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Review

Management of cryptogenic stroke

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Abstract

Cryptogenic stroke(CS) is defined as cerebral ischemia of obscure or unknown origin. The cause of CS remains undetermined because the event is transitory or reversible, investigations did not look for all possible causes, or because some causes truly remain unknown. One third of the ischemic strokes is cryptogenic. CS is more frequent in younger than older patients and most frequently due to cardiac embolism, followed by vasculopathy, and coagulopathy. The most frequent causes of cardiac embolism include paradoxical embolism from upstream veins via a patent foramen ovale(PFO), paroxysmal atrial-fibrillation, valvular heart-disease, and atrial septal aneurysm. The most frequent vascular causes of CS are complex aortic plaques and Fabry's disease. Diagnostic work-up for CS includes transesophageal echocardiography, long-term ECG-recordings, CT-/ MR-angiography of the aorta, transcranial Doppler-sonography, imaging for venous thrombosis in case of paradoxical embolism, and blood chemical investigations and coagulation tests. Recurrence rate and prognosis of CS is under debate. Primary and secondary stroke prevention in CS is not at variance from stroke of known cause. If the cause of CS can be identified, appropriate treatment is indicated. A PFO requires antiplatelet medication, OAC if there are other indications for OAC, and closure in case of recurrent CS under OAC.

Key words: Cryptogenic stroke; stroke of undetermined cause; cerebral ischemia; pathogenesis, cause of stroke; patent foramen ovale; paroxysmal atrial fibrillation.

Introduction

The term "cryptogenic" means that the cause of a condition is of obscure or unknown origin and thus remains to be determined. Though the term is frequently used together with disease, there is no human disease without a cause, thus no stroke without an aetiology (cryptogenic stroke (CS) (Table 1). The cause of an ischemic stroke may remain cryptogenic because 1. the event is transitory or reversible and diagnostic work-up is not carried out in due time, 2. investigations do not look for all known causes of stroke, or 3. some causes of stroke truly remain unknown (1). The rate of CS thus depends on the definition of the term "complete" and how extensive and how rapid the diagnostic work-up is carried out (Table 2). The likelihood to detect the cause of a CS, however, increases if methods beyond routine diagnostic tools (carotid ultrasound, transthoracic echocardiography (TTE), 24h-Holter-monitoring) are applied. Delineation of CSs from stroke of undetermined cause is arbitrary why both terms should be used synonymously (2). As with strokes of known cause, causes of CS can be classified as cardiac, vascular, hemodynamic, or thrombophilic. CS most frequently occurs in patients < 55 y of age (juvenile stroke) as compared to stroke in the elderly, which is most frequently due to atrial fibrillation (AF) or atherosclerosis (1, 3). This minireview wants to give a short overview on the knowledge and most recent findings concerning the frequency, aetiology, pathogenesis, diagnosis, and treatment of CS.

Review criteria

The database in which it was searched for appropriate articles was MEDLINE. The period during which it was searched for appropriate publications was 1966 to December 2009. The search terms were "cryptogenic stroke", "stroke of undetermined cause", "ischemic stroke", and "cardioembolic stroke". The vast majority of the selected papers were full-text papers written in English. The vast majority of the papers reported studies on humans but animal studies were also included if relevant for the topic. Reference lists of identified papers were further searched for further leads.

