Stroke in children and sickle-cell disease

Baltimore–Washington Cooperative Young Stroke Study

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Article abstract—*Background/Purpose:* The Baltimore–Washington Cooperative Young Stroke Study is the largest biracial urban-suburban population-based study to examine the etiology of strokes in children. *Methods:* We identified all children aged 1 to 14 years discharged from all 46 hospitals in central Maryland and Washington, DC with a diagnosis of ischemic stroke and intracerebral hemorrhage in the years 1988 and 1991. Each medical record was reviewed by two neurologists for appropriateness of the diagnosis of stroke and for information on the patient's history, clinical presentation, pertinent investigations, hospital stay, and outcome at time of discharge. *Results:* Eighteen children with ischemic infarction and 17 with intracerebral hemorrhage were identified. The most common cause of ischemic stroke was sickle-cell disease (39%), followed by vasculopathic (33%) and indeterminate (28%) causes. Causes of intracerebral hemorrhages were arteriovenous malformation (29%), hematologic (23%), vasculopathy (18%), surgical complication (12%), coagulopathy (6%), and indeterminate (12%). The overall incidence for childhood stroke was 1.29 per 100,000 per year, with ischemic stroke occurring at a rate of 0.58 per 100,000 and intracerebral hemorrhage occurring at a rate of 0.71 per 100,000. The incidence of stroke among children with sickle-cell disease was estimated to be 0.28% or 285 per 100,000 per year. *Conclusion:* Sickle-cell disease plays a disproportionately high role in childhood stroke when a biracial population is surveyed.

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Cardiac disease, infective vasculitis, coagulopathies, hematologic and metabolic diseases, vascular anomalies, and arterial dissection are considered common causes of stroke in children.[1] However, the relative contribution of these factors in childhood stroke is based largely on single-center case series.[2-5] There are also many reports that discuss the clinical presentation and outcome in children with stroke, but as with the data on etiology, they are biased by their dependency on single-center study results. A further confounding issue is the reported high risk of stroke in children with sickle-cell disease.[6] Because of this risk factor, the racial distribution of a particular population would be expected to influence the distribution of stroke causes among children. The importance of race in childhood cerebrovascular disease has never been defined either in terms of incidence or etiology beyond the more specific issue of sickle-cell disease. However, even when dealing with the issue of sickle-cell disease, there are no population-based studies to confirm or deny the espoused high incidence of stroke.[6]

Available data from the three population-based studies of childhood stroke that were conducted with primarily white populations reported the incidence rates but not the distribution of stroke etiologies, clinical features, or outcomes.[5,7,8] The only community-based study of childhood stroke to include a biracial (black/white) population did not survey all hospitals within the study areas.[9] Furthermore, although various etiologies were reported, sickle-cell disease was not identified as a contributing factor in that population.

The Baltimore–Washington, DC metropolitan area has a childhood (1 to 14 years) population of more than 770,000. Among this population, the black/white racial mix is nearly 50/50. There are an estimated 1 to 3 children with sickle-cell disease for every 337 black children in the population. The Baltimore–Washington Cooperative Young Stroke Study is the largest and essentially the only epidemiologic study to evaluate etiology, clinical presentation, morbidity, and mortality in childhood stroke comprehensively. It is the only study of its kind to address the issue of race and specifically sickle-cell disease in childhood stroke.

Subjects and methods. The Baltimore–Washington Cooperative Young Stroke Study[10] is a regional, hospital-

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based registry designed to study the incidence and etiology of strokes in children (1 to 14 years) and young adults (15 to 44 years). We retrospectively identified all hospital cases for the calendar years 1988 and 1991. Our study registry covered all hospitals (including pediatric hospitals) within the catchment area for a total number of 46 hospitals. Because of referral patterns, it was believed unlikely that a child with a stroke who was residing in the study region would be hospitalized outside the area of surveillance. The total population for the study region was 1,436,166. The population of children under age 15 years was 773,016 (411,537 white and 361,479 nonwhite) based on the 1990 census data for Maryland and Washington, DC.[11] In children under age 15 years in the Baltimore–Washington, DC study area it is estimated that one child with sickle-cell disease exists for every 337 to 351 African American children, giving an estimated number between 1,028 and 1,072 children with sickle-cell disease. The estimate of sickle-cell disease in the population was determined using the *National Newborn Screening Report*, which is a publication of the Newborn Screening Committee, the Council of Regional Networks for Genetic Service.

