Cryptogenic Stroke

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Cryptogenic stroke (CS) is defined as the infarction of the brain that is not attributable to a source of definite cardioembolic (CE), large artery atherosclerosis (LAA), or small artery disease (SAD) despite extensive vascular, cardiac and serologic evaluation. The term Cryptogenic stroke (CS) was first used in the National Institute of Neurologic Disease and Stroke (NINDS) Data bank. The TOAST (trial of ORG10172 in Acute Stroke Treatment) classification of subtypes of acute ischaemic stroke conceived the term 'Stroke of Undetermined etiology'. Similar terminology in the literature includes cryptogenous stroke, infracts of unknown, uncertain, or undetermined cause.

Larger epidemiologic studies report 30-40% of all strokes as cryptogenic. In a sizeable subset of patients with stroke, we are unable to identify the etiology because: 1. the cause is reversible and the workup is not performed at the appropriate time, 2. the cause of the stroke not fully investigated, 3. some causes of stroke remain unknown. In the TOAST classification, the stroke is designated as one of undetermined etiology when the presence of multiple, concomitant risk factors force the physician to be unable to determine a final diagnosis.

**PATHOPHYSIOLOGY OF CS**

1. **Reversible events**
   - **Atrial fibrillation (AF):** Atrial fibrillation accounts for 10% of all strokes and 50% of the cardioembolic events. Frequently, AF, being asymptomatic in up to 30% cases remains undiagnosed. A quarter of stroke patients with AF never had a diagnostic label of AF. AF is intermittent in 30% of cases with strokes. A single standard ECG recording therefore may miss the diagnosis. The Event loop recorder (ELR) designed to capture heart rhythm in ambulatory patients for a week or longer improves detection of AF. In a recent study ELR captures AF in 22 out of 149 (14.8%) patients with an acute stroke or stroke. Standard ECG detects such arrhythmia in only 6.7% cases. Thirty day cardiac monitor (30-DEM) improves the detection of intermittent AF even further and proves useful in the work-up of patients with CS.
   - **Vasospasm:** It plays a role in infarcts related to migraine. It can be reversible as well as transient. It may resolve by the time cerebral ischaemia presents itself.
   - **Embolism:** Embolus may disappear without residual evidence when the patient with CS is evaluated by CT, MRI or MRA.

2. **Inadequate work-up**
   - In the study of Bang et al the recurrence rate of stroke following a CS is about 30% and most of these strokes are large artery strokes. They have postulated that the underlying mechanism of CS is a variation of large artery disease (LAD). The work up often does not include the thorough evaluation of the large artery, for example the aortic arch. As detailed further below, the studies have shown the aortic arch atheroma to be a significant risk factor for the ischaemic stroke.
   - Some causes remain unknown and often the etiologic association can be inferred only on the basis of epidemiologic
studies, for example, patent foramen ovale (PFO). Several mechanisms have been adduced for a presumed PFO-related stroke: paradoxical embolism from the peripheral venous system, embolization from thrombi formed within the atrial septum and thrombus formation as a result of transient atrial arrhythmias.4 (see below).

**CLINICAL FEATURES**

Cryptogenic stroke most commonly presents with superficial infarction in 62-84% of cases.2,12 In The PFO-ASA study, cortical signs were present in 27% and abrupt onset in 59%.13 In this study 56% of patients had superficial infarcts. Forty percent of the CS in Stroke Data Bank were found to have cortical infarcts. Larger subcortical strokes (more than 15mm) also tend to be either CS or cardioembolic in origin. The German stroke study found that parenchymal haemorrhagic transformation occurred in 2.4% of patients with stroke of unknown etiology in first 7 days, comparable to the percentage among cardioembolic stroke suggesting an embolic mechanism.14 Lacunar syndromes are rare, less than 5%. The severity of initial presentation varies but in general, less severe than cardioembolic strokes and worse than lacunar ones.