Table 1

Causes of cryptogenic stroke

- Cardiac
  - Frequent
    - PFO*
    - Atrial septal defect*
    - Atrial septal aneurysm (ASA)*
    - Atrial fibrillation
    - Heart valve disease*#
    - Regional myocardial dyskinesia
    - Dilated left atrium
  - Rare
    - Right atrial Chiari network*
    - Prominent Eustachian valve* (conducts the blood from the caval vein directly into the right atrium)
    - Spontaneous echocontrast within the right atrium*
    - Ventricular thrombus*
    - Left atrial appendage thrombi*
    - Dilative cardiomyopathy*
    - Restrictive cardiomyopathy*
    - Takotsubo syndrome*
    - Left ventricular hypertrabeculation*
    - Endomyocardial fibrosis
    - Left atrial bands*
    - Papillary fibroelastoma*
    - Atrial myxoma*
- Lung
  - Hereditary teleangiectasia Rendu-Osler (paradoxical embolism from pulmonary AV-shunts)
- Vascular
  - Atherosclerosis
    - Large arteries (aortic plaques*), small arteries
  - Fabry's disease
  - Aortic dissection*
  - Mural thrombi over dissected aortic segments*
- Coagulopathic
  - Arterial hypercoagulability
    - Antiphospholipid antibody syndrome
    - Elevated lipoprotein (a)
    - Tissue factor mutation
    - Hyperhomocysteinemia
  - Venous hypercoagulability
    - Inherited
      - Antithrombin-III deficiency
      - Protein-S deficiency
      - Protein-C deficiency
      - Factor II deficiency
      - Heparin cofactor II deficiency
      - Prothrombin mutations
      - Activated protein C (APC)-resistance
      - Fibrinolytic system abnormalities (plasminogen or tissue plasminogen activator deficiency, elevated plasminogen activator inhibitor)
      - Hereditary hyperhomocysteinemia
      - Factor XIII polymorphisms
    - Acquired
      - Acquired hyperhomocysteinemia
      - Neoplasm

*: detected on TTE or TEE, #: heart valve disease include thickened valves, mitral prolapse syndrome, aortic valve strands, aortic valve stenosis, mitral valve strands, mitral valve stenosis, mitral valve ring calcification, valve thickening, aortic valve sclerosis, Libman-Sacks endocarditis, marantic endocarditis, Lambl's excrescences

Table 2

Diagnostic work-up for CS

- Useful
  - TEE
  - Long-term ECG-recording
  - CT- or MR-angiography of the aorta and its thoracic branches
  - TCD
  - Venous ultrasound, MR-venography, phlebography
  - Ordinary blood investigations
    - Blood cell count (polycythemia vera, thrombocytosis) (82), D-dimer, urine protein
  - Coagulation test
    - Arterial hypercoagulability (lupus anticoagulant, anticardiolipin antibodies, lipoprotein A, tissue factor mutations, hyperhomocysteinemia)
    - Venous hypercoagulability (activated-protein-C (APC)-resistance, deficiency of protein-C, protein-S, or antithrombin-III, heparin cofactor II deficiency, prothrombin gene mutations, fibrinolytic system abnormalities (factor XIII polymorphisms), hyperhomocysteinemia (67))
  - Alpha galactosidase (GLA genetics)
- Questionable
  - 3D-MRI
  - Multidirectional 3D-MRI velocity mapping
  - FDG-PET
  - Cardiac MRI
  - Intracardiac echocardiography
  - Biological assays

Operational definition

A common binding definition of CS is not available. However, CS is most commonly defined as an ischemic cerebrovascular event of which the cause remains undetermined in the absence of smoking, if arterial hypertension, diabetes, and hyperlipidaemia are well controlled or absent, and if carotid ultrasound, transthoracic echocardiography (TTE), routine ECG, determination of the thrombocyte count, alpha-galactosidase, long-term ECG, coagulation studies, transcranial ultrasound (TCD), or transesophageal echocardiography (TEE), have been proven normal.

Frequency

Despite a complete work-up the cause of ischemic stroke remains undetermined in 20-40% of the cases (1-10). In a study of 130 consecutive stroke patients with a patent foramen ovale (PFO) the prevalence of CS was even 67% (11).

Pathogenesis

A. Cardiac causes

The most common cause of CS is presumably cardiac embolism. A cardiac cause of embolism can be eventually detected in at least half of the patients with CS (4,10). Though there are a large number of cardiac sources of embolism involved in the pathogenesis of CS, a few are more prevalent than others. The most common causes of cardiac embolism in CS include paradoxical embolism originating from crural or pelvic veins via a PFO, atrial septal aneurysm (ASA), paroxysmal AF (pAF), or valvular heart disease (Table 1). More rare causes of CS from cardiac embolism are listed in Table 1 (4, 12). Recently, enlargement of the left atrium and development of AF were proposed as the common pathomechanism of cardioembolic CS in patients with a PFO and ASA (13).

