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Cryptogenic stroke: too many suspects to find a culprit?

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A cerebral stroke is a heterogeneous entity and—in the context of this heterogeneity—a cryptogenic stroke, that is, of unknown origin at the time of diagnosis, finds a worthy position. Cryptogenic strokes are ∼25% of ischaemic strokes and in hindsight, they often appear to be of obvious or highly presumptive origin. Knowledge of the causes of a cerebral stroke that are not immediately evident is, therefore, fundamental for the purposes of correct secondary and, hopefully, primary prevention. Certainly, in fact, a cryptogenic stroke may require appropriate treatment, which is similar to a stroke whose origin is immediately evident. Equally certainly, however, cryptogenic stroke can benefit from specific treatments, which the lack of diagnosis of origin is destined to nullify. Therefore, it must unfortunately be accepted that a minority of cryptogenic strokes remain without a culprit and, therefore, without a specific corrective treatment. However, the insistent deepening of the diagnostic process in 'obscure' cases must also be pursued. Only the unyielding examination of these cases, in fact, is destined to identify a covert vasculitis, Fabry disease, occult atrial fibrillation, or one of the many pathologies, often far from rare, which require a therapy as specific as it is life-saving. In this brief review, therefore, we will try to fully expand on the identifiable causes of cryptogenic stroke.

Rationale

Stroke—whether ischaemic or haemorrhagic—represents a clear problem for public health, the affected individual, and their families.[1]

According to the Ministry of Health and data published by the Cardio-Cerebrovascular Alliance,[1] in Italy, stroke is second only to ischaemic heart disease as a cause of death, being responsible for ∼10% of all deaths.[1] Every year, in Italy, there are just under 100 000 hospitalizations for stroke, of which ∼20% are recurrences. A total of 20–30% of people affected by stroke die within a month of the event, 40–50% within the first year. Only 25% of patients who survive a stroke recover completely, while a good 75% survive, but with some form of disability. Of these survivors with disabilities, ∼50% are found to have a deficit so severe as to imply the loss of self-sufficiency.[1]

Cryptogenic stroke

A stroke is a heterogeneous entity. This is not only due to the morphology and size of the damaged area, which can be tiny or enormous, but also due to its origin. About 9 out of 10 strokes are ischaemic, while the remainder are haemorrhagic (*Figure 1*).[2,3,4] Among ischaemic strokes, almost a quarter—often originating from small vessels—are lacunar.[3,4] Among non-lacunar strokes, cardio-embolic stroke is extremely common, but above all—perhaps surprisingly—strokes of unknown origin (*Figure 1*).[3,4] Further complicating the picture, on the other hand, is the complexity of what lies behind the term cryptogenic, at least in the case of stroke. The term, as is known,

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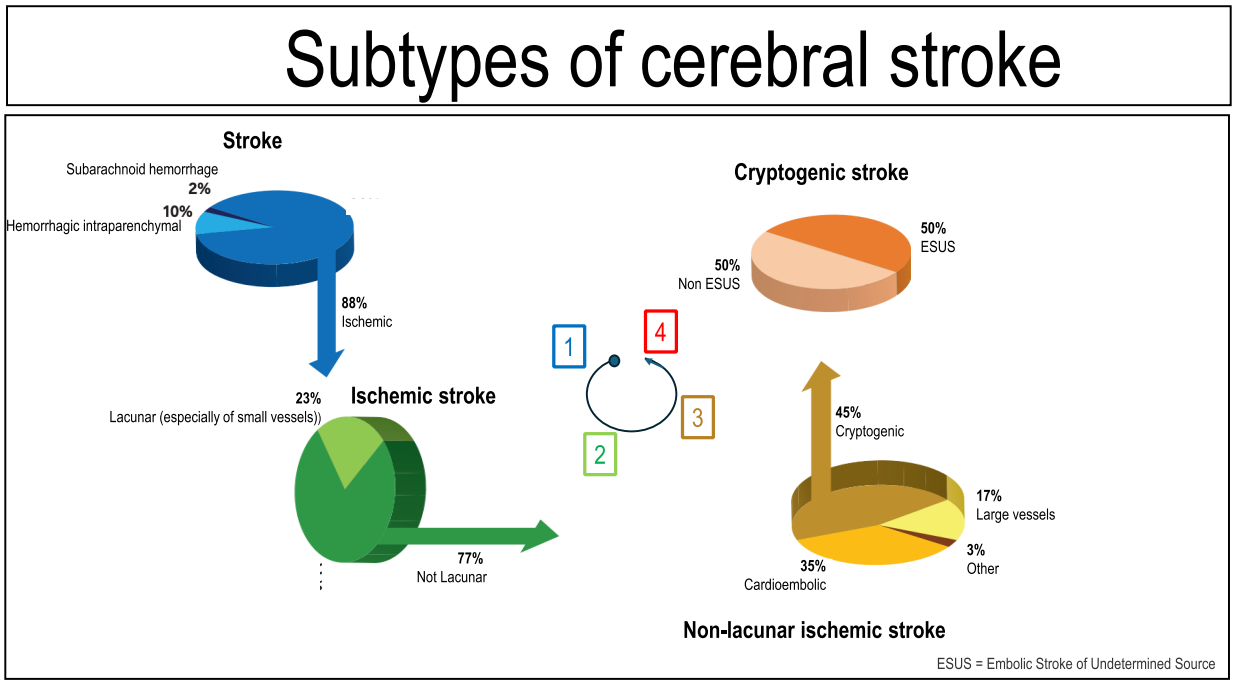

Figure 1 Subdivision of cerebral stroke. Modified from Kleindorfer DO, Towfighi A, Chaturvedi S, *et al*. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke. 2021;52:e364-e467.

comes from the fusion of kryptós (κρυπτός, 'hidden') with gĕnĕsis (γένεσις, creation, from which the adjective γενετικός) and indicates something whose origin is mysterious, but not secret and never traceable. Despite this, a cryptogenic stroke can have many suspects and, not infrequently, end with no culprit.

Starting from the definition, the American Heart Association and American Stroke Association Guidelines for the Prevention of Stroke in Patients After Stroke or TIA define cryptogenic stroke as a stroke confirmed and demonstrably of unknown origin after performing at least careful imaging, an echocardiogram, prolonged monitoring of cardiac rhythm and key laboratory tests, such as lipid profile and glycosylated haemoglobin.[4] The causes to be investigated, in particular, are listed below.

Patent foramen ovale

According to a European position statement,[5] patent foramen ovale is implicated in several human pathologies. Closure of patent foramen ovale may be followed by significant benefit in cryptogenic stroke.[6,7,8,9,10] Therefore, it seems extremely reasonable to investigate the possible presence of patent foramen ovale in every patient with cryptogenic stroke. In accordance with this, as already specified, it is estimated that about half of strokes of unknown origin are cardio-embolic, with a prevalence of patent foramen ovale of ~25%. This implies that 4% of cases—55% considering only those aged <60 years—of cryptogenic stroke actually originate from the formal patent foramen ovale and the consequent paradoxical thromboembolism (*Figure 2*).[11]

Occult atrial fibrillation

Atrial fibrillation is a well-known cause of cerebral stroke, even cryptogenic, when it is paroxysmal and occult.[12] In a consecutive series of 127 Italian patients affected by cryptogenic stroke of cardio-embolic origin, but with unknown nature of cardio-embolism at the time of diagnosis of stroke, 26% were affected by occult episodes of paroxysmal atrial fibrillation detected by the implantable loop recorder.[12] Cerebral infarcts were more often of relatively modest size and involved the posterior cerebral circulation and the cerebellum.[12] Predictive factors of occult atrial fibrillation as a cause of a cryptogenic stroke of cardio-embolic nature are advanced age, diabetes mellitus, left atrial dilation, obesity, elevation of NT-pro-BNP, or troponin T.[12]

Thrombophilia

A thrombophilic state—either congenital or acquired—is a not uncommon cause of cryptogenic stroke.[4] In a consecutive series of patients with cerebral stroke ($n = 196$, age 18-65 years), a previously unknown thrombophilic state was found in 85 cases (43%, 95% confidence interval = 36-51%). Among the 111 cases of cryptogenic stroke, 49 (44%) were affected by a thrombophilic state. The most common causes of thrombophilia were hyperhomocysteinaemia or mutation of methylenetetrahydrofolate-reductase or factor V. Even after excluding these patients, however, a thrombophilic state was still observable in 24% of 11 patients.[13] Therefore, the presence of a thrombophilic state must always be carefully sought after in a patient

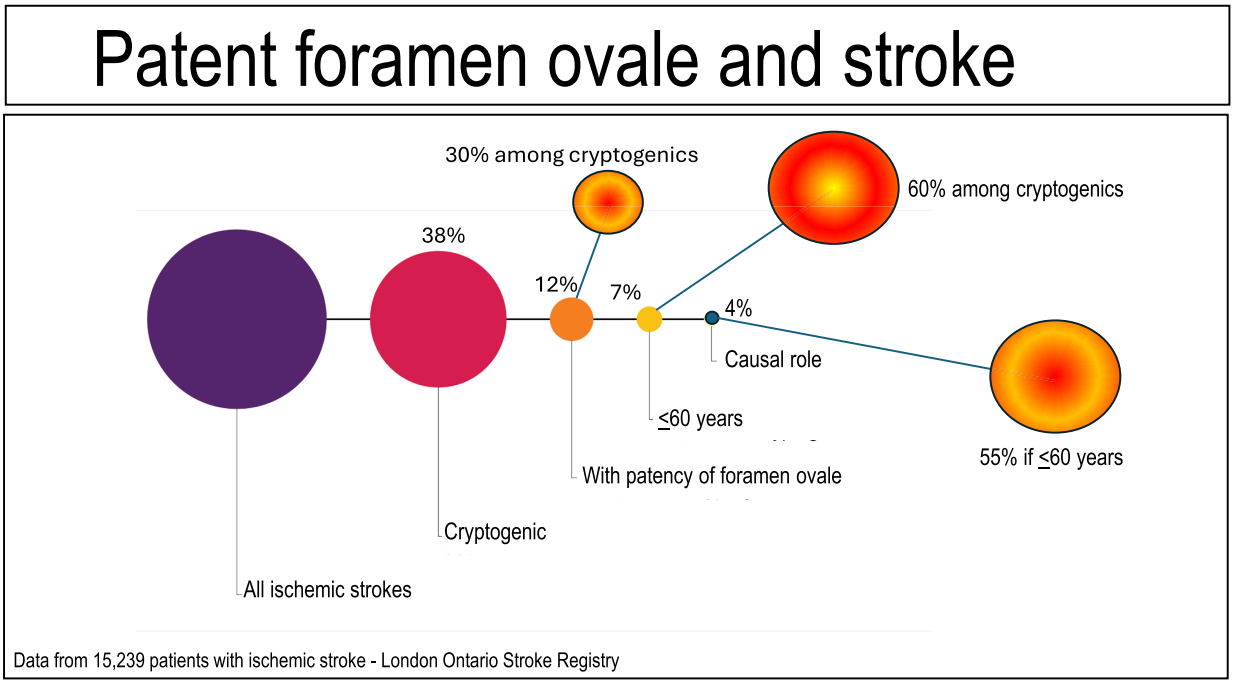

Figure 2 An occult patent foramen ovale is often the cause of cryptogenic stroke in young people or adults. Data from the London Ontario Stroke Registry. Modified from: Sposato LA, Albin CSW, Elkind MSV, Kamel H, Saver JL. Patent foramen ovale management for secondary stroke prevention: state of the art appraisal of current evidence. Stroke. 2024;55(1):236-247.

with cryptogenic stroke and never limited to the most common causes.

Aortic atheromasia

A cause—certainly minor epidemiologically speaking—of cryptogenic stroke can be found in the presence of atherosclerotic lesions of the aortic arch.[14] Obviously, it is difficult to separate patients with aortic atheromasia in whom the stroke—as well as other ischaemic lesions in other districts—was caused by a cardio-embolism of aortic origin and patients in whom the marked aortic atheromasia is an evident marker of more advanced vascular pathology, even multi-district.[14] Despite this, the observation of 934 patients (72 ± 9 years; 37% men) recruited in the Cardiovascular Abnormalities and Brain Lesion study allowed to detect aortic arch plaques in 645 participants (69.1%), which were of the large type (>4 mm) in 114 (12.2%). During a mean follow-up period of 11.3 ± 3.6 years, 236 patients (25.3%) experienced a cardiovascular event (n.76 patients = ischaemic stroke; n.27 patients = myocardial infarction; n.133 patients = death from cardiovascular causes). The presence of large plaques located at the level of the aortic arch was an independent risk factor for the abovementioned events (adjusted hazard ratio, 2.19; 95% confidence interval, 1.40-3.43), but not for stroke considered alone (adjusted hazard ratio, 1.09; 95% confidence interval, 0.50-2.38). The overall risk appeared paradoxically higher in patients receiving statins (adjusted hazard ratio, 2.57; 95% confidence interval, 1.52-4.37), but this was most likely simply a reflection of their higher baseline risk (higher body mass index, higher prevalence of hypertension, diabetes mellitus, and/or coronary heart disease) compared with those not receiving statins. Therefore, the aortic arch should always be visualized in patients with cryptogenic stroke, but how much this actually influences the final diagnostic 'refinement' and/or *ad hoc* therapeutic procedures remains to be determined.

Cardiac tumours

A cause—which it is not entirely appropriate to define as cryptogenic, since its identification, at least a posteriori, is generally not difficult—is linked to rare cardiac tumours. As is known, these tumours are more commonly benign—the most frequently described (50-80% of cases) is certainly the atrial myxoma—but they often end up being, at least in a certain sense, malignant in their clinical manifestations.[15] From 15% to about half of patients with cardiac tumours may have acute neurological symptoms, most often secondary to ischaemic stroke, but also to intracranial haemorrhages, major and/or minor epileptic episodes, and other forms of encephalopathy.[15] In general, benign 'non-myxoma' isolated cardiac tumours can be: fibromas (typical in paediatric age, mainly neonatal), rhabdomyomas (also typical in paediatric age, frequently combined with complex syndromes such as tuberous sclerosis, often characterized by spontaneous regression), haemangiomas, lipomas, teratomas, and papillary fibroelastomas of the aortic and mitral cardiac valves (but also observed in other cardiac districts); multifocal

myxomas. The rare malignant tumours are mainly sarcomas and lymphomas, as well as metastatic tumours (the heart is generally 'resistant' to metastases, but the literature and clinical practice are full of descriptions of cardiac metastases of lung tumours, breast tumours, etc.).

Arterial dissection

Dissection—or dissection—of the carotid or vertebral artery is a rare, but unfortunately well-known cause of cryptogenic stroke.[16] In the general population, dissection causes ischaemic stroke in no more than 2% of cases. However, if we limit our attention to younger patients (<50 years), this percentage can rise to 25%.[16] The average age at diagnosis is around 45 years and is generally slightly earlier among women, who, however, manifest this pathology less commonly than men.

The factors determining dissection are both congenital and, above all, acquired. Among the congenital diseases are: collagen diseases such as Ehlers–Danlos syndrome, fibromuscular dysplasia, Marfan syndrome, and osteogenesis imperfecta; extravascular anatomical variants such as Eagle syndrome (also called 'hypertrophic styloid process', commonly identified by a length of this process > 30 mm. The syndrome exists in two main forms: the classic form, due to the involvement of the nervous system, and the so-called stylo-carotid form, which also or predominantly involves the vascular system. Eagle syndrome classically presents with a sensation of a foreign body in the throat, dysphagia, unilateral neck-facial pain; all due to the involvement of cranial nerves V, VII, IX, and/or X. In addition, syncopal episodes and true ischaemic attacks—transient or not—may also be present due to involvement of the carotid arteries); or vascular anatomical variants such as vessel tortuosity or the subclavian steal syndrome (which can certainly be linked to dysembryogenesis, to atherosclerotic disease or overt vasculitis, such as Takayasu's disease; but in which the 'conflict' between the clavicle and the first rib is often a significant cause or contributory cause of compression of the subclavian artery and, therefore, of the consequent reduction in flow, with symptomatic haemorrhage affecting the vertebral district).

Not infrequently, a recent infection can be described with an accurate anamnesis of the patient. This is true not only for the onset of inflammatory phenomena at the vascular level, but also because the infection can be combined with retching or coughing fits, which can acutely disturb the cerebral flow.

A positive history of minor trauma is decidedly common, especially in the case of vertebral dissections.[16] In this area, are anecdotal reports of multiple cases of dissections resulting from common 'whiplash' and sports injuries, up to the rarer forms resulting from both rapid and prolonged extensions of the neck, such as can occur during physiotherapy practices, chiropractic sessions, oesophago-gastroscopies, prolonged procedures on the dentist's chair, equally prolonged painting of a ceiling. Among the causes that have even interested the lay press, but which cannot fail to interest the astute clinician, there is the positive anamnesis for completely peculiar traumas, such as those linked to playful moments spent on a roller coaster or at the hairdresser (while washing the head with the neck hyperextended).

Non-cardiac neoplasia

Neoplasia are characterized—as is unfortunately well known—by a thrombophilic state, and stroke can, therefore, be one of the preventable consequences.[17] Roughly speaking, 15% of patients with ischaemic stroke have a known or unknown tumour, while 40% have a clear acquired thrombophilic state resulting from the tumour.[17] Among patients with stroke, but without a known diagnosis of neoplasia, a tumour form can be found in 2.1% to 4.3% of cases, much more commonly cardio-embolic of unknown origin.[17] This is a clear demonstration of how the patient affected by neoplasia should be carefully receive anti-aggregant and/or anticoagulant treatment—especially in the presence of conditions that further aggravate the thrombotic risk, but also that in the absence of more evident and certain causes of ischaemia; the presence of an occult neoplasm should be carefully excluded. This is true not only before

Table 1 Major causes of vasculitis with neurologic involvement and possible ischaemic stroke

Large-vessel arteritis
Takayasu arteritis
Giant cell arteritis (also known as 'Horton' or 'temporal')
Hughