BECAUSE only 3% of cerebral infarctions (CI) occur in patients under the age of 40, few clinicians have wide experience in evaluation and management of young adults with CI. Nevertheless, a thorough diagnostic search to prevent recurrence is of paramount importance in the young stroke victim. Common etiologies of CI in young adults may also apply to stroke in older patients in whom atherosclerosis predominates. The elucidation of stroke mechanisms in young patients may thus further our understanding of stroke in all patients.

The wide array of diagnostic considerations in young adults with CI (Table 1) necessitates a systematic approach to evaluation. We present a survey of CI in 100 young adults, a review of the recent literature highlighting major causes, and a practical approach to the evaluation and management of stroke in patients under 40.

**Differential Diagnosis**

Despite the lengthy differential diagnosis of CI in young adults (Table 1), several predominant etiologies account for the majority of cases. Subdivision into general categories based on several reports from Western cultures is shown in Table 2.

The category of uncertain etiology includes patients with CI associated with mitral valve prolapse, migraine, and oral contraceptive use. Each of these conditions is frequent enough in healthy young adults that causality cannot be assumed until other causes of CI have been eliminated. Although attributing CI to any of these three factors is largely diagnosis by exclusion, certain clinical features lessen this hazard, as described below.

Further subdivision of diagnoses in the initial 100 patients of our population-based, retrospective survey in young adults under 40 years old, excluding trauma, postoperative CI, and CI associated with subarachnoid hemorrhage, is shown in Table 3. Based on this distribution of etiologies, a rational approach to evaluation of CI in young adults can be constructed.

**Cerebrovascular atherosclerosis** was assumed to be the cause of CI if angiography revealed any type or degree of plaque in the appropriate proximal arteries and if other probable causes were absent. Although arteriographically visible, asymptomatic cerebrovascular atherosclerosis is relatively uncommon in people under 40, it is possible that some patients classified by our criteria had asymptomatic plaques and CI of other etiology. All 18 patients in this category were either juvenile-onset diabetics or males over 35 years old with one or more cerebrovascular risk factors (e.g., hypertension, heavy tobacco use, abnormal serum lipids). A history of transient ischemic attacks and evidence of generalized vascular disease were often present.

**Cerebral embolism** of recognized origin, usually cardiac, accounted for almost one-third of all CI. In most patients previously identified cardiac disease was the obvious source, but in eight patients cerebral embolism was the presenting feature of previously unrecognized cardiopulmonary disease (Table 3). In one instance a soft murmur of mitral stenosis was detected only by the cardiology consultant and later confirmed by echocardiography. Pulmonary arteriovenous malformations with presumed paradoxical embolism were visible on routine chest x-ray in two patients. In two instances demonstrated atrial septal defects were assumed to have permitted paradoxical embolization in the presence of a right-to-left intracardiac shunt, which may have transiently occurred with Valsalva maneuver.

In the absence of a recognized source, embolic CI can be suspected from characteristic arteriographic findings, consisting of intraluminal obstruction convex toward the lumen, especially involving single or multiple cerebral branch arteries in the absence of proximal atherosclerosis. Such occlusions can be demonstrated in over 75% of patients with cerebral embolism who undergo arteriography within 48 hours of ictus, but clot lysis and/or distal migration of embolism usually results in a normal arteriogram if the procedure is delayed. Although cerebral branch artery occlusion is characteristic of embolism, embolic obstruction can occur proximally at the common carotid bifurcation or at the internal carotid siphon. Cerebral branch artery occlusion has also been seen in association with migrainous vasospasm and use of oral contraceptives on a presumably nonembolic basis. It is our experience that neither computed tomography (CT) nor CSF examination is reliable in distinguishing the minimally hemorrhagic, embolic CI often seen at autopsy from pale, nonembolic infarction. When hemorrhagic CI is demonstrated by computed tomography in a patient with no coagulation or platelet abnormalities, an embolic source should be strongly suspected.
TABLE 1  Differential Diagnosis of Cerebral Infarction in Young Adults*

