

Diagnostic Strategies in Young Patients with Ischemic Stroke in Canada

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ABSTRACT: Background: A preliminary national survey of ischemic stroke in the young (15-45 years) undertaken by the Canadian Stroke Consortium indicated that in 44% of 356 patients, no cause was found. **Objective:** To determine the reason for this high incidence of diagnostic uncertainty in young patients with ischemic stroke. **Methods:** Neurologists in the ten Canadian stroke centers completed a detailed questionnaire for patients aged 15-45 years admitted to hospital between January 1993 and December 1997. Using a step-wise diagnostic algorithm incorporating clinical, neuroimaging, neurovascular and laboratory data, we divided patients into three groups: (1) those with established cause for the ischemic stroke, (2) those who remained unexplained despite adequate investigation, (3) those who remained unexplained but were, in our opinion, under-investigated. **Results:** In 197 patients (56%), an identified cause was established including cardioembolic sources (14%), extracranial arterial dissection (13%), lacunar infarcts (8%) atherosclerosis (6%). A miscellaneous group of 15%, included cerebral venous thrombosis, coagulopathies, vasculitis and others. In 159 patients (44%) with no apparent cause for their stroke, we considered only 81 (23%) adequately investigated, and 78 (21%) inadequately investigated. **Conclusion:** About one in five young patients was inadequately investigated by a stroke-oriented group of neurologists. The major problem appears to be restriction of investigations to neuroimaging alone (usually computerized cerebral tomography), without further tests such as cerebral angiography and cardiac imaging.

RÉSUMÉ: Stratégies diagnostiques chez des patients jeunes qui ont subi un accident vasculaire cérébral ischémique au Canada. Introduction: Une enquête nationale préliminaire sur l'accident vasculaire cérébral (AVC) ischémique chez les jeunes (15 à 45 ans) sous l'égide du Canadian Stroke Consortium indique qu'aucune cause n'a été mise en évidence chez 44% des 356 patients étudiés. **Objectif:** Déterminer la raison de ce haut taux d'incertitude diagnostique chez des patients jeunes qui ont subi un AVC ischémique. **Méthodes:** Les neurologues des dix centres canadiens de l'AVC ont complété un questionnaire détaillé sur leurs patients âgés de 15 à 45 ans qui avaient été hospitalisés entre janvier 1993 et décembre 1997. Nous avons séparé les patients en trois groupes selon un algorithme diagnostique pas à pas incorporant les données cliniques, neuroradiologiques, neurovasculaires et biochimiques: (1) les patients dont la cause de l'AVC ischémique était établie; (2) ceux dont l'étiologie de l'AVC demeurait inexpliquée malgré une investigation adéquate; (3) ceux dont l'étiologie de l'AVC demeurait inexpliquée mais dont l'investigation était inadéquate à notre avis. **Résultats:** Chez 197 patients (56%), la cause a été identifiée: une source d'embolie chez 14%; une dissection artérielle extracrânienne chez 13%; un infarctus lacunaire chez 8%; l'athérosclérose chez 6%. Un groupe hétérogène composé de 15% des patients comprenait des patients ayant subi une thrombose veineuse, des patients atteints de coagulopathies, de vasculite ou d'autres pathologies. Des 159 patients (44%) n'ayant aucune cause apparente de leur AVC, nous avons considéré que seulement 81 patients (23%), avaient été investigués adéquatement et 78 (21%) ne l'avaient pas été. **Conclusion:** Environ un jeune patient sur cinq avait été mal investigué par un groupe de neurologues travaillant dans le domaine de l'AVC. Le problème majeur semble être une investigation limitée à la neuroimagerie (habituellement une tomographie cérébrale assistée par ordinateur), sans autre test comme une angiographie et une imagerie cardiaque.

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Although stroke is a leading cause of death and disability in developed countries, ischemic stroke below the age of 50 years is relatively infrequent. In Canada in 1991, the incidence of cerebral infarction in persons below 54 years was about 13/100,000, compared to 180/100,000 in those aged 55-65.¹ Consequently there are few studies with sufficiently large populations of young stroke patients on which to base adequate epidemiological data. The etiological spectrum is different in older patients where atherosclerosis is a major cause, while cardioembolism and arterial dissection are the main documented causes in the young.²⁻⁵ In up to one third of these young patients

no cause was found, yet etiological attributions were often made, for which little or no evidence-based data were available.

