Cryptic Loss of Consciousness in a 36-Year-Old Woman

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Case Description

A 36-year-old woman was found unconscious in her work place in an industrial area. Her relatives reported that she had complained of blurred vision earlier that day. On initial evaluation by the paramedic team, she reacted to painful stimuli and was able to localize, but did not open her eyes when prompted. She was not able to produce any meaningful speech; hence her Glasgow Coma Scale was 8. There were no signs of trauma, epileptic seizures, or exposure to chemicals. She had no cardiorespiratory compromise, was normothermic, slightly hypoglycemic and her blood pressure was 153/99 mm Hg. The initial brain computed tomography, taken in a regional hospital, was normal. The patient remained unconscious, was intubated, and transported to a university hospital emergency unit with a working diagnose of either intoxication, hypoglycemia, or status epilepticus.

The patient had a medical history of migraine without aura with a low attack frequency. Her only medication was oral contraceptive pills containing estrogen. She did not smoke or drink excessive amounts of alcohol. Two weeks earlier, she was treated for sinusitis with oral cephalaxin. She had severe long-lasting financial distress. She had no family history of stroke, but both maternal grandparents had ischemic heart disease at a later age.

On admission to the university hospital, brain computed tomography and computed tomography angiogram covering intra and extracranial arteries were unremarkable. Toxicology and infection screen was negative, she remained normoglycemic and normotensive with no epileptic seizures. Magnetic resonance imaging on day 3 showed bilateral thalamic infarcts (Figure [A]). Magnetic resonance angiography of the neck and brain vessels revealed no abnormalities (Figure [B]). Transesophageal echocardiogram with a contrast study was negative for any cardiac source of emboli other than a patent foramen ovale (PFO) with moderate right-to-left shunt after Valsalva maneuver (Figure [C] and in the online-only Data Supplement Movie). A transcranial Doppler bubble study demonstrated severe right-to-left shunt (60 microembolic signals) at rest and a curtain-like burst of microemboli after Valsalva maneuver (Figure [D]). ECG telemetry and 48-hour Holter monitoring were unremarkable. Ancillary blood tests remained normal and detected hypercoaguable work-up was unremarkable.

The patient became gradually improved with intermittent fluctuations in her mental status until the time of discharge. In accordance with secondary stroke prevention guidelines, clopidogrel and atorvastatin were started. She underwent neuropsychological and occupational rehabilitation in an outpatient unit. At follow-up visit 3 months later, she reported increased fatigue but was able to return to work and her usual activities.

Discussion

This case represents 2 diagnostic challenges. First, the presentation of a patient who requires urgent multidisciplinary assessment to determine the cause of coma. Several neurological and non-neurological diseases must be considered in the differential diagnosis, including intracerebral and subarachnoidal hemorrhage, basilar artery occlusion, status epilepticus, brain trauma or neoplasm, sepsis, infection of the central nervous system, intoxication, hypoglycemia, and somatization. Bilateral paramedian thalamic infarcts, as detected on day 3, are a well-known cause for decreased consciousness. The second diagnostic challenge is determining the cause of infarction in a young otherwise healthy patient. Three-fifths of young patients remain without a clear cause for their stroke or have common conditions, such as PFO, which may or may not be associated with the event. Our patient had several conditions that have been associated with stroke, although no high risk factors. Ultimately, the cause of this stroke remains cryptogenic.

In young patients, the most prevalent modifiable risk factors are the same as those seen in older individuals and include dyslipidemia, smoking, and hypertension. However, certain risk factors or conditions can be regarded as age-specific because they mainly or solely seem in young patients, or the strength of association with stroke is greater among young when compared with old individuals. Such risk factors include oral contraceptive use, pregnancy, puerperium, illicit drug use, and idiopathic intracranial hypertension.
use, and PFO. Furthermore, recent acute or chronic infections may be more commonly found in younger individuals. These factors can either be present in isolation or in combination. Presumably multiple factors will further increase the total risk.

