Focal Cerebral Arteriopathy
Do Steroids Improve Outcome?

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Background and Purpose—Focal cerebral arteriopathy accounts for up to 35% of arterial ischemic stroke (AIS) in children and is the most important predictor of stroke recurrence. The study objective was to compare outcomes for children with focal cerebral arteriopathy treated with combined corticosteroid antithrombotic treatment (CAT) to those receiving antithrombotic treatment (AT) alone.

Methods—This multicenter retrospective Swiss/Australian cohort study analyzed consecutive children, aged 1 month to 18 years, presenting with first AIS because of a focal cerebral arteriopathy from 2000 to 2014. Children with CAT were compared with those treated with AT. Primary outcome was the presence of neurological deficits at 6 months post–AIS as measured by the Pediatric Stroke Outcome Measure. Secondary outcomes included resolution of stenosis and stroke recurrence. Analysis of covariance was used to adjust for potential confounders (baseline pediatric National Institute of Health Stroke Scale and concomitant acyclovir use).

Results—A total of 73 children (51% males) were identified, 21 (29%) of whom received CAT. Mean (SD) age at stroke for the entire group was 7.9 years (4.7). Median (interquartile range) pediatric National Institute of Health Stroke Scale was 3 (2.0–8.0) in the CAT group and 5 (3.0–9.0) in the AT group (P=0.098). Median (interquartile range) Pediatric Stroke Outcome Measure 6 months post-AIS was 0.5 (0–1.5) in the CAT group compared with 1.0 (0.5–2.0) in the AT group (P=0.035), the finding was sustained after adjusting for potential confounders. Complete resolution of stenosis at last MRI was noted in 17 (81%) in the CAT group compared with 24 (59%) in the AT group (P=0.197). Stroke recurrence occurred in 1 patient in each group.

Conclusions—Corticosteroid treatment may provide additional benefit over AT for improved neurological outcome in childhood AIS because of focal cerebral arteriopathy. Larger prospective studies are warranted to further investigate these differences and understand mechanisms by which steroids modify outcome. **(*Stroke*. 2017;48:2375-2382. DOI: 10.1161/STROKEAHA.117.016818.)**

Key Words: acyclovir ■ inflammation ■ ischemic attack, transient ■ pediatric ■ prospective studies ■ stroke

Approximately half of arterial ischemic stroke (AIS) in childhood are because of an arteriopathy,[1–3] of whom one third show an underlying focal cerebral arteriopathy (FCA).[4] The course of FCA is dynamic, sometimes with initial worsening of stenosis, followed by stabilization or improvement in the longer term.[5,6] Clinical characteristics of AIS because of FCA include preceding transient ischemic attack, stuttering symptom onset, predominantly affecting the proximal anterior circulation—with involvement of M1 segment of the middle cerebral and distal carotid arteries—leading to ischemic infarction of subcortical structures, including the basal ganglia.[1,5–7] FCA is increasingly considered to be an inflammatory arteriopathy, most likely triggered by infection in a predisposed child.[8,9] There is little available histopathologic data, but an inflammatory mechanism is supported by 2 major observations.[10,11] First, there is growing evidence that FCA occurs in the context of recent infections.[1,9,12–14] Second, the radiological findings of vessel wall enhancement lead to the assumption of an underlying acute inflammatory process.[15–17]

As a consequence, there is increasing use of corticosteroids in children with AIS because of FCA. However, clinical equipoise exists for use of anti-inflammatory treatments to improve outcome in this patient population based on a paucity of published data and limited understanding of disease pathogenesis. In particular, it is unclear whether FCA is an inflammatory arteriopathy, and if so, whether it is idiopathic, provoked by

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active viral infection, or because of post-viral inflammation. Therefore, the objective of this study was to analyze the effect of additional corticosteroid treatment by comparing clinical outcomes, arteriopathy dynamics, and recurrence rates in children with AIS because of FCA. Based on the presumed inflammatory pathogenesis, we hypothesize that children receiving additional corticosteroid treatment will show a better clinical outcome and a lower recurrence rate compared with children receiving antithrombotic treatment (AT) alone.