1. Patent foramen ovale (PFO)

a) General

The cardiac abnormality most frequently associated with CS is the PFO, particularly in subjects < 55y (2, 14, 15), although some studies reported an association between CS and PFO also in patients > 55y (16-18). A PFO can be detected in 40-50% of the patients with CS (3, 10, 18-24) but in single studies extreme figures of 22% (4) respectively 88% (25) have been reported. Investigating 227 patients with CS, a PFO was found in 43.9% of the young patients and in 28.3% of the old patients (18). Patients > 65y of age have a 3 times higher risk to develop a stroke if a PFO is present (3). PFO is more prevalent in men than women with CS (26). With only 15-30% of the normal population having a PFO (24, 27-30) the frequency of PFO is higher in CS patients as compared to healthy controls (10, 24). In CS patients PFOs are larger, have longer tunnels, and are more frequently associated with atrial septal aneurysm (ASA) as compared to patients with stroke of known cause (31). Since the source of embolism in the presence of a PFO is usually not the heart but the upstream veins, a PFO usually constitutes a risk factor for CS but not the cause of CS (2). Accordingly, the association of stroke and PFO is not sufficient to diagnose paradoxical embolism (32) and investigations of the peripheral veins for thrombosis and coagulation tests are necessary. Since PFO is a tunnel-like structure with possibly stagnant flow, also in situ thrombus formation may occur (24).

b. Diagnosis

PFO can be detected with the same accuracy by TEE as by TCD (23). In case of diagnosing CS and PFO the upstream particularly crural and pelvic veins need to be investigated for thrombosis by Doppler ultrasound, MR-venography, or phlebography immediately after the event. Clinical clues to the diagnosis of paradoxical embolism include the coexistence of deep venous thrombosis, pulmonary embolism, migraine, recent prolonged travel, sleep apnea, waking up with a transitory ischemic attack (TIA) or stroke, or a Valsalva manoeuvre (32). The morphological pattern of a PFO may be classified as simple (central/superior eccentric shunt or with valve mechanism), reduced (widely redundant septum primum), entire atrial septal aneurysm (EASA), cribriform, or as tunnel between septum primum and secundum > 10mm (33). Risk factors of paradoxical embolism in addition to a PFO are the presence of an ASA, Eustachian valve, or a Chiari network, which can be best detected by intracardiac echocardiography (34,35). The risk of stroke is particularly increased in young patients with a PFO (36). The only prothrombotic marker related to PFO size is the presence of antiphospholipid antibodies (37).

c. Arguments for a causative role of PFO

There are a number of arguments in favour and against a contributing role of PFO in CS, why no final decision can be made with regard to the pathogenicity of a PFO for CS. Arguments in favour of a causative role are: 1. PFO is more frequent in CS patients than in the normal population (38). 2. PFO is more frequent in patients with CS than in stroke patients with known cause. In a study of 130 stroke patients a PFO was found in 41% of the young and in 25% of the old patients with CS but only in 14.3% of the patients with a stroke of known cause (11). 3 In CS patients the presence of a PFO is associated with a low atherosclerotic burden, as measured by carotid intima media thickness (21). It was assumed that in patients with a PFO a non-atherosclerotic mechanism is involved, whereas in CS patients without a PFO an atherosclerosis-mediated mechanism prevails (21). 4. The recurrence rate of CS in patients with a PFO is lower after PFO-closure than in patients without (Table 3) (39, 40).

d. Arguments against a causative role of PFO

Arguments against a contributing role of PFO in CS are: 1. the recurrence risk of stroke in patients with a history of CS and PFO is not increased com-