I. Cerebrovascular atherosclerosis (thrombotic or embolic)

II. Embolism

A. Cardiac source
1. Valvular (mitral stenosis, prosthetic valve, infective endocarditis, marantic endocarditis, Libman-Sacks endocarditis, mitral annulus calcification, mitral valve prolapse, \( ^{20, 21} \) calcific aortic stenosis)
2. Atrial fibrillation and sick-sinus syndrome
3. Acute myocardial infarction and/or left ventricular aneurysm
4. Left atrial myxoma
5. Cardiomyopathy

B. Paradoxical embolism and pulmonary source
1. Pulmonary arteriovenous malformation (including Osler-Weber-Rendu syndrome)\(^{24} \)
2. Atrial and ventricular septal defects with shunt
3. Patent foramen ovale with shunt\(^{25} \), \(^{24} \)
4. Pulmonary vein thrombosis
5. Pulmonary and mediastinal tumors

C. Other
1. Aortic cholesterol embolism
2. Transient embolicognic aortitis
3. Emboli distal to unruptured aneurysm
4. Fat embolism syndrome

III. Arteropathy

A. Inflammatory
1. Takayasu’s disease
2. Allergic (Churg-Strauss) and granulomatous
3. Infective — specific: syphilis, mucormycosis, ophthalmic zoster, TB, malaria; nonspecific: severe tonsillitis or lymphadenitis
4. Associated with amphetamine use
5. Associated with systemic disease (lupus, Wegener’s, polyarteritis nodosa, rheumatoid arthritis, Sjogren’s, scleroderma, Dego’s, Behcet’s, acute rheumatic fever, inflammatory bowel disease)\(^{11} \)

B. Noninflammatory
1. Spontaneous dissections
2. Post-therapeutic irradiation
3. Fibromuscular hyperplasia
4. Moya-moya and progressive arterial occlusion syndrome
5. Congophilic (amyloid) angiopathy
6. Thromboangiitis obliterans\(^{1} \)
7. Familial: homocysteinuria, Fabry’s pseudoxanthoma elasticum\(^{24} \)
8. Neoplastic angioendotheliosis

IV. Vasospasm associated with:

A. Migraine\(^{13, 17} \)
B. Subarachnoid hemorrhage
C. Hypertensive encephalopathy
D. Cerebral arteriography

V. Hematological disease and coagulopathies

A. Hyperviscosity
1. Polycythemia and myeloproliferative
2. Dysproteinemia (myeloma, Waldenstrom’s, cryoglobulinemia)

B. Coagulopathy
1. Thrombotic thrombocytopenic purpura
2. Chronic diffuse intravascular coagulation
3. Paroxysmal nocturnal hemoglobinuria
4. Oral contraceptive use/peripartum/pregnancy\(^{\dagger} \)
5. Thrombocythemia
6. Sickle cell and hemoglobin C disease
7. Lupus anticoagulant
8. Nephrotic syndrome
9. \( C \); deficiency (familial)
10. Protein C deficiency (familial)

C. Controversial associations
1. Platelet hyperaggregability
2. Fibrinolytic insufficiency
3. Increased factor VIII
4. Antithrombin III deficiency
5. Vitamin K and antifibrinolytic therapy
6. Acute alcohol intoxication

VI. Miscellaneous

A. Trauma (direct, indirect, rotation and extension injuries)
B. Mechanical (cervical rib, atlanoaxial subluxation)
C. Related to systemic hypotension
D. Iatrogenic (perioperative and periprocedural including air and foreign particle embolism)
E. Cortical sinus or vein thrombosis

*Complete reference list available upon request.
\( \dagger \)Association of uncertain significance, although often cited.
\( \ddagger \)Mechanism probably multifactorial, including endothelial hyperplasia and embolism in individual instances.