The involvement of the following arteries is considered marker of embolic events:
- posterior division of MCA
- distal PCA
- ACA
- superior cerebellar artery (SCA)

A significant proportion of CS adhere to the embolic infarct topography on CT/MRI.

**EVALUATION OF CS**

**TOE**

Although the standard transthoracic echocardiogram with bubble contrast can reveal significant abnormalities, it appears that the trans-oesophageal echo (TOE) is superior in the evaluation of patients with CS.15 TOE is a useful investigation in the diagnostic armamentarium for the CS, especially in the young (less than 50) and few or no risk factors for the stroke.16 The chances of finding a potential cardiac source embolism is higher than that for the transthoracic echocardiogram. The following abnormalities have been described in the context of CS:
- atrial appendage thrombus
- enlarged left atrium
- spontaneous echo contrast

PFO
- Atrial septal aneurysm
- large thoracic aortic plaques
- valvular strands
- mitral valve prolapse

The assessment of PFO on TOE depends on counting the number of microbubbles (MBs) moving from the right atrium (RA) to the LA through the PFO after VM within the first three cardiac cycles. A PFO is diagnosed if at least one MB was detected in the LA. MBs appearing after the first 3 cardiac cycles were classified as pulmonary shunt.15

Although the cutoff of three cardiac cycles has been widely used, some authors have defined early RLS as those appearing within 3 cardiac cycles and late as those at 4th or 5th cardiac cycle.17 Transpulmonary shunting is assessed by the bubble movements as well further clarified by following the bubble movements with a frame-by-frame analysis and assessing each pulmonary vein origin for bubble entry during each TOE/TTE contrast study.

A contrast test is performed using an agitated saline mixed with urea-linked gelatine (Haemaccel). The content of the 2 syringes (one with 2 ml of saline solution and one with 2 ml of Haemaccel) are rapidly mixed until a homogeneous solution is obtained (CSL). This is injected as a rapid bolus (5 seconds) via a 21-gauge intravenous catheter inserted in the right antecubetal vein.

In one study of the 237 patients without recognised cause of TIA and/or stroke potentially treatable cardioembolic sources were detected in 146 (61%) patients: PFO with right to left shunt (n=59), left atrial clot (n=6), left atrial appendage clot (n=8), severe thoracic aortic atherosclerotic plaque disease (plaque thickness >4mm) (n=79) of which 56 had an ulcerated plaques and 4 had mobile plaque.18

In general, the most frequently identified abnormalities in CS includes: PFO, ASA and aortic atheromas. The timing of TOE - <72 h versus >72 h in relation to the index event- does not alter the sensitivity of the testing.

**Transcranial Doppler (TCD)**

TCD appears to be an attractive alternative to TOE in the evaluation of the CS, especially to look for a PFO.15 Transcranial doppler examination is done with the patient in supine position. the side of the cranium with the superior temporal window is chosen and the middle cerebral artery
(MCA) is identified with colour Doppler bilaterally. An 8mm pulsed Doppler sample volume and a low gain provided settings for distinguishing the microembolic signals (MES) from the background spectrum.

TCD is deemed positive if at least one MES is recorded on the TCD spectrum within the first three cardiac cycles from contrast injection. The Doppler spectrum is continuously recorded for 40 seconds after valsalva is completed. The results are classified as follows:

- 0 MES: test negative.
- 1-10 MES: small shunt
- >10 MES: medium shunt
- > 10 MES plus curtain effect: large shunt

The combination of contrast TOE with contrast TCD is slated to become the gold standard for the detection and assessment of the PFO.19

**MRI of the aortic arch**
The overall number of high risk plaques detected by MRI (n=74) was substantially higher compared with TOE (n=47). Most noticeably, MRI identified aortic high risk pathologies in 8/26 (30.8%) patients with cryptogenic stroke after standard diagnostics, including TOE.20