Incidence cases were identified by the primary and secondary hospital discharge diagnoses. Charts with International Classification of Diseases, 9th Revision (ICD-9) codes 431.00 to 438.00, 671.50 to 671.54, and 674.00 to 674.04 were reviewed by trained neurologic nurses who abstracted each chart. ICD-9 code 430.00, which represents subarachnoid hemorrhage, was not included in this study. The abstracts contained a narrative summary of the current neurologic event. The abstracting process placed specific emphasis on identifying the evolution of the neurologic symptoms and signs, emergency room evaluation and management, hospital course and management, and discharge status. Included in the abstraction process were specific questions dealing with prior neurologic events, TIAs, and strokes. Information on past medical and surgical events, demographics, risk factors, neuroimaging, laboratory studies, therapies, and autopsy data were also collected. Based on this information, cases considered to represent a possible acute stroke were independently reviewed by two board-certified neurologists who classified the event as an ischemic cerebral infarction, intracerebral hemorrhage, or other diagnosis. Stroke was defined according to the criteria of the World Health Organization.[12] The definitions of ischemic cerebral infarction and intracerebral hemorrhage were based on the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank.[13] Placement into a particular category was based on an agreement between a pair of neurologists who reviewed the case. Disagreement was resolved by a consensus conference. Stroke occurring as an immediate consequence of trauma was excluded. Cerebral infarction associated with subarachnoid hemorrhage was also excluded. Assessment of functional neurologic status at the time of discharge was based on the Glasgow Outcome Scale (GOS).[14] GOS rankings are as follows: 1 = a full and independent life with or without minimal neurologic deficits; 2 = neurologic or intellectual impairment but independent; 3 = conscious but totally dependent on others to get through the activities of the day; 4 = vegetative survival; 5 = dead.

Each patient with an ischemic cerebral infarction was further classified by a pair of neurologists into nine categories according to written criteria developed by the study physicians for the project.[15] The categories were divided into "higher priority" diagnoses (atherosclerotic vasculopathy, nonatherosclerotic vasculopathy, cardiac/transcardiac embolism, hematologic/other) and "lower priority" diagnoses (lacunar infarct, migrainous stroke, oral contraceptive related, other drug related, and indeterminate). Higher priority diagnoses were conditions for which well-defined positive criteria exist (atherosclerotic and nonatherosclerotic vasculopathy) or the probable mechanism of stroke is known (cardiac/transcardiac embolism, hematologic), or both. Lower priority diagnoses included those of undetermined cause (indeterminate, lacunar infarct), those for which the mechanism is obscure (migrainous stroke), and those associated with conditions that often coexist with or are weakly linked with stroke (oral contraceptive related, other drug related).

For intracerebral hemorrhage, each case was placed into 1 of 13 specific etiologic categories: hypertension, aneurysm, arteriovenous malformation (AVM), hematologic, coagulopathy, anticoagulant/thrombolytic therapy, arterial/venous vasculopathy, collagen disorder, drug associated, neoplasm, surgical complications, other, and indeterminate.[15] The category of "other" was reserved for any case with a clear probable cause that did not fall into any of the more specific categories. Any case for which a "probable" cause could not be identified was placed into the "indeterminate" category. Some cases may have had more than one probable cause. In that event, all causes are discussed in the body of the text, but for display in the tables the most likely cause was used for categorization.

Only first-ever strokes were used to establish annual incidence rates. All CIs were calculated from the exact incidence using the Poisson distribution.[16]

Results. A total of 35 patients were identified in the 2-year period in the study region. Table 1 summarizes the clinical characteristics and investigations for the 18 children with ischemic stroke. Three children (nos. 4, 7, and 10) reported a prior stroke. Ischemic strokes fell into three diagnostic categories. The most common probable cause was hematologic, with all seven children having a history of sickle-cell disease. Angiography in three children demonstrated severe intracranial large artery occlusive disease in each case. Carotid duplex sonography was performed in two patients and revealed proximal internal carotid artery (ICA) stenosis in one (no. 7). Two patients had no cerebrovascular evaluation.