In a preliminary national registry of young stroke patients undertaken by the Canadian Stroke Consortium (CSC), we were

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surprised by the large number of patients who, on hospital discharge, had no established cause for their cerebral infarction. This study was undertaken to evaluate the reason for high incidence of diagnostic uncertainty in young patients with ischemic stroke.

METHODS

Members of the CSC reviewed the records of all patients aged 15-45 years, using ICD-9 codes (433, 434, 436, 437) with a diagnosis of ischemic stroke, who were admitted between January 1993 and December 1997 to Canadian hospitals. After completing a special case record form, data were stored centrally by computer at the coordinating centre in Toronto. All identified arterial and venous strokes were included. We excluded transient ischemic attack (in view of the uncertainty of diagnosis), strokes secondary to surgical procedures, and patients with subarachnoid hemorrhage. In those who had more than one stroke during the study period, we included only the first episode.

Data included demographic factors, putative risk factors, clinical features, final hospital diagnosis, and all diagnostic and laboratory procedures such as computed cranial tomography (CCT) or magnetic resonance imaging (MRI), 24 hour monitoring of cardiac rhythm (Holter), hematological testing, transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE), carotid ultrasound, and all forms of cerebral angiography.

We studied the frequency and types of CCT, MRI, carotid doppler, TTE, and TEE, and determined how frequently specific hematological work-up were performed when these other tests proved negative.

We considered patients adequately investigated according to a step-wise, progressive, diagnostic algorithm if they had brain, neurovascular and cardiac imaging, as well as specific hematological testing including lupus anticoagulant (LA) and antiphospholipid antibodies (APLA), antithrombin III, protein C, protein S, activated protein C resistance (factor V Leiden), hyperhomocystinemia, cholesterol and sickle cell factor. We

Table 1: Cause of stroke

Cause	Total n = 356	15-30 years n = 76	31-45 years n = 280
Unknown	159 (44%)	35 (47%)	124 (43%)
Miscellaneous	54 (15%)	18 (23%)	36 (13%)
Cardioembolic	51 (14%)	15 (20%)	36 (13%)
Dissection of extracranial artery	44 (13%)	7 (9%)	37 (14%)
Small vessel disease	27 (8%)	0 (0%)	27 (10%)**
Large artery disease	21 (6%)	1 (1%)	20 (7%)*

* $p < 0.01$ compared with 15-30 years old subgroup

** $p < 0.05$ compared with 15-30 years old subgroup

Table 2: Cardiac causes of stroke (n = 51)

	n	%
Acquired (n=27)		
Ischemic heart disease	17	33
Rheumatic heart disease	4	8
Bacterial endocarditis	3	6
Atrial fibrillation	2	4
Atrial myxoma	1	2
Congenital (n = 24)		
Patent Foramen Ovale	15	29
Mitral valve prolapse	3	6
Valvular heart disease	3	6
Atrial septal defect	3	6

considered them inadequately investigated if the cause remained unexplained and only some of these investigations had been performed.

Risk factors were deemed present in patients already receiving treatment for hypertension, diabetes, hypercholesterolemia, ischemic heart disease and migraine and all drugs were documented including current use of contraceptive pills. Migrainous stroke was only diagnosed when the stroke occurred during or immediately after a migraine attack as defined by the International Headache Society (IHS) criteria.⁶ The diagnosis of arterial dissection was accepted only in the presence of angiographic imaging (catheter or MRI), in view of the limited value of Doppler.⁷

Strokes were classified into modified TOAST classification:⁸

1. Large artery atherosclerosis; 2. Cardioembolic; 3. Small vessel disease; 4. Dissection; 5. Miscellaneous (migraine, vasculitis, venous thrombosis, coagulopathies etc.); and 6. Unknown causes (Cryptogenic). In patients with more than one potential cause, we chose the most potent etiological factor and ascribed only one cause.