**Patent Foramen Ovale (PFO)**
Analysis of pooled data from the autopsy studies shows an average prevalence of 26% (range 17-35%) amongst general population while echocardiographic studies estimates it at 3.2%-18%.22 Interestingly, PFO seems to be associated with CS in younger patients (less than 55) rather than older (more than 55). A met analysis of case control studies demonstrates increased prevalence of PFO in patients with CS in younger age group (OR 5.01, 95% CI 3.24-7.75) but not in patients older than 55 (OR 1.20 95% CI 0.56-2.56).23

Mechanism of stroke in the context of PFO is not always clear. Paradoxical embolism appears to be the most appealing explanation. For paradoxical embolism to happen, a right to left pressure gradient is required such as that happens during valsalva maneuver and pulmonary hypertension. This may often be transient and a venous source of embolism may not always be identified. Stollemberg shows venography of lower limbs reveals a DVT in 24 out of 42 patients with arterial embolism and PFO. DVT was located exclusively in the calf veins in 13 of the patients. In the PELVIS study, MR venography of the pelvic veins shows thrombosis in 20% of CS with PFO.

**Aortic Arch Atheroma**
Aortic arch atheroma is an under recognised cause of the CS. TOE detects the presence of the aortic arch atheroma. The arch atheroma itself is an independent risk factor for stroke as well as it reflects a generalized vascular disease.

In a study of consecutive 147 patients with ischemic cerebrovascular disease including ischaemic stroke and transient ischaemic attacks, 56 patients had aortic complex lesion defined as an aortic intima-media thickness (IMT) greater than 4mm, mobile plaque, and/or ulcers.24

Carorid IMT as defined by carotid duplex is closely linked with aortic IMT.

Amarencro and colleagues25 have shown that atheromatous plaques thicker than 4 mm in the aortic arch is associated with ischaemic stroke, especially those with a presumed undetermined etiology. The risk of stroke is increased if there is severe atheroma of the aortic arched defined by the following characteristics: mobile, thickness more than 4mm and ulcerated. The odds ratio for the stroke of peripheral embolism in patients with severe arch atheroma is 4 and those with mobile atheroma is greater than 12.26

The prevalence of severe arch atheroma in patients presenting with stroke is 20%, comparable with those of carotid atherosclerosis and atrial fibrillation.27 Patients with severe atheroma tend to have recurrent vascular events which is estimated at 14.2% per year. Therefore, these patients need more aggressive anticoagulation strategy and the ARCH (Aortic Arch Related Cerebral Hazard) Study 28 a multicentre currently looks at whether aspirin and clopidogrel combination is superior to warfarin (INR 2-3).

The French Study of Aortic Plaques in Stroke (FSAPSG) 29 prospectively studied 331 consecutive stroke patients older than 60 who underwent evaluation by TEE for proximal aortic plaques. The risk of stroke recurrence varies with the plaque size: the risk of recurrence was 12.9% per year in larger plaques (more than 4mm) while it is 3.5% in smaller (1-3.9mm) plaques and 2.8% in patients with no plaques. TCD further clarifies the role of the aortic arch atheroma.30 It detects (high intensity transient signals) HITS more frequently in patients with atheromas: 56% of patients with AAA vs. 20% in those without (odds ratio 5.0 and 95% CI 0.98-26.9, p=0.064. In the subset of patients with AAA, HITS were more frequent in those with complex morphology as
opposed to non-complex: OR 2.6, 95% CI 1.7-3.9, p=0.005. Multidetector computed tomogram (MDCT) is another useful technique for the assessment of the aortic arch and delineation of atheroma.\(^{31}\)

More recently\(^{32}\) the relationship between arch plaques and recurrent events has been studied in 516 patients with ischemic stroke who were double-blindly randomized to treatment with warfarin or aspirin as part of the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), based on the Warfarin-Aspirin Recurrent Stroke Study (WARSS). The risk of vascular events was highest among cryptogenic stroke patients, both for large plaques (HR, 6.42; 95% CI, 1.62 to 25.46) and large complex plaques (HR, 9.50; 95% CI, 1.92 to 47.10). Event rates were similar in the warfarin and aspirin groups in the overall study population (16.4% versus 15.8%; P=0.43).

