



Clinical Reasoning: An 87-year-old woman with left-sided numbness

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SECTION 1

An 87-year-old woman with a history of hypertension, hyperlipidemia, and peripheral vascular disease presented with acute left paresthesias. On evaluation, blood pressure was 152/77 mm Hg and heart rate 78 and regular. Physical examination had normal results. On neurologic examination, she had normal mental status, decreased sensation on the left face, and normal strength, tone, and reflexes. Cerebellar examination and gait were normal. There was reduced light touch and pinprick sensation of the left arm and leg, with no extinction. Complete blood count and comprehensive metabolic panel were within normal limits, and ECG showed normal sinus rhythm. Head CT scan was

unremarkable. She was prescribed aspirin and admitted for evaluation. Symptoms lasted 48 hours. Brain MRI showed no acute infarction. Magnetic resonance angiography showed normal intracranial vessels and mild bilateral internal carotid disease. Echocardiography showed an ejection fraction of 55%–60% and no structural abnormalities, though the left atrium was not visualized. On telemetry, she had 2 self-limited episodes of asymptomatic paroxysmal supraventricular tachycardia. She started a low dose β -blocker.

Questions for consideration:

1. What is your differential diagnosis?
2. How would you evaluate and manage the patient?

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SECTION 2

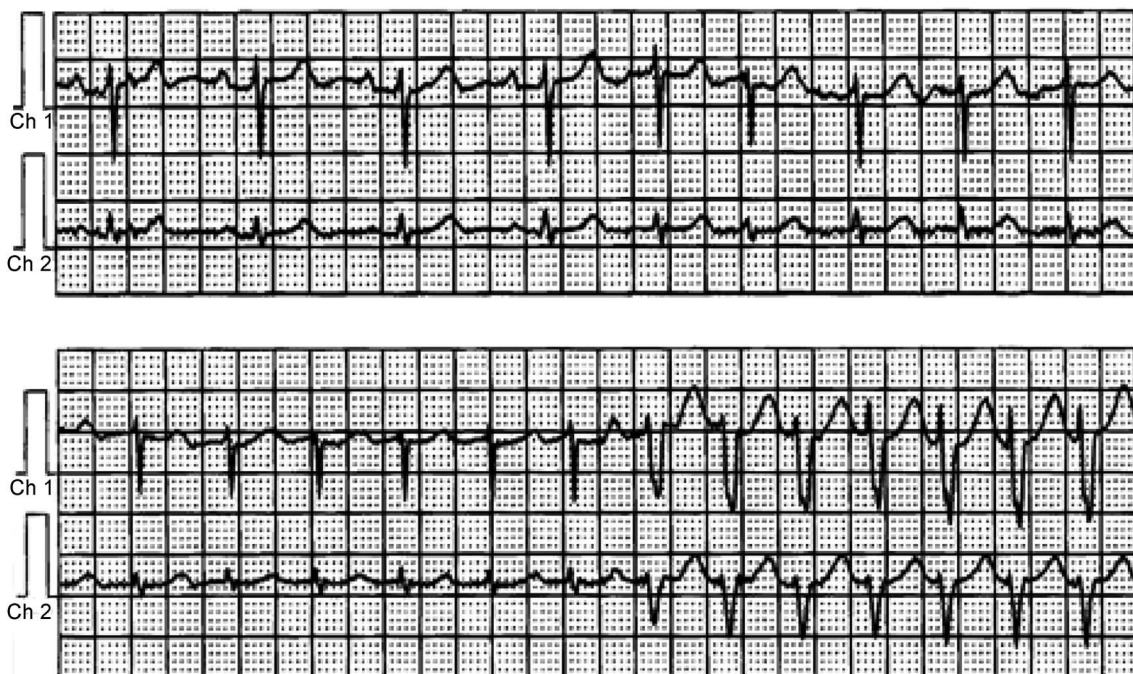
Given the acuity of symptoms, her focal neurologic deficits, and the fact that her deficits lasted over 24 hours, a clinical stroke was diagnosed.¹ The CT scan did not reveal hemorrhage. Although her brain MRI did not show evidence of infarction, this did not eliminate the diagnosis of stroke as a negative diffusion-weighted imaging (DWI) MRI sequence can be seen in up to 20% of patients with ischemic stroke.² Absence of DWI signal abnormality is more common in patients with small subcortical strokes.² In some instances, repeat MRI detects infarcts even when initial MRI scan is negative.²

