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Incidence of Recurrence in Posterior Circulation Childhood Arterial Ischemic Stroke

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Abstract

IMPORTANCE—Childhood arterial ischemic stroke (CAIS) affects approximately 1.6 per 100 000 children per year, while stroke recurs in up to 20%of patients at 5 years. Factors determining the risk of recurrence are incompletely understood.

OBJECTIVE—To investigate the incidence of the recurrence of CAIS in the posterior and anterior circulations to determine if the risk differs between the 2 locations.

DESIGN, SETTING, AND PARTICIPANTS—A retrospective analysis of CAIS was conducted among children enrolled in a single-center prospective consecutive cohort at The Children's Hospital of Philadelphia between January 1, 2006, and January 1, 2015. Children with confirmed CAIS occurring between 29 days and 17.99 years were evaluated for inclusion. Patients were excluded if infarcts were located in both the anterior and posterior distributions or if CAIS occurred as a complication of intracranial surgery or brain tumor.

MAIN OUTCOMES AND MEASURES—Stroke recurrence.

RESULTS—The study population included 107 patients (75 boys [70.1%] and 32 girls [29.9%]; median age at AIS, 7.7 years [interquartile range, 3.1–13.6 years]). Sixty-one children had anterior circulation CAIS (ACAIS) and 46 had posterior circulation CAIS (PCAIS). Median follow-up was

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Study concept and design: Uohara, Beslow, Ichord.
Acquisition, analysis, or interpretation of data: All authors.
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20.9 months (interquartile range, 8.7–40.4 months). For ACAIS, recurrence-free survival was 100% at 1 month and 96%(95%CI, 85%–99%) at 1 and 3 years. For PCAIS, recurrence-free survival was 88%(95%CI, 75%–95%) at 1 month and 81%(95% CI, 66%–90%) at 1 and 3 years. The hazard ratio for recurrence after PCAIS compared with ACAIS was 6.4 (95%CI, 1.4–29.8; P = .02) in univariable analysis and 5.3 (95%CI, 1.1–26.4; P = .04) after adjusting for sex and cervical dissection.

CONCLUSIONS AND RELEVANCE—We identified a subgroup of patients that comprise more than 80% of recurrences of CAIS. Three years after incident stroke, 19% of children with PCAIS had a recurrence compared with 4%of patients with ACAIS. Different mechanisms of stroke may account for this difference. Children with PCAIS may warrant increased monitoring. This study highlights the necessity for further research focused on recurrence prevention.

Childhood arterial ischemic stroke (CAIS) affects 1.6 per 100000 children per year and is an important cause of neurologic morbidity.[1] In a population-based cohort study, recurrent ischemic events occurred in 19% of children at 5 years.[2] Although previous consideration has been given to risk factors for recurrence of CAIS, relatively little attention has been given to how distinct pathophysiological mechanisms may differentially affect the anterior circulation compared with the posterior circulation, resulting in differences in the risk of recurrence.[2,3]

Arterial ischemic stroke isolated to the posterior circulation is less common than arterial ischemic stroke in the anterior circulation, accounting for approximately 20% of cases in large multicenter prospective cohorts.[4] Clinical observations suggest that CAIS in the posterior circulation tends to recur at higher rates than does CAIS restricted to the anterior circulation, but this possibility has yet to be adequately investigated. In previously reported small cohort studies of 22 and 27 children with posterior circulation childhood arterial ischemic stroke (PCAIS), recurrent stroke was estimated to occur in 23% and 52% of patients, respectively.[2,5,6] In these studies, analysis of the risk of recurrence comparing children with PCAIS with those with anterior circulation childhood arterial ischemic stroke (ACAIS) was not performed. In this study, we aimed to compare the risk of recurrence in children with PCAIS with that seen in children with ACAIS. Furthermore, we hope that this study will provide the basis for further investigation into the mechanisms of stroke unique to each distribution that may influence their rates of recurrence.

Methods

Study Design

We conducted a retrospective analysis of a single-center, prospectively enrolled consecutive cohort of children with CAIS who presented to The Children’s Hospital of Philadelphia, a tertiary care center, between January 1,2006, and January 1, 2015. Written informed consent was obtained from all participants’ parents, and assent was obtained from the children when appropriate. The study was approved by The Children’s Hospital of Philadelphia Committees for the Protection of Human Subjects (institutional review board). Results of acute neuroimaging were assessed for infarct location and distribution. All available records were assessed for clinical and radiographic evidence of stroke recurrence.

