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Cerebral infarction in young adults

The Baltimore-Washington Cooperative Young Stroke Study

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Article abstract—*Background:* Few reports on stroke in young adults have included cases from all community and referral hospitals in a defined geographic region. *Methods:* At 46 hospitals in Baltimore City, 5 central Maryland counties, and Washington, DC, the chart of every patient 15 to 44 years of age with a primary or secondary diagnosis of possible cerebral arterial infarction during 1988 and 1991 was abstracted. Probable and possible etiologies were assigned following written guidelines. *Results:* Of 428 first strokes, 212 (49.5%) were assigned at least one probable cause, 80 (18.7%) had no probable cause but at least one possible cause, and 136 (31.8%) had no identified probable or possible cause. Of the 212 with at least one probable cause, the distribution of etiologies was cardiac embolism (31.1%), hematologic and other (19.8%), small vessel (lacunar) disease (19.8%), nonatherosclerotic vasculopathy (11.3%), illicit drug use (9.4%), oral contraceptive use (5.2%), large artery atherosclerotic disease (3.8%), and migraine (1.4%). There were an additional 69 recurrent stroke patients. *Conclusions:* In this hospital-based registry within a region characterized by racial/ethnic diversity, cardiac embolism, hematologic and other causes, and lacunar stroke were the most common etiologies of cerebral infarction in young adults. Nearly a third of both first and recurrent strokes had no identified cause.

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Few data are available from populations in the United States regarding the clinical spectrum of stroke in young adults.¹⁻³ In particular, few studies have reviewed cases derived from a broad cross-section of community and referral hospitals in a specific geographic region using a classification system of known interobserver reliability. We evaluated the causes of cerebral arterial infarction among young adults 15 to 44 years of age presenting to all 46 hospitals in the Baltimore-Washington region.

Methods. The Baltimore-Washington Cooperative Young Stroke Study is a regional hospital-based registry initiated to study the incidence and causes of stroke in young adults.⁴⁻⁶ The study region encompasses Baltimore City; Washington, DC; and five central Maryland counties (Anne Arundel, Baltimore, Howard, Montgomery, and Prince Georges). The total population of this region in 1990 was 3,935,910. The population of young adults 15 to 44 years of age was 2,077,825; of these, 57% were white, 38% black, 4% Asian, and 1% of other racial and ethnic groups.^{7,8}

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All 44 acute care hospitals and both rehabilitation hospitals in the study region participated in the study. During 1988 and 1991, there were 2470 hospital discharges of persons 15 to 44 years of age with a primary or secondary diagnosis reflecting a possible cerebral infarction or intracerebral hemorrhage; specifically, International Classification of Diseases—Ninth Revision (ICD-9) codes 431.00 to 438.00 (cerebrovascular disease except subarachnoid hemorrhage), 671.50 to 671.54 (cerebral venous thrombosis), and 674.00 to 674.04 (cerebrovascular complications of the puerperium). Of these cases, medical records from 2309 (93%) were reviewed by an experience-trained nurse.

The abstracting process yielded a narrative summary for each patient that described past strokes and episodes of transient ischemic attacks as well as presenting neurologic symptoms and signs and their evolution. In addition, the data recorded demographic characteristics, stroke risk factors, laboratory results including neuroimaging findings and, if available, autopsy reports. For the purpose of classifying an event as an incident or recurrent stroke, a history of prior stroke in the medical record was accepted as true (unless it occurred during the study years and was available for abstraction).

The abstract on each possible acute stroke was reviewed by two neurologists who classified the event according to the criteria of the World Health Organization⁹ and the National Institute of Neurological Disorders and Stroke (NINDS).¹⁰ We excluded cerebral arterial infarctions occurring as an immediate consequence of trauma or associated with subarachnoid hemorrhage and strokes due to cerebral venous thrombosis.

Each cerebral infarction was further classified by a pair of neurologists into nine categories according to written predefined criteria of known interobserver reliability.⁶ The one exception to our previously reported criteria is that patients with total occlusion of a large artery proximal to an infarction, without evidence of atherosclerotic disease in any other vessel or other identifiable disease process, were classified as indeterminate. 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, illicit drug-related, and indeterminate).

