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Clinical and Radiological Recurrence After Childhood Arterial Ischemic Stroke

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Background—Data on rates and risk factors for clinical and radiological recurrence of childhood arterial ischemic stroke (AIS) might inform secondary prevention strategies.

Methods and Results—Consecutive Great Ormond Street Hospital patients with first AIS were identified retrospectively (1978–1990) and prospectively (1990–2000). Patients underwent repeat neuroimaging at the time of clinical recurrence or, if asymptomatic, at least 1 year after AIS. Cox and logistic regression analyses were used to explore the relationships between risk factors and clinical and radiological recurrence, respectively. A total of 212 patients were identified, of whom 97 had another prior diagnosis. Seventy-nine children had a clinical recurrence (29 strokes, 46 transient ischemic attacks [TIAs], 4 deaths with reinfarction 1 day to 11.5 years (median 267 days) later); after 5 years, 59% (95% confidence interval, 51% to 67%) were recurrence free. Moyamoya on angiography and low birth weight were independently associated with clinical recurrence in the whole group. Genetic thrombophilia was associated with clinical recurrence in previously healthy patients, independent of the presence of moyamoya. Sixty of 179 patients who had repeat neuroimaging had radiological reinfarction, which was clinically silent in 20. Previous TIA, bilateral infarction, prior diagnosis (specifically immunodeficiency), and leukocytosis were independently associated with reinfarction. Previous TIA and leukocytosis were also independently associated with clinically silent reinfarction.

Conclusions—Clinical and radiological recurrence are common after childhood AIS. The risk of clinical recurrence is increased in children with moyamoya and, in previously healthy patients, in those with genetic thrombophilia. Preexisting pathology, including immunodeficiency, and persistent leukocytosis are risk factors for radiological recurrence, which suggests a potential role for chronic infection. **(*Circulation*. 2006;114:2170-2177.)**

Key Words: stroke ■ pediatrics ■ cerebrovascular disorders ■ cerebrovascular circulation ■ cerebral infarction ■ infection

Arterial ischemic stroke (AIS) is increasingly recognized as a serious pediatric problem, with a significant rate of recurrence,[1] but the lack of causal homogeneity presents problems for predicting and preventing it. Physicians faced with a previously well child in whom a risk factor such as recent varicella-zoster infection or a prothrombotic abnormality has been identified have few data with which to counsel the family on the risk of recurrence or any benefit of prophylactic treatment. We previously reported on the risk factors for first AIS encountered in a large cohort of patients from a single institution.[2] The aim of the present study was to report longitudinal data from the same patients on the rates of and risk factors for clinical and radiological recurrence.

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Methods

Patients

Great Ormond Street Hospital is the tertiary pediatric neurology center serving north London, United Kingdom (pediatric population 650 000). As previously reported,[2] patients presenting to the pediatric neurology service after a first acute AIS between 1978 and 2000 were eligible for a study of origin and outcome of first AIS. Patients presenting between 1978 and 1990 were identified by a retrospective search of the hospital discharge database for *International Classification of Diseases* (*ICD*), 9th Revision, codes 434 to 437 and *ICD*, 10th Revision, codes 160 to 169. From 1990 onward, patients presenting to the pediatric neurology service were identified and included prospectively; an *ICD* code search of discharge diagnoses was also performed for this period. Ethical permission for review of all charts was granted by the Research Ethics Committee of Great Ormond Street Hospital.

Acute AIS was defined as an acute focal neurological deficit with evidence of cerebral infarction in an arterial distribution on brain imaging, regardless of duration of clinical symptoms. Children with hemorrhagic stroke, congenital hemiplegia, and asymptomatic ("silent") infarction were excluded. Patients from outside north London (the local region) were included unless only referred after recurrence. Patients were allocated to 1 of 2 mutually exclusive groups; those with a recognized medical diagnosis before AIS were allocated to the "prior diagnosis" group, whereas the rest formed the "previously healthy" group.

From 1990 onward, clinical, radiological, and laboratory data selected to enable identification of cerebral arterial disease and

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potentially modifiable risk factors for AIS were collected prospectively, even if there appeared to be an obvious diagnosis, with approval from the Research Ethics Committee. Children who had had first AIS before 1990 were invited by letter to reattend for investigation.