The mechanism of stroke remained uncertain. Vessel imaging did not show significant large artery intracranial atherosclerotic disease, no cardioembolic etiology was identified on transthoracic echocardiography, and no atrial fibrillation (AF) was detected on inpatient telemetry. The patient's presentation with a pure sensory syndrome was suggestive of a clinical lacunar stroke affecting the right lateral thalamus, despite her negative diffusion imaging. Although lacunar strokes are classically attributed to intrinsic small vessel disease, up to 25% are due to other mechanisms of stroke, including cardioembolism.³

Cryptogenic, or unexplained, stroke comprises about 30%–40% of ischemic strokes.⁴ Potential stroke mechanisms in cryptogenic stroke include paroxysmal AF, substenotic atherosclerotic plaque, and other low-risk cardiac sources such as patent foramen ovale (PFO) and aortic arch atheroma. Paroxysmal

AF is one of the most common causes identified in patients with cryptogenic stroke.⁴ Admission ECG or 24-hour telemetry is useful in the diagnosis of persistent or paroxysmal frequent AF, with a yield up to 7% in ischemic stroke patients.⁴ These tests, however, are not very useful in detecting infrequent paroxysmal episodes of AF. Recent evidence from the 30-day cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) study supports the superiority of mobile continuous outpatient telemetry (MCOT) over inpatient telemetry or 24-hour Holter monitoring in detecting AF in patients with cryptogenic stroke (16.1% vs 3.2% detection).⁵ In addition, the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) study randomized patients with cryptogenic stroke and negative transesophageal echocardiography to either an implantable loop recorder or standard of care. This study showed higher detection rates of paroxysmal AF with implantable loop recorders (detection rates of 8.9% vs 1.4%).⁶ Although outpatient cardiac monitoring is therefore more likely to detect AF than inpatient telemetry and ECG, the optimal duration and monitoring method remain unclear in the absence of trials comparing different methods and durations of outpatient monitoring. Atrial ectopy also predicts detection of AF with monitoring. In the EMBRACE study, for example, patients who had AF detected during 30 days of monitoring had significantly more atrial premature beats.⁷

Figure Mobile continuous outpatient telemetry shows a 6-second episode of paroxysmal atrial fibrillation vs paroxysmal supraventricular tachycardia with aberrancy



Noninvasive testing in patients with cryptogenic stroke via transcranial Doppler with agitated saline may also be useful in detecting PFO.

Because of the absence of confirmed subcortical stroke on MRI, and the presence of atrial ectopy on telemetry, the patient underwent further cardiac monitoring after discharge. MCOT showed a single equivocal

episode of paroxysmal supraventricular tachycardia, vs AF, lasting for less than 6 seconds (figure).

Questions for consideration:

1. How would you treat the patient?
2. What is your next step, if any, in evaluating this patient?

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SECTION 3

There was uncertainty about whether the patient had experienced paroxysmal AF (PAF) or paroxysmal supraventricular tachycardia (PSVT) with aberrancy, and the episode was very brief. Recent evidence suggests the possibility of an increased risk of stroke in patients with PSVT. In a study using administrative inpatient data, patients with PSVT had a higher risk of stroke in the absence of AF after adjusting for stroke risk factors (hazard ratio, 2.10; 95% confidence interval, 1.69–2.62).⁸ In the absence of trials of specific antithrombotic regimens among patients with PSVT, however, there is no evidence supporting the use of anticoagulants for stroke prevention

in those patients. The benefit of chronic anticoagulation in patients with AF episodes lasting less than 30 seconds is also unclear. There is evidence to suggest, however, that episodes of AF lasting ≥ 5 minutes are associated with a 2-fold increase in risk of stroke or death.⁹ Given the uncertainty that the episode was AF and its brief duration, the patient was maintained on aspirin and another 3 weeks of MCOT was prescribed, during which she had clear episodes of AF. She had no contraindications to anticoagulation.

Question for consideration:

1. How would you manage the patient now?

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SECTION 4

The patient was diagnosed with PAF. The risk of ischemic stroke could now be calculated using well-accepted risk stratification schemes. The congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke (CHADS₂) and congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/TIA, vascular disease, age 65–74 years, sex category (CHA₂DS₂-VASc) scores predict the risk of stroke in patients with AF (table). For each point of the CHADS₂ score, there is an approximate 2% increase in absolute risk of stroke or systemic thromboembolism. A limitation of the CHADS₂ score is that it discriminates poorly among those at the lower end of the risk spectrum. The CHA₂DS₂-VASc score incorporates additional risk factors, including levels of age, sex, and other atherosclerotic and vascular diseases that increase stroke risk. Those with CHA₂DS₂-VASc scores of 0–1 appear to be at very low risk of stroke. In large cohorts analyzed thus far, the CHA₂DS₂-VASc score demonstrated better predictive value than

the CHADS₂ score. However, the predictive value of all scores remains limited, and these scores are based on analyses of prior cohorts of patients, and current risks may be lower due to advances in treatment and increasing use of other preventive medications, such as statins.

