CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Cryptogenic Stroke

Jeffrey L. Saver, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

After a gym workout, a 48-year-old man had sudden ataxia, nausea, and diplopia, followed by persistent inability to see the upper left quadrant of space with either the left or right eye. He did not have neck pain. His medical history included hypertension and migraines with aura. Magnetic resonance imaging (MRI) showed a right occipitotemporal and thalamic infarct. Magnetic resonance angiography showed an abrupt cutoff of a distal segment of the right posterior cerebral artery. The complete blood count, prothrombin time, and partial-thromboplastin time were normal. Transthoracic echocardiographic results suggested a possible right-to-left shunt. Cardiac telemetry during the first 2 inpatient days revealed no dysrhythmias. How should this case be further evaluated?

From the Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine at the University of California, Los Angeles (UCLA), Los Angeles. Address reprint requests to Dr. Saver at the UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095, or at jsaver@mednet.ucla.edu.

THE CLINICAL PROBLEM

CRYPTOGENIC ISCHEMIC STROKES ARE SYMPTOMATIC CEREBRAL INFARCTS for which no probable cause is identified after adequate diagnostic evaluation. More expansive definitions add strokes in patients who are incompletely evaluated and in those with more than one probable cause identified, but these are better considered to be separate entities. Among strokes of undetermined cause, useful further distinctions are between those that are cryptogenic after standard evaluation and those that are cryptogenic after additional, specialized evaluation and between those that are "highly cryptogenic" (i.e., with no probable and no possible cause discovered) and those "of possibly determined origin" (i.e., with no probable, but one or more possible, causes identified).

Cryptogenic mechanisms account for 10 to 40% of all ischemic strokes.[1-4] This range reflects varying definitions across series, evolution in diagnostic technology, differing conceptions of adequate etiologic investigation, and the fact that there are more than 200 known causes of ischemic stroke potentially requiring exclusion.[5,6] In general, the percentage of ischemic strokes that are classified as cryptogenic has declined over time as diagnostic testing has advanced, from 40% in the 1970s[1] to 10 to 15% today for highly cryptogenic stroke in advanced centers performing extensive testing.[3,4] However, stroke that is cryptogenic after a standard diagnostic evaluation remains a common clinical challenge, accounting for 20 to 30% of all ischemic strokes[7] and therefore occurring in 120,000 to 180,000 patients each year in the United States.

The most common determined causes of ischemic stroke, identified during routine initial evaluation, are large-artery atherosclerosis, cardioembolism, and

An audio version of this article is available at NEJM.org

KEY CLINICAL POINTS

CRYPTOGENIC STROKE

- One quarter of patients with ischemic stroke have no probable cause found after standard workup, including echocardiography, inpatient cardiac telemetry or 24-hour Holter monitoring, magnetic resonance imaging or computed tomographic (CT) imaging of topographic features of the infarct in the brain, and magnetic resonance or CT angiographic assessment of neck and brain arteries. Additional investigation identifies a likely mechanism in more than half these patients.
- Most cryptogenic ischemic strokes are embolic in origin, arising from proximal arterial sources, the heart, or venous sources (with right-to-left shunts).
- Investigation in patients with cryptogenic stroke typically includes evaluation for atherosclerotic and nonatherosclerotic arteriopathies, cardiac sources of embolism (structural and rhythm abnormalities), and disturbances of coagulation.
- Patent foramen ovale is found in up to half of young adults with cryptogenic stroke but is also found in one quarter of healthy persons.
- Occult, low-burden, paroxysmal atrial fibrillation is increasingly recognized as a source of cryptogenic stroke, especially in older patients.

---

small-vessel disease, each of which accounts for approximately 25% of cases.[8] In patients with ischemic stroke that is considered to be cryptogenic after standard evaluation, causes that are most often found after more specialized testing include occult atherosclerosis, including nonstenosing but unstable plaques at intracranial and cervical sites or stenosing plaques at the thoracic origins of the common carotid and thoracic vertebral arteries[9]; nonatherosclerotic arteriopathies, such as dissection or vasculitis; hypercoagulable states; cardioembolism from medium-grade sources, such as low-burden paroxysmal atrial fibrillation or dilated cardiomyopathy of moderate degree; and paradoxical embolism (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The age of the patient influences the likelihood of various causes. In young adults 18 to 30 years of age, dissection is most common, but thrombophilias and congenital cardiac disease are also noteworthy causes. In persons 31 to 60 years of age, early-onset atherosclerosis and acquired structural cardiac disease are increasingly common. In patients older than 60 years of age, occult atrial fibrillation becomes more frequent.