Information regarding ethnicity was routinely recorded from parents on admission of their children to the hospital, and patients were categorized as white, black, or Asian (the latter includes Far Eastern and South Asian). Birth weight was obtained from parent interview. Body mass index (BMI; weight/height^2) was calculated from admission weight and height. Blood pressure (BP) was entered from the follow-up visit or last inpatient measurement; hypertension was defined as BP >90th percentile for age and height.[3] Persistent iron deficiency was defined as mean cell volume and/or mean cell hemoglobin concentration <2 SDs below the mean for age or >4% hypochromic cells on follow-up testing, provided that the red cell count was not >2 SDs above the mean.[4] Leucocytosis was defined as total white cell count >2 SDs, and leucopenia as total white cell count <2 SDs of mean for age. The upper limit of the normal range was 5.4 mmol/L for cholesterol and 1.4 μmol/L for triglycerides. The range of normal values for fibrinogen was 1.7 to 4 g/L.

Clinical Recurrence

Clinical recurrence after initial presentation with AIS included the mutually exclusive categories of transient ischemic attack (TIA; if symptoms resolved within 24 hours) and clinical stroke (if symptoms lasted >24 hours[5] or the patient died due to the neurological event, with radiological evidence of reinfarction). Deaths unrelated to stroke were censored. Clinical recurrence was identified at re-presentation to our institution. Patients identified prospectively were followed up at 6-month intervals in a cerebrovascular clinic. They were specifically asked about symptoms suggestive of recurrence at these visits. In addition, parents were asked about symptoms of recurrence as part of an outcome study,[6] but data were only included if substantiated by chart review.

Neuroradiological Follow-Up

Patients investigated prospectively underwent brain magnetic resonance imaging or computerized tomography after clinical recurrence or, if asymptomatic, at least 1 year after first AIS. All imaging studies were reviewed by 2 neuroradiologists. Overt and clinically silent reinfarction were defined as new areas of infarction with or without accompanying clinical symptoms, respectively.

Management Strategies to Prevent Recurrence

An institutional protocol for AIS management was established in 1990.[7] Patients with sickle cell disease (SCD) were offered regular blood transfusion. Anticoagulation was recommended if arterial dissection was diagnosed acutely. Revascularization surgery was available for moyamoya. For the remainder of the children, advice about diet and nutritional supplementation and decisions regarding aspirin therapy or anticoagulation were made by physicians on an individual basis; some patients seen before 1990 received no prophylaxis.

Statistical Analysis

All statistical analyses were undertaken with SPSS (version 12) software (SPSS Inc, Chicago, Ill). Hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical recurrence (TIA/stroke/death with reinfarction) were calculated with Cox regression for the whole group and separately for the previously healthy group. The proportional hazards assumption necessary for valid implementation of these models was assessed graphically after model fitting.[8] Deaths were censored if clearly attributable to a cause unrelated to stroke recurrence. The influence of the following factors (for which data were available in at least 75% of the patients) on recurrence was examined: (1) demographic and clinical factors: age, ethnicity, gender, prior diagnosis, previous TIA, birth weight, BMI, hypertension, and chickenpox within the preceding 12 months; (2) radiological factors: any cerebral arterial abnormality and unilateral or bilateral infarction; and (3) laboratory factors: hemoglobin (FUHb), leukocyte (FUWBC), and platelet count at follow-up or persistent iron deficiency. The laboratory data were obtained at follow-up when all children with SCD were in a transfusion program. Additional factors considered in previously healthy patients were echocardiography results, thrombophilia mutations (factor V Leiden [FVL], prothrombin 20210, and homozygosity for thermolabile methylene tetrahydrofolate reductase [MTHFR-TT]), fibrinogen, random serum cholesterol, and triglycerides.

Protein C, protein S, antithrombin, and plasminogen levels were not considered in the analysis because they were never persistently abnormal.[2] Creatinine, anti-cardiolipin antibodies, homocysteine, factors VIII and XII, von Willebrand factor, and lipoprotein (a) were not analyzed because data were available for <70% of patients.[2]

Z scores adjusted for age and sex were calculated for birthweight (*z*BWt) and BMI (*z*BMI) with a computer program based on growth data from normal UK children (Castlemead[9,10]) and for FUHb (*z*FUHb) and FUWBC (*z*FUWBC) with the mean and SD for various ages and both sexes from normal hematologic data. Each variable was entered into a univariate analysis, and significant variables ($P<0.05$) were then entered into a multivariate analysis. Variables nonsignificant in the univariate analyses were added to the multivariate model to verify that they remained nonsignificant after correction for other important factors. The multivariate models allowed the independent effects of related predictors to be quantified.

In the majority of patients, only 1 further scan was performed, a variable duration after the initial, diagnostic scan. If the second scan showed new infarcts, it was not possible to precisely identify the timing of these, and therefore, standard survival analysis techniques could not be undertaken. Logistic regression analysis, adjusted for time between diagnostic and final neuroimaging, was therefore performed to identify risk factors for radiological recurrence.