Our patient had both migraine without aura and oral contraceptive use. Migraine with aura roughly doubles the risk of ischemic stroke when compared with the general population, but such an increase has not been consistently documented for migraine without aura. The combination of oral contraceptives and migraine with aura increases the risk of ischemic stroke 5- to 17-fold. Our patient also had recent infection and increased stress, which may have contributed to a prothrombotic state. Importantly, none of these factors by themselves are sufficient to explain the patient's stroke.

The prevalence of PFO is about 25% in the general population. Its role as a causal factor for stroke remains hard to prove in individual patients, although case-control studies consistently show a statistical association between PFO and otherwise cryptogenic stroke. This association is higher in young patients, in patients with large right-to-left shunts, and in patients with structural heart abnormalities, such as atrial septal aneurysms, and in patients with large right-to-left shunts. However, also contradictory evidence exists, especially when it comes to the size of PFO. Our patient had a PFO and her stroke may have been caused by paradoxical embolism. However, there was no evidence of a prothrombotic state. In this case, there was no evaluation for deep vein thrombosis or pulmonary embolus, which if found would have increased suspicion for paradoxical embolization. Young patients with cryptogenic transient ischemic attack or stroke and PFO should be evaluated for lower extremity or pelvic venous thrombosis, which would also be an indication for anticoagulation.

According to recent randomized trials, prolonged ECG monitoring detects paroxysmal atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack at a rate of about 10% per year. However, this rate includes patients with traditional risk factors and likely overestimates the incidence of atrial fibrillation in young patients without risk factors for atherosclerotic disease. It should be noted that intracardiac thrombus may be missed on echocardiography either because it is small or it has already embolized. Arterial dissections can heal and may not be present when imaging is completed weeks or months after the stroke.

According to ASCO classification, our case had eventual phenotype of A0-S0-C3-O0. This classification takes into account all the possible causes of an ischemic stroke, not just the most likely one. The categories of ASCO classification are as following: A for atherosclerosis, S for small vessel disease, C for cardiac source, and O for other cause. Each of the subtypes is further graded into 4 groups according to its likelihood of being the cause of the ischemic stroke or into group 9 if certain category cannot be graded. The prevalence of cryptogenic stroke is mainly influenced by the completeness and quality of the diagnostic work-up, as well as our understanding of stroke mechanisms.

Figure. A, Magnetic resonance imaging of the brain with diffusion-weighted imaging showing bilateral paramedian thalamic infarcts (hyperintensive areas). B, Magnetic resonance angiography of the brain vessels revealed no abnormalities (The same was the case for the neck vessels, not shown). C, Transesophageal echocardiogram with a contrast study demonstrating a patent foramen ovale with a moderate right-to-left shunt after Valsalva maneuver. No atrial septal aneurysm was detected. D, Transcranial Doppler bubble test showing severe right-to-left shunt at rest (60 microemboli) and a curtain-like burst of microemboli after Valsalva maneuver. LA indicates left atrium; and RA, right atrium.
These cryptogenic strokes are a considerable challenge to the stroke community. Studies with comprehensive standardized investigations, imaging protocols, and longer follow-up are needed to more accurately identify risk factors, optimal investigations, and long-term therapy of cryptogenic strokes. Given the heterogeneity of ischemic stroke mechanisms in younger protocols for the evaluation of stroke in patients without strong risk factors should be developed. The ongoing Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome study (NCT01934725) is attempting to better define causes of strokes in these patients and establish such protocols.

**Disclosures**

Dr. Putaala received funding from The Finnish Medical Foundation and Helsinki University Central Hospital for related research (significant). The other authors report no conflicts.

**TAKE-HOME POINTS**

- Bithalamic infarcts are a well-known cause of depressed level of consciousness. Several other neurological and non-neurological conditions must be considered in the differential diagnosis.
- As many as 3 of 5 young ischemic stroke cases remain cryptogenic despite thorough diagnostic work-up.
- Apart from well-documented vascular risk factors, young stroke patients frequently harbor less established and age-specific risk factors, such as oral contraceptive use, pregnancy, puerperium, illicit drug use, or patent foramen ovale.
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SUPPLEMENTAL MATERIAL

Video legend: Bubbles are passing atrial septum through patent foramen ovale in bubble test during Valsalva maneuver.