Nonatherosclerotic cerebral vasculopathy (e.g., fibromuscular hyperplasia, dissections, arteritis) required arteriography for diagnosis and was identified in ten patients. Our two patients with vertebral artery injury due to abrupt cervical rotation have been previously reported.\(^8 \) There were no patients in our series with fibromuscular hyperplasia or infarction distal to unruptured aneurysm. Arteritis confined to the central nervous system (two patients in our series) is usually multifocal and progressive but may occasionally mimic stroke early in the course.\(^9 \)

Systemic diseases and coagulopathies accounted for nine patients with CI. Four patients, all with a prior diagnosis of systemic lupus erythematosus (SLE), presented with sudden, focal deficits (not cerebritis). In three of these patients, evidence for the lupus anticoagulant (prolonged partial thromboplastin time with incomplete correction with 50/50 mix) was found. The presence of this inhibitor is not limited to patients with SLE and has been shown to be associated with thrombosis.\(^10 \) Collagen vascular diseases only rarely have stroke as their initial manifestation.\(^11 \)

Peripartum CI, occurring within two weeks of parturition, accounted for five cases. Most peripartum CI are the result of arterial occlusion, usually of obscure pathogenesis, although vasospasm, altered coagulability, and embolism have been postulated.\(^12, 13 \) We have seen several other patients in the final months of pregnancy with transient numbness and weakness associated with headache and visual scintillations that appeared to be pregnancy-related exacerbation of lifelong common migraine.

Of the 27 patients with CI of uncertain etiology, 9 of 19 women (47%) were using oral contraceptives, compared with 15 to 20% of the general female population of childbearing age.\(^14 \) Oral contraceptive use has been associated with ninefold increased risk of CI.\(^15 \) We found that a prior history of migraine could be elicited in the majority of patients whose oral contraceptive use was associated with CI, supporting this widely held clinical association. Arteriography has
been reported to show arterial occlusion of the carotid, middle cerebral, and branch arteries, attributed to in situ thrombosis, vasospasm, and/or emboli from pulmonary veins.\textsuperscript{3, 13} Pathological study has shown intimal hyperplasia compromising the lumen of cerebral vessels.\textsuperscript{16}

The association of migraine with CI in young adults is widely accepted but difficult to assess statistically.\textsuperscript{17} Vasospasm with or without thrombosis potentiated by platelet hyperaggregability is the assumed mechanism.\textsuperscript{13, 18} Onset of ischemia with migraine-associated CI most often coincides with typical headache but may occur in its absence. Although a lifelong history of migraine usually antedates CI, severe headache at the time of stroke may occasionally be the initial episode of migraine, only later to be followed by recurrent common or classic migraine. In such instances the possibility that subsequent vascular headaches are the sequelae of CI or other cause must be considered.\textsuperscript{19} Anecdotally, it appears that patients with a combination of migraine and states of altered, albeit ill-defined, coagulability (e.g., use of oral contraceptives, lupus anticoagulant, Crohn’s disease) are at special risk for CI.

Mitrval valve prolapse (MVP) is present in 5 to 10% of the general population of young adults (depending on diagnostic criteria) but has recently been shown to be present in 20 to 40% of young adults with unexplained CI.\textsuperscript{20, 21} Cerebral arteriography, if done acutely, frequently shows embolic occlusion of the middle cerebral artery or its branches.\textsuperscript{20} Infarction in such instances is presumable due to embolism of valvular thrombi, but prolapse-associated atrial fibrillation or bacterial endocarditis are other considerations. Auscultatory findings are present in most patients, but echocardiography (especially two-dimensional) will detect occult cases (10 to 20%). In our retrospective series three of eight patients with no other explanation for CI who had echocardiography showed evidence of mitral valve prolapse.

There remains 10% of young adults with CI in our series termed idiopathic CI, with no recognized predisposition for stroke.