The second most common identified cause of ischemic stroke was vasculopathy (excluding sickle-cell disease), which includes both atherosclerotic and nonatherosclerotic causes of stroke. Angiography in five children revealed large artery intracranial vasculopathy. The etiologies for the vasculopathy were Lyme vasculitis (no. 9), bilateral vertebral artery dissection (no. 11), collagen disease associated with Ehlers-Danlos syndrome (no. 12), and uncertain (nos. 8 and 13). The vasculopathy in the last two children (nos. 8 and 13) was mild focal irregular stenosis that was limited to the infarct-related artery subserving the infarct site. Extensive histories and laboratory studies for coagulopathy, collagen vascular disease, and lipid disorders were done in both children and were unremarkable. Transthoracic echocardiography with (no. 13) and without (no. 8)

Table 1 *Clinical features and investigations for each child with ischemic stroke*

Pt no.	Age/race, gender*	Etiology†	Pertinent history	General investigations‡	Lesion by CT/MRI§	Presentation¶					Outcome‖		
						F	H	P	S	L	D	P	G
1	2 y 5 mo/B, F	Hemato	Sickle-cell	Ang (bil ICA occlusion)	MCA: C	+	+	+	+	A	13	H	1
2	2 y 11 mo/B, M	Hemato	Sickle-cell		None	−	−	+	−	A	3	H	2
3	4 y 3 mo/B, M	Hemato	Sickle-cell	Ang (left MCA occlusion)	MCA: C	−	−	+	−	A	13	R	3
4	5 y 6 mo/B, M	Hemato	Sickle-cell, prior stroke	Carotid duplex	MCA: C	+	+	+	+	A	11	H	3
5	6 y 3 mo/B, M	Hemato	Sickle-cell	Ang (left ICA stenosis)	MCA: B	+	−	+	−	A	17	H	1
6	6 y 8 mo/B, M	Hemato	Sickle-cell		None	+	−	+	−	A	4	H	2
7	12 y 4 mo/B, M	Hemato	Sickle-cell, prior stroke	Carotid duplex (proximal ICA stenosis)	MCA: C	−	−	+	−	A	4	H	2
8	7 y 7 mo/W, M	Vasculo		LP, Echo, Ang (left ICA, left MCA stenosis)	MCA: I/B	−	−	+	−	A	7	H	1
9	8 y 1 mo/W, M	Vasculo		Echo, LP (↑ WBC), Ang (vasospasm), lab (⊕ Lyme)	PCA/BA: T/Cb	−	+	+	+	L	7	H	1
10	8 y 8 mo/B, M	Vasculo	Irradiation, prior stroke	LP (↑ WBC)	MCA: C	+	−	+	−	L	11	R	3
11	14 y 7 mo/B, M	Vasculo		LP, Ang (bil VA dissection)	VA: Cb	−	+	−	−	L	8	H	3
12	3 y 8 mo/W, F	Vasculo	Ehlers-Danlos	Echo, Ang (left ICA occlusion)	MCA: C	−	−	+	−	L	27	D	5
13	7 y 2 mo/W, F	Vasculo		Echo, Ang (right MCA stenosis)	MCA: I/B	−	−	+	−	A	8	R	3
14	2 y 0 mo/W, M	Indeter		Ang, LP, Echo, PS, PC, AT, ANA, Lyme	MCA: B	−	−	+	−	A	8	H	3
15	2 y 1 mo/B, M	Indeter		LP, Echo	MCA: C	+	−	+	−	L	7	H	3
16	10 y 4 mo/B, M	Indeter		Ang, Echo, ANA, ACA, RPR, PC, PS, AT	MCA: I/B	−	−	+	−	A	10	H	3
17	1 y 10 mo/W, M	Indeter		Ang, LP, Echo, ANA, RPR, PC, PS	MCA: I/B	+	−	+	−	A	6	H	2
18	10 y 2 mo/B, F	Indeter		Ang, LP, Echo, ANA, ACA (⊕), RPR, Lyme, HIV	MCA: I	−	−	+	−	A	4	H	2

* B = black; W = white.

† Cases are grouped according to their probable etiology. Hemato = hematologic; Vasculo = vasculopathy; Indeter = indeterminate.

‡ Absence of an investigational procedure indicates that it was not done. A positive finding on an investigation is identified in the parentheses. Ang = angiogram; bil = bilateral; ICA = internal carotid artery; MCA = middle cerebral artery; LP = lumbar puncture; Echo = echocardiogram; WBC = white blood count; Lyme = Lyme titer; VA = vertebral artery; PS = protein S; PC = protein C; AT = antithrombin III; ANA = antinuclear antibody; ACA = anticardiolipin antibody; RPR = rapid plasma reagent.

§ The infarction as identified by CT or MRI is reported according to the vascular territory (MCA = middle cerebral artery; PCA = posterior cerebral artery; BA = basilar artery; VA = vertebral artery) and the gross anatomic distribution (C = cortical ± subcortical areas; B = basal ganglia; I = internal capsule; T = thalamus; Cb = cerebellar).

¶ At presentation, the presence (+) or absence (−) of specific symptoms was noted. F = febrile illness; H = headache; P = paresis; S = seizure; L = level of consciousness; A = alert; L = lethargic. A child was considered to have a concomitant or prodromal illness (F) if a fever was documented in the emergency room or a history of illness with fever occurred within 3 days before the stroke.