Analyses are reported in relation to rates and risk factors for (1) clinical recurrence in all patients, (2) clinical recurrence in the previously healthy group, (3) reinfarction in patients who were reimaged, (4) reinfarction in patients from the previously healthy group who were reimaged, and (5) clinically silent reinfarction in patients who were reimaged. Unless stated otherwise, figures in parentheses represent 95% CIs.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Two hundred twelve patients were included (46 seen before 1990 and 166 identified prospectively from 1990 onward). Age at first AIS ranged from 21 days to 19.5 years (median 5 years); 115 (54%) were male. One hundred fifty-two patients were white, 41 were black, and 19 were Asian.

The risk factors for AIS in these patients have been reported previously.[2] In summary (Table 1), 97 patients had a previous diagnosis associated with increased AIS risk (prior diagnosis group); the remaining 115 formed the previously healthy group. Of the prior diagnosis group, 35 had SCD, 26 had cardiac disease, 6 had immunodeficiency (human immunodeficiency virus [HIV] infection in 2 cases and Omenn syndrome, severe combined immunodeficiency, Schimke immuno-osseous dysplasia, and T-cell immunodeficiency in 1 case each), and 30 had other diagnoses (brain tumor in 4; skin hemangioma in 5;

TABLE 1. Clinical and Radiological Recurrence

	All Patients (n=212)	Previously Healthy Group (n=115)	Previous Diagnosis			
			SCD (n=35)	Cardiac Disease (n=26)	Immune Deficiency (n=6)	Other (n=30)
Age,* y	5	5	8.5	2.5	4.5	4
Range	(21 d–19 y)	(3 mo–17 y)	(1–19 y)	(21 d–16 y)	(3 mo–13 y)	(26 d–15 y)
Follow-up*	2.2	2	2.5	3	9 mo	1.5
Range	(1 d–21 y)	(1 d–13.5 y)	(7 d–11 y)	(4 d–21 y)	(11 d–4 y)	(4 d–13 y)
Clinical recurrence, n (%)	79 (37)	34 (30)	18 (51)	9 (31)	3 (50)	15 (50)
Stroke, n (%)	29 (14)	8 (7)	9 (26)	5 (19)	3 (50)	4 (13)
TIA, n (%)	46 (22)	25 (22)	8 (23)	3 (12)	0	10 (33)
Death with reinfarction, n (%)	4 (2)	1	1	1	0	1
Prophylaxis†						
None	29/81	16/46	4/7	4/16	2/2	3/10
Aspirin	16/64	9/47	...	1/3	0/2	6/12
Anticoagulation	15/33	7/19	...	4/7	1/2	3/5
Revascularization	5/6	2/3	...	...	...	3/3
Blood transfusion	14/28	...	14/28	...	...	...

Data are presented for all patients, for the previously healthy group, and for the prior diagnosis group by subcategory.

*Median, expressed in years unless otherwise noted.

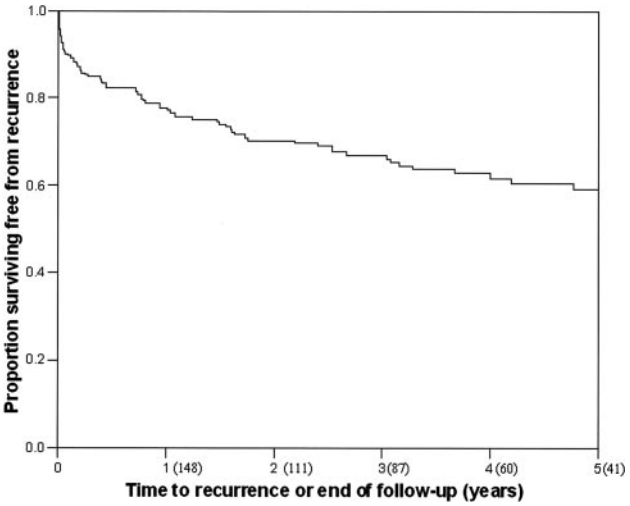
†For the data presented under "Prophylaxis," the numerator is the number of patients who had recurrence while undergoing that treatment, and the denominator is the total number of patients undergoing that treatment at the end of follow-up.

meningitis in 6; hematologic malignancy in 3; hydrocephalus, Down syndrome, Crohn's disease, and hemolytic uremic syndrome in 2 cases each; and malignant hypertension, athetoid cerebral palsy, neurofibromatosis type 2, and aplastic anemia in 1 case each).