For an individual event, the diagnosis of stroke subtype could be either probable or possible depending on the strength of clinical evidence. Two probable diagnoses were allowed if criteria were met for two conditions of equal priority. A lower priority diagnosis could not be coded as probable when a higher priority probable or possible diagnosis was present; the lower priority diagnosis had to be assigned a possible label. This system was intended to approximate the process of clinical diagnosis while preserving information about secondary, contributing, or multiple causes. The use of probable and possible labels preserved the ability to access data when a less likely but plausible (possible) cause was present.⁶

Results. We identified 493 patients with a cerebral arterial infarction. The 493 patients sustained 503 stroke events, 428 first stroke events, and 75 recurrent stroke events. Of those with first stroke, 51.4% were women, 60.5% were black, 36.2% were white, and 19.6% were

younger than 30 years of age. Those with prior stroke were slightly more likely to be women (59.4%), more likely to be of black race (68.1%), and less likely to be younger than 30 years of age (15.9%).

Of the 428 patients with a first stroke, 212 (49.7%) were assigned a probable cause, 80 (18.5%) only a possible cause, and 136 (31.8%) no probable or possible cause. Of patients with at least one probable stroke cause, less than 2% had more than one probable cause. Of the patients with no probable cause identified, 38% had more than one possible etiology. Of 428 patients, the distribution of probable causes were: cardiac embolism, 66 (15.4%); lacunar, 42 (9.8%); hematologic and other, 38 (8.9%); nonatherosclerotic vasculopathy, 24 (5.6%); illicit drug use 20 (4.7%); oral contraceptive use, 11 (2.6%); large artery atherosclerosis, 8 (1.9%); and migraine, 3 (0.7%). Four persons with a probable hematologic and other cause and also nonatherosclerotic vasculopathy (2) and cardiac embolism (2) were counted with the latter two diagnoses to maintain a denominator of people rather than diagnoses.

For the 212 persons assigned a probable cause, the mean (and median) age of persons in the different etiologic categories were, in ascending order of age in years: oral contraceptive-associated, 31.2 (29); nonatherosclerotic vasculopathy, 31.7 (31); migrainous stroke, 31.7 (33); hematologic and other causes, 33.4 (34.5); illicit drug-associated, 34.7 (34); cardiac embolism, 35.8 (38); atherosclerotic, 39.4 (40); and lacunar, 39.9 (41.5). These mean age differences were highly significant ($p < 0.001$) by analysis of variance; the significant ($p < 0.05$) contrasts, controlling for multiple comparisons, were that persons with lacunar strokes were older than persons with cardiac embolism, hematologic and other causes, nonatherosclerotic vasculopathy, and oral contraceptive-associated stroke.

Of the 75 recurrent stroke events, 65 occurred among patients who had their first stroke outside of the study years (not during 1988 and 1991), 4 occurred among the 428 patients who had their first stroke within the study years, and 6 occurred among five patients who had a prior recurrent stroke within the study years. Four patients had two recurrent strokes and one patient had three recurrent strokes. The etiologies represented in these five patients were large artery atherosclerosis in one, cardiac embolism in three, and indeterminate in one. For the sake of simplicity, and to maintain persons rather than strokes as the denominator, all subsequent analyses of recurrent stroke are based on the first recurrence during the study years. Of the 69 patients with first recurrent stroke, 27 (39.1%) were assigned a probable cause, 19 (27.5%) only a possible cause, and 23 (33.3%) no probable or possible cause. Of patients with at least one probable stroke cause, none had more than one probable cause. Of the patients with only possible cause identified, 4 of 20 (20%) had more than one possible etiology. Table 1 shows a summary of probable and possible causes for first and recurrent stroke.

The remainder of the results pertain to the 428 persons with first cerebral infarction. Cardiac embolism was the probable cause of stroke in 66 individuals and the possible cause of infarction in another 41. The specific causes of cardioembolism are detailed in table 2. Endocarditis, prosthetic valves, and cardiomyopathy were the three leading probable causes.

There were 42 cases of lacunar stroke in the absence of

Table 1 Probable and possible etiologies among 428 persons with first and 69 persons with recurrent cerebral infarction*

Episode	Etiology								
	Ath	Non Ath	Lac	Emb	Heme/Oth	Mig	OC	Illicit drugs	Indet
First (n = 428)									
Probable	8	24	42	66	42	3	11	20	136
Possible	25	7	12	41	19	5	11	31	—
Recurrent (n = 69)									
Probable	4	2	4	9	8	0	0	0	23
Possible	5	0	2	13	6	0	0	2	—

* Cells indicate the number of persons with each designated etiology. As described in the text, a given event may have multiple probable or possible etiologies.