‖ Outcomes are given as follows: D = total number of hospital days; P = placement at time of discharge; G = score on Glasgow Outcome Scale. Placement (P) includes the following: H = home; R = inpatient rehabilitation; D = the child died while in the hospital.

⊕ = positive laboratory finding.

air contrast did not identify any potential cardioembolic source. The sixth child (no. 10) had a history of intracerebral hemorrhage secondary to an AVM several years previously. Nine months before the present stroke, he had proton beam irradiation of the AVM; the radiated region was the site of infarction. His clinical presentation and lumbar puncture findings of increased white cell count were consistent with radiation-induced vasculopathy.

In the remaining five children, the etiology of ischemic stroke was indeterminate. Four of the five children had angiographic evaluations and lumbar punctures. All cases had transthoracic echocardiography, but only two (nos. 14 and 17) had contrast. The blood studies done in each case were variable and included one or more of the following special laboratory studies: antinuclear antibody (ANA), anticardiolipin antibody (ACA), rapid plasma reagent, protein C, protein S, antithrombin III, Lyme titer, and HIV assay. The only abnormal laboratory finding (no. 18) was a

***Table 2** Clinical features and investigations for each child with intracerebral hemorrhage*

Pt no.	Age/race, gender*	Etiology†	Pertinent history	General investigations‡	Lesion by CT/MRI§	Presentation¶					Outcome‖		
						F	H	P	S	L	D	P	G
19	12 y 8 mo/B, F	AVM		Ang (AVM)	C/IV	−	−	−	−	St	2	D	5
20	1 y 8 mo/W, F	AVM		Autopsy (AVM)	Cb	−	−	−	+	St	1	D	5
21	6 y 0 mo/B, M	AVM	Factor VII deficiency, prior stroke	Ang (AVM), lab (PT = 27 sec)	B/IV	−	+	−	−	L	12	H	1
22	13 y 4 mo/W, M	AVM		Ang (AVM)	C/IV	+	+	+	−	A	7	H	1
23	13 y 8 mo/W, M	AVM		Ang (AVM)	C/IV	−	+	−	−	L	10	H	2
24	4 y 10 mo/B, F	Hemato	Aplastic anemia/ thrombocytopenia	Echo, lab (↓ Hb, ↓ Plt)	C	−	+	−	−	L	47	R	4
25	10 y 4 mo/B, F	Hemato	Sickle-cell, prior stroke	Ang (bil ICA stenosis with moyamoya)	B/IV	−	−	−	+	C	78	C	4
26	14 y 11 mo/ B, M	Hemato	Sickle-cell	Autopsy (no AVM, no aneurysm)	C/B/IV	−	+	−	−	C	2	D	5
27	4 y 3 mo/W, F	Hemato	Thrombocytopenia	Lab (↓ Plt)	S	+	+	−	−	A	2	H	1
28	14 y 6 mo/B, F	Vasculo	Systemic lupus erythematosus	Ang (vasculitis), Echo	C/IV	−	+	−	+	L	31	H	1
29	11 y 8 mo/W, M	Vasculo	Bone-marrow transplant, graft-vs-host disease	LP *(Aspergillus)*, lab (↓ Plt)	C	+	−	+	+	L	4	H	1
30	5 y 10 mo/W, M	Vasculo		Autopsy (sagittal sinus thrombus)	C	+	+	+	+	St	3	D	5
31	1 y 11 mo/W, F	Coagulo	Prosthetic valve, on heparin	Echo, lab (PTT > 150 sec)	C/IV	−	−	−	−	St	13	D	5
32	5 y 6 mo/W, M	Surgical	Intraventricular shunt removal		C/IV	+	−	−	−	L	90	R	3
33	10 y 0 mo/W, F	Surgical	Cerebellar cyst resected	Ang	IV	−	+	−	−	L	25	H	2
34	5 y 0 mo/B, F	Indeter			C	−	+	−	−	L	1	D	5
35	1 y 4 mo/B, F	Indeter	AIDS, thrombocytopenia	Echo (global hypokinesis), LP, labs (CMV, ↓ Plt)	C	+	−	−	−	St	54	D	5

* B = black; W = white.

† Cases are grouped according to their probable etiology. AVM = arteriovenous malformation; Hemato = hematologic; Vasculo = vasculopathy; Coagulo = coagulopathy; Surgical = surgical complication; Indeter = indeterminate.