Cerebral infarction was bilateral in 52 patients. Cerebrovascular imaging had been performed in 185 patients (87%; 88 conventional and 97 with magnetic resonance angiography); abnormalities were identified in 139 (75%; dissection in 14, stenosis in 65, occlusion in 30, moyamoya in 26, and vasculitis in 4). Twenty-eight children had had a TIA before the initial AIS. Systolic BP was >90th percentile in 104 of 208 patients for whom the data were available. Thirty-three of 173 patients for whom data were available had had chickenpox within the previous 12 months. Data on *z*BWt were available for 192 patients, and data on BMI were available for all 212. Mean *z*BWt for the whole group was −0.28, significantly lower that the expected average (zero) in the population ($P=0.001$). Mean *z*BWt was significantly lower in the prior diagnosis group than in the previously healthy group (−0.48 compared with −0.12, $P=0.03$). Data on *z*FUHb, *z*FUWBC, and platelet count were available for 211, 211, and 210 patients, respectively. Thirty-five of the 41 black patients had SCD. As would be expected, *z*FUHb was significantly lower in patients with SCD than in the remainder (−3.85 compared with −0.92, $P<0.001$). Thirty-five patients had iron deficiency (as previously defined).

Rate and Risk Factors for Clinical Recurrence in the Whole Group (n=212)

The interval between first AIS and recurrence or end of follow-up ranged from 1 day to 21 (median 2.2) years (Table 1). Seventy-nine patients (37%) had a clinical recurrence (TIA n=46, stroke n=29, and death at time of reinfarction n=4) a median of 267 days (range 1 day to 11.5 years) after initial AIS. Twenty-one patients had a clinical recurrence (11 TIAs, 8 strokes, and 2 deaths with reinfarction) within 30 days of initial AIS. Four patients died of causes unrelated to stroke (nonneurological complications of congenital cardiac disease in 3 and polyarteritis nodosa in the other) and were censored from the analysis. Five patients died later after having been censored at the time of a recurrent event. Total mortality was 13 (6%) of 212 patients. Figure 1 shows the proportion of patients free of clinical recurrence against time



Proportion of patients surviving free of clinical recurrence (stroke or TIA) for the first 5 years of follow-up after first AIS. The numbers in parentheses indicate the number of patients surviving free of recurrence at each time point.

TABLE 2. Multivariate HRs and 95% CIs From Cox Regression Analysis for Prediction of Clinical Recurrence (TIA, Stroke, or Death With Reinfarction) for the Whole Group

Variable	n	HR (95% CI)	*P*
*z*BWt	192	0.76 (0.61–0.95)	0.016
Vascular diagnosis	...	...	0.013
None*	46/185	...	...
Dissection	14/185	0.75 (0.21–2.68)	0.66
Occlusion	30/185	1.07 (0.45–2.57)	0.88
Stenosis	65/185	1.43 (0.71–2.87)	0.31
Vasculitis	4/185	2.16 (0.48–9.73)	0.32
Moyamoya	26/185	3.26 (1.55–6.84)	0.002

The 4 deaths unrelated to stroke (see text for details) were censored. Proportions in the column marked "n" indicate the number of patients with the factor as a proportion of the number of patients for whom data were available. Where a proportion is not indicated, the number refers to the number of patients for whom the continuous data were available. For *z*BWt, the hazard is the change per unit increase in the variable.

*Denotes the reference category.

in the 5 years after first AIS. The estimated percentage of patients free of any clinical recurrence (stroke, TIA, or death with reinfarction) at the end of 5 years was 59% (95% CI, 51% to 67%), and the percentage free of recurrent clinical stroke was 82% (95% CI, 75% to 89%).

In the univariate analyses, vascular diagnosis (dissection [HR, 0.62; 95% CI, 0.18 to 2.15; $P=0.45$], occlusion [HR, 0.89; 95% CI, 0.40 to 1.98; $P=0.77$], stenosis [HR, 1.24; 95% CI, 0.65 to 2.34; $P=0.51$], vasculitis [HR, 1.41; 95% CI, 0.31 to 6.39; $P=0.65$], moyamoya [HR, 2.78; 95% CI, 1.41 to 5.49; $P=0.003$]), previous TIA (HR, 1.96; 95% CI, 1.15 to 3.36; $P=0.014$), low *z*BWt (HR, 0.71; 95% CI, 0.57 to 0.88; $P=0.002$), and bilateral infarction (HR,1.71; 95% CI, 1.07 to 2.73; $P=0.02$) were significantly associated with clinical recurrence and were therefore entered into the multivariate model. Age, gender, ethnicity, prior diagnosis, BMI, hypertension, chickenpox within the preceding 12 months, FUHb, FUWBC, platelet count at follow-up, and persistent iron deficiency were nonsignificant in the univariate analysis. Low *z*BWt and a vascular diagnosis of moyamoya were independently associated with time to clinical recurrence (Table 2). The interaction was nonsignificant. No other factors were additionally predictive.