Inclusion and Exclusion Criteria

Inclusion criteria were age at stroke onset of 29 days to 17.99 years, confirmed diagnosis of acute CAIS, and availability of results from diagnostic studies of stroke risk factors, including complete vascular imaging (head and neck) and cardiac evaluation, sufficient to assign a stroke subtype. Children were excluded from the study if infarcts were located in both the anterior and posterior distributions or if AIS occurred as a complication of intracranial surgery or brain tumor.

Key Points

Question

Does the incidence of stroke recurrence differ between posterior circulation childhood arterial ischemic stroke (PCAIS) and anterior circulation childhood arterial ischemic stroke (ACAIS)?

Findings

In this cohort study of children with arterial ischemic stroke, recurrence of PCAIS was 19% at 1 and 3 years compared with 4%recurrence for ACAIS at 1 and 3 years.

Meaning

In our cohort, the recurrence of PCAIS exceeded that of ACAIS; thus, patients with PCAIS may warrant additional monitoring aimed at minimizing the risk of recurrence.

Definitions

Acute CAIS was defined as the presence of an acute focal neurologic deficit conforming to a vascular territory with an acute infarct seen on diagnostic imaging (computed tomography or magnetic resonance imaging [MRI]) corresponding to the deficit.[7] *Isolated ACAIS* was defined as parenchymal infarction located only within regions supplied by the carotid system. *Isolated PCAIS* was defined as parenchymal infarction located only within regions supplied by the vertebrobasilar system. *Transient ischemic attack* (TIA) was defined as a brief episode of focal neurologic dysfunction conforming to a vascular territory caused by cerebral ischemia but not resulting in cerebral infarction (diffusion restriction seen on MRI or hypodensity seen on computed tomography).[8] Acute imaging was assessed for the presence of clinically silent infarction (encephalomalacia or volume loss) not otherwise attributable to a past clinical event.

Stroke subtypes were classified by 2 of us (M.Y.U. and R.N.I.) using the Childhood AIS Standardized Classification System and Diagnostic Evaluation (CASCADE) criteria (Table 1).[9] Classification of cervical artery dissection was determined by consensus involving the stroke neurologist (R.N.I.) and vascular neuroradiologist on review of imaging and clinical data based on 1 or more of the following findings[7,9]: (1) angiographic findings of a double lumen, intimal flap, or pseudoaneurysm, or, on axial T1 fat saturation MRI images, a “bright crescent sign” in the arterial wall; (2) the sequence of cervical or cranial trauma, neck pain, or head pain less than 6 weeks preceding angiographic findings of segmental arterial stenosis (or occlusion) located in the cervical arteries; or (3) angiographic findings of

segmental stenosis (or occlusion) of the vertebral artery at the level of the C2 vertebral body, even without known traumatic history. Suspected cervical vertebral dissection was determined based on the findings of multiple posterior circulation infarcts of varying ages present at the time of initial presentation in the setting of a history of cervical or cranial trauma within the preceding 6 weeks. The classification of suspected cervical vertebral artery dissection was changed to confirmed dissection if follow-up imaging showed new vascular abnormalities meeting 1 of the criteria described above.

Decisions regarding diagnostic testing and treatment were determined according to an institutional stroke pathway based on published guidelines for childhood stroke.[10,11] All patients initially underwent noninvasive imaging with MRI and magnetic resonance angiography of the head and neck or with computed tomography and computed tomography angiography if MRI was contraindicated. In cases in which MRI findings were equivocal for cervical dissection, computed tomography angiography was performed. Catheter angiography is rarely performed acutely at The Children's Hospital of Philadelphia in cases of suspected cervical dissection because decisions regarding antithrombotic treatment are rarely altered by the findings; we treat all suspected dissections in the same manner as confirmed ones.

Acute antithrombotic treatment was administered unless there was a specific contraindication. Treatment was classified as systemic anticoagulation (low-molecular-weight heparin sodium or warfarin sodium), antiplatelet therapy (aspirin), or both. Patients with suspected or confirmed cervical artery dissection were generally treated with systemic anticoagulation as initial therapy. Treatment of patients with recurrent stroke while being treated with the initial single agent (antiplatelet therapy or anticoagulation alone) was typically escalated to dual antithrombotic therapy (combined antiplatelet therapy and anticoagulation) and continued for 3 to 12 months, after which aspirin monotherapy was then maintained for a minimum of 2 additional years.