Methods

Study Design and Study Population

This is a retrospective analysis of 2 prospective consecutive patient cohorts in Switzerland and Melbourne, comparing outcomes for children with FCA treated with combined corticosteroid antithrombotic treatment (CAT), to those receiving AT alone. Included were consecutive children and adolescents aged 1 month to 18 years diagnosed with an AIS because of FCA ascertained from searches of the Swiss Neuropaediatric Stroke Registry (SNPSR) from 2000 until 2014 and the Royal Children's Hospital Melbourne institutional stroke registry from 2003 until 2014. The SNPSR is a nationwide prospective registry, including all children living in Switzerland having AIS. More details on the SNPSR have been given in previous publications.[18,19] Excluded were children with neonatal stroke, underlying systemic conditions, and stroke because of other pathogeneses (eg, arterial dissection, Moyamoya disease, cardioembolism, and sinus venous thrombosis). Childhood AIS was defined as new focal neurological deficit with acute ischemic lesion on MRI in the corresponding vascular territory. FCA was defined as focal stenosis or irregularity affecting medium to large vessels of anterior or posterior circulation.[20]

Collected Variables at Stroke Onset

Clinical: sex, age at stroke, stroke severity (measured with the pediatric National Institute of Health Stroke Scale[21]; cases before 2011 were scored retrospectively[22]), preceding transient ischemic attack, seizures during acute stroke, time from symptom onset to MRI diagnosis (<6, <12, <24, and >24 hours), history of recent infection (categorized into 0=no history of infection, 1=history of varicella infection during the past 12 months, 2=history of nonvaricella infection during the past 4 weeks, such as fever, upper respiratory tract infections, including infectious symptoms [such as cough, vomiting, and diarrhea],[23,24] 3=combination of 1 and 2), cardiac work up, analysis of cerebrospinal fluid examination during acute AIS, treatment of AIS (antiplatelet, anticoagulation, steroid treatment [oral, intravenous, and duration measured in weeks]). Neuroimaging: type of vascular imaging (time of flight or contrast magnetic resonance angiography [MRA], computed tomographic angiography, conventional catheter cerebral angiography, or ultrasound), affected vessel, vessel status (complete occlusion or stenosis), dynamic evolution of vessel (worsening or improvement of stenosis, defined as decrease or increase in patent vessel diameter on follow-up MRA), infarction topography (thalamus, basal ganglia, internal capsule, caudate, cortex and white matter, cerebellum, and brain stem), time from first MRI to second and last MRI (measured in days and years, respectively).

Collected Variables During Follow-Up

Clinical: time from AIS onset to last follow-up (measured in years), neurological deficit (as measured by the Pediatric Stroke Outcome Measure [PSOM]),[25,26] clinical recurrence during follow-up period (defined as new focal neurological deficit with new infarction on MRI in the corresponding vascular territory). Neuroimaging: radiological recurrence during follow-up time (defined as new silent infarction on MRI without clinical manifestation), degree of stenosis at last follow-up MRI, evolution to a progressive arteriopathy (defined as progression of unilateral arteriopathy beyond 6 months or development into bilateral arteriopathy).[1]

Outcome

Primary outcome was the neurological/neurocognitive deficit at 6 months post-AIS as measured by the PSOM. A summary score of a maximum of 10 points (=worst outcome) can be reached. Secondary outcomes included resolution of arteriopathy at last follow-up MRI, dynamics of arteriopathy (progression/nonprogression), and clinical or radiological stroke recurrence.