Clinical Recurrence in the Previously Healthy Group (n=115)

In the previously healthy group, 8 of 104 children investigated with echocardiography had an abnormal study. The prothrombotic mutations FVL, PT20210, and MTHFR-TT were identified in 5 of 85, 2 of 81, and 13 of 81 patients tested, respectively. Random cholesterol and triglycerides were elevated in 7 and 24 of 84 patients, respectively. Data on fibrinogen were available in 97 patients.

Thirty-four of the 115 children in the previously healthy group had a clinical recurrence (25 TIAs, 9 strokes). Of the factors examined in univariate analyses, only the presence of the PT20210 mutation was significantly associated with clinical recurrence (HR 7.89, 95% CI 1.78 to 34.92, $P=0.007$). Age, gender, ethnicity, prior diagnosis, previous TIA, *z*BWt, BMI, hypertension, vascular diagnosis, bilateral infarction, chickenpox within the preceding 12 months, FUHb, FUWBC, platelet count at follow-up, persistent iron deficiency, abnormal echocardiogram, high cholesterol, high triglycerides, high fibrinogen, and the presence of the prothrombotic mutations FVL and MTHFR-TT were nonsignificant on univariate analysis. The presence of at least 1 of FVL, PT20210, or MTHFR-TT (n=15 with 1, 1 with 2, and 1 with 3) was associated with decreased time to clinical recurrence (HR, 2.25; 95% CI, 1.01 to 5.02; $P=0.048$). This was independent of vascular diagnosis (adjusted HR, 2.60; 95% CI,1.14 to 5.95; $P=0.02$). Seventeen of the 34 previously healthy patients with clinical recurrence for whom data were available had either moyamoya (n=7), a genetic polymorphism predisposing them to thromboembolism (n=9), or both (n=1). One other patient, who developed a widespread vasculitis, had raised cholesterol and fibrinogen levels, but the other 16 children were negative for the laboratory factors examined, although only 3 had lipoprotein(a)[11] measured.

Rate and Risk Factors for Reinfarction (n=179)

Repeat neuroimaging was performed in 179 patients (84%). The interval between AIS and final imaging was 1 day to 14.9 years (median 1.6 years); at final imaging, 76 patients had had clinical recurrence (of whom 3 had had clinically silent reinfarction on interim scans), and 103 remained asymptomatic. Of the 33 children who were not reimaged, 20 were previously healthy, and 13 had prior diagnoses (8 cardiac disease, 1 SCD, 1 immunodeficiency, and 3 other diagnoses). Two of these patients died of nonneurological causes. Three previously healthy children had recurrent TIAs but were not reimaged; 1 had arterial stenosis at presentation, but vascular imaging was normal in the other 2; 2 had the MTHFR-TT mutation. Of the 179 reimaged patients, 60 (34%) had new areas of infarction: 30 (91%) of 33 patients with recurrent stroke, 10 (23%) of 43 with recurrent TIA, and 20 (19%) of 103 reimaged asymptomatic children.

Time to repeat imaging was included in all univariate logistic regression analyses. In the univariate analyses, the risk of reinfarction was related to time to reimaging (OR, 0.86; 95% CI, 0.76 to 0.86; $P=0.01$); ethnicity (white=reference category, black [OR, 4.80; 95% CI, 2.12 to 10.85; $P<0.001$], Asian [OR, 2.39; 95% CI, 0.79 to 7.30; $P=0.13$]); prior diagnosis (SCD [OR, 8.87; 95% CI, 3.51 to 22.37; $P<0.001$], cardiac [OR, 3.15; 95% CI, 1.02 to 9.69; $P=0.05$], immunodeficiency [OR, 14.15; 95% CI, 1.47 to 136.5; $P=0.02$], other diagnoses [OR, 4.09; 95% CI, 1.59 to 10.53; $P=0.004$]); bilateral infarction at presentation (OR, 5.23; 95% CI, 2.54 to 10.80; $P<0.001$); previous TIA (OR, 4.62; 95% CI, 1.90 to 11.24; $P=0.001$); vascular diagnosis (normal vessels=reference category, dissection [OR, 0.35; 95% CI, 0.06 to 1.92; $P=0.23$], occlusion [OR,1.46; 95% CI, 0.50 to 4.27; $P=0.50$], stenosis [OR,1.08; 95% CI ,0.42 to 2.76; $P=0.88$], vascu-

TABLE 3. Multivariate ORs and 95% CIs for Prediction of Radiological Recurrence With Logistic Regression Analyses With Time to Reimaging Included to Adjust for Variable Times When All Other Factors Were Examined