The need for follow-up imaging was determined clinically by the treating pediatric stroke neurologist. A recurrent ischemic event was defined as either a new clinical symptom conforming to an arterial distribution and confirmed radiographically or a clinically asymptomatic new infarction identified on follow-up surveillance imaging. Typical follow-up surveillance imaging was performed in accordance with the institutional stroke protocol, which recommends follow-up MRI at 3 to 6 months and 12 months after the incident stroke, regardless of the presence of new clinical symptoms. For this analysis, TIA was not considered a recurrent event. Any changes in antithrombotic treatment after stroke recurrence were abstracted.

Statistical Analysis

All analyses were conducted with STATA, version 12.0 (Stata Corp). Kaplan-Meier methods were used to estimate recurrence-free survival. Survival was calculated from the date of incident CAIS to the date of recurrence; patients without recurrence were censored at the last clinic visit. Cox proportional hazards regression models were used to compare the risk of recurrence between PCAIS and ACAIS in both univariable and multivariable analyses.

Given our sample size, factors with $P < .20$ in univariable analyses were included in the multivariable model. $P \leq .05$ was considered statistically significant.

Results

One hundred thirty-four children with CAIS were identified from the institutional stroke registry. Of these children, 13 were excluded because infarcts were located in both the anteriorand posterior distributions, and 14 were excluded because AIS occurred as a complication of intracranial surgery or brain tumor, leaving 107 participants in the study cohort (eFigure in the Supplement). Table 1 provides details of the study population; 61 patients (57.0%) had isolated ACAIS and 46 (43.0%) had isolated PCAIS (eFigure in the Supplement). Median follow-up was 20.9 months (interquartile range, 8.7–40.4 months).

Demographics

Seventy-five children (70.1%) were male; 72 (67.3%) were white, 21 (19.6%) were African American, 8 (7.5%) were other or unspecified race, and 6 (5.6%) were Hispanic. Median age at AIS was 7.7 years (range, 0.2–18.0 years). Six patients (5.6%) died during the study. All deaths occurred before hospital discharge and were not directly attributable to the patients' strokes.

Stroke Subtype (CASCADE Classification)

Of all CAIS, 28 (26.2%) were classified as cervicoaortic arteriopathy, 24 (22.4%) as cardiogenic, 19 (17.8%) as unilateral focal cerebral arteriopathy, 17 (15.9%) as indeterminate, 9 (8.4%) as bilateral cerebral arteriopathy, 7 (6.5%) as small vessel disease, 2 (1.9%) as multifactorial, and 1 (0.9%) as "other" (sickle cell disease without vasculopathy) (Table 1 and the eTable in the Supplement). Of the 28 with cervicoaortic arteriopathy, 24 had suspected or confirmed cervical dissections: 19 vertebral and 5 carotid.

Vertebral Artery Dissection

Of 19 vertebral dissections, 10 (52.6%) were confirmed and 9 (47.4%) were suspected. All patients underwent vascular imaging (either magnetic resonance angiography or computed tomography angiography) (Table 2).

Multiple Infarcts

Six patients (5.6%; 4 with ACAIS and 2 with PCAIS) had evidence of prior infarction at initial presentation. Of those with evidence of prior infarction, 4 had moyamoya disease (1 of the 4 also had sickle cell anemia), 1 had cervical dissection, and 1 had acute systemic disease.

Treatment

Ninety-nine of 107 patients (92.5%) received acute antithrombotic treatment. Of these patients, 56 (56.6%) received aspirin, 42 (42.4%) received anticoagulation, and 1 (1.0%) received both (Table 1). The eTable in the Supplement displays information about acute antithrombotic treatment. All patients with recurrent AIS were receiving antithrombotic therapy at the time of recurrence. Table 3 shows treatment changes after recurrence.