The patient had a CHADS₂ score of 4 (corresponding to annual stroke or systemic thromboembolism risk of 8.5%) and a CHA₂DS₂-VASc score of 7 (annual stroke or thromboembolism risk of 11.2%). Anticoagulation has been shown in randomized controlled trials to be superior to antiplatelet therapy in primary stroke prevention in patients with AF who are considered to be at high risk of stroke, i.e., those with CHADS₂ score >1 or CHA₂DS₂-VASc score >1 , and for secondary stroke prevention in patients with AF.

Recent evidence suggests that non-vitamin K oral anticoagulants (NOACs) are as effective as vitamin K antagonists (VKAs) such as warfarin in the prevention of stroke and systemic embolism in patients with AF with a lower risk of intracranial hemorrhage. As compared to warfarin, dabigatran was associated with reduced risk of ischemic stroke and systemic embolism as well as intracranial hemorrhage, but with a higher rate of gastrointestinal hemorrhage.¹⁰ Apixaban was similarly superior to warfarin in the prevention of stroke and systemic embolism with a lower risk of intracranial hemorrhage. Rivaroxaban had a similar efficacy in the prevention of stroke and systemic embolism but lower risk of intracranial hemorrhage when compared to warfarin.¹⁰ Dabigatran is the only NOAC thus far associated with reduced risk of ischemic stroke as compared to warfarin, whereas only apixaban was superior to warfarin in reducing major bleeding risks.¹⁰ Furthermore, in patients with AF deemed unsuitable for warfarin, the Apixaban vs Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial showed that apixaban was superior to aspirin in reducing risk of stroke and embolic events (hazard ratio, 0.45; 95% confidence interval, 0.32–0.62) with similar risk of major bleeding events and intracranial hemorrhage.¹¹ Taking the available evidence together, in our patient, apixaban was chosen for its reduced risk of stroke and its lower risk of hemorrhagic complications than warfarin. Aspirin was stopped given the increased risk of bleeding when aspirin is used with anticoagulation.

DISCUSSION Cryptogenic stroke constitutes 30%–40% of ischemic strokes and up to 30% of those are due to PAF. The detection of AF appears higher among those with evidence of atrial ectopy.⁷ MCOT and loop recorders increase detection rates in patients with cryptogenic stroke when compared to inpatient telemetry and ECG. The detection of AF in those patients is an indication for the use of oral

Table Commonly used stroke and thromboembolism risk prediction schemes for atrial fibrillation

CHADS ₂ items	Points	CHA ₂ DS ₂ -VASc items	Points
C = Congestive heart failure	1	C = Congestive heart failure	1
H = Hypertension	1	H = Hypertension	1
A = Age ≥ 75 y	1	A ₂ = Age ≥ 75 y (double value)	2
D = Diabetes mellitus	1	D = Diabetes mellitus	1
S ₂ = history of stroke, TIA, or thromboembolism (double value)	2	S ₂ = History of stroke, TIA, or thromboembolism (double value)	2
		V = Vascular disease (prior myocardial infarction, peripheral arterial disease, aortic plaque)	1
		A = Age 65–74 y	1
		Sc = sex category (female sex)	1
Range	0–6		0–9
Annual risk of stroke and systemic embolism per CHA ₂ DS ₂ -VASc and CHADS ₂			
CHADS ₂		CHA ₂ DS ₂ -VASc	
0: 1.9% per year		0: 0.2% per year	
1: 2.8% per year		1: 0.6% per year	
2: 4% per year		2: 2.2% per year	
3: 6% per year		3: 3.2% per year	
4: 8.5% per year		4: 4.8% per year	
5: 12.5% per year		5: 7.2% per year	
6: 18% per year		6: 9.7% per year	
		7: 11.2% per year	
		8: 10.8% per year	
		9: 12.2% per year	

Abbreviations: CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/TIA, vascular disease, age 65–74 years, sex category; CHADS₂ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke.

anticoagulants for secondary stroke prevention. NOACs have a better safety profile than VKAs, and may be considered as alternatives to warfarin.

AUTHOR CONTRIBUTIONS

Dr. Yaghi: manuscript preparation and literature review. Dr. Elkind: literature review, manuscript revision, supervision.

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