Statistics

Continuous variables are summarized as mean (SD) or median (interquartile range) as appropriate, and categorical variables are given as frequencies (%). Comparison of outcome variables was performed using univariate analysis. Categorical outcome variables were assessed using χ^2/Fisher exact test and continuous variables using Wilcoxon rank-sum test. Adjustment for potential confounders (baseline pediatric National Institute of Health Stroke Scale and use of concomitant acyclovir) was performed using an ANCOVA. Confounders were chosen according to clinical importance. A $P<0.05$ was considered statistically significant. Analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC). The Swiss registry was approved by the cantonal ethic boards and by the Swiss Ministry of Health. The Royal Children's Hospital Melbourne stroke registry was approved by the institutional Human Research Ethics Committee (reference number 34097A).

Results

A total of 73 children (28 from the Royal Children's Hospital Melbourne and 45 from the SNPSR) with FCA (37 male, 50.7%) were included in the study, of whom 21 (29%) received CAT (8 from the Royal Children's Hospital Melbourne and 13 from the SNPSR). Although additional corticosteroids were used in 20% to 30% of children diagnosed with FCA in the first decade of the study period, treatment increased for the past 3 years (Figure 1). Details on the initial clinical presentation of the children are given in Table 1. A history of varicella infection in the previous 12 months was more frequent in the patients in the CAT group (P=0.037; Table 1). Cerebrospinal fluid analysis was performed in 29 (39.7%) children, of whom 14 (66.7%) were in the CAT group (P=0.003). Six children (20.7%) had a mononuclear pleocytosis (range, 16–39 cells) 5 (17.2%) had elevated protein (range, 0.61–0.83 g/L), with no difference between the 2 treatment groups. Cerebrospinal varicella zoster virus polymerase chain reaction and antibody testing were positive in 5 (28%) and 6 (86%) of respective children tested, once again, with no difference in the 2 groups (Table 1). Acyclovir was given more frequently in the CAT group (P<0.001). Corticosteroids (intravenous, oral, or combined) were given at the discretion of the treating physician (Table 1). The median (interquartile range) duration of corticosteroid treatment was 10 (2–16) weeks. Almost half of these children received initial high-dose intravenous methylprednisolone (10–20 mg/kg per dose, up to a maximum of 1 g per day) for 3 to 5 days, followed by an oral taper for several weeks.

A total of 67 (91.8%) children received at least 1 follow-up MRI after a median (interquartile range) of 42 (7–105) days. More than 1 follow-up MRI was recorded in 46 (63.0%) children after a median of 15 (7–31) months. The dynamic of the arteriopathy in the 2 different treatment groups is given in Figure 2A and 2B. Worsening of stenosis at first follow-up MRI/MRA was observed in 15 (22.4%) children while 4 (6.0%) and 26 (38.6%) showed normalization or improvement,