Stroke Recurrence

Table 3 provides details on the 11 patients (10.3%) with recurrent AIS. Recurrence-free survival in the entire cohort at 1 month was 95% (95% CI, 88%–98%) and at 1 and 3 years was 90% (95%CI, 82%–94%). Ten of the 11 patients (90.9%) experienced recurrence within the first 6 months after AIS, of which 5 (45.5%) recurred within the first month (Figure). No patient with recurrent AIS had severe direct head or neck trauma, boney abnormalities, or connective tissue disease. Several patients with and without recurrence had a history of minor trauma or incidents of forceful or repetitive neck motion preceding their initial stroke. One patient with sickle cell anemia and an abnormal anatomical variant of the vertebrobasilar system had a recurrent stroke 40 months after the incident stroke. Before recurrence, this patient was prescribed aspirin and regular transfusions; this treatment was modified to include anticoagulation following the recurrence. Ten of 11 recurrences remained within the same arterial distribution as the incident infarction. One recurrence was in the same distribution as the incident stroke (posterior circulation), but additional scattered punctate foci of ischemia were also present in the anterior circulation. Ten of 11 recurrences were discovered in the setting of new clinical symptoms, which prompted neuroimaging. One clinically silent recurrence was seen on surveillance MRI.

Table 4 shows univariable Cox proportional hazards regression models to evaluate risk factors for recurrence. Ten of 11 recurrent strokes (90.9%) were in males. Of 19 patients with CASCADE focal intracranial cerebral arteriopathy, only 2 (10.5%) had recurrent stroke. Among 19 patients with cervical vertebral artery dissection, 5 (26.3%) had recurrence. However, in univariable and multivariable analyses, only posterior circulation location was a risk factor for recurrence. Nine recurrent strokes were in patients with PCAIS and 2 were in children with ACAIS. Recurrence-free survival after PCAIS at 1 month was 88% (95% CI, 75%–95%) and at 1 and 3 years was 81% (95% CI, 66%–90%) (Figure). Of PCAIS recurrences, 5 of 9 patients (55.6%) had cervical dissections (2 with concomitant thrombophilia), 2 (22.2%) had cardiogenic AIS (1 with concomitant thrombophilia), 1 (11.1%) had sickle cell anemia, and 1 (11.1%) had no risk factor identified. Two of 9 patients with PCAIS (22.2%) had multiple recurrences. Of these 2 patients, 1 had a cervical dissection with thrombophilia (elevated lupus anticoagulant), while the other child's etiologic factors were indeterminate. Recurrence-free survival after ACAIS at 1 month was 100% and at both 1 and 3 years was 96% (95% CI, 85%–99%). Of ACAIS recurrences, 1 patient had probable small vessel disease, and the other had focal cerebral arteriopathy and thrombophilia (elevated lipoprotein a).

In univariable analysis, the hazard ratio for recurrence after PCAIS compared with that after ACAIS was 6.4 (95%CI, 1.4–29.8; $P = .02$). In a multivariable analysis including sex and cervical dissection, the hazard ratio for recurrence after PCAIS compared with that after ACAIS was 5.3 (95% CI, 1.1–26.4; $P = .04$).

Discussion

We examined recurrence-free survival in a prospective cohort of children with CAIS and examined recurrence in patients with posterior circulation stroke compared with those with anterior circulation stroke. In the entire cohort, recurrence was estimated to occur in 10.3%

of patients at 3 years. Recurrence was more common after CAIS isolated to the posterior circulation than after CAIS isolated to the anterior circulation, even after adjusting for sex and the presence of cervical dissection (hazard ratio, 5.3). In fact, at 3 years after the incident stroke,19%of those with PCAIS had a recurrent stroke while only 4% of those with ACAIS had recurrence.

Our findings that PCAIS is more likely to recur than ACAIS cannot be viewed without discussion of the pathologic findings distinct to each distribution that may affect the risk of recurrence. Although dissection was not independently associated with recurrence risk, 20.8%of children with cervical artery dissection (5 of 24) in this cohort had recurrence (5 of 19 [26.3%] with vertebrobasilar dissection). These findings support those by Fullerton et al[12] that reported recurrent stroke in 7 of 47 patients (15%) with posterior cerebral artery dissection and 4 of 73 patients (5%) with anterior cerebral artery dissection. The Cervical Artery Dissection in Stroke Study (CADISS) demonstrated that risk of recurrent stroke after adult dissection was low as seen in 4 of 250 patients at 3 months.[13] Our finding that 20.8% of children with dissection had recurrence may indicate that cervical dissection in children is a different pathophysiological process than in adults, with a different risk of recurrence, and suggests that management implications from the CADISS study, or other similar studies in adults, may not be generalizable to children. To further distinguish stroke caused by dissection in children from that in adults, our results also indicate that, in children, vertebrobasilar dissection is more common than carotid dissection, a phenomenon that is reversed in adults.[13,14]