Table 3

Recurrence rates of CS in patients with or without PFO in various studies

Study	NOP	FUP	RR	RRY	RFR
No PFO					
Palomeras 2009 (6)	121	1y	2.8	2.8	NG
Mas 2001 (50)	581	4y	4.2	1.1	NG
PFO, no closure					
Mas 2001 (only PFO) (50)	581	4y	2.3	0.6	None
Mas 2001 (PFO + ASA) (50)	581	4y	15.2	3.8	Presence of PFO + ASA
Serena 2008 (45)	486	729d	5.8	2.9	None (neither PFO nor ASA)
Van de Wyngaert 2008 (95)#	66	100pat.y	16.6	11.1	NG
Nedelchev 2002 (20)	159	29m	13.4	5.5	Previous stroke
Ford 2009 (92)	150	6y	0.9-2.8	0.2	Increased PP, APC-resistance,
PFO, after closure					
Harrer 2006 (91)	41	10y	NG	2.1-2.9	Large shunts, pulmonary embolism, previous stroke, ASA no pedictor
Spies 2008 (15)*	423	18m	NG	1.8	NG
Spies 2008 (15)#	423	18m	NG	1.3	NG
Luermans 2008 (48)	83&	0.7-31y	1.2	NG	NG
Van de Wyngaert 2008 (95)#	66	3.73y	0	0	None
Ford 2009 (92)	352	6y	0.9-2.8	NG	Increased PP, APC-resistance, protein-S deficiency
Gasiavelis 2004 (96)	33	99m	6	0.7	NG

NOP: number of included patients, FUP: follow-up period, RR: recurrence rate in percent, RRY: recurrence rate per year in percent, RFR: risk factors for recurrence, NG: not given, PP: pulmonary pressure, *: patients >55y, #: patients <55y, & only 59% had a CS

pared to those without a PFO (41). 2. about one third of the patients with CS and PFO would not profit from closure of the PFO (14). 3. the lesion pattern on cerebral MRI is not at variance in patients with PFO and CS as compared to those with CS but without a PFO (42). 4. the risk of stroke is not increased in patients with a PFO alone or a PFO with ASA as compared to controls (29). 5. the combined presence of PFO and anti-phospholipid syndrome does not increase the risk of subsequent cerebrovascular events in patients with previous CS (43). 6. right-to-left shunt is no independent risk factor for stroke in patients with CS (22). 7. the prevalence of prothrombin mutations is higher in patients with a PFO as compared to stroke patients without a PFO (44). 8. neither PFO nor ASA are independent risk factors for recurrence of stroke in CS patients (45).

2. Atrial septal aneurysm (ASA)

The definition of ASA is under debate but most frequently it is defined as > 10mm excursion of the intra-atrial septum and affects ~2% of the general population (30, 46). An ASA can be detected in up to 50% of the cases with a PFO. ASA is independently associated with ischemic cerebral events possibly interacting with thrombophilia (20, 47,48), In some studies stroke recurrence is particularly increased if both PFO and ASA are present (Table 3) (49,50). Generally, the association between CS and ASA with PFO is independent of age (18). ASA is usually associated with a large PFO, prominent Eustachian valve, or prominent right atrial filamentous strands (51). In a study of 121 patients with CS, ASA was present in 24% of them (19).

3. Intermittent or paroxysmal AF (pAF)

AF is the most common cause of embolic stroke in industrialized countries (52,53). AF may be classified as permanent, intermittent or paroxysmal (pAF). pAF is assumed to play also a dominant role in the pathogenesis of CS. It is speculated that in a number of patients CS is due to intermittent or pAF (7). In a study of 121 CS patients pAF was recorded on standard ECG in 6.4% during a one-year follow-up (6). The longer and the more intensively it is searched for pAF, the more likely it is detected. If pAF cannot be detected by standard ECG, 24h-Holter, 48h-Holter, 7d-Holter, or telemetry, it may be detected

Table 4

Treament options for stroke prevention in patients with CS (30)

Abnormality	Treatment
PFO alone	APM
PFO + AF or SD	OAC
PFO + AF or SD but CI for OAC	PFO-closure
PFO and recurrent CS under OAC	PFO-closure
PFO + ASA	OAC
AF, pAF, atrial flutter	OAC
Aortic plaques	APM, statins, OAC if there is AF or SD
Arterial dissection (extracranial)	OAC for 3-6 months
Arterial dissection + recurrent CS	Stenting
Thrombophilia + thrombosis + CS	OAC
APLABS (only antibodies) + CS	APM
APLABS (clinical manifestations) + CS	OAC
Fabry	Enzyme replacement therapy

PFO: patent forame ovale, APM: antiplatelet medication, OAC: oral anticoagulation, AF: atrial fibrillation, APLABS: antiphospholipid antibody syndrome, SD: systolic dysfunction, CI: contra-indication

by an event recorder or by loop recording. pAF may be indirectly predicted by application of the STAF score. If the score exceeds a value of 5, pAF is quite likely (53). Items, which constitute the STAF score include age > 62y (2 points), NIHSS ≥1, atrial dilation (2 points), absence of intra- or extra-cranial atrial stenosis > 50%, or a clinical or radiological lacunar syndrome (3 points) (53).