As compared with strokes of determined origin, cryptogenic ischemic strokes typically result in less severe presenting neurologic deficits, less final disability, and lower mortality.[10] In most[11,12] though not all[13] long-term follow-up studies, patients with cryptogenic ischemic stroke have a lower risk of recurrence than those with stroke of identified cause. In the largest long-term study to date, among patients 18 to 55 years of age who had a stroke that was cryptogenic and who were treated with aspirin, the recurrence rate was 1.9% in the first year after the stroke and 0.8% per year in years 2 to 4.[11] This low recurrence rate comports with the absence of an easily discovered cause of major stroke that would place the patient at elevated risk.

STRATEGIES AND EVIDENCE

ASSESSMENT OF THE PATIENT WITH CRYPTOGENIC ISCHEMIC STROKE

Cryptogenic stroke is a diagnosis of exclusion, arrived at by ruling out known causes. Particularly informative aspects of the patient's history and physical examination are shown in Table 1, and a strategy for laboratory and imaging workup is outlined in Figure 1 and in Table S2 in the Supplementary Appendix.

In contemporary practice, the routine evaluation of the patient with ischemic stroke includes several components. The topographic features of the stroke (infarct location, volume, and multiplicity) are assessed by MRI of the brain, including diffusion sequences (which are more sensitive to small lesions and lesions in the brain stem and cerebellum) or computed tomography (CT) of the brain (when MRI is not available). The topographic features provide important etiologic clues: infarcts in multiple territories suggest emboli from a proximal aortocardiac source; infarcts of different ages in a single territory suggest emboli of arterial origin; infarcts along the borders between brain artery territories suggest systemic hypotension or multiple emboli; and a small,

Table 1. Suggestive Findings on History and Physical Examination in Patients with Cryptogenic Stroke.*

Variable	Potential Clinical Implication
Historical feature	
Neck trauma or manipulation	Carotid or vertebral artery dissection
Migraine	Migrainous infarction or CADASIL
Intravenous drug use	Endocarditis, HIV infection, vasculitides, paradoxical emboli, or vasospasm
Dental procedure or systemic bacterial infection	Endocarditis, septic emboli, or coagulopathy
Airplane travel or Valsalva maneuver at stroke onset	Paradoxical embolism
Family history of early myocardial infarction or ischemic stroke	Genetic accelerated atherosclerosis
Pregnancy and peripartum	Cerebral venous thrombosis or eclampsia
Sickle-cell disease	Secondary moyamoya disease
Physical finding	
Asymmetric arm pressures	Coarctation of aorta, aortic dissection, Takayasu's disease, or premature atherosclerosis
Skin	
Needle tracks	Intravenous drug use or HIV infection
Livedo reticularis	Sneddon's syndrome, antiphospholipid antibody syndrome, or systemic lupus erythematosus
Xanthoma or xanthelasma	Hyperlipidemia
Adenopathy	HIV infection, sarcoid, or Tangier disease
Heart murmur	Endocarditis, ventral septal defect, or myxoma
Vessels	
Diminished pulses	Premature atherosclerosis, coarctation of aorta, aortic dissection, or Takayasu's disease
Bruit	Premature atherosclerosis, fibromuscular dysplasia, or arterial dissection
Venous thrombosis in the legs	Hypercoagulable state

* CADASIL denotes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and HIV human immunodeficiency virus.

deep infarct along with white-matter hyperintensities suggests intrinsic small-vessel disease. The brain, neck, and thoracic arteries are assessed by CT or magnetic resonance angiography (which have similar sensitivity and specificity) or, if these are contraindicated or unavailable, carotid duplex ultrasonography and transcranial Doppler ultrasonography.

The presence of structural cardiac disease is evaluated by means of echocardiography. Transthoracic echocardiography (TTE), which is better at ventricular imaging, is used first in patients with coronary artery disease, congestive heart failure, or other ventricular disease that is evident from history or electrocardiogram (ECG).