‡ Absence of an investigational procedure indicates that it was not done. A positive finding on an investigation is identified in the parentheses. Ang = angiogram; PT = prothrombin time; Echo = echocardiogram; Hb = hemoglobin; Plt = platelet count; bil = bilateral; ICA = internal carotid artery; LP = lumbar puncture; PTT = partial thromboplastin time; CMV = cytomegalovirus.

§ Hemorrhagic site as identified by CT or MRI is reported according to the gross anatomic distribution. C = cortical; IV = intraventricular; Cb = cerebellar; B = basal ganglia; S = subcortical.

¶ At presentation, the presence (+) or absence (−) of specific symptoms was noted. F = febrile illness; H = headache; P = paresis; S = seizure; L = level of consciousness; St = stuporous; L = lethargic; A = alert; C = comatose. A child was considered to have a concomitant or prodromal illness (F) if a fever was documented in the emergency room or a history of illness with fever occurred within 3 days before the stroke.

‖ Outcomes are given as follows: D = total number of hospital days; P = placement at time of discharge; G = score on Glasgow Outcome Scale. Placement (P) includes the following: D = the child died while in the hospital; H = home; R = inpatient rehabilitation; C = inpatient chronic nursing care.

weakly positive ACA titer with a negative ANA titer. This finding was not considered sufficient to classify it as a probable cause of stroke, and its relevance is uncertain.

Table 2 summarizes clinical characteristics and investigations for the 17 children with intracerebral hemorrhage. Two children (nos. 21 and 25) reported a prior ischemic or intracerebral hemorrhagic stroke. There were five children with AVMs, making this the single most common cause. One child (no. 21) also had a second probable cause—a factor VII deficiency with a prothrombin time of 27 seconds. The second most common category was hematologic: aplastic anemia (no. 24), sickle-cell disease (nos. 25 and 26), and idiopathic thrombocytopenia (no. 27).

In the category of arterial/venous vasculopathy (non–sickle-cell) there were three patients. One child (no. 28) had a history of systemic lupus erythematosus and had vasculitic findings on angiography. The probable cause was considered nonatherosclerotic vasculopathy related to underlying connective tissue disease. The second child (no. 29) had had a bone marrow transplant for leukemia, which

was complicated by graft-versus-host disease. The admission lumbar puncture demonstrated *Aspergillus,* and laboratory studies showed mild thrombocytopenia (90×10^3/cumm). The probable cause of the hemorrhage was considered to be an infective vasculopathy, although the thrombocytopenia may have been a contributing factor. The last child (no. 30) presented with a lobar hemorrhage. However, bilateral, multifocal ischemic infarctions developed several days later. Autopsy demonstrated sagittal sinus thrombosis. This case is classified as an intracerebral hemorrhagic stroke because the initial presentation was an intracerebral hemorrhage.

A young girl (no. 31) had a mitral valve prosthesis and was being treated with heparin while being converted to warfarin. Before the neurologic event the activated partial thromboplastin time was markedly elevated (>150 seconds) on two sequential testings. An echocardiogram done within 24 hours of the event did not identify any thrombus. The case was thus classified as a probable coagulopathy. There were two cases under the category of surgical complication. One child (no. 32) had chronic hydrocephalus and had a shunt revision the day before the hemorrhage, which occurred along the tract of the removed shunt. A 10-year-old girl (no. 33), who underwent removal of a cerebellar cyst 4 days before her stroke, had widespread intraventricular hemorrhage with no clear parenchymal involvement. Angiogram was normal. The temporal relation to the surgery was considered sufficient to register the probable cause as a surgical complication.

There were two cases of indeterminate etiology. The first child (no. 34) died within 24 hours. No investigations or autopsy were performed beyond the initial CT, which showed a massive left parieto-occipital hemorrhage with intraventricular and subarachnoid blood. An AVM was documented in the chart as the most probable cause; however, there were insufficient studies to prove that suspicion adequately. The second child (no. 35) presented with staphylococcal septicemia and was found to have global hypokinesis on echocardiogram; she had a diagnosis of AIDS and thrombocytopenia. Serology was positive for cytomegalovirus. Lumbar puncture was done, but documentation of the results could not be found. Although a probable cause could not be assigned based on the available information, a possible cause or causes would include septic arteritis, cardioembolic event, or hematologic disorder.