Our study cohort was 70.1% male, a slight overrepresentation compared with previous studies.[2,5,15] Although the predominance of recurrent stroke observed in males in this study was not statistically significant (10 of 11 recurrences), these results support the proposition by Golomb et al[15] that behavioral differences or X-linked disorders may contribute to the increased incidence of stroke among males and to differences in rates of recurrence. Another possible explanation for these findings is that the rate of arterial dissection, previously shown to be higher in males than in females, is in part responsible.[12,15] In our study, 5 of 9 recurrences of PCAIS were in patients with dissections (2 had concurrent thrombophilia), and all were male. Patients with PCAIS and those with vertebral artery dissections were highly represented in our study, comprising 43.0% and 17.8% of our overall cohort, respectively, which may represent referral bias to our tertiary center.

Most recurrences occurred within 6 months following acute stroke, with the highest risk in the first month. Most patients with recurrent AIS had a single recurrence, which prompted treatment modification; subsequently, the patients remained recurrence free. Despite several studies demonstrating the safety of anticoagulation, to our knowledge, there have been no randomized clinical trials that address its efficacy in CAIS.[16–18] In our study, nearly all patients (92.5%) and all patients with recurrence were treated acutely with an antithrombotic medication, and most patients received monotherapy (98 of 99 [99.0%]). Among those with recurrent stroke, 4 were receiving anticoagulation therapy and 7 were taking aspirin at the time of recurrence. However, it was not possible to evaluate the efficacy of aspirin vs anticoagulation therapy in this observational study. Although antithrombotic therapy probably reduces the risk of recurrence, it clearly does not prevent all recurrentevents.[2,10,19]

Our results raise a question as to whether current protocols that use antithrombotic monotherapy are sufficient to prevent recurrent strokes in children with PCAIS. Furthermore, results of this study suggest that children with PCAIS may benefit from a different approach to secondary stroke prevention. One such area that deserves further investigation is treatment with both an anticoagulant and antiplatelet agent. However, systematic evaluation of safety and efficacy of this dual approach warrants specific study before it is widely adopted because hemorrhagic transformation is common following CAIS, and dual therapy could increase the risk for hemorrhagic transformation.[20] Although the purpose of our study was not to evaluate the safety of dual antithrombotic therapy, 6 children in our cohort were treated with dual therapy following recurrence. Of these children who received dual therapy, none had hemorrhagic transformation or systemic bleeding complications.

Limitations

This study has several limitations. First, because this study was observational, decisions to perform repeat neuroimaging studies were made clinically; thus, we may have underestimated recurrence. Second, ascertainment of dissection was based mainly on results of noninvasive imaging, which may have resulted in underestimation. This limitation is inherent in our institutional practice of minimizing exposure of patients to invasive diagnostic procedures that will ultimately have limited or no effect on our treatment decisions because our practice is to treat all suspected dissections as though they were confirmed. Many centers use catheter angiography safely and effectively to confirm the diagnosis of dissection.[21] Furthermore, we excluded patients with strokes that affected both the carotid and vertebrobasilar systems; hence, more investigation is needed to describe this subgroup. Also, differences between our study and other cohorts might limit the generalizability. Recurrence among children with moyamoya disease in previously published studies is as high as 29%[3,5,22,23]; however, of the 10 children with moyamoya disease in our study, all of whom had ACAIS, none had recurrence. Although the lack of recurrent stroke among the patients in our study with moyamoya disease may highlight the success of advances in medical care and surgical interventions, the rate of recurrence in patients with ACAIS may be higher in other cohorts. Another difference between our study and other published cohorts is the low rate of recurrence in our patients with focal cerebral arteriopathy (10.5%). Risk of recurrence has been described as high as 25% in such patients.[24] Last, this study was not a randomized clinical trial, and acute treatment decisions were made by one of several clinicians. The lack of a trial design and confounding by indication make it impossible to evaluate treatment effects.