Variable	n	OR (95% CI)	*P*
Time to reimaging	179	0.83 (0.72–0.97)	0.016
Diagnosis	...	...	0.028
Previously healthy*	95/179	...	...
SCD	34/179	2.06 (0.62–6.74)	0.23
Cardiac disease	18/179	3.40 (1.0–11.57)	0.05
Immunodeficiency	5/179	20.91 (1.98–220.72)	0.01
Other	27/179	3.082 (1.07–8.87)	0.04
Previous TIA	179/179	5.48 (1.95–15.43)	0.001
Bilateral infarction†	50/179	2.78 (1.18–6.58)	0.02
*z*FUWBC	178	1.22 (1.04–1.42)	0.02

Data include all reimaged patients (n=179). Deaths unrelated to stroke are censored. Proportions in the column marked "n" indicate the number of patients with the factor as a proportion of the number of patients for whom data were available. Where proportions are not mentioned, continuous data were available for the number indicated. For continuous variables, the ORs are the change per unit increase in the variable.

*Denotes the reference category.

†Compared with unilateral infarction.

litis [OR, 0.72; 95% CI, 0.06 to 8.26; $P=0.79$], and moyamoya [OR, 4.39; 95% CI, 1.35 to 14.30; $P=0.014$]); lower *z*BWt (OR, 0.69; 95% CI, 0.50 to 0.94; $P=0.02$); and higher *z*FUWBC (OR, 1.26; 95% CI, 1.10 to 1.44; $P=0.001$). Age, gender, BMI, hypertension, chickenpox within the preceding 12 months, FUHb, platelet count at follow-up, and persistent iron deficiency were nonsignificant in the univariate analyses. After multivariate analysis, the risk of reinfarction was significantly related to prior diagnosis, previous TIA, bilateral infarction, and higher *z*FUWBC (Table 3). There were no significant interactions. After we accounted for these factors, no other significant associations emerged.

Rate and Risk Factors for Reinfarction in the Previously Healthy Group (n=95)

Ninety-five (83%) of the 115 patients in the previously healthy group had repeat magnetic resonance imaging, and 16 (17%) had a recurrent infarct, which was clinically silent in 9. In addition to shorter time to final neuroimaging (OR, 0.64; 95% CI, 0.44 to 0.93; $P=0.018$), for which the other factors were adjusted, bilateral infarction on initial neuroimaging (OR, 6.14; 95% CI, 1.34 to 28.20; $P=0.02$) and lower *z*BWt (OR, 0.50; 95% CI, 0.27 to 0.95; $P=0.03$) were associated with a higher risk of reinfarction in the univariate analysis. These variables were entered into the multivariate analysis. Age, gender, ethnicity, previous TIA, vascular diagnosis, BMI, hypertension, chickenpox within the preceding 12 months, FUHb, FUWBC, platelet count at follow-up, persistent iron deficiency, *z*FUWBC, and echocardiogram results were nonsignificant in univariate analysis. Although there was a trend for an effect of FVL, the presence of at least 1 of the 3 genetic polymorphisms was not associated in this small data set (n=73; OR, 1.07; 95% CI, 0.35 to 3.29; $P=0.91$). After we took account of the presence of bilateral infarction on the initial scan, none of the other variables were independently associated with recurrent infarction. The next most important independent effect identified was for FVL (OR, 9.07; 95% CI, 0.96 to 86.02; $P=0.055$) for the 76 patients in whom this was available.

Rate and Risk Factors for Clinically Silent Reinfarction (n=103)

Reinfarction was identified in 20 (19%) of the 103 children who remained asymptomatic after initial AIS and who were reimaged between 1 day and 11.1 years (median 1.5 years) later. Twelve of them had prior diagnoses (7 with SCD; 1 with a double-inlet univentricular heart and transposition who had had a Glenn procedure and Blalock shunt and was in 2:1 heart block; 1 with HIV infection; 1 with hemolytic-uremic syndrome; 1 with meningitis; and 1 with a skin hemangioma). The child with HIV subsequently had a recurrent stroke; 4 others (3 with SCD and another with posterior circulation stroke and a homocysteine level of 101.4 [reference <13.5] μmol/L)[12] subsequently had TIAs; and 1 with SCD died after a bone marrow transplantation without clinical recurrence.

Time to repeat imaging was included in all univariate analyses. Black ethnicity (OR, 7.2; 95% CI, 2.1 to 24.5; $P=0.002$), SCD (OR, 7.49; 95% CI, 1.9 to 29.6; $P=0.004$), previous TIA (OR, 5.4; 95% CI, 1.3 to 23.2; $P=0.02$), bilateral infarction (OR, 3.6; 95% CI, 1.2 to 11.0; $P=0.026$), and higher *z*FUWBC (OR, 1.40; 95% CI, 1.12 to 1.75; $P=0.003$) were associated in univariate analysis. Age, gender, *z*BWt, *z*BMI, hypertension, chickenpox within the preceding 12 months, vascular diagnosis, FUHb, FUWBC, platelet count at follow-up, and persistent iron deficiency were nonsignificant on univariate analysis. In the multivariate analysis, previous TIA (OR, 8.4; 95% CI, 1.9 to 38.11; $P=0.006$) and higher *z*FUWBC (OR, 1.4;

95% CI, 1.12 to 1.75; $P=0.003$) were independently associated with clinically silent reinfarction; after we accounted for these, none of the other variables were predictive. There were no significant interactions.

