (20.4)	6 (30)	1.08 (0.24–4.79)	0.92
AIS classification (CASCADE)				0.02[b]
2B. Unilateral FCA: anterior circulation without collaterals	20 (40.8)	4 (20)	Reference	Reference
3A. Bilateral cerebral arteriopathy: with collaterals	3 (6.1)	6 (30)	10.00 (1.73–57.72)	0.01
4A. Aortic/cervical arteriopathy: dissection	2 (4.1)	1 (5)	2.50 (0.180–34.67)	0.50
4C. Aortic/cervical arteriopathy: other	1 (2.0)	0	0.00 (0.00)	>0.99
5A. Cardioembolic: definite	1 (2.0)	2 (10)	10.00 (0.72–138.68)	0.09
6A. Other: undetermined aetiology	15 (30.6)	2 (10)	0.67 (0.11–4.13)	0.66
6B. Other: unclassifiable	6 (12.2)	5 (25)	4.17 (0.84–20.64)	0.08
7. Greater than one anatomical site of disease	1 (2.0)	0	0.00 (0.00)	>0.99
Wallerian degeneration	7 (14.3)	12 (60)	8.14 (2.44–27.15)	0.001
Length of follow-up, y:mo, median (IQR)	2:10 (16:0)	4:2 (12:0)	1.14 (0.98–1.34)	0.09

[a]*p*-value calculated using logistic regression unless otherwise stated. [b]*p*-value calculated using Fischer's exact test. OR, odds ratio; CI, confidence interval; AIS, arterial ischemic stroke; CASCADE, Childhood AIS Standardized Classification and Diagnostic Evaluation; FCA, focal cerebral arteriopathy; IQR, interquartile range.

selected adults.[29,30] However, children have a much wider range of risk factors, including non-atherosclerotic arteriopathies. The lesion pattern in children is most commonly perforator territory infarction, as opposed to occlusion being relatively common in adults and neonates.[31] As such, this may be why ASPECTS is predictive of outcome in the latter two groups only. Our data reinforce that children with bilateral arteriopathies, specifically moyamoya, are likely to have a worse prognosis than those with a unilateral arteriopathy.[32] Whilst thrombectomy has generally been shown to have poor outcomes in moyamoya,[33] the risks versus benefits of this in other non-atherosclerotic, likely inflammatory arteriopathies is not known.

In this retrospective study we did not have advanced imaging techniques available (in particular perfusion weighted images), so the penumbra of salvageable brain tissue could not be evaluated as in adult trials and current practice.[29,30,34] Perfusion images have to be obtained using dynamic-susceptibility contrast enhanced magnetic resonance perfusion which can be challenging in children because of the need for adequate venous access and a power injector.[35,36]

This study shows poor correlation between ASPECTS on acute MRI and outcome in children with MCA stroke. It is therefore important to plan prospective studies using contrast perfusion techniques (e.g. dynamic-susceptibility contrast perfusion) in children using custom administration of a standard dose of contrast and a reproducible technique as recently suggested.[37]

In paediatric stroke, acute downstream involvement of the ipsilateral CST (pre-Wallerian degeneration) predicts poor outcome;[18] Wallerian degeneration as a predictor of poor outcome has been confirmed by the univariate logistic regression analysis in our cohort. Diffusion tensor images represent a more powerful diffusion technique able to identify early pathological changes in the CST after stroke.[38–41] Diffusion tensor images will be a promising prospective approach together with appropriate perfusion imaging in order to evaluate motor outcome and neuroplasticity after brain damage.[42,43]

We did not find a correlation between ASPECTS on acute MRI and long-term motor outcome. Although widely used in adults, ASPECTS has several limitations related to reproducibility, evaluation of the anterior circulation territory only, and correlation with stroke volume depending on location of the damage.[17,44,45] Although more rigorous methods of assessing infarct volume are available, a good correlation between DWI and ASPECTS modified for paediatric MRI and volume of infarction in children has been shown.[17]

The way forward is probably more standardized use of advanced techniques in a homogenous population (e.g. MCA ischemia only, patients with moyamoya, patients with combined anterior+posterior circulation stroke, etc.) in distinct age groups with specific guidelines for each. This approach will need large, multicentre studies and strong reproducible radiological methods of assessment given the rarity of AIS in children.

ACKNOWLEDGEMENTS

The authors have stated they have no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared by request from any qualified investigator.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Receiver operating characteristic curve for ASPECT scores.

Table S1: Univariate logistic regression for acute predictors of eventual outcome using global RRQ.

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