4. Valvular heart disease

In a study of 702 patients with CS valvular abnormalities were the second most frequent echocardiographic abnormality, found in 15.8% of the cases (4). Aortic valve sclerosis was found in 9.4%, mitral prolapse syndrome in 2.1%, aortic valve strands in 0.9%, aortic valve stenosis in 0.7%, mitral valve strands in 0.7%, and mitral valve stenosis in 0.14% of the cases (4). More rare valve abnormalities associated with CS are listed in Table 1 (54). Valve thickening may be an indicator of an anti-phospholipid antibody syndrome (43).

B. Vascular causes

The most frequent types of vasculopathy associated with CS are atherosclerosis and arteriopathy from Fabry's disease. Atherosclerosis affects all sizes of arteries (small, medium-sized, large arteries) why the proximal cardiac arteries (e.g. complex plaques in the aortic arch), the extra-cranial arteries (e.g. vertebral artery origin stenosis), the intracranial arteries (e.g. middle cerebral artery stenosis), or the small intraparenchymatous arteries may be affected (55). Atherosclerosis is usually progressive resulting in narrowing of the luminar diameter, stenosis, occlusion, or mural thrombus formation with consecutive arterial embolism (56).

1. Atherosclerosis

Aortic plaques

Complex aortic plaques or complex atheroma (i.e. plaques with attached thrombus) upstream to the left subclavian artery or the right truncus brachiocephalicus constitute a frequent pathomechanism of CS (2). How often embolism from complex aortic plaques is responsible for CS is unknown but it is estimated that up to one fifth of the CSs are due to embolism from aortic plaques. Aortic plaques are frequently found in patients with CS > 60y (2). Among patients with embolic events, aortic atheromas are found in about one quarter of them (57). Aortic plaques can be visualized by TEE, CT- or MR-angiography, or multidirectional 3D-MRI (58). In a subgroup analysis of 40 patients with CS, plaques in the aortic arch were detected by CT-angiography in 20.5% of them (8). With 3D-MRI the aortic arch can be investigated with high accuracy and complex plaques can be most effectively visualized (58). 3D-MRI provides exact plaque localization and can be combined with multidirectional 3D-MRI velocity mapping (58). There

are some indications that the risk of stroke is increased only if the thickness of a plaque is > 4 mm (2, 59). In single cases, dissection of the aorta with a mural thrombus may lead to cerebral embolism (9, 55, 60). In a study of 26 patients with CS aortic dissection was detected on 3D-MRI in two of them and 6 others had plaques > 4mm (61).

Small- and medium-sized arteries

Frequently, atherosclerosis and stenosis of the medium- or small-sized intra-cerebral arteries remain unrecognized in CS. Meanwhile, however, previously undetected abnormalities may be detectable by high-resolution MRI. An argument for atherosclerosis to play a pathogenetic role in the development of CS is that moderate stenoses of the carotid artery are more frequently found in patients with CS than in patients with stroke of definite cause (2). Intracranial stenosis may be detected upon MR-angiography or by TCD.

2. Arteriopathy from Fabry's disease

Fabry's disease is an X-linked recessive lysosomal storage disease resulting from deficient alpha-galactosidase and leading to accumulation of glyco-sphingolipids and storage of the material in the vascular endothelium with consecutive micro- and macroangiopathy and enlargement of the arteries (62, 63). In a study of 721 patients with CS, mutations in the alpha-GAL gene were found in 4.9% of the male patients and in 2.4% of the female patients with CS (62). The disease manifested clinically in 1.2% of all patients and was more frequent in the vertebro-basilary artery system than in the anterior circulation (62). This explains why these patients had an increased frequency of dolichoectatic pathology of the basilary artery (62, 63). The figures about the prevalence of Fabry's disease in CS have been recently challenged.

C. Coagulopathies

In a small number of CS patients inherited or acquired hypercoagulability can be found if systematically looked for (64, 65). Generally, coagulopathies may be classified according to the preferentially affected vascular bed into venous or arterial hypercoagulability or according to the pathogenesis into hereditary or acquired forms.