Recurrence With Prophylactic Treatment

One hundred thirty-one children had received treatment to prevent another stroke; 50 of them (38%) had a clinical recurrence, compared with 29 (35%) of 81 who were untreated. Of 14 children with arterial dissection, 9 underwent anticoagulation therapy, 4 received aspirin, and 1 was not treated. Twenty-eight of 35 children with SCD were regularly transfused; 9 had radiological moyamoya, but none were revascularized. Six of the other 15 children with moyamoya had had revascularization (usually superficial temporal artery to middle cerebral artery anastomosis) before first recurrence; 5 of these patients had further TIA (n=4) or stroke (n=1); 3 were treated with aspirin, and 6 were not treated. Of the 27 patients with no vascular imaging, most of whom were seen before 1990, only 3 were treated (1 with aspirin and 2 with anticoagulants).

Excluding SCD, 108 children had abnormal cerebral arteries: 11 with cardiac disease, 5 with immunodeficiency, 16 with other underlying pathologies, and 76 previously healthy children. As long-term prophylaxis, 64 of these patients were treated with low-dose aspirin (1 mg/kg body weight); 33 patients were given anticoagulation therapy, and 74 received no treatment. After adjustment for the underlying and vascular diagnoses, neither aspirin nor anticoagulation significantly influenced the incidence of clinical recurrence compared with no prophylaxis, although there was a trend for an effect of aspirin (HR, 0.55; 95% CI, 0.26 to 1.16; $P=0.11$ for aspirin; HR, 1.06; 95% CI, 0.45 to 2.51; $P=0.89$ for anticoagulation).

Discussion

Clinical and radiological recurrence are common after first childhood AIS. The most important associations with clinical recurrence were moyamoya and low birth weight. For the previously healthy group, the presence of at least 1 genetic thrombophilia mutation was also associated with a higher risk of clinical recurrence. In addition to the presence of previous TIA and bilateral infarction at initial presentation, which implies previous pathology, radiological recurrence was associated with prior immunodeficiency and leukocytosis, which suggests a potential role for chronic infection, as for primary stroke in adults.[13] In a previous study reporting on the associations with first AIS in the same group of patients, the most frequently observed associations were cerebral arterial abnormalities, anemia, trauma, and previous varicella infection. As would be expected, the overlap with risk factors for recurrence is limited because the latter identify a high-risk subgroup, but the high prevalence of arterial disease is a common theme. Despite the large number of patients in the present study and the amalgamation of subgroups where clinically meaningful, the numbers in some of the subgroups were small, as reflected in the wide confidence intervals for some ORs and HRs.

The risk factors that have emerged from the present study have generated some important trends that cross the borders of etiological entities. Most previous studies reporting associations with recurrence of childhood stroke did not perform vascular imaging in unselected consecutive patients and therefore could not estimate the relative influence of arterial pathology on risk. A recent study[11] that reported a recurrence rate of 6.6% included a smaller proportion of children with preexisting diagnoses and specifically excluded children with previous vascular events (for example, TIA) and those with SCD. We may, therefore, be reporting data from a relatively higher-risk population but one in which the risk factors associated with recurrence in the previous study, ie, high lipoprotein(a) and low protein C levels,[11] are rare. In addition, we included recurrent TIA and stroke confirmed on neuroimaging in our definition of clinical recurrence, and patients in the present study were followed up longer. The presence of another medical condition previously identified as a risk factor for recurrence[14] is related to the risk of radiological recurrence. Although there may be a spectrum of severity for moyamoya,[15,16] from these and other data,[17,18] the risk of recurrence is significantly higher in this group. Investigation of the cerebral circulation appears to be justified in all children presenting with stroke and should probably be undertaken in the acute phase so that sinovenous thrombosis, which may be associated with cortical infarction in the frontal, parietal, and occipital lobes mimicking an arterial distribution,[19] is excluded. This will also be important for future studies investigating risk factors for recurrence, because relatively fewer patients with sinovenous thrombosis have recurrences, and prothrombotic disorders may be more common.[20] The contribution of specific arterial pathologies to recurrence requires further elucidation. We adopted a broad definition of arteriopathy and included patients with arterial occlusion alone, in whom abnormal imaging may have reflected thromboembolic disease rather than true arterial pathology. This may account for the observation that the rate of recurrence in patients with arterial occlusion was similar to that in patients with no vasculopathy. It is more surprising that the risk of recurrence in the 14 patients with dissection was lower than in those without arteriopathy; this may reflect more chronic risk factors in the latter patients or early treatment for all but 1 of those with dissection, but it awaits confirmation in other cohorts.