The anatomic localization and vascular distribution for the ischemic infarcts and the intracerebral hemorrhages are described in the respective tables, under the column heading "Lesion by CT/MRI." The middle cerebral artery (MCA) is overwhelmingly the most commonly involved vascular territory (78%) for ischemic strokes, with equal involvement of the right and left hemispheres. Of clinical relevance is that cortically based ischemic foci were more likely related to a defined cause (73%) than to an indeterminate etiology (20%). Cortical/lobar events are the most common anatomic site (65%) for intracerebral hemorrhage in children, in contrast to intracerebral hemorrhage in adults where basal ganglia and thalamic sites predominate.

Table 1 contains information on the clinical presentation and outcome measures for children with ischemic stroke, and table 2 contains this information for hemorrhagic events. The most common clinical sign on presentation with an ischemic event was hemiparesis (94%), whereas only 21% of children with hemorrhagic insults presented with hemiparesis. Of the children with an intracerebral hemorrhage, 88% presented with altered mental status compared with 28% of children with an ischemic stroke. Headaches were relatively more common in children with primary hemorrhagic events (59%) than with ischemic events (22%). Seizures were also slightly more common on presentation with intracerebral hemorrhages (29%) than with ischemic (16%) infarction. However, the presence of a fever or prodromal illness was roughly equal between stroke types and ranged between 35 and 40%.

The outcomes for intracerebral hemorrhages were notably more severe than with ischemic stroke—the average hospital stay was 27 days versus 9 days and mortality was 41% versus 5%. However, despite this higher mortality, a good outcome, as indicated by a score of 1 or 2 on the GOS, was seen in 41% of children with an intracerebral hemorrhage compared with 50% of children with an ischemic stroke.

The incidence of stroke was determined according to the type of stroke, race, and gender. There were 30 children with first-ever clinical strokes. Based on home address, 10 of these patients were identified as living outside our designated population area. Therefore, estimation of stroke incidence was based on the 20 children with first-ever strokes who resided within our study area. The overall incidence of childhood stroke in the Greater Baltimore–Washington, DC area was 1.29 per 100,000 per year (CI: 0.83 to 2.11). The incidence per 100,000 for ischemic stroke was 0.58 (CI: 0.37 to 1.34) and for intracerebral hemorrhage was 0.71 (CI: 0.28 to 1.17). Gender, race, or gender × race interactions did not significantly contribute to the risk of ischemic stroke or intracerebral hemorrhage in our population. However, the risk of stroke in children with sickle-cell disease was found to be substantially higher than in the general childhood population. During the 2 years of surveillance, there were six children with a history of sickle-cell disease for whom this was their first stroke—five with ischemic strokes (nos. 1, 2, 3, 5, and 6) and one with an intracerebral hemorrhage (no. 26). The overall stroke incidence rate for those with sickle-cell disease was approximately 285 per 100,000 per year (95% CI: 105 to 622). The incidence rate for ischemic stroke was 238 per 100,000 (95% CI: 78 to 556) and for intracerebral hemorrhage was 47.5 per 100,000 (95% CI: 1.2 to 266). For blacks without sickle-cell disease, the overall incidence of stroke was 0.83 per 100,000, which was comparable with the incidence of 0.97 per 100,000 found among whites.

Discussion. The causes of ischemic stroke in children are quite varied and commonly include cardiac disease, infective vasculitis, connective tissue disease, hematologic and metabolic disorders, coagulopathies, and arterial dissection.[1] Although cardiac disease has been found to be the most common cause for childhood stroke in many single-center data series,[1,5,17,18] in the present study the most frequent cause was sickle-cell disease. The present population-based survey of childhood stroke in a large metropolitan area highlights the importance of this disorder in its contribution to cerebrovascular disease among children. Our estimated incidence of stroke among those with sickle-cell disease was 0.28% per year,

which is comparable with 0.35% per year reported among Jamaican children with sickle-cell disease.[19] A somewhat higher incidence of 0.77% was reported by the Sickle Cell Cooperative Study at the Children's Hospital of Philadelphia.[6] The higher incidence may be because that hospital is a referral-based center for sickle-cell disease. Secondly, and probably more importantly, their definition of stroke included TIAs and subclinical cerebrovascular events that were based on positive CT findings only.