Conclusions

We demonstrated that the risk of recurrence after PCAIS exceeds that after ACAIS; the subgroup of patients with PCAIS comprised 81.8%of the recurrences. Children with PCAIS may warrant increased monitoring. This study highlights the necessity for further research focused on prevention of recurrence, including the safety and efficacy of dual antithrombotic therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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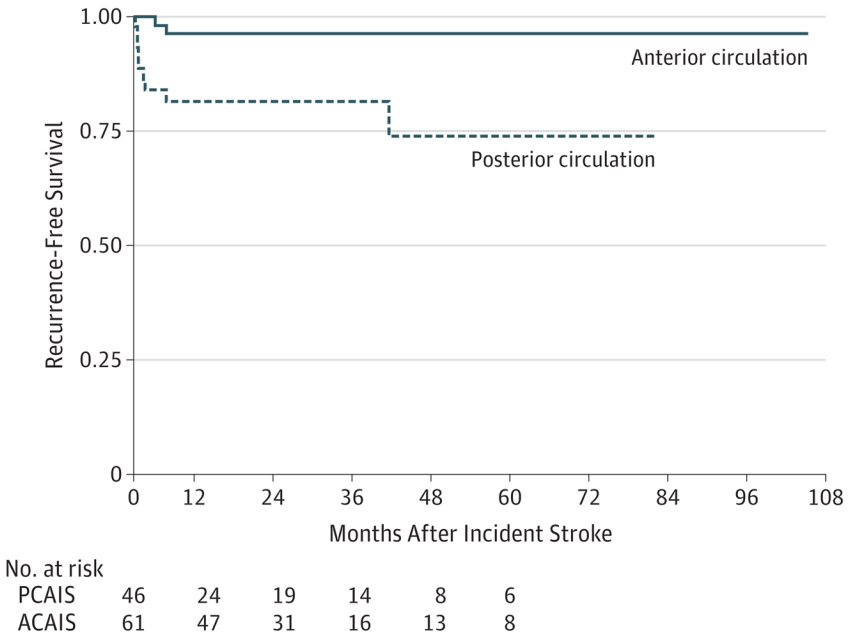

Figure. Kaplan-Meier Survival Curve

Recurrence-free survival of patients with posterior circulation childhood arterial ischemic stroke (PCAIS) and anterior circulation childhood arterial ischemic stroke (ACAIS).

Table 1

Patient Characteristics

Characteristic	Value[a]		
	ACAIS	PCAIS	Overall
Total	61 (57.0)	46 (43.0)	107
Demographics			
Age, median, y	7.2	9.2	7.7
Male	40 (65.6)	35 (76.1)	75 (70.1)
Stroke subtype (CASCADE)			
Cardiogenic	16 (26.2)	8 (17.4)	24 (22.4)
Intracranial vasculopathy			
Focal cerebral arteriopathy	12 (19.7)	7 (15.2)	19 (17.8)
Steno-occlusive	8 (13.1)	1 (2.2)	9 (8.4)
Small vessel disease	4 (6.6)	3 (6.5)	7 (6.5)
Extracranial vasculopathy, cervico-aortic	8 (13.1)	20 (43.5)	28 (26.2)
Other	0	1 (2.2)	1 (0.9)
Indeterminate	12 (19.7)	5 (10.9)	17 (15.9)
Multifactorial	1 (1.6)	1 (2.2)	2 (1.9)
Treatment			
Anticoagulation monotherapy	18 (29.5)	24 (52.2)	42 (39.3)
Aspirin monotherapy	37 (60.7)	19 (41.3)	56 (52.3)
Anticoagulation and aspirin	0	1 (2.2)	1 (0.9)
None	6 (9.8)	2 (4.3)	8 (7.5)
Acute imaging			
MRI	58 (95.1)	44 (95.7)	102 (95.3)
CT only	3 (4.9)	2 (4.4)	5 (4.7)

Abbreviations: ACAIS, anterior circulation childhood arterial ischemic stroke; CASCADE, Childhood AIS Standardized Classification System and Diagnostic Evaluation; CT, computed tomography; MRI, magnetic resonance imaging; PCAIS, posterior circulation childhood arterial ischemic stroke.

[a]Data are presented as number (percentage) of patients unless otherwise indicated.