<table>
<thead>
<tr>
<th>TABLE 2 Causes of Cerebral Infarction in Young Adults*</th>
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<tbody>
<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Embolism†</td>
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<tr>
<td>Arteropathy</td>
</tr>
<tr>
<td>Coagulopathy/systemic‡</td>
</tr>
<tr>
<td>Peripartum</td>
</tr>
<tr>
<td>Uncertain cause§</td>
</tr>
<tr>
<td>Oral contraceptives</td>
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<tr>
<td>Idiopathic</td>
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</tbody>
</table>

*Aggregate data from 318 patients from references 1, 3, 20, 29, and the present study.
†Embolism with recognized source.
‡Includes causes listed in group V of Table 1 plus systemic arteropathies.
§Includes CI associated with migraine, mitral valve prolapse, and oral contraceptive use; idiopathic means no recognized predisposition for stroke.

<table>
<thead>
<tr>
<th>TABLE 3 Causes of Infarction in 100 Young Adults*</th>
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<tbody>
<tr>
<td>I. Cerebrovascular atherosclerosis</td>
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<tr>
<td>II. Cerebral embolism</td>
</tr>
<tr>
<td>A. Previously known cardiac disease (e.g., rheumatic heart disease, valve prosthesis)</td>
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<tr>
<td>B. Previously unrecognized source</td>
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<tr>
<td>Left atrial myxoma</td>
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<tr>
<td>Pulmonary arteriovenous malformation</td>
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<tr>
<td>Atrial septal defect</td>
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<tr>
<td>Occult mitral stenosis</td>
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<tr>
<td>Idiopathic cardiomyopathy</td>
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<tr>
<td>III. Nonatherosclerotic cerebral vasculopathy (angiographic diagnosis)</td>
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<tr>
<td>Spontaneous carotid dissection</td>
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<td>Post neck irradiation</td>
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<tr>
<td>Idiopathic venous sinus thrombosis</td>
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<tr>
<td>Cerebral vasculitis</td>
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<td>Vertebral artery injury 2° neck turning</td>
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<td>IV. Coagulopathy and systemic inflammation (serological diagnosis)</td>
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<tr>
<td>SLE with/without lupus anticoagulant</td>
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<tr>
<td>Lupus anticoagulant without SLE</td>
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<tr>
<td>Homocysteinuria</td>
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<tr>
<td>Systemic vasculitis (unclassified)</td>
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<tr>
<td>Coagulopathy with thrombocytosis (unclassified)</td>
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<tr>
<td>Severe Crohn’s disease</td>
</tr>
<tr>
<td>V. Peripartum</td>
</tr>
<tr>
<td>VI. Uncertain etiology (8 males, 19 females)</td>
</tr>
<tr>
<td>Associated with migraine only</td>
</tr>
<tr>
<td>Associated with OC use only</td>
</tr>
<tr>
<td>Migraine and OC use</td>
</tr>
<tr>
<td>Mitral valve prolapse only</td>
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<tr>
<td>&quot;Idiopathic”/no association (5 males, 5 females)</td>
</tr>
</tbody>
</table>

*5 additional patients not included because of inadequate evaluation (e.g., no angiography or incomplete studies) to allow classification.
†24 of 27 had cerebral angiography including all 10 of "idiopathic/no association.”
‡5 of 10 had either echocardiograms or cardiac catheterization without evidence of MVP.

Abbreviations: OC = oral contraceptive; SLE = systemic lupus erythematosus.

disposition for stroke after thorough evaluation. Reports that such strokes occur primarily in winter months (nine of ten patients in our series had CI between November and March) have prompted speculation about the role of infection causing pulmonary venous thromboembolism or local endarteritis via direct viral invasion or immunological mechanism.\textsuperscript{22} In a recent report acute alcohol intoxication preceded 40% of CI in young adults, presumably causing alterations in coagulation, cerebral dysautoregulation or cardiac dysrhythmia with embolism ("holiday heart").\textsuperscript{23}

Other authors have stressed the importance of cryp-
togenic cerebral embolism, based on arteriographic findings suggestive of embolic obstruction but without identified source. In our series as well as Marshall's, almost half of patients with no recognized predisposing factors for CI had arteriographic findings suggestive of embolic obstruction. Paradoxical embolism via a patent foramen ovale (present in 15 to 30% of adults) with transient left-to-right intracardiac shunt during Valsalva maneuver has been reported but is of uncertain over-all importance as a cause of stroke.