Arterial hypercoagulability

The most frequent condition associated with arterial hypercoagulability is the antiphospholipid antibody syndrome (66). The antiphospholipid antibody syndrome is an acquired form of arterial and venous hypercoagulability associated with thrombocytopenia, livedo reticularis, and increased frequency of pregnancy-related complications, such as miscarriage, stillbirth, abortions. or preeclampsia. The syndrome is due to the production of autoimmune antibodies against phospholipids, cardiolipin, or beta-glycoprotein I. The condition is diagnosed upon the clinical presentation and the presence of antiphospholipid and anti-cardiolipin antibodies (67). More rare causes of arterial hypercoagulability with increased risk of cerebrovascular ischemic events, include the acquired hyperhomocysteinemia, the tissue factor polymorphism + 5466A> G (66), and high lipoprotein A (68).

Venous hypercoagulability

Inherited and acquired disorders with venous hypercoagulability are listed in Table 1 (65). Whether any of these hypercoagulabilities is indeed associated with CS is so far unknown. In a recent study of 167 patients with ischemic stroke, prothrombin and factor XIII polymorphisms were not associated with any thromboembolic event but the prevalence of the Leyden mutation was increased (64). A study of 89 patients with stroke and PFO showed that also altered fibrin clot structure and resistance to fibrinolysis are associated with CS (69).

Diagnostic work-up

Patients with CS need to undergo a number of investigations to eventually find the cause of CS. The most important of these investigations are TEE, long-term ECG recording, MR- or CT-angiography of the aorta, TCD, search for upstream venous thrombi by venous ultrasound, MR-angiography, or phlebography in case of a PFO, and blood investigations, including investigations for hypercoagulability (Table 2).

Transesophageal echocardiography (TEE)

TEE is indicated in CS patients if TTE is non-diagnostic (61, 70). TEE detects relevant abnormalities in about half of the young patients with CS (4, 71), although figures up to 100% have been reported (61). Relevant findings in patients with CS include PFO (22-29%) with spontaneous or provocable (Valsalva manoeuvre) right-to-left shunt after application of contrast medium or a bubble test (4), previously undetected valve disease (16%) (4), ASAs (1%), aortic plaques, regional myocardial dyskinesia, or

dilated left atrium (Table 1) (4). TEE may also reveal more rare sources of embolism as listed in Table 1. In a study of 231 consecutive CS patients TEE detected a major cardiac risk factor with indication for OAC in 16% of the cases (72). Some authors preferentially recommend TCD instead of TEE for PFO detection in patients with CS since the concordance of recognition is high and since TCD is more simple and non-invasive (23). Generally, TEE findings may change the treatment in about one third of the CS patients (61). In a retrospective study of 54 patients with CS TEE findings changed the management in 1 out of 3 patients (73). In a study of 100 patients with CS, however, TEE changed the management even in 90% of the patients with abnormal TEE and suggested PFO closure in 38 of them, surgery in three patients, and OAC in five patients (71).

Long-term ECG recording

Long-term ECG recording is strongly recommended in CS patients, particularly when they report palpitations, when the morphological stroke-pattern on MRI suggests an embolic cause (7), or when there is enlargement of the left atrium (STAF score). The longer the period, during which an ECG is recorded, the more likely a relevant rhythm abnormality may be detected. Long-term ECG recording may be particularly helpful to detect pAF. Long-term ECG recording can be carried out by 24h-, 48h-, 7d-Holter, mobile cardiac outpatient telemetry, event recorders (allow up to 30d ECG-monitoring), or loop-recorders (recording up to 2y) (2, 7, 74). 24- or 48h Holter monitoring detects new onset AF in 1-5% of the stroke patients (75, 76). If Holter-monitoring is extended to 7d, occult AF may be detected in up to 26% of the CS patients (77). The rate of newly-diagnosed pAF during inpatient cardiac monitoring by telemetry ranged between 4-8.4% (78). In a study of 56 patients with CS pAF could be detected in 23% by 21d mobile outpatient telemetry (74). In a study of 60 stroke patients 6.7% showed pAF upon event-recording during an average of 70h, of which one third went undetected by conventional ECG or ordinary Holter-monitoring (79). In a study of 36 patients with CS 20 patients were evaluated by means of a 30d-event recorder and in 20% of them pAF was recorded (7). In a study of 149 stroke patients new-generation event recorders detected pAF in 5.7% of them (80).