Ath = atherosclerotic vasculopathy; Non Ath = nonatherosclerotic vasculopathy; Lac = lacunar; Emb = cardiac/transcardiac embolism; Heme/Oth = hematologic/other; Mig = migraine; OC = oral contraceptive use; Indet = indeterminate.

any other probable or possible stroke etiology: 1 case in association with a probable hematologic/other cause and 11 cases in association with another possible cause. Hypertension was present in 73.2% of lacunar strokes, compared with 40.1% of nonlacunar strokes.

There were 42 stroke cases with a probable and 19 stroke cases with a possible hematologic/other cause. The specific conditions are shown in table 2. The three most common conditions were systemic lupus erythematosus, eclampsia or preeclampsia, and complications of procedures, particularly neck surgery.

There were 24 cases of probable and 7 cases of possible nonatherosclerotic vasculopathy. The specific conditions are shown in table 2. Vasculitis and dissection were equally common and accounted for over half of the cases in this category.

There were 20 cases of stroke in temporal association with illicit drug use in the absence of another probable or possible cause, 20 cases in association with a probable cause, and 11 cases in association with another possible

cause. The specific conditions are shown in table 2. Cocaine use within 48 hours of the ictus was present in 80% of the probable causes in this category.

There were 11 cases where oral contraceptive use was the only identified contributing cause: six cases in association with a probable cause and four cases in association with another possible cause.

There were eight cases of probable atherosclerotic vasculopathy, in five women and three men aged 31 to 44 years. All had at least one risk factor for atherosclerotic disease (cigarette smoking, 7; hyperlipidemia, 5; diabetes mellitus, 2; and hypertension, 2). No patient had coronary artery disease. Extracranial carotid artery disease occurred in seven patients; two had coexistent atherosclerotic disease in the middle cerebral artery. One individual had basilar artery atherosclerosis. Aortic arch studies were available for six patients, only one of whom demonstrated atherosclerosis. An additional 25 cases had detectable, but not more than 60%, atherosclerotic stenosis proximal to their stroke; of these, 3 had another probable cause and 13

Table 2 Summary of etiologies of 428 first strokes: The Baltimore-Washington Cooperative Young Stroke Study*

Etiology	Probable cause	Possible cause
Cardioembolic	Endocarditis (20), prosthetic valve (14), cardiomyopathies/diffuse hypokinesis (9), intracardiac thrombus (7), akinetic segment (5), atrial fibrillation (4), other (7)	Mitral valve prolapse (16), hypokinetic segment (8), remote myocardial infarction (4), aortic valve or mitral annular calcification (4), other (9)
Lacunar stroke	(42)	(12)
Hematologic/other	Hematologic (16), systemic lupus erythematosus (7), eclampsia/preeclampsia (5), other systemic diseases (6), complications of neck surgery (3), other complications of procedures (5)	Hematologic (15), systemic disease (3), complication of procedure (1)
Nonatherosclerotic vasculopathy	Takayasu vasculitis (3), other vasculitis (6), carotid dissection (9), other (6)	Vasculitis (4), vertebral dissection (1), other (2)
Illicit drug-associated	Cocaine (8), other drugs (3), multiple drugs (9)	Cocaine (18), other drugs (7), multiple drugs (6)
Oral contraceptive-associated	(11)	(10)
Atherosclerotic vasculopathy	Extracranial carotid (7), basilar stenosis (1)	(25)
Migrainous stroke	(3)	(5)

* Categories are not mutually exclusive; more than one probable or possible cause is permitted. No probable or possible causes were noted in 136 patients (indeterminate).

had another possible cause. Four cases of total occlusion without other evidence for cerebral atherosclerosis were classified in the indeterminate category.

There were three probable cases of migrainous stroke without any other possible contributing cause, one possible case in association with a probable cause, and four possible cases in association with another possible cause.