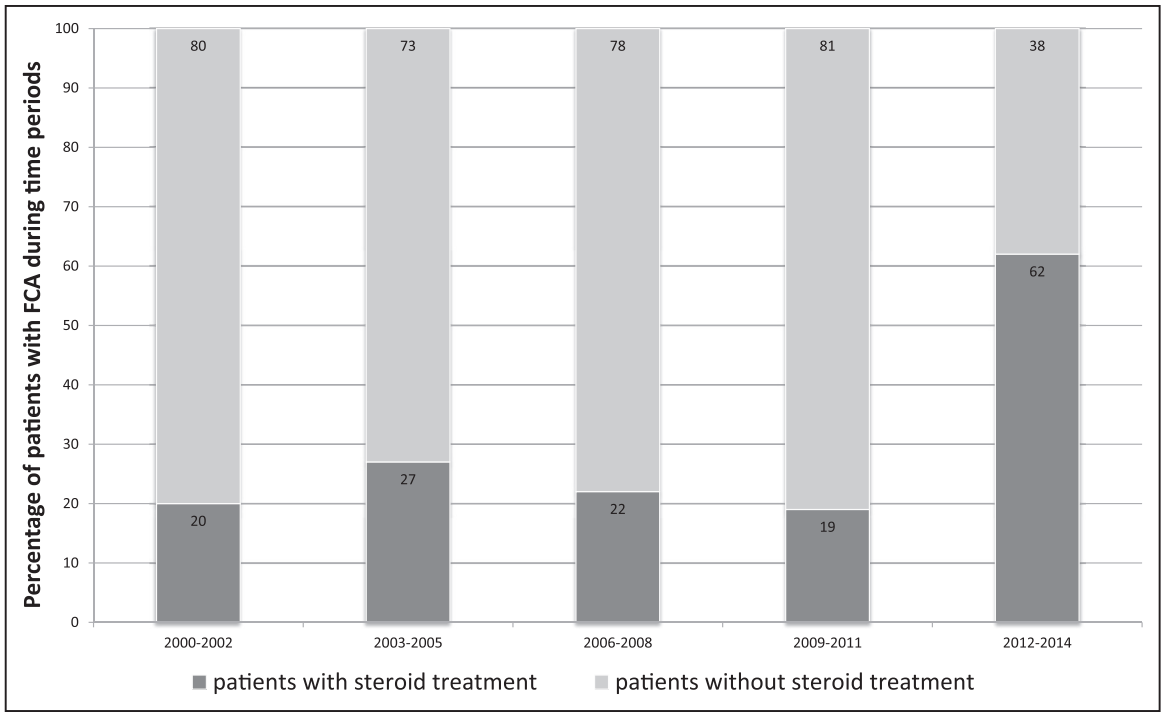

Figure 1. Use of steroids in arterial ischemic stroke (AIS) because of focal cerebral arteriopathy (FCA) over time. It shows the proportional increase of corticosteroid use since 2012 in children and adolescents having AIS because of FCA.

respectively (Figure 2A and 2B). Median duration of follow-up time and time point of performed MRI with regards to diagnosis did not differ between the 2 groups. At last follow-up, overall 9 (19.6%) children (8 in the AT group) had normal vascular imaging; however, the difference between the 2 groups was not statistically significant (P=0.400). Two children in the CAT group had radiological worsening of the arteriopathy on follow-up MRA >12 months after acute stroke. Both children were clinically stable, with no recurrent events or increase in infarct volume over time. One patient's initial follow-up scan during the first week suggested improvement, but a follow-up scan >12 months from diagnosis demonstrated worsening of the arteriopathy. The second child's first follow-up scan 3 months from diagnosis demonstrated worsening of the arteriopathy, which was then followed by Doppler ultrasonography showing persisting increased velocities in the right middle cerebral artery and lack of flow in the right anterior cerebral artery. The next MRI performed >12 months after acute stroke showed worsening of the arteriopathy compared with the previous MRA. The 2 groups did not differ with regards to the frequency of clinical recurrence—with 1 event in each group—(P=0.757) or for complete resolution of arteriopathy (P=0.400; Table 2). No child in either group had silent radiological recurrence during the follow-up period. Hemorrhagic transformation occurred in 6 children (8.2%), of whom 1 (4.8%) was in the CAT group.

Children treated with CAT showed a better clinical outcome compared with children treated with AT alone in the overall PSOM (P=0.035; Table 2). This finding was most pronounced for the cognitive/behavioral subscale of the PSOM (P=0.007) while the remaining subscales of the PSOM did not differ between the 2 treatment groups (Table 2). Better outcomes (overall PSOM and cognitive/behavioral subscale) persisted following adjustment for potential confounders (baseline pediatric National Institute of Health Stroke Scale and acyclovir use; Table 3). There was no association between mode of intravenous steroid treatment (intravenous, oral, or combination regimes) and outcome, for overall PSOM (P=0.502) or a cognitive/behavioral subscale scores (P=0.904). Outcomes in the 6 children in the CAT group receiving additional acyclovir did not differ for any PSOM subdomain compared with those receiving steroids alone.