We have reported the incidence of any clinical recurrence, even when this occurred very soon after the initial stroke. The temporal distinction between an extension of the original stroke and a completely separate event has not been defined clearly, but both are potentially preventable if modifiable risk factors can be defined. More than one fourth of the whole group had clinical recurrence >30 days after the initial stroke, including 23 with an additional stroke, thus making it unlikely that the relatively high rate of recurrence in patients in the present study is entirely due to lack of distinction between extension and recurrence. The potential for referral bias is an important consideration and might explain in part the higher incidence of recur-

rence in the present study compared with others.[11,14] However, patients who were only referred to our center after recurrence were excluded from the study, and there was no evidence of any differences in patients referred from other regions.[2] Because a proportion of the patients were identified retrospectively, it is possible that the incidence of recurrence was underestimated in them.

Cerebral infarction is found in most children with clinical stroke and in many with transient or no symptoms. Clinically silent reinfarction has not been reported previously in children with AIS, other than in those with SCD[21] or moyamoya, in whom it may be associated with cognitive morbidity.[22] The present data suggest that even asymptomatic patients should be reimaged after an interval, particularly if they have preexisting disease. Our observations suggesting that chronic infection is associated with reinfarction might have parallels in elderly adults and should be further explored in larger pediatric cohorts. Although intercurrent infection is common in children, a recent study has demonstrated endothelial dysfunction in the acute and convalescent phases of childhood infection.[23] It is possible that persistent infection, the host response, immunodeficiency (which may be a consequence of hyposplenism in SCD in addition to those with specific diseases), or other factors lead to more permanent arterial changes.

A large number of laboratory tests have been recommended in the evaluation of young adults and children with stroke, although the prevalence of abnormalities varies between populations,[2,11] and few studies have examined any association with recurrence.[11,14] The yield of comprehensive investigation may be low, but the implications of abnormal results may be important for individual patients, which presents a dilemma for the clinician in terms of cost-effectiveness. The present data would suggest that priority should be given to careful clinical history and examination, characterization of the cervical and cerebral arteries, and relatively simple laboratory investigations such as complete blood count. Although there is no evidence-based management, screening for thrombophilia may be justified in previously healthy patients. Dietary advice should be considered; for example, vitamin B supplementation in patients who are homozygous for the T-MTHFR mutation has no known side effects,[12] although it is of unproven benefit.

Although formal evaluation of the efficacy of secondary prevention strategies was not possible, children with SCD may have recurrent stroke despite regular blood transfusion.[18] Even though antithrombotic treatment in childhood AIS appears to be safe,[24] the importance of hemodynamic mechanisms, especially in the presence of arterial disease, has not been explored systematically. Future randomized trials should be undertaken in well-characterized, homogenous groups of patients, in whom the proposed treatment is appropriate to the pathophysiology of stroke and recurrence.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Arterial ischemic stroke (AIS) is a serious problem in children, with an estimated annual incidence of 3 in 100 000, but the rates of and risk factors for clinical or radiological recurrence, which might inform investigation and management, have received little attention. In the present study, we report the rates of clinical and radiological AIS recurrence in 212 children with first AIS seen at a single tertiary pediatric neurology center. Ninety-seven children had another diagnosis before AIS; the rest were previously well. Median time to recurrence or death was 267 days (range 1 day to 11.5 years). Seventy-nine children had a clinical recurrence (29 strokes, 46 transient ischemic attacks [TIAs]), and 4 deaths with reinfarction). Clinical recurrence was associated with moyamoya and low birth weight and, in previously healthy patients, with genetic thrombophilia. Sixty of 179 patients who had repeat neuroimaging had radiological reinfarction, which was clinically silent in 20 children. Previous TIA, bilateral infarction, prior diagnosis (specifically immunodeficiency), and leukocytosis were independently associated with reinfarction. Previous TIA and leukocytosis were also independently associated with clinically silent reinfarction. There was a trend for a reduction in clinical recurrence with aspirin therapy. These data confirm that clinical and radiological recurrence are significant problems after first AIS in childhood. Vascular imaging is an essential component of diagnostic evaluation. Ongoing pathology (indicated by the relationship with prior diagnoses, previous TIA, and leukocytosis) appears to have a role in recurrent events. Further studies should examine the efficacy of secondary prophylaxis.