Discussion. Our study examines the clinical spectrum of cerebral arterial infarction in a young heterogeneous metropolitan population and is the largest American series reported to date. Because this study includes all patients hospitalized in a defined geographic region, it is less subject to selection bias than most prior series. A further distinguishing feature is that African Americans account for a substantial proportion of the population in the study region.

Cardiac sources of embolism account for the largest group of probable causes of stroke in young patients. Overall, 66 of 428 (15.4%) first stroke patients and 9 of 69 (13.0%) recurrent stroke patients could be assigned this diagnosis. Importantly, air-contrast echocardiography was infrequently used and transesophageal echocardiography was not readily available. Therefore, with current technology, more patients might have been assigned a cardiac diagnosis.

Few series^{2,3,11-14} have assigned a diagnosis of lacune. Because the relative frequency of this etiology of stroke in our series is fairly substantial (54 of 493, or 11.0% of first strokes), we believe this category must be considered in future studies. We recognize, given our definition of "lacune" as a syndrome, that the underlying pathologic stroke mechanisms may be diverse. Our results support the usefulness of the lacune concept in young adults in that, of the 54 lacunes among the first strokes, only one coexisted with a higher priority probable cause. Hypertension was more common in lacunar than nonlacunar strokes, but over 25% of lacunar stroke patients did not have a history of hypertension.

The hematologic/other category represents a large, heterogeneous group. The strength of the association of some of the conditions to stroke is poorly defined; for these cases, some investigators might argue with our designation of probable or possible causes or might prefer inclusion in the indeterminate category. With further insights into the contribution of coagulation disorders to stroke causation, we expect the proportion of patients assigned to this category to grow in the future.

Nonatherosclerotic vasculopathy was three times more common than atherosclerosis as a probable cause of first cerebral infarction. Our patients with atherosclerotic disease had readily identified risk factors, with a high proportion of cigarette smoking. Interestingly, none had documented coronary artery disease, and the majority were women. The disease was usually extracranial. Both nonatherosclerotic and atherosclerotic vasculopathy may have been underestimated, as angiography was performed in only

32% of incident stroke cases and magnetic resonance angiography was not widely employed.

Oral contraceptive-associated stroke or illicit drug-associated stroke does not imply a causal relationship. The design of this study cannot address whether oral contraceptive or illicit drug use (or any specific characteristic) confers an excess stroke risk. In fact, one recent study failed to find a statistically significant association between ischemic stroke and oral contraceptive use,¹⁵ although another international study found an association, particularly among smokers or hypertensive patients.¹⁶

Similarly, some¹⁷ but not all¹⁸ studies have found recent illicit drug use to be associated with stroke in young adults. Our diagnostic paradigm may underestimate the true impact of illicit drug use on stroke. For instance, endocarditis was assigned to the cardiac group, but could have been precipitated by drug abuse.

We used strict criteria in assigning a diagnosis of migraine-associated stroke. As the International Headache Society's (IHS) 1988 criteria for migrainous stroke¹⁹ were not published until after the design of the study, they were not used. Chart reviews may not provide enough information to warrant a diagnosis of migrainous stroke by strict criteria. Therefore, the diagnosis of migraine-associated stroke is likely underestimated by this study; such patients may have been placed in the indeterminate category.

The patients with an indeterminate cause of stroke are an especially interesting group. A more thorough evaluation may have permitted a definitive diagnosis. The evaluation of stroke in young patients can be quite complicated and there is no generally accepted algorithm for approaching the problem, although some have been suggested.²⁰ Furthermore, some patients may have died or were so close to death that diagnostic evaluation was precluded. Nevertheless, even in the series by Adams et al.,² where comprehensive evaluations were conducted at a single institution and classification used predefined criteria, 34.3% of strokes were considered to be of indeterminate cause. With advancing knowledge, we expect the proportion of young stroke patients within the indeterminate category to shrink progressively; developments in hematology and genetics will be particularly important to monitor. Finally, 33.3% of patients with a prior stroke had no identified probable or possible cause for their cerebral infarction, suggesting that a "negative workup" does not preclude recurrent events.

An important limitation for our study was that patient evaluations were conducted by multiple physicians in diverse hospital settings; there was no uniform protocol. Management was based on each physician's approach to patient care and reflected 1988 and 1991 knowledge and technology. We were further hampered by the retrospective nature of the information obtained and the possibility that subsequent outpatient data would have permitted a more precise diagnosis.

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