Table 2

Vertebral Artery Dissections

Sex/Age, y	Suspected or Confirmed[a]	Imaging Type	Repeat Imaging	Time to Imaging, d	Acute Treatment	Pertinent Imaging Findings
M/4.9	Confirmed (definitions 1 and 2)	MRI and MRA	Angiography	0	Aspirin	PCA occlusion with traumatic damage to vertebral arteries of the upper cervical spine level
M/5.0	Confirmed (definition 3)	MRI and MRA	None	0	LMWH	Complete absence of flow in the left vertebral artery
M/6.9	Confirmed (definition 3)	MRI and MRA	None	2	LMWH	Markedly decreased signal in the vertebral artery; T1 of the neck showing thrombus within the cervical portion of the right vertebral artery
M/12.9	Suspected	MRI and MRA	CTA	0	Aspirin	Occluded basilar artery with patent vertebral arteries; bilateral PCAs filled via posterior communicating arteries
M/5.7	Suspected	MRI and MRA	None	0	LMWH	Scattered areas of cerebral infarction of different chronicity in posterior circulation; questionable area of irregularity at the posterior-medial aspect of the left vertebral artery's origin
M/8.3	Suspected	MRI and MRA	None	5	LMWH	Multifocal infarcts within the brain parenchyma; absent flow in the PCA
F/8.3	Suspected	MRI and MRA	None	5	LMWH	Focus of cystic encephalomalacia at the mesencephalic-pontine junction; absent posterior communicating artery
M/4.4[b]	Confirmed (definitions 1 and 3)	MRI and MRA	Angiography	23	LMWH	Multiple infarcts in temporal lobe and bilateral thalami; repeat catheter angiography showed dissection with near occlusion of the cervical left vertebral artery
M/4.1	Suspected	MRI and MRA	None	2	LMWH	Multiple infarcts in the cerebellar hemispheres with history of prior trauma
M/2.0	Confirmed (definition 1)	MRI and MRA	None	1	Aspirin	Irregularity of the lumen of the left vertebral artery at the level of C2
F/13.6	Suspected	MRI and MRA	None	2	Aspirin	Multiple areas of infarction seen as restricted diffusion involving the inferior cerebellar hemisphere cortex and dorsal medulla
M/7.4[b]	Confirmed (definition 3)	MRI and MRA	Angiography	1	LMWH	Multiple areas of infarction in the cerebellar hemisphere, thalamus, and para median occipital and parietal lobes; filling defect in the left vertebral artery at the level of C2–C3 consistent with a nonocclusive thrombus
M/6.9	Confirmed (definition 3)	MRI and MRA	None	1	None	Multiple areas of infarction in the cerebellum, thalamus, and parietal lobe; high-grade stenosis of the vertebral artery consistent with prior dissection
M/17.0[b]	Confirmed (definition 3)	CTA	Angiography	0	Aspirin[c]	Basilar artery thrombosis; received intra-arterial thrombolysis with mechanical thrombectomy
M/5.5[b]	Confirmed (definition 3)	MRI and MRA	Angiography	0	LMWH	Multiple infarcts in the lateral thalamus and occipital lobe; low-flow signal in the P1 segment of the PCA; repeat angiography showed a diminutive vertebral artery that appeared narrow throughout its length; portions were not discretely visualized
M/11.5	Suspected	MRI and MRA	None	27	Aspirin	Brain MRI showing multiple small areas of hyperintensity and restricted diffusion involving the temporal lobe and thalamus

Sex/Age, y	Suspected or Confirmed[a]	Imaging Type	Repeat Imaging	Time to Imaging, d	Acute Treatment	Pertinent Imaging Findings
M/15.4	Suspected	MRI and MRA	None	1	LMWH	Infarcts in the thalamus with history of recent trauma; hypoplastic vertebral artery
M/5.3[b]	Suspected	MRI and MRA	Angiography	0	LMWH	Multiple infarcts involving the cerebellar hemispheres, brachium pontis, and occipital lobe; angiography results consistent with basilar tip thrombus and stenosis involving the ostia of the SCAs bilaterally with distal thrombus identified
M/0.7	Confirmed (definition 3)	MRI and MRA	CTA	1	Aspirin	Multiple infarcts of the bilateral cerebellar hemispheres and occipital lobe; subacute infarcts of the medial temporal lobes and thalamus; vertebral artery occlusion

Abbreviations: CTA, computed tomography angiography; LMWH, low-molecular-weight heparin; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; SCA, superior cerebellar artery.