Transesophageal echocardiography (TEE), which is better at atrial and aortic-arch imaging, is preferred in patients with nonlacunar infarct and no evidence of ventricular disease and as an additional test in patients with unrevealing TTE results. TEE identifies potentially salient abnormalities in approximately 50 to 75% of young patients with otherwise cryptogenic stroke,[14,15] including patent foramen ovale, atrial septal aneurysm, endocarditis, aortic atherosclerosis, regional myocardial-wall dysfunction, dilated left atrium, and atrial appendage thrombi. Cardiac dysrhythmias are initially assessed by 12-lead ECG and inpatient cardiac telemetry or 24-hour Holter monitor. Hematologic disorders are screened
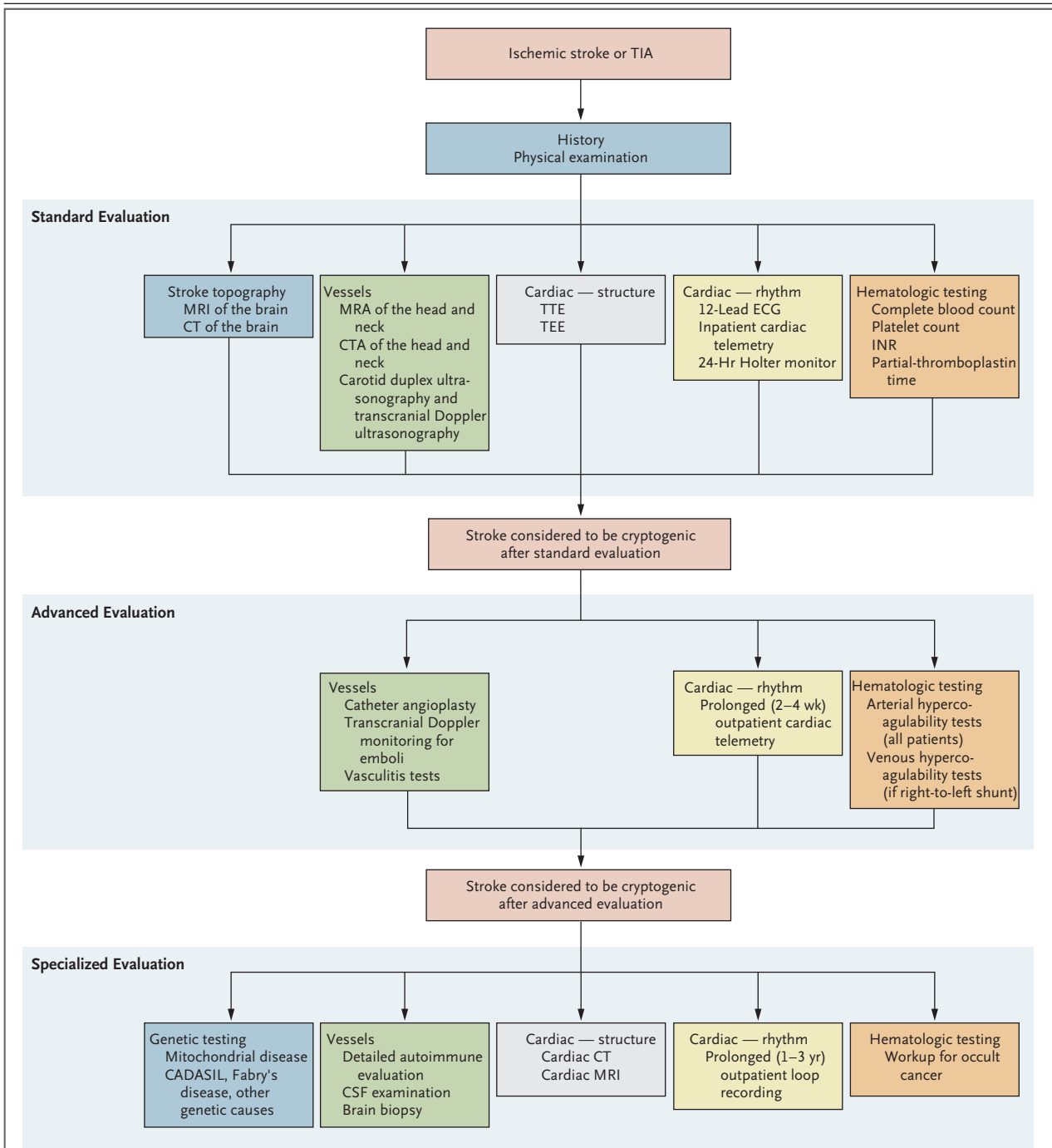
Ischemic stroke or TIA

History
Physical examination

Standard Evaluation

Stroke topography
MRI of the brain
CT of the brain

Vessels
MRA of the head and
neck
CTA of the head and
neck
Carotid duplex ultra-
sonography and
transcranial Doppler
ultrasonography

Cardiac — structure
TTE
TEE

Cardiac — rhythm
12-Lead ECG
Inpatient cardiac
telemetry
24-Hr Holter monitor

Hematologic testing
Complete blood count
Platelet count
INR
Partial-thromboplastin
time

Stroke considered to be cryptogenic
after standard evaluation

Advanced Evaluation

Vessels
Catheter angioplasty
Transcranial Doppler
monitoring for
emboli
Vasculitis tests

Cardiac — rhythm
Prolonged (2–4 wk)
outpatient cardiac
telemetry

Hematologic testing
Arterial hyperco-
agulability tests
(all patients)
Venous hyperco-
agulability tests
(if right-to-left shunt)

Stroke considered to be cryptogenic
after advanced evaluation

Specialized Evaluation

Genetic testing
Mitochondrial disease
CADASIL, Fabry's
disease, other
genetic causes

Vessels
Detailed autoimmune
evaluation
CSF examination
Brain biopsy

Cardiac — structure
Cardiac CT
Cardiac MRI

Cardiac — rhythm
Prolonged (1–3 yr)
outpatient loop
recording

Hematologic testing
Workup for occult
cancer

Figure 1. Algorithm for the Identification and Diagnostic Evaluation of Patients with Cryptogenic Ischemic Stroke or Transient Ischemic Attack (TIA).