Finally, hyperaggregability of platelets, fibrinolysin insufficiency, and increased factor VIII and platelet antiaggregates in migraine patients with CI have been reported in young patients with unexplained CI, but further data are required to differentiate their role in genesis and/or propagation of stroke from their appearance as acute phase changes (epiphemomena).

**Evaluation**

Based on the frequency of causes of CI in young adults outlined in Tables 2 and 3, a diagnostic approach begins with a careful history and examination, seeking evidence of systemic disease (Fig. 1). Patients in whom there is strong evidence for cardiogenic cerebral embolism (e.g., nonorganic prosthetic heart valve, atrial myxoma, infective endocarditis) or obvious systemic disease (e.g., sickle cell, polyarteritis nodosa) need not always undergo cerebral arteriography. In patients with uncertain diagnosis, cerebral arteriography is usually warranted. We prefer early arteriography (within days) to seek potentially treatable structural disease (e.g., dissection) and evidence of unsuspected embolism which may not be apparent if arteriography is delayed. As previously stated, attributing CI to oral contraceptives, mitral valve prolapse, or migraine can be safely done only after excluding other disease, which usually requires arteriography.

Arteriography in patients with migraine is sometimes reported to carry increased risk of complications. We feel that the risk of cerebral arteriography in migraine patients is acceptably low if carefully carried out and is usually justified by the importance of establishing an accurate diagnosis in young stroke victims. Arteriography is probably best avoided during an acute migraine attack.

Cerebral biopsy seeking arteritis confined to the CNS is rarely indicated. This disorder is typically subacute, multifocal, and progressive, and biopsy is not indicated in single, uncomplicated instances of acute CI.

Hypercoagulability has often been suspected in CI but remains a nebulous entity of uncertain importance, as has been stated in recent reviews. Clinically useful laboratory markers of hypercoagulability that allow prediction of future stroke risk are not yet available for most patients. Several specific states of altered coagulation associated with stroke are listed in Table 1. Antithrombin III deficiency, for example, is known to be associated with recurrent venous thrombosis but was not present in a large series of young adults with CI. Further prospective data on the role of altered coagulation factors, platelet function, and fibrinolytic mechanisms in young adults with CI are urgently awaited.

**Management**

Management of CI in young adults obviously depends on accurate diagnosis. Patients with "premature" atherosclerosis have a high risk of recurrent ischemia. Risk factors should be modified and vigorous medical or surgical management undertaken. Management of cardiogenic embolism depends on the underlying source. The risk of recurrent stroke in patients with the lupus anticoagulant is unknown; there has been no recurrence during brief follow-up of our patients.

In patients with CI associated with oral contraceptive use, permanent discontinuation results in a low incidence of recurrent stroke. Ergot preparations and oral contraceptives should probably be avoided in patients with migraine headaches and CI. We have used platelet antiaggregates in migraine patients with CI, based on reports of platelet hyperaggregability in migraine and the relative safety of these agents. Management of patients with mitral valve prolapse and CI is controversial. Multiple episodes of ischemia have
occurred in several patients with prolapse-associated CI. Platelet antiaggregation agents are recommended for initial therapy; recurrent embolism during treatment with these agents may necessitate anticoagulation with warfarin.

The idiopathic subgroup is reported to have low risk of recurrent stroke. However, three of ten patients with idiopathic CI had a prior history of CI (occurring one, two, and five years previously). In those patients whose CI followed alcohol intoxication, avoiding acute intoxication seems prudent, given the available information. The long-term use of platelet antiaggregation agents in patients with idiopathic CI seems reasonable but should not reassure the physician or patient to any great extent. The importance of thorough diagnostic evaluation of the young adult with CI to establish an accurate diagnosis cannot be overemphasized.

References

Cerebral infarction in young adults: a practical approach.
R G Hart and V T Miller

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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