We divided the patients into two groups, 15-30 years of age, and 30-45 years of age, since the putative etiologies change during the three decades of age used in this study. Atherosclerosis, for example, is rare below age 30.⁹

Statistical evaluations were made by means of t test to determine significant differences between means ($P < 0.05$), and the χ^2 test was used to determine significant differences between proportions. Data were stored on SPSS (version 7.5 for windows) software.

RESULTS

Records from a total of 356 patients in 10 centres were examined: 58% (207) were men, mean age 36 ± 8 years, and 42% (149) were women, mean age 35 ± 7 years.

Hypertension was present in 29%, hypercholesterolemia in 10%, cardiac disease in 14%, diabetes in 12%, migraine in 29%

Table 3: Miscellaneous causes of stroke (n = 54)

Cause	n	%
Venous thrombosis	13	24
APLAand LA*	8	15
Migraine	7	13
Vasculitis	6	11
Substance abuse	4	8
Pregnancy or peri-partum	4	8
Moya-Moya disease	2	4
Meningitis/ vasculitis	2	4
Other**	8	15*

*APLA indicates antiphospholipid antibody syndrome. LA indicates lupus anticoagulant.

**Single cases of Susac's microangiopathy, HIV, MELAS, homocystinemia, sickle cell crisis, subclavian steal, radiation arteritis and Epstein-Barr virus associated lymphoid granulomatosis were documented.

of women and in 12% of men. Eighteen percent of women were taking oral contraceptives and 12% were pregnant or within six weeks post-partum.

Patients with established cause of stroke

A cause for the patients stroke was found in 197 cases (56%), the largest identified group being cardioembolic (14%) [Table 1]. Arterial dissection was the second major cause (13%) and in 25% of these cases, a recent history of cervical trauma was present, but since this is a retrospective study, the incidence of minor trauma may be underestimated. In patients 31-45 years, dissection was the commonest identified cause of ischemic stroke.

Lacunae and carotid stenosis, were almost absent in the younger age group (<30 years) (Table 1).

Twenty-seven patients had acquired cardiac lesions and 24 had congenital cardiac lesions as the presumed cause of stroke (Table 2). In this group ischemic heart disease accounted for 33% (17/51) of the cases, followed by rheumatic heart disease (8%), bacterial endocarditis (6%), atrial fibrillation (4%) and atrial myxoma (2%). Patent foramen ovale (PFO) was the leading congenital cause of cardioembolic stroke (29%, 15/51). In the absence of proof of a concomitant venous source, such as deep venous thrombosis (DVT), this cause must remain speculative, and we found no evidence of clinical and laboratory testing to confirm either a diagnosis of DVT or a concomitant coagulopathy. Atrial or ventricular septal defect and mitral valve prolapse were other congenital cardiac causes of stroke, each representing 6% (3/51).

The miscellaneous group (Table 3) consisted of cerebral venous thrombosis as the most common cause (24%), followed by APLA syndrome (15%), and 13% with an ischemic cerebral lesion accompanied by a migraine attack. One patient, presenting initially with stroke but both negative CT and cerebral angiography, was readmitted three months later with another "transient ischemic attack (TIA)" when MR scanning immediately identified the typical plaques of multiple sclerosis.

Patients with unknown cause

Among 159 patients (44%) where no cause for their stroke was found, 81 (23%) were adequately investigated according to our predefined criteria, but 78 (21%) were inadequately investigated. There was no significant difference in the frequency when carotid duplex was used, or in cardiac imaging studies (Table 4), but inadequately investigated patients had significantly less angiography ($p < 0.001$), TEE and TTE than patients with established causes of stroke. There was no significant difference in the frequency of investigations between patients with established causes of stroke and those who remained unexplained even after adequate investigation, so there still remains a group of unexplained cause in spite of complete neurological, vascular and hematological investigations (81/159 = 55% of the cryptogenic group) (Table 4).