Table S2 in the Supplementary Appendix lists additional considerations regarding advanced and specialized tests. CADASIL denotes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CSF cerebrospinal fluid, CTA computed tomographic angiography, ECG electrocardiogram, INR international normalized ratio, MRA magnetic resonance angiography, TEE transesophageal echocardiography, and TTE transthoracic echocardiography.

by means of red-cell and platelet counts and measurement of the prothrombin time and partial-thromboplastin time.

The stroke may be considered to be cryptogenic after standard evaluation when clinical examination and brain imaging suggest a superficial or large, deep cerebral infarct, but none of the above routine vessel-imaging, cardiac, or hematologic tests has revealed a probable cause. Patients with a small, deep infarct also may be considered to have cryptogenic stroke if they are younger than 50 years of age, have no standard vascular risk factors, and have no white-matter hyperintensities or prior small, deep infarcts.[16] More extensive diagnostic testing is then pursued (Figs. 1 and 2, and Table S2 in the Supplementary Appendix).

Several formal diagnostic algorithms have been developed to categorize ischemic strokes according to cause or as cryptogenic (Table S3 in the Supplementary Appendix). The long-established Trial of Org 10172 in Acute Stroke Treatment (TOAST) diagnostic algorithm[17,18] is beginning to be superseded by the newer ASCOD (atherosclerosis, small-vessel disease, cardiac, other, dissection) and Causative Classification of Stroke (CCS) systems, which take a more nuanced approach when multiple contending causes are identified.[17-20] As compared with the TOAST criteria, both the ASCOD and CCS systems identify fewer patients as having had cryptogenic stroke.[21,22] These instruments are essential for the classification of patients in clinical trials and can be useful in clinical practice.

Space constraints for this review preclude detailed attention to all causes of cryptogenic ischemic stroke. Focused consideration will be given to three topics of recent interest: occult atrial fibrillation, patent foramen ovale, and embolic stroke of undetermined source.

OCCULT ATRIAL FIBRILLATION

Manifest atrial fibrillation is a common cause of ischemic stroke, accounting for one quarter of all cerebral infarcts and more than one half of those of cardioembolic origin. In the standard evaluation of ischemic stroke, approximately 15% of patients have a known history of chronic or paroxysmal atrial fibrillation predating the stroke, approximately 8% receive a new diagnosis of atrial fibrillation on the basis of the results of the first ECG, and another 5% receive a new diagnosis, after initial presentation in sinus rhythm, on the basis of results of inpatient cardiac telemetry or 24-hour Holter monitoring.[8,23,24]

Technology to detect infrequent paroxysmal atrial fibrillation has dramatically improved over the past decade, with the development of mobile cardiac telemetry systems that may be worn externally for 2 to 4 weeks, subcutaneous loop recorders with battery lives enabling detection for 1 to 3 years, and in patients needing therapeutic internal pacemakers or defibrillators, implantable therapeutic devices with the capability to detect atrial fibrillation for 3 years or more. These technological advances unveiled a long-surmised, but infrequently identified, group of patients with low-burden paroxysmal atrial fibrillation. Patients with low-burden paroxysmal atrial fibrillation have a lower risk of stroke than patients with chronic or high-burden paroxysmal atrial fibrillation. However, their risk of stroke is higher than that among persons without atrial fibrillation.[25] As little as a single 1-hour episode of atrial fibrillation during 2 years of monitoring has been associated with a doubling in the risk of ischemic stroke.[26]

Among patients whose ischemic strokes are cryptogenic after conventional inpatient evaluation, prolonged outpatient cardiac monitoring detects low-burden atrial fibrillation in 15%.[23,27,28] In the multicenter Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial, the frequency of the detection of paroxysmal atrial fibrillation was 9% at 6 months, 12% at 1 year, and 30% at 3 years.[27] The characteristics of patients that increase the likelihood that protracted monitoring will uncover low-burden atrial fibrillation include older age and higher CHA_2DS_2-VASc score (on which scores range from 0 to 9, with higher scores indicating greater risk),[29,30] cerebral infarct topographic features (such as multiple vascular territories and cortical location),[29,31] and indexes of left atrial cardiopathy,[32] including left atrial dilatation,[32,33] strain, and reduced emptying fraction, left atrial appendage size and single-lobe morphologic features,[34,35] p-wave dispersion on ECG,[36] frequent atrial premature beats,[30] and elevated N-terminal pro–brain natriuretic peptide serum levels.