The importance of subclinical or silent stroke is exemplified by the natural history study in sickle-cell disease reported by Armstrong et al.[20] Concurrent MRI evaluation of 135 children with sickle-cell disease identified 30 children with cerebral infarction—9 children had a history of stroke and 21 had no clinical history of stroke but had an abnormal MRI consistent with a previous stroke. The clinical importance of silent cerebral infarction was seen on neuropsychological tests; children with silent infarction had an overall poorer performance than did children with normal MRI. Therefore, depending upon the definition of stroke or the extent of clinical evaluation, the incidence of stroke in children with sickle-cell disease lies between 280 and 770 per 100,000 children per year. This range contrasts sharply with the much lower incidences of two to three cases of stroke per 100,000 children per year.[5,7,8] In fact, the incidence for sickle-cell disease-associated stroke is closer to that estimated for adults in the Framingham Study, which was approximately 0.5% in adults over age 35 years.[21] Despite the high incidence of stroke among blacks with sickle-cell disease, for children without sickle-cell disease the incidences were similar in the two racial groups. Therefore, unlike stroke in the adult population, for whom rates of stroke were reportedly higher for blacks,[10,22,23] cerebrovascular events among children of black/white racial groups were comparable.

An important finding in studies that have examined the issue of stroke in sickle-cell disease is the high incidence of first-time stroke among younger children. Roughly 60 to 80% of those with sickle-cell disease who will eventually have a stroke will have it before the age of 10 years.[6,19] The mean age for first-time stoke in our study was 6 years 3 months, which was similar to that found in the Jamaican study.[19] The incidence of first-time stroke falls off rapidly after childhood whereas that for second- and third-time stroke climbs.[6] This finding highlights the importance of early (age $\leq$2 years) screening for any stroke prevention initiative that might be planned for those with sickle-cell disease.

One of our more surprising findings is the marked prevalence of boys in the group with sickle-cell disease. Of the total of nine children with sickle-cell disease, only two were girls. The sickle-cell literature on the whole tends to report minor or no differences between sexes in terms of stroke prevalence. The Children's Hospital of Philadelphia study reported that 57.6% of all sickle-cell patients with cerebrovascular disease were males.[6] More impressive differences were reported in the Jamaican sickle-cell disease population where 73.3% of those with ischemic strokes were males.[19] Clearly our sample is relatively small, and random variability may account for some of the gender difference. However, our findings, along with the Jamaica study, suggest that boys under age 15 years may be at greater risk for stroke then their female counterpart.

In sickle-cell disease, both angiographic and postmortem studies have demonstrated the primary vascular lesion to be occlusive disease of the distal ICA or proximal middle cerebral artery or anterior cerebral artery.[24-26] Only three of the children in our study had an angiogram, and all three demonstrated occlusion or severe stenosis of the ICA or MCA. Of particular note is that one child (no. 5), although having a basal ganglia infarct on CT, demonstrated severe distal ipsilateral ICA stenosis. Thus the assumption that the underlying pathology is either large vessel or small vessel based solely on CTs or MRI[27,28] may be tenuous. The preponderance of ischemic stroke over intracerebral hemorrhage in sickle-cell disease is fairly well recognized and follows as a consequence of the underlying vascular pathology.

The next most common category of stroke etiology was vasculopathy (non–sickle-cell disease). Within this category were various causes: infection, arterial dissection, connective tissue disorders, and radiation-induced vasculopathy. Two children had no specific cause outside of focal ipsilateral cerebrovascular changes found on angiogram. Both of these children had basal ganglionic infarctions compared with the other four children in this group who had cortical or cerebellar infarctions. This is consistent with the series of children with acute basal ganglionic infarction described by Zimmerman et al.,[29] who found 10 of 11 angiograms to be positive. Of the 10 positive angiograms, 7 had specific findings (arterial dissection, aneurysm, embolus, moyamoya), but three children had only focal ipsilateral intracranial stenosis similar to what was found in our two children (nos. 8 and 13). Blennow et al.[30] also reported similar findings of focal intracranial arterial irregularities in a small subgroup of children under investigation for their stroke. He speculated that "... since atherosclerosis can hardly be implicated, these luminal irregularities may tentatively represent regional arteritis." However, neither study helps clarify the etiology of this focal intracranial process or its importance to future events. Zimmerman et al.[29] suggest extensive laboratory evaluation in these cases may yield more definitive cause. Despite a very exhaustive assessment in our two cases, no specific etiology was identified, although homocysteine metabolism was not assessed.

Congenital or acquired heart disease is often identified as a leading cause of stroke in children.[1,5,17,18] In our cohort of patients only two had underlying heart disease (nos. 31 and 35), but in neither of these children was the stroke necessarily related to the

heart disease. Dusser et al.[2] reported on a series of 44 infants and children who had a cerebrovascular event. Cardiac disease was considered the primary cause in six infants (<2 years) and two children (2 to 14 years). This gave a proportion of 38% in infants and 7% in children. In a series of 87 children (age range 0 to 14), Hilal et al.[3] reported a cardiac cause in 8%, but separate event rates for infants and children were not reported. These two series represent, as do many others, the experience of large referral centers and are not population-based studies. In a survey of the pediatric hospitals in the Cincinnati, Ohio, area, two of seven ischemic strokes were attributed to a cardiac cause.[9] Cardiac events appear to be much higher in infancy (0 to 2 years) than in childhood (2 to 14 years)[2] and, by limiting the case selection in the Baltimore–Washington, DC study to the 1 to 14 age range, we have probably limited the contribution of cardiac disease.