[a]Definition 1 = angiographic findings of a double lumen, intimal flap, or pseudo aneurysm, or, on axial T1 fat saturation MRI images, a “bright crescent sign” in the arterial wall; Definition 2 = the sequence of cervical or cranial trauma, or neck pain, or head pain less than 6 weeks preceding angiographic findings of segmental arterial stenosis (or occlusion) located in the cervical arteries; Definition 3 = angiographic segmental stenosis (or occlusion) of the vertebral artery at the level of the C2 vertebral body, even without known traumatic history.

[b]Recurrence.

[c]Following intra-arterial thrombolysis with mechanical thrombectomy.

Table 3

Stroke Recurrences

			Recurrence			Treatment	
Sex/Age, y	**Location of First Stroke**	**Stroke Risk Factors**	**Months**	**Location**	**Type**	**Acute**	**Change**
Posterior—Circulation Recurrences							
M/4.4	Left temporo-occipital, bilateral thalami	Vertebral dissection, thrombophilia (positive lupus anticoagulant)	1.5	Bilateral cerebellar, left thalamus, left temporo-occipital, (punctate infarctions bilateral frontal)	Clinical and radiographic	LMWH	Added aspirin, steroids
M/7.4	Left cerebellum, left thalamus, bilateral temporo-occipital	Vertebral dissection, thrombophilia (homozygous for plasminogen activator inhibitor, heterozygous for MTHFR C677T)	0.5	Right midbrain	Clinical and radiographic	LMWH	Added aspirin
M/17.0	Brainstem, left temporal	Vertebral dissection	0.2	Left cerebellar	Covert	Aspirin	Switched to LMWH
M/1.3	Right occipital	Unknown (incidentally discovered Chiari 1 anomaly)	0.6	Right occipital	Clinical and radiographic	Aspirin	Added LMWH
M/5.5	Right thalamus, right occipital	Vertebral dissection	1.9	Right cerebellum	Clinical and radiographic	LMWH, transition to aspirin	Restarted LMWH
M/8.1	Bilateral temporal, brainstem (pons)	Fibroelastoma, thrombophilia (decreased protein C, elevated lipoprotein A)	5.0	Brainstem (pons), right cerebellum	Clinical and radiographic	LMWH, transition to aspirin	Restarted LMWH[a]
M/5.3	Bilateral cerebellum, right occipital	Vertebral dissection	0.7	Right cerebellum	Clinical and radiographic	LMWH	Added aspirin
F/9.9	Left cerebellum, brainstem	Hemoglobinopathy (sickle cell anemia)	39.9	Brainstem, left cerebellum, left thalamus	Clinical and radiographic	Aspirin, regular transfusions	Added LMWH
M/0.3	Left occipital	Cardiogenic (HLHS)	0.8	Right temporo-occipital	Clinical and radiographic	LMWH	Switched to aspirin and clopidogrel
Anterior—Circulation Recurrences							
M/4.8	Left frontal-parietal	Intracranial vasculopathy, thrombophilia (elevated lipoprotein a)	3.4	Left MCA division	Clinical and radiographic	LMWH, transition to aspirin	Restarted LMWH

			Recurrence			Treatment	
Sex/Age, y	Location of First Stroke	Stroke Risk Factors	Months	Location	Type	Acute	Change
M/12.9	Right basal ganglia	Probable small-vessel disease	5.1	Right deep white matter	Clinical and radiographic	Aspirin	Added LMWH

Abbreviations: HLHS, hypoplastic left heart syndrome; LMWH, low-molecular-weight heparin; MCA, middle cerebral artery.

[a]Patient was later transitioned to warfarin sodium, clopidogrel bisulphate, and aspirin.

Table 4

Risk Factors for Recurrence of Stroke

Characteristic	Hazard Ratio (95% CI)	*P* Value
Univariable		
PCAIS vs ACAIS	6.4 (1.4–29.8)	.02
Etiologic factors		
Dissection	2.9 (0.9–9.7)	.08
Cardiac	0.4 (0.05–3.1)	.37
Male sex	4.1 (0.5–32.2)	.18
Multivariable		
PCAIS vs ACAIS	5.3 (1.1–26.4)	.04
Etiologic factors		
Dissection	3.2 (0.4–25.8)	.20
Male sex	0.7 (0.4–4.9)	.57

Abbreviations: ACAIS, anterior circulation childhood arterial ischemic stroke; PCAIS, posterior circulation childhood arterial ischemic stroke.