Unusual association of diseases/symptoms

Cryptogenic stroke in low-risk patients, consider a cardiac shunt at your peril

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Summary

Patent foramen ovale (PFO) as a cause of cryptogenic stroke from paradoxical embolisation remains a controversial issue. The optimal care between medical and surgical management of these patients for the attending clinician remains a conundrum. We report a case of cryptogenic stroke in a woman aged 59, with a PFO, concomitant venous thrombosis and cryptogenic stroke. The case highlights the difficulty in diagnosing and managing such patients, particularly as recent evidence challenges the clinical practice of percutaneous closure and pathophysiological rationale.

BACKGROUND

The incidence of cerebrovascular events (transient ischaemic attacks and stroke) in UK general hospitals and worldwide remains high. Our case highlights the importance of careful clinical examination and the need to consider paradoxical embolisation at atrial shunt level in low-risk patients presenting with cerebrovascular events.

CASE PRESENTATION

A 59-year-old Caucasian woman was admitted with a gradual onset right-sided occipital headache, visual disturbance and left leg pain. She reported having similar symptoms a few days prior to admission, which had fully resolved. On examination she was in sinus rhythm. Blood pressure was mildly raised at 150/100 mm Hg. Her left leg was not swollen but was significantly tender. She had inattention of her left side and loss of left visual field in a quadrantanopic pattern. Fundoscopy was normal. The rest of the cranial nerves were otherwise intact. Motor and sensory examinations were intact in the upper and lower extremities.

Her medical history included migraine, sacroiliitis and depression, for which she was taking mirtazapine and citalopram. She had a very strong family history of ischaemic heart disease, cerebrovascular disease and pulmonary embolism. She had never smoked, drank alcohol occasionally and lived independently with her husband on a farm.

INVESTIGATIONS

Blood results on admission were essentially normal, apart from a raised D-dimer of 4235 and a slightly raised C-reactive protein of 17. Her coagulation screen was normal. ECG showed a normal sinus rhythm. An ultrasound Doppler of her left calf confirmed a small thrombosis in the distal calf area with no distal flow. Subsequent cranial MRI showed an acute infarct in the right parieto-occipital cortex.

Incidentally, her chest x-ray was reported as having bilateral prominent hilar lymphadenopathy. A thoracic CT

suggested bulky pulmonary arteries with possible filling defects. The patient underwent a CT pulmonary angiogram, despite her Well's score being low. This excluded pulmonary emboli but the presence of dilated pulmonary arteries, and persistent contrast in the superior vena cava after prolonged delay suggested a cardiac shunt. An outpatient left-sided bubble contrast echocardiogram confirmed the presence of a patent foramen ovale (PFO) with left-to-right shunt.

DIFFERENTIAL DIAGNOSIS

- ▶ Ischaemic stroke
- ▶ Venous sinus thrombosis
- ▶ Migraine

TREATMENT

She was given a loading dose of aspirin, but on confirmation of the deep vein thrombosis this was stopped and therapeutic dose enoxaparin was given until warfarin had reached its therapeutic range. Simvastatin was started as her total cholesterol was raised (6.2 mmol/l). She was referred to an interventional cardiologist to consider closure of the defect.

OUTCOME AND FOLLOW-UP

Three months following discharge, her vision has returned to normal and she is doing well. She is currently awaiting percutaneous PFO closure.

DISCUSSION

A PFO is a connection between the two atria of the heart caused by a failure of the atrial septum to fuse post-partum. It is a type of atrial septal defect and has been found to have an overall incidence of 27.3% in an autopsy study.¹ The link between a PFO, paradoxical embolism and cryptogenic stroke was first proposed in 1877.² The pathophysiological basis suggests that the presence of a PFO can theoretically allow embolisation into the left

atrium and the cerebral vasculature, during transient high right atrial pressure situations.

Over the decades, multiple case series and non-randomised studies have highlighted an association between a PFO and cerebrovascular events. A study in 2003 looked at the recurrence of cerebrovascular events following closure of the PFO.³ In this study of 457 patients, the incidence of recurrent embolic events was 1.9%, compared to 3.2% prior to the procedure. Similarly, in 2004, Braun *et al*⁴ conducted a study of 308 patients. Only five patients (1.6%) experienced a recurrence of stroke/transient ischaemic attack (TIA)/peripheral embolism, which translated to an annual recurrence risk of 0.6% for TIA and 0% for stroke.⁴ However, the case series mentioned include follow-up of only 12 months³ and 24 months,⁴ respectively and are only single-arm studies, which is a common problem with all previous studies.

The CLOSURE I trial published in 2012 is a landmark study as the first randomised trial comparing outcomes between medical and percutaneous device closure.⁵ It concludes that there are no significant advantages of percutaneous device closure over medical management.⁵

This calls into question the established National Institute for Clinical Excellence (NICE) guidance which recommends bubble contrast echocardiography in cryptogenic stroke age <55 and hence subsequent consideration for percutaneous closure. CLOSURE I trial reignite the clinical debate in the light of a systematic review by NICE which quotes a major and minor complication rates of 1.5% and 7.9%, respectively.⁶

Major complications include:⁶

- ▶ Death
- ▶ Haemorrhage requiring blood transfusion
- ▶ Cardiac tamponade
- ▶ Need for surgical intervention
- ▶ Pulmonary embolus.

Minor complications include:⁶

- ▶ Bleeding
- ▶ Arrhythmia—especially atrial fibrillation, (as seen in the CLOSURE I trial⁵)
- ▶ Device arm fracture
- ▶ Device embolisation
- ▶ Air embolism
- ▶ Arteriovenous fistula formation.

Although well designed, the CLOSURE I trial has its own limitations. The study population of 909 patients is statistically significant but represent less than a tenth of the number of patients included in all observational studies.⁷ As the recurrence rate of cerebrovascular accident is low, a median follow-up period of 2 years may not reflect the benefits of closure over medical management.⁷

With regard to the association of a PFO and stroke/transient ischaemic attack, the evidence remains poor. To date, much of the debate has centred on management, with positive surgical interventions speculatively being associated with treating the cause/source of paradoxical embolisation. Nevertheless, while the pathophysiological mechanism is plausible, many of the cases reported to date fail to have one or more of the elements necessary for a diagnosis of paradoxical embolism.⁸

We reviewed the population-based, prospective study by Meissner *et al*⁹, which found 140 of the 585 contributors had a PFO. Over a 5-year period, 41 of the 585 had a

cerebrovascular event.⁹ On analysis, a PFO was not found to be an independent risk factor for future cerebrovascular events.⁹ Conversely, according to the literature review by Kent and Thaler² PFO was an important risk factor for stroke recurrence after an initial cryptogenic stroke. However, this was through indirect evidence and statistical calculations.²

Alternative mechanisms underpinning the association of PFO with embolic cerebrovascular accident has been suggested, in particular, in situ thrombus formation within the interatrial septum,⁸ or increased susceptibility to atrial fibrillation.^{2 5 8} This challenges the clinical practice of closure device, as potential clinical benefit remains narrow.²

In conclusion, the role for foramen ovale closure with percutaneous device is weak compared to medical therapy. The equivocal results of the CLOSURE I trial question the justification of percutaneous risk exposure. Clinical practice should reflect ongoing evidence.

Learning points

- ▶ Establishing a cause in cryptogenic stroke is difficult but important to aid treatment and prevent recurrence.
- ▶ Good history and examination can often highlight additional risk factors, which may lead to a diagnosis of patent foramen ovale (PFO).
- ▶ Bubble contrast echocardiogram remains the gold standard investigation when a PFO is suspected.
- ▶ Suitable patients should be considered for ongoing randomised controlled studies such as the Gore REDUCE clinical trial.¹⁰

Competing interests None.

Patient consent Obtained.

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