MR- or CT-angiography and FDG-PET

MR- or CT-angiography should be carried out in patients in whom complex aortic plaques or aortic dissection are suspected (60). Available techniques include multi-detector CT (52), high-resolution MRI, 3D-MRI, multidirectional 3D-MRI, or FDG-PET. In a study of 26 CS patients 3D-MRI identified aortic high risk pathologies in 8 patients. In two patients aortic dissection and in 6 cases plaques with a thickness of > 4 mm were found (61). Multi-directional 3D-MRI velocity mapping is a new method, which allows the demonstration of retrograde flow paths originating from complex plaques of the descending aorta resulting in a potential hemodynamic stroke mechanism (58). FDG-PET may be useful to detect plaques in the carotid artery (2). Noninvasive FDG-PET has a complementary value for the evaluation of atherosclerotic plaque composition and activity since lipid-rich plaques are more inflamed than calcified or collagen-rich plaques (81).

Detection of venous thrombosis

If there are indications of paradoxical embolism or deep venous thrombosis or thrombosis of the more proximal veins, search for venous thrombi by means of a Doppler ultrasound of the crural veins, MR-venography, or even phlebography needs to be carried out. One problem with determining the cause of CS is that mobile intracardiac or luminal thrombi may have disappeared at the time of the investigation (55).

Blood investigations

If venous thrombosis with paradoxical embolism or sinus venous thrombosis are suspected, determination of the D-dimer may be helpful. If Fabry's disease is suspected, the urine should be investigated for increased protein and for serum levels of alpha-galactosidase (62). If the alpha-galactosidase is reduced the GLA gene should be sequenced for point mutations or screened for deletions by MLPA. If an anti-phospholipid antibody syndrome is suspected the thrombocyte count, the lupus anticoagulant, and the anti-cardiolipin antibodies should be determined (43). Concerning the search for hypercoagulability, there is no consensus about the usefulness of such investigations. Since there is a lack of studies comparing OAC with anti-platelet therapy in patients with CS and thrombophilia, laboratory screening for thrombophilia remains of questionable value in CS patients (65). Other groups, however, recommend to individualize the decision on the therapeutic consequences and to screen for arterial and venous hypercoagulability (82).

Treatment

Drug treatment

OAC for secondary prevention of stroke is indicated if there is pAF (52), if the morphological stroke pattern suggests an embolic cause, or in case of intracardiac thrombus formation (83). If OAC is given in these indications it reduces the risk of recurrent stroke by 2-8% per year (3). Whether OAC is indicated for primary or secondary prevention of stroke in patients with a PFO is unsolved (10, 35, 84). Among 576 patients treated with acetyl-salicylic acid (ASS) or OAC the recurrence risk of cardioembolic events was similar in both groups (85). There was also no difference between the two treatments concerning the prevention of death or the rate of major bleedings (85). When comparing event rates between patients under ASS and under OAC there was no significant difference (21). In another study, however, the 2y rate of stroke recurrence or death was lower in patients receiving OAC than in patients receiving antiplatetelet medication (86). According to recent guidelines OAC is reasonable for high-risk patients only if they have other indications for OAC (30). In the majority of the cases antiplatelet treatment is reasonable to prevent a recurrent event (30). The best medical treatment of patients with CS or PFO plus ASA is OAC (10). Whether OAC is also superior to antiplatelet drugs in patients with antiphospholipid syndrome is under debate (65). There is no consensus on antiplatelet drugs vs. OAC for secondary stroke prevention according to a study of 519 patients with severe aortic plaques of whom 111 experienced an embolic event (87). Statins have been proven beneficial in complex aortic atheroma.