Whether patients with low-burden atrial fibrillation are best treated with anticoagulant or
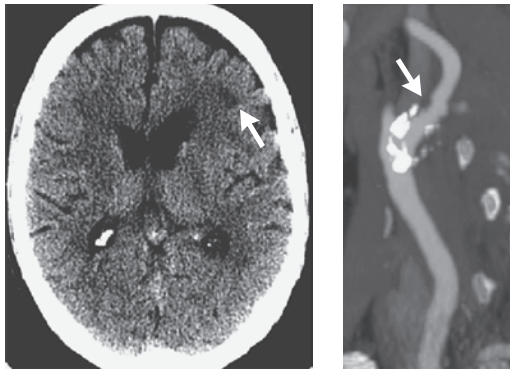
A Nonatherosclerotic Arteriopathy and the Reversible Cerebral Vasoconstriction Syndrome

B Cancer Causing Hypercoagulable State or Cerebral Arteriopathy
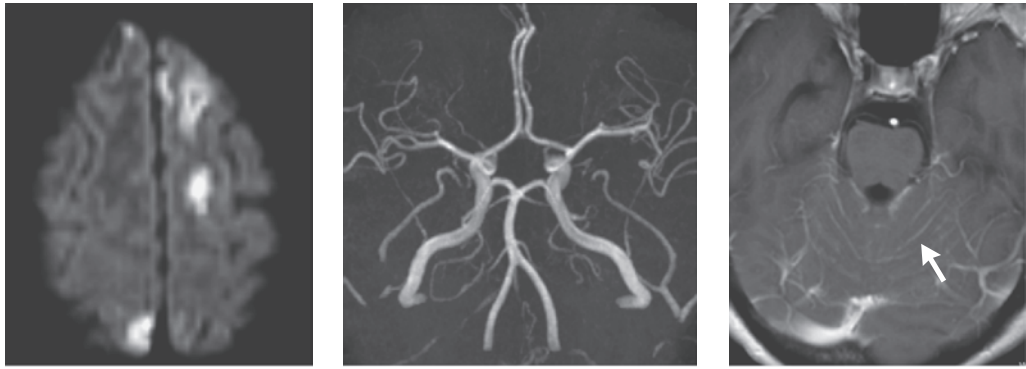
C Nonhemodynamically Significant Carotid-Artery Atherosclerosis

antiplatelet agents is currently unknown. In some patients, the infrequent atrial fibrillation is probably not causally related to the stroke, and clinical trials to inform decision making are sparse. One recent randomized trial involving persons with implanted defibrillators showed no significant reduction in a composite outcome of stroke, systemic embolism, and major bleeding with a strategy of using the detection of occult atrial fibrillation or flutter to guide warfarin use, as compared with routine clinical care.[37] However, few patients had a history of cerebral ischemia, many in the control group received anticoagulation, and warfarin was withdrawn in the monitoring group after periods of 1 to 3 months without atrial fibrillation. Pending the

Figure 2 (facing page). Examples of Evaluation and Causes of Cryptogenic Stroke.

A 38-year-old woman who presented with confusion and slurred speech received a diagnosis of nonatherosclerotic arteriopathy and the reversible cerebral vasoconstriction syndrome (Panel A). An MRI showed a right hemisphere infarct (left panel), and CT angiography revealed narrowed middle cerebral arteries bilaterally (middle panel, arrows) and a narrowed basilar artery. A catheter angiogram showed multifocal stenoses in the right supraclinoid internal carotid artery (right panel, arrow) and middle cerebral artery (arrowhead). A 33-year-old woman with a history of breast cancer who presented with new weakness in the right leg received a diagnosis of cancer causing a hypercoagulable state or cerebral arteriopathy (Panel B). An MRI showed bilateral infarcts in the territories of the anterior cerebral arteries bilaterally (left panel), a magnetic resonance angiographic scan showed normal proximal intracranial arteries (middle panel), and an MRI with the use of contrast material showed enhancement in multiple cerebellar folia (right panel, arrow), which was due to carcinomatous meningitis. A 72-year-old man who presented with transient episodes of weakness in the right arm and loss of vision in the left eye received a diagnosis of nonhemodynamically significant carotid-artery atherosclerosis (Panel C). CT of the brain with the use of contrast material showed a small left frontal infarct (left panel, arrow). A CT angiogram showed calcifications, mild stenosis, and ulcer (right panel, arrow) at the origin of the left internal carotid artery.

completion of ongoing trials, a provisional suggested management algorithm is shown in Table S4 in the Supplementary Appendix.