**Other Sources of Cardiac Embolism in CS**

A novel MR protocol has been developed to evaluate retrograde embolism from descending thoracic aorta, another under recognized cause of CS.\(^{33}\) The protocol has 3 components. Briefly, plaque localization was based on T1-weighted fat-saturated 3D gradient echo MRI (T1 3D-GRE, spatial resolution 0.8x1.1x1.1 mm\(^3\)). The distance of complex DAo plaques to the outlet of the left subclavian artery (LSA) was determined using the CE-MRA data. The time-resolved contrast-enhanced MR angiography (CE-MRA) covering the entire thoracic aorta and supra-aortic branches was performed (0.05 mL/kg gadobenate dimeglumine at 3.5 mL/s). For the assessment of blood flow in the thoracic aorta ECG synchronized and respiration controlled time resolved multidirectional 3D velocity mapping was employed (spatial resolution=2.1x3.2x3.5 mm\(^3\), temporal resolution=48.8 ms).

The retrograde flow from the complex plaques in descending thoracic aorta (thickness 4 mm or more, ulcerated, or superimposed thrombi) contributes to cardioembolic stroke. In a recent study by Harloff et al potential embolisation from DAo plaques was identified in 19 of 57 patients (33.3%) with determined and in 9 of 37 (24.3%) with CS.\(^{34}\) Retrograde flow from the DAo plaques reached the left subclavian artery (58.5%), left common carotid artery (24.5%) and the brachiocephalic trunk (13.8%).

Pacemaker lead thrombosis has been reported as a cause of CS in a patient referred for percutaneous closure of the PFO.\(^{35,36}\)

**MANAGEMENT IMPLICATIONS OF CS**

The issue of PFO closure is controversial. Until further data available from randomized trials, it would make sense to consider closure in cases of PFO with the following risk factors: large separation of more than 4mm, increased left to right shunting, increased septal mobility, and atrial septal aneurysm.\(^{37}\) Percutaneous techniques and devices for the PFO closure have come of age and surgery is rarely required these days. The Amplatzer device seems to be safer and less prone to have complications compared to the CardioSEAL devices.\(^{38,39}\) The Occlutech Figulla PFO and ASD Occluder, a novel device for this purpose has recently been reported to be a safe alternative.\(^{40}\)

**RECOMMENDATIONS**

For the vast majority of patients with CS, antiplatelet therapy is recommended as the mainstay of antithrombotic therapy for secondary prevention. According to stroke prevention guidelines, risk factor modification and other measures of secondary stroke prevention are applicable to most patients with CS (ie, control of hypertension and diabetes, smoking cessation, lipid lowering therapies, weight loss, moderate alcohol consumption, and adequate physical activity).

**SUMMARY AND CONCLUSIONS**

- Cryptogenic stroke (CS) is defined as brain infarction that is not attributable to a source of definite cardioembolism (CE), large artery atherosclerosis (LAA), or small artery disease (SAD) despite extensive vascular, cardiac, and serologic evaluation (see “Definition” above).
- CS accounts for about 30 to 40 percent of ischemic stroke (see “Epidemiology” above), and the prevalence of CS may be higher in blacks and Mexican-Americans compared with white populations in the United States.
- The risk factors for CS are not clearly different from the risk factors for other types of ischemic stroke, although hypertension may be less common in patients with CS compared with other ischemic stroke types.
- The pathophysiology of CS is likely heterogeneous, and proposed mechanisms include paradoxical embolism from atrial septal abnormalities such as patent foramen ovale (PFO), occult cardiac embolism secondary to aortic atheromatous disease or other cardiac sources, hypercoagulable states, preclinical or subclinical cerebrovascular disease, and inflammatory processes.
REFERENCES