Discussion

This study assessed the impact of additional corticosteroid treatment on clinical and radiological outcomes in children with AIS because of FCA compared with those treated with AT alone. The key finding was that children treated with additional corticosteroid treatment had better clinical outcomes than the AT treatment group particularly in the cognitive and behavior subdomain on the PSOM. In contrast, rates of recurrent stroke were low, with no difference between children receiving additional corticosteroid treatment and those who did not. Our study confirmed the association between FCA and recent varicella zoster virus infection,[12,27] previous radiological studies reporting the early dynamic behavior of the stenosis, with worsening of the arteriopathy during the first 6 months after diagnosis, and the high frequency of basal ganglia infarction ranging from 62% to 78%.[1,6]

As previously reported, the proximal MCA is the most frequently involved vessel in children with AIS because of FCA, but the vertebrobasilar circulation can also be affected.[1,6,28] Multiple stenoses within the same vascular territory were seen in ≈20% of our children. Conversion of FCA to a progressive arteriopathy

Table 1. Clinical, Radiological, and Treatment Characteristics of the Study Population at Presentation of Acute Stroke

	Whole Cohort (n=73)	CAT (n=21)	AT (n=52)	*P* Value
Age, median (IQR)	6.9 (4.4–12.1)	7.3 (5.3–13.7)	6.8 (4.0–11.6)	0.538
Sex, m (%)	37 (50.7)	10 (47.6)	27 (51.9)	0.800
PedNIHSS, median (IQR)	4 (2.0–8.5)	3 (2.0–8.0)	5 (3.0–9.0)	0.098
History of VZV infection, n (%)	19 (26.1)	9 (42.9)	10 (19.2)	0.037*
CSF VZV antibodies positive, n (%)/n children tested	6 (85.7)/7	3 (100)/3	3 (75.0)/4	0.350
CSF VZV PCR positive, n (%)/n children tested	5 (27.8)/18	3 (27.3)/11	2 (28.6)/7	0.964
Seizure at presentation, n (%)	7 (9.6)	0	7 (13.5)	0.077
TIA before acute stroke, n (%)	18 (24.7)	8 (38.1)	10 (19.2)	0.091
Affected vessel				0.734
ICA	15 (20.5)	4 (19.0)	11 (21.2)	
MCA	40 (54.8)	13 (61.9)	27 (51.8)	
ACA	5 (6.8)	2 (9.5)	3 (5.8)	
PCA	9 (12.4)	1 (4.8)	8 (15.4)	
BA	4 (5.5)	1 (4.8)	3 (5.8)	
Vessel affection				0.189
Occlusion, n (%)	22 (30.1)	4 (19.0)	18 (34.6)	
Stenosis, n (%)	51 (69.9)	17 (81.0)	34 (65.4)	
Multiple stenosis	14 (19.2)	5 (23.8)	9 (17.3)	
Lesion location				0.547
Thalamus	12 (16.4)	2 (9.5)	10 (19.2)	
Basal ganglia	45 (61.6)	15 (71.4)	30 (57.7)	
Cortex/WM	32 (43.8)	6 (28.6)	26 (50.0)	
Cerebellum	6 (8.2)	1 (4.8)	5 (9.6)	
Brain stem	5 (6.8)	1 (4.8)	4 (7.7)	
Acute therapy, n (%)				0.315
Antiplatelet only	39 (53.4)	11 (52.4)	28 (53.8)	
Anticoagulation only	17 (23.3)	7 (33.3)	10 (19.3)	
Combined	17 (23.3)	3 (14.3)	14 (26.9)	
Acyclovir given, n (%)	7 (9.6)	6 (28.6)	1 (1.9)	<0.001
Steroids given per epoch, n (%)/n children diagnosed with FCA		…	…	0.078
2000–2002	1 (20)/5			
2003–2005	3 (27)/11			
2006–2008	5 (22)/23			
2009–2011	4 (19)/21			
2012–2014	8 (62)/13			
Steroid regimen	…		…	…
Intravenous only		2 (9.5)		
Oral only		9 (42.9)		
Combined		10 (47.6)		

ACA indicates anterior cerebral artery; AT, antithrombotic treatment; BA, basilar artery; CAT, combined corticosteroid antithrombotic treatment; CSF, cerebral spinal fluid; FCA, focal cerebral arteriopathy; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCR, polymerase chain reaction; pedNIHSS, pediatric national institute of health stroke scale; TIA, transient ischemic attack; VZV, varicella zoster virus; and WM, white matter.