Table 4: Frequency of investigations (n = 356)

Investigations	Established n = 197	Unknown ("Cryptogenic") n = 159	Unknown with completely investigated n = 81	Unknown with inadequately investigated n = 78
Angiogram	138 (70%)*	77 (49%)	57 (70%)	20 (25%)
Duplex	75 (38%)	70 (44%)	46 (57%)	24 (31%)
TTE	125 (64%)**	108 (68%)	81 (100%)	27 (35%)
TEE	54 (27%)**	36 (22%)	31 (38%)	5 (6%)
Hematology	177 (90%)	106 (67%)	80 (99%)	26 (34%)

* $p < 0.001$ compared with unknown

** $p < 0.001$ compared with inadequate investigation

DISCUSSION

In published studies of young stroke patients, the etiology remains completely unexplained in 23-50% of the cases.²⁻⁵ Some of these etiological discrepancies between published series of ischemic stroke in the young may represent regional differences, such as the relative high occurrence of stroke induced by drug abuse in large cities in the USA¹⁰ or by alcohol in Finland.² However, we believe a major reason so many remain unexplained is either the lack of adequate neurovascular investigation or the incorrect perception of the weighting of risk factors. For instance, in a pooling of data in three German data banks, of 1564 patients with stroke or TIA, 17% were attributed to cardiogenic causes. Patients investigated by TEE compared to those without this investigation had much higher rates of cardiac thrombus (11% vs 2.4%), mitral valve prolapse (22% vs 0.6%) and PFO (7.4% vs 0%), yet the authors concluded that this investigation did not appreciably aid in determining the cause of the stroke.¹¹

Cardiac lesions previously considered benign, such as asymptomatic chronic atrial fibrillation, are now recognized as powerful sources of cardioembolic stroke, with an annual frequency of about 4% of ischemic strokes.¹² Although one in five otherwise normal people have detectable PFO this is increasingly recognized as an established cause of paradoxical embolism.¹³ Although the presence of PFO alone (or associated abnormalities such as atrial septal aneurysm) does not justify a causal relationship, recent data indicate that the majority of patients with stroke have evidence of deep vein thrombosis (evident on imaging but not necessarily clinically).¹⁴ Therefore, when a PFO is considered as a possible cause of cerebral embolism, besides a clinical search for DVT venography, radionuclide or ultrasound imaging are also mandatory,¹⁵ and failing that, hematological testing for coagulopathy defects should be performed.

Arterial dissection, previously believed a rare phenomenon, has been increasingly recognized due to safer neurovascular imaging, both by catheter or MR angiography, and in one series was the most frequent determined etiology.² Though sometimes visualized by ultrasound methods, the specificity of the Doppler technique alone is often inadequate for a reliable diagnosis.⁷

Abnormalities of blood coagulation were rare in this study, APLA elevations were present in only 4%, and homocystinemia in 1% of patients, in keeping with previous published figures.¹⁶ Coagulopathy studies can be deferred until after the initial diagnostic imaging has proven negative.

In older stroke populations (>45 years) the major cause of ischemic stroke is atherosclerosis of large arteries, lacunar infarction due to small artery disease, and cardioembolic stroke predominantly due to atrial fibrillation. Together, these comprise 40-50% of all cases.¹⁷ In young patients there should be a different approach to prevention of recurrence, since the common causes are congenital cardiac lesions and extracranial arterial dissection, with less frequent involvement of small and large cerebral or extracranial arterial disease. In the Baltimore-Washington study of traditional risk factors for ischemic stroke, in 296 young patients compared with controls, an increased prevalence of hypertension, diabetes and cigarette smoking were found significant, but unfortunately no data regarding stroke types are available, so the relevance of the relationship remains uncertain.⁴

The routine use of aspirin as the ubiquitous stroke prophylaxis is rarely indicated in young patients with ischemic stroke when there is no evident cause after complete investigation. In young patients with ischemic stroke, when all investigations have been proven negative, there is a tendency to prescribe aspirin nonspecifically. This is not evidence-based and raises the question of how long the medication should be administered? Aspirin is not devoid of adverse effects and should not be prescribed without pharmacological justification. No patient should be abandoned diagnostically until the full range of cerebral, neurovascular and cardiac imaging, in conjunction with hematological testing is utilized. We believe that if these steps had been undertaken in our patients, the cause of stroke may have been identified in up to 21% more cases, leading to improved treatment and prevention of further episodes.

APPENDIX

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