PATENT FORAMEN OVALE

Paradoxical embolism is the passage of a clot or other embolic particle from the venous circulation to the arterial circulation through a right-to-left shunt, such as an atrial or ventricular septal defect and pulmonary arteriovenous malformation. The most common cause of a right-to-left shunt is a patent foramen ovale. This interatrial passage typically closes within 3 months after birth but may persist throughout life and potentially allow venous thromboemboli to avoid filtration in the pulmonary vasculature and enter the systemic arterial circulation.[38] The mean diameter of a patent foramen ovale is 4.9 mm, which is more than sufficient to permit the passage of emboli that are large enough to occlude the trunk of the middle cerebral artery (3 mm) and major cortical branches (1 mm). Atrial sep-

tal aneurysm — a hypermobile interatrial septum that protrudes alternately into the right and left atria — is a related abnormality that has been associated with increased risk of stroke in patients with a patent foramen ovale.[11]

A patent foramen ovale is present in approximately one quarter of the general patient population but in one half of patients with cryptogenic stroke.[38,39] A Bayesian attributable risk analysis of pooled data from 12 studies suggested that among patients with cryptogenic stroke who had a patent foramen ovale, the patent foramen ovale is probably causally related to the stroke in approximately half.[40] Features that increase the likelihood of a causal relationship include younger age[39]; Valsalva maneuver at the onset of stroke[41]; extended airplane or car travel preceding the stroke[41]; concomitant venous thrombosis in the leg or pelvis[41,42]; coexisting venous hypercoagulable state; coexisting atrial septal aneurysm; history of migraine with aura[41]; cortical location, multiplicity, and large size of cerebral infarcts[39,43,44]; and absence of hypertension, diabetes, and smoking.[39]

The diagnosis of patent foramen ovale relies on ultrasonography with the use of agitated saline ("bubble") contrast material (see video). TTE detects only approximately half the instances of patent foramen ovale that are found on TEE or transcranial Doppler ultrasonography; transcranial Doppler ultrasonography does not simultaneously provide information on other structural cardiac lesions and aortic-arch atherosclerosis. TEE is accordingly the preferred method. Transcranial Doppler ultrasonography with the use of bubble contrast material is used if the patient has contraindications to TEE and if TTE is unrevealing. In patients with a patent foramen ovale, supporting evidence that the patent foramen ovale is causally related to the stroke may be further sought by testing for a venous hypercoagulable state and for the presence of covert deep venous thrombi with the use of ultrasonography of the legs and pelvic MRI or CT.

Antiplatelet therapy is a first-line treatment option in patients with cryptogenic stroke who have patent foramen ovale; aspirin at a dose of 300 mg daily is associated with low rates of recurrent stroke among persons with patent foramen ovale.[11] Meta-analyses of data from observational and randomized trials suggest that war-

A video showing a transesophageal echocardiogram is available at NEJM.org

farin has efficacy that is similar to or greater than aspirin, particularly among patients with superficial territory infarcts.[45,46] Newer, direct oral anticoagulants have not been formally tested in patients with patent foramen ovale, but their efficacy in the prevention and treatment of venous of thromboembolism suggests a possible benefit with regard to paradoxical embolism.

The percutaneous endovascular placement of closure devices can eliminate the patent foramen ovale. Complications, although less frequent with newer-generation disk-occluder devices than with older, umbrella-occluder devices,[47] include atrial fibrillation (in approximately 0.7% of patients per year) and periprocedural device embolization, cardiac tamponade, and femoral hematoma (each occurring in <0.5% of participants in clinical trials).[16,47,48] Three randomized trials (one that used an umbrella-occluder device and two that used a disk-occluder device) did not show significantly lower rates of recurrent ischemic stroke with device therapy than with medical therapy alone.[16,48,49] However, a subsequent analysis of pooled individual patient data showed a significant reduction in the risk of recurrent ischemic stroke with the disk occluder, from approximately 6 to approximately 2 strokes per 100 patients treated over a period of 5 years.[50] Other trials are ongoing (ClinicalTrials.gov numbers, NCT00738894 and NCT00562289).

EMBOLIC STROKE OF UNDETERMINED SOURCE

Cryptogenic ischemic strokes that are superficial, or deep but large, are almost always due to emboli arriving in the brain from an arterial, cardiac, or transcardiac source. Intrinsic large artery diseases, such as in situ thrombosis or vasospasm, are uncommon causes. Recently, this long-standing clinical insight was formalized as the clinical construct "embolic stroke of undetermined source." Embolic strokes of undetermined source are operationally defined as nonlacunar brain infarcts without substantial proximal arterial stenosis or major cardioembolic sources,[7] and they represent 80 to 90% of all cryptogenic ischemic strokes.

Diverse low-risk sources are the presumed origin of thromboemboli causing infarcts in embolic strokes of undetermined source, including mild left ventricular dysfunction, mitral annular calcification, low-burden paroxysmal atrial fibrillation, patent foramen ovale, aortic-arch athero-

sclerosis, and nonstenosing atherosclerotic plaques in cervical and intracranial arteries. The relative benefits of anticoagulation versus antiplatelet therapy have not been well established for any of these entities. Large, international trials comparing new, direct oral anticoagulants and aspirin in patients with embolic stroke of undetermined source have recently been launched (NCT02239120, NCT02313909, and NCT02427126). Pending their completion, initial treatment with either antiplatelet agents or direct oral anticoagulants is reasonable, while more detailed etiologic investigation proceeds.