*Statistically significant value.

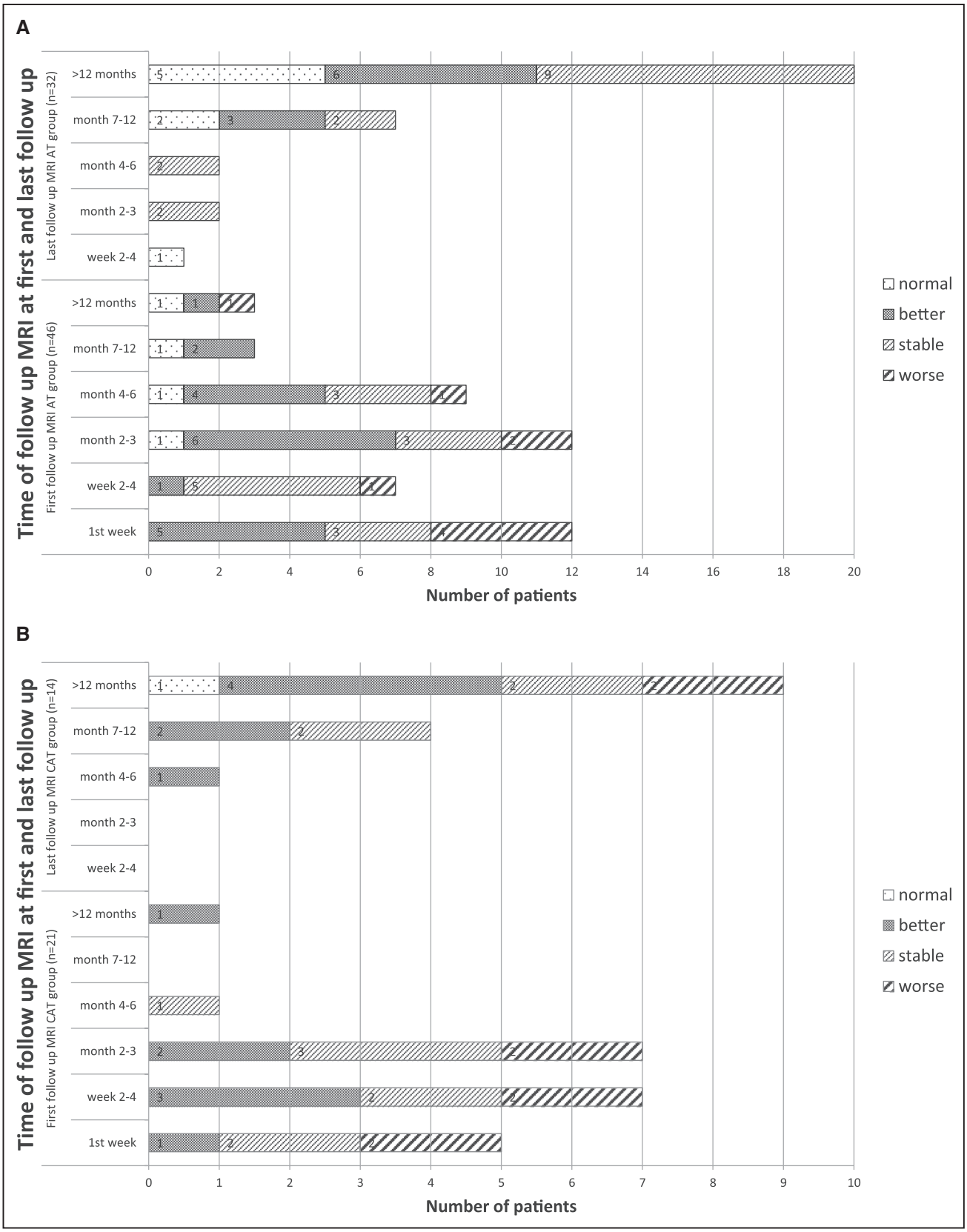

Figure 2. Evolution of arteriopathy during follow-up time in the antithrombotic treatment (AT) group (**A**) and in the corticosteroid antithrombotic treatment (CAT) group. It shows the dynamics of the arteriopathy in (**A**) the AT group and (**B**) in the CAT group.

Table 2. Comparison of Outcomes Between the 2 Groups

	Whole Cohort (n=73)	CAT (n=21)	AT (n=52)	*P* Value
Pediatric stroke outcome measure				
PSOM, median (IQR)	1.0 (0.5–1.5)	0.5 (0–1.5)	1.0 (0.5–2.0)	0.035†
PSOM SMR, median (IQR)	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)	0.579
PSOM SML, median (IQR)	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)	0.165
PSOM language production, median (IQR)	0 (0)	0 (0)	0 (0–0.5)	0.362
PSOM language comprehension, median (IQR)	0 (0)	0 (0)	0 (0)	0.899
PSOM cognition/behavior, median (IQR)	0.5 (0–1.0)	0 (0–0.5)	0.5 (0–1.0)	0.007†
Dynamics of the arteriopathy				
Initial progression of arteriopathy, n (%)	15 (22.4%)	6 (28.6)	9 (17.3)	0.281
Complete resolution of stenosis, n (%)*	9 (19.6)	1 (7.1)	8 (25.0)	0.400
Recurrence, n (%)	2 (2.7)	1 (4.8)	1 (2.0)	0.757

AT indicates antithrombotic treatment; CAT, combined corticosteroid antithrombotic treatment; IQR, interquartile range; PSOM, pediatric stroke outcome measure; SML, sensorimotor left; and SMR, sensorimotor right.

*For last follow-up, MRI n=46 for the whole cohort, n=14 in the CAT and n=32 in the AT group.

†Statistically significant value.

is described in 6% to 20% of cases,[1,6] particularly in children with occlusion or posterior circulation arteriopathy at initial diagnosis. We observed low rates of radiologically progressive arteriopathy, which were similar to a previous European study with comparable duration of follow-up (1.25 versus 1.4 years).