Intracerebral hemorrhage represents roughly one-half the total number of strokes in our cohort. The Cincinnati study[9] also found hemorrhagic strokes to be roughly one-half the total number of strokes. This is in stark contrast to adults for whom intracerebral hemorrhage represents only approximately 10% of strokes.[31] In the Baltimore–Washington, DC study, 29% of intracerebral hemorrhages were associated with an AVM, making this the leading cause of intracerebral hemorrhagic stroke in children. Forty-three percent of intracerebral hemorrhages (excluding subarachnoid hemorrhage) in the Cincinnati cohort[9] also were attributable to AVM. Again, this contrasts with findings in adults in whom less than 5% of intracerebral hemorrhages are attributable to AVM and in whom hypertension accounts for nearly 50% of this type of stroke.[31]

Ischemic strokes and intracerebral hemorrhages in children differed in their clinical presentation and outcomes. Hemiplegia is the most common presentation for an ischemic event, whereas it is uncommon with a primary hemorrhagic event.[2,5,9,32] Altered mental status was the leading clinical presentation for intracerebral hemorrhage (88% of children). However, altered mental status was present on initial examination in only 28% of ischemic patients. Keidan et al.[32] also found that approximately 75% of children presenting with intracerebral hemorrhages had an altered level of consciousness, but he reported that one-half the ischemic group also had this finding.

Our finding of a higher mortality for intracerebral hemorrhages compared with ischemic strokes agrees with earlier reports.[5,9,32] However, despite the higher mortality in those with intracerebral hemorrhages, there appears to be less of a disparity in morbidity between survivors of the two stroke types—41% of the hemorrhagic and 50% of the ischemic groups had good outcomes. Similarly, Schoenberg et al.[5] found slightly less residual disability in those with intracerebral hemorrhages compared with ischemic strokes, and Keidan et al.[32] reported no difference in disability between hemorrhagic and ischemic groups with an average follow-up period of 4.2 years.

The reported range of incidences for childhood (0 to 14 years) stroke is 2.5 to 3.1 per 100,000,[5,7,8] which is substantially higher than our finding of 1.25 per 100,000. However, it should be noted that the confidence intervals for those incidence rates are inclusive of our study findings. The incidence of 2.52 per 100,000 (CI: 0.69 to 6.45) reported for Rochester, Minnesota, is derived from four cases found over a 10-year period.[5] The Oxfordshire Community Stroke Project[7] identified only two cases over a 5-year period and reported an incidence of 3.0 per 100,000 but did not report the confidence interval. In Iceland, the incidence of childhood stroke is 3.1 per 100,000 (CI not given), and this represents 22 cases found over a 10-year period.[8] The only study comparable with ours in terms of size, race, and metropolitan population is the Greater Cincinnati Metropolitan study.[9] The authors of that study identified 16 infants or children with stroke over a 2-year period and reported an overall incidence for stroke in children of 2.6 per 100,000 (CI: 1.2 to 4.1). The lower incidence rate (1.25/100,000) reported here is likely because our study excluded infants and subarachnoid hemorrhage. All four of the studies cited above included subarachnoid hemorrhage and infants (age <12 months) in their case collection. The addition of subarachnoid hemorrhage will clearly increase the stroke incidence by increasing the number of cases defined as stroke. Reported case series of childhood stroke from various centers indicate that anywhere from 37 to 78% of cases of childhood stroke are under the age of 2 years.[3,32-34] Therefore, the inclusion of infants in the population to be studied is likely to increase the overall estimated incidence of stroke in childhood. If the same exclusion criteria used in our study were applied to the Cincinnati study,[9] there would be five cases excluded out of their original 16—two with subarachnoid hemorrhage and three with ages under 12 months—for an incidence of 1.79 per 100,000 children.

Although strokes occur in children, the overall rate of occurrence is low. When a stroke occurs in children, those with an intracerebral hemorrhage have a higher mortality than that seen with ischemic stroke. Unlike the adult population, intracerebral hemorrhage and ischemic stroke occur in about equal proportion with approximately the same outcome in survivors. Among children with sickle-cell disease there is a disproportionately higher incidence of stroke with rates similar to those for the adult population.

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