AREAS OF UNCERTAINTY

Increasingly specialized, expensive tests, of diminishing yield, are often pursued in patients with cryptogenic ischemic stroke. The most cost-effective approach to evaluation and the usefulness of highly specialized investigations have not been well studied. The most effective duration to pursue ambulatory monitoring for low-burden atrial fibrillation is unknown. Extended etiologic investigation should not delay the initiation of a reasonable treatment plan. Further study is needed to help clinicians discriminate when low-burden paroxysmal atrial fibrillation is likely to be stroke-related or merely incidental. For patients with patent foramen ovale and cryptogenic stroke, a risk score has been developed to estimate the likelihood that the patent foramen ovale is causal, but its potential to guide therapy requires further exploration.[40] Data are needed from rigorous clinical trials comparing antiplatelet and anticoagulant therapy in patients with embolic stroke of undetermined source and in those with occult atrial fibrillation; data are also needed from further trials comparing antiplatelets, anticoagulants, and device therapy in patients with cryptogenic stroke that has been attributed to patent foramen ovale.

GUIDELINES

Guidelines for the diagnostic evaluation of ischemic stroke and treatment of cryptogenic ischemic stroke have been published by the American Heart Association–American Stroke Association and American Academy of Neurology.[51-54] The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The man described in the vignette presents with a stroke that is attributable to an embolus that briefly lodged in the basilar artery and then traveled further to persistently occlude a branch of the right posterior cerebral artery. For this embolic stroke with source not yet determined, leading etiologic considerations include aortic-arch atherosclerosis, patent foramen ovale with atrial septal aneurysm, occult atrial fibrillation, and prothrombotic states. As next steps in the evaluation of this patient, I would obtain TEE, arterial hypercoagulability laboratory assessments, and given a possible right-to-left shunt on TTE, venous hyper-

coagulability laboratory assessments, and I would plan 4 weeks of ambulatory cardiac monitoring. His hypertension should be controlled, and for antithrombotic therapy, I would treat the patient initially with aspirin while additional tests are obtained to guide the choice between long-term antiplatelet or anticoagulant therapy.

REFERENCES

1. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. Ann Neurol 1989;25:382-90.
2. Li L, Yiin GS, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol 2015;14:903-13.
3. Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. JAMA Neurol 2013;70:51-7.
4. Wolf ME, Grittner U, Böttcher T, Norrving B, Rolfs A, Hennerici MG. Phenotypic ASCO characterisation of young patients with ischemic stroke in the prospective multicentre observational sifap1 study. Cerebrovasc Dis 2015;40:129-35.
5. Bogousslavsky J, Caplan LR, eds. Uncommon causes of stroke. 2nd ed. Cambridge, United Kingdom: Cambridge University Press, 2008.
6. Saver JL, Tamburi T. Genetics of cerebrovascular disease. In: Pulst S-M, ed. Neurogenetics. Oxford, United Kingdom: Oxford University Press, 1999:403-31.
7. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429-38.
8. Paciaroni M, Agnelli G, Caso V, et al. Atrial fibrillation in patients with first-ever stroke: frequency, antithrombotic treatment before the event and effect on clinical outcome. J Thromb Haemost 2005; 3:1218-23.
9. Freilinger TM, Schindler A, Schmidt C, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. JACC Cardiovasc Imaging 2012;5:397-405.

10. Scullen TA, Monlezun DJ, Siegler JE, et al. Cryptogenic stroke: clinical consideration of a heterogeneous ischemic subtype. J Stroke Cerebrovasc Dis 2015;24: 993-9.
11. Mas J-L, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740-6.
12. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. Circulation 2002;105:2625-31.
13. Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. Ann Neurol 2003;54:227-34.
14. Knebel F, Masuhr F, von Hausen W, et al. Transesophageal echocardiography in patients with cryptogenic cerebral ischemia. Cardiovasc Ultrasound 2009;7:15.
15. Rus Mansilla C, Mesa Rubio D, Suárez de Lezo Cruz Conde J, Rodríguez Almodovar A, Durán Torralbo C, Delgado Ortega M. Utility of transesophageal echocardiography in young patients with cryptogenic stroke and low cardiovascular risk. Med Clin (Barc) 2008;130:241-5. (In Spanish.)
16. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092-100.
17. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial — TOAST: Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
18. Lee LJ, Kidwell CS, Alger J, Starkman S, Saver JL. Impact on stroke subtype di-

agnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. Stroke 2000;31: 1081-9.
19. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). Cerebrovasc Dis 2013;36:1-5.
20. Arsava EM, Ballabio E, Benner T, et al. The Causative Classification of Stroke system: an international reliability and optimization study. Neurology 2010;75: 1277-84.
21. Marnane M, Duggan CA, Sheehan OC, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin Population Stroke Study. Stroke 2010;41:1579-86.
22. Chatzikonstantinou A, Wolf ME, Hennerici MG. Ischemic stroke in young adults: classification and risk factors. J Neurol 2012;259:653-9.
23. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2015;14:377-87.
24. Lazzaro MA, Krishnan K, Prabhakaran S. Detection of atrial fibrillation with concurrent Holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. J Stroke Cerebrovasc Dis 2012;21: 89-93.
25. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9.
26. Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients

from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). Eur Heart J 2014;35:508-16.

27. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-86.

28. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014; 370:2467-77.

29. Favilla CG, Ingala E, Jara J, et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. Stroke 2015;46: 1210-5.

30. Suzuki S, Sagara K, Otsuka T, et al. Usefulness of frequent supraventricular extrasystoles and a high CHADS2 score to predict first-time appearance of atrial fibrillation. Am J Cardiol 2013;111:1602-7.

31. Chiti A, Giannini N, Terni E, et al. "Cardioembolic profile" in patients with ischemic stroke: data from the analysis of 1037 cases. J Stroke Cerebrovasc Dis 2015; 24:1287-90.

32. Kamel H, Okin PM, Longstreth WT Jr, Elkind MS, Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. Future Cardiol 2015;11:323-31.

33. Yaghi S, Moon YP, Mora-McLaughlin C, et al. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. Stroke 2015;46:1488-93.

34. Taina M, Vanninen R, Hedman M, et al. Left atrial appendage volume increased in more than half of patients with cryptogenic stroke. PLoS One 2013;8(11): e79519.

35. Korhonen M, Muuronen A, Arponen O, et al. Left atrial appendage morphology in patients with suspected cardiogenic stroke without known atrial fibrillation. PLoS One 2015;10(3):e0118822.

36. Acampa M, Guideri F, Tassi R, et al. P wave dispersion in cryptogenic stroke: a risk factor for cardioembolism? Int J Cardiol 2015;190:202-4.

37. Martin DT, Bersohn MM, Waldo AL, et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. Eur Heart J 2015;36:1660-8.

38. Saver JL. Cryptogenic stroke in patients with patent foramen ovale. Curr Atheroscler Rep 2007;9:319-25.

39. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? Stroke 2009;40:2349-55.

40. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology 2013;81:619-25.

41. Ozdemir AO, Tamayo A, Munoz C, Dias B, Spence JD. Cryptogenic stroke and patent foramen ovale: clinical clues to paradoxical embolism. J Neurol Sci 2008; 275:121-7.

42. Cramer SC, Rordorf G, Maki JH, et al. Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study. Stroke 2004;35: 46-50.

43. Huang YY, Shao B, Ni XD, Li JC. Differential lesion patterns on T2-weighted magnetic resonance imaging and fluid-attenuated inversion recovery sequences in cryptogenic stroke patients with patent foramen ovale. J Stroke Cerebrovasc Dis 2014;23:1690-5.

44. Thaler DE, Ruthazer R, Di Angelantonio E, et al. Neuroimaging findings in cryptogenic stroke patients with and without patent foramen ovale. Stroke 2013;44: 675-80.

45. Kent DM, Dahabreh IJ, Ruthazer R, et al. Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis. Eur Heart J 2015;36:2381-9.

46. Kitsios GD, Dahabreh IJ, Abu Dabrh AM, Thaler DE, Kent DM. Patent foramen ovale closure and medical treatments for secondary stroke prevention: a systematic review of observational and randomized evidence. Stroke 2012;43:422-31.

47. Hornung M, Bertog SC, Franke J, et al. Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale. Eur Heart J 2013;34:3362-9.

48. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083-91.

49. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366:991-9.

50. Kent DM, Dahabreh IJ, Ruthazer R, et al. Device closure of patent foramen ovale after stroke: pooled analysis of completed randomized trials. J Am Coll Cardiol 2016;67:907-17.

51. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-236.

52. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2013; 44:870-947.

53. Culebras A, Messé SR, Chaturvedi S, Kase CS, Gronseth G. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82:716-24.

54. Singhal AB, Biller J, Elkind MS, et al. Recognition and management of stroke in young adults and adolescents. Neurology 2013;81:1089-97.

Copyright © 2016 Massachusetts Medical Society.

NEJM CLINICAL PRACTICE CENTER
Explore a new page designed specifically for practicing clinicians,
the NEJM Clinical Practice Center, at NEJM.org/clinical-practice-center.
Find practice-changing research, reviews from our Clinical Practice series,
a curated collection of clinical cases, and interactive features
designed to hone your diagnostic skills.