[1] None of the 3 children (4.1%) in the current study with radiological worsening of the vasculopathy beyond 6 months of time had clinical deterioration or recurrent events. One child did not undergo follow-up imaging until 12 months after presentation, and another underwent imaging at 3 and 12 months poststroke. We could not, therefore, determine the time at which worsening of the vasculopathy occurred in these 2 children, leaving us with 1 patient who demonstrated continued worsening of the arteriopathy on all follow-up scans up to 84 months post-event. There may, however, be a small proportion of children who have worsening beyond >6 months with subsequent stabilization and no clinical deterioration. Thus, continued radiological surveillance is important to confidently differentiate children at risk of progressive worsening, from those whose arteriopathy is improving, to guide further investigation and treatment with additional immunosuppressive treatment.

Recurrent events were low in our study (2.7%) similar to the 4% rates reported in a recent Korean study but lower than the 18% rates reported in a European study.[1,6] These differences may relate to variation in acute treatment protocols, such as immediate use of aspirin and anticoagulant therapies as secondary prophylaxes. There was no difference in recurrent stroke between children receiving additional corticosteroid treatment and those who did not. We did not identify a significant difference in baseline characteristics of the 2 treatment groups—in our study, the initial pediatric National Institute of Health Stroke Scale was even lower in the CAT group (median 3 versus 5; *P*=0.098)—making a confounding by indication bias unlikely. In summary, although of high clinical impact, fortunately recurrence of stroke does not seem to be a frequent event to worsen outcome of these children.

Children receiving additional corticosteroid treatment showed better clinical outcomes compared with children receiving AT alone, particularly in the cognitive/behavioral domain on the PSOM. This finding persisted after adjusting for potential confounders. Cognitive problems are reported in 11% to 19% of pediatric stroke survivors in population-based[29,30] and large single-center studies[25] and suggest that even small improvements, such as shown in our study, are of importance to the affected families.[31]

Despite the potential positive effect of CAT, there is limited understanding of pathophysiology underlying FCA because of limited histopathologic studies,[10,11] and therefore, the role and mechanism of action of corticosteroid therapy on improving outcomes are unclear. Because steroids are implemented when stroke is already apparent, a direct beneficial impact on the ischemic lesion is unlikely. Steroids might rather influence the inflammatory cascade in the vessel wall, assuming less progression or faster regression of the arteriopathy, or early vascular remodeling may result in better cerebral perfusion. For children with focal arteriopathy, it is unknown, whether persistence of severe stenosis increases the volume of infarction in the subacute phase, or has a negative impact on early reorganization process, and thus adversely influences the outcome of these children.

Clinical outcome is more suitable for primary outcome than stroke recurrence for possible treatment trials given the low rates of recurrent events in the current study. The possible importance of early reperfusion for faster recovery and thus

Table 3. Analysis of Covariance of the Effect of Treatment on Outcome (PSOM Total)

	Coefficient	SE	*P* Value
CAT (vs AT)	−0.456	0.223	0.045*
Baseline PedNIHSS	0.100	0.020	<0.001*
No acyclovir use (vs acyclovir use)	−0.258	0.365	0.482

Multiple R^2: 0.323. AT indicates antithrombotic treatment; CAT, combined corticosteroid antithrombotic treatment; pedNIHSS, pediatric national institute of health stroke scale; and PSOM, pediatric stroke outcome measure.

*Statistically significant value.

better outcome may make time to clinical recovery within the first few months after the event a useful secondary outcome measure.

The role of concomitant antiviral therapy in FCA treated with steroids is unclear. There were higher rates of varicella zoster virus infection in the CAT group, but we did not find a difference in outcomes between children treated with steroids and those treated with steroids and acyclovir, and the beneficial effect of steroids was not confounded by use of acyclovir. The small sample size, however, limits interpretation of the study findings. There are concerns about the immunosuppressive effect of steroids in children with herpes group viral infection and the majority of pediatric neurologists surveyed using a Delphi consensus process felt that acyclovir treatment should be used in future trials of steroids for FCA, until active infection by herpes and varicella virus was excluded.[32]

The study has other limitations. The small sample size, variation in corticosteroid protocols, and low frequency of follow-up neuroimaging may explain the negative findings for stroke recurrence or early radiological progression of arteriopathy. Weekly or fortnightly MRA may be required to address the question of radiological progression, but the need for sedation in young children makes repeated imaging in the first days to weeks challenging. It was also not possible to assess the effect of corticosteroids on cerebral perfusion because perfusion MRI was not routinely done in the first week after diagnosis. Furthermore, volumetric assessments were not performed. Finally, the retrospective study design that introduced selection bias, heterogeneity, and variation in treatment protocols, for both AT and CAT groups, limited our ability to explore more factors predictive of better outcome.

In conclusion, use of steroids in children with AIS because of FCA may be associated with improved neurological outcomes, but the effect is relatively small, and the inherent limitations associated with the retrospective study design mean the findings need to be confirmed in future studies. In contrast, there were low overall rates of recurrence in this multicenter cohort of children with FCA, with no benefit demonstrated from additional corticosteroid therapy over standard AT. Therefore, large international randomized controlled trials are needed to investigate whether the use of additional corticosteroids is beneficial in this patient population. The study design agreed on within a group of European Australian experts in the field of pediatric stroke is a randomized controlled trial with high-dose steroids and aspirin, compared with aspirin alone, in the acute phase of stroke because of a FCA.[32]

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