Patent foramen ovale closure

Though PFO-closure by percutaneous devices or open surgical repair suggests to be an alternative or additive to medical therapy with antiplatelet agents or OAC for secondary prevention of CS, it is under debate if a PFO in a CS patient should be closed at all or if such a patient should receive other treatment (10, 88, 89). According to recent guidelines PFO closure is indicated only in patients with recurrent CS caused by presumed paradoxical embolism through a PFO who have failed therapeutic dosages of OAC (24, 30, 89). Closure may be also considered if MRI suggests multiple or recurrent CSs or when the onset of CS is associated with elevation of right atrial pressure (30, 89). Further arguments for closure of a PFO are that in single cases OAC are contra-indicated (90) and that there are studies favouring closure when comparing outcome and recurrence rates of CS in patients with PFO treated with antiplatelet agents, OAC, or PFO closure (Table 3) (19,45). Arguments against PFO closure are that recurrence rates of CS between patients with and without PFO treated with warfarin or ASS did not differ (PICSS study) (86), that recurrence rates of CS were not different between the medically treated and the closure group (91), and that closure also carries a procedural risk and does not prevent recurrence of embolic events in each case (92). Before closure of a PFO in a patient with CS, however, other potential causes of CS, such as arterial or venous hypercoagulability have to be carefully ruled out not to expose the patient against a procedural risk without minimizing the risk of stroke recurrence (93).

Prognosis

There are only limited data concerning the prognosis of CS available. Most data about the prognosis of patients with CS have been collected during studies of patients after PFO-closure. Studies on this matter, however, are difficult to compare because of non-uniform inclusion criteria, for varying definitions of CS and TIA, because of variable age, selection bias, for absent blinded adjudication of events, for a prolonged period between index event and closure, and for insufficient account of medical treatment in patients undergoing closure in some studies (24). Generally, the prognosis of CS is dependent on the size of the stroke, the degree of disability resulting from CS, and the management of the underlying cause. Whether recurrence rates are different between CS patients with and without a PFO and if an ASA in CS patients with a PFO increases the risk of recurrence is under debate (24). Some studies showed that the risk of recurrence is increased in the presence of a PFO, whereas other studies found that an unclosed PFO does not increase the recurrence risk of stroke (Table 3). Recurrence of CS in patients without a PFO ranges between 1.1 and 2.8%. per year (Table 3) (6, 50). In a study of 943 patients being either on ASS or OAC the annual stroke rate was 1.98% (24). Some studies showed that the recurrence risk is significantly increased in the presence of an ASA (30, 50), whereas others did not confirm these results (Table 3) (40, 91). In CS patients with an untreated PFO recurrence rates of stroke range between 0.2 and 11.1% per year (Table 3). According to a number of studies (50,94) the risk of stroke recurrence in patients with a medically treated PFO increases with the time after the index event (10). CS patients with a closed PFO have a recurrence rate of 0-7.8% per year (Table 3) (94). Except for two studies the recurrence rate of CS is similar

in patients with untreated PFO and in patients with a closed PFO (Table 3). Whether the rate of recurrence or adverse outcome is different between CS and stroke of determined cause is unsolved. Some studies report a higher rate of recurrence in CS (1) whereas others show the opposite.

Conclusions

To determine the cause of CS at the moment, patients should, in addition to routine diagnostic work-up (carotid ultrasound, TTE, 24h-Holter-monitoring), undergo TEE to look for a PFO or other cardiac sources of embolism, long-term ECG recording to detect pAF or atrial flutter, CT- or MRI-angiography of the proximal aorta to detect aortic plaques with mural thrombi or aortic dissection, TCD to look for intracranial artery stenosis, imaging for venous thrombosis in case of paradoxical embolism, or blood chemical investigations or coagulation studies to look for arterial or venous coagulopathy, anti-phospholipid antibody syndrome, or Fabry's disease. To increase the accuracy of TTE and to lower the high inter-observer variability clear-cut criteria for the diagnosis of PFO and ASA have to be provided. Additionally, national and international neurological and rehabilitational societies are asked to clearly define CS, determine which tools routine and additional diagnostic work-up should include, at which point further diagnostic measures are indicated, and to recommend an algorithm for the diagnostic work-up of CS. To provide convincing evidence with regard to available and upcoming treatment options, more randomised, controlled studies are needed. In the upcoming years, new diagnostic tools may hopefully determine, which pathologies are definitively causally related to CS and well-designed therapeutic trials may provide evidence for the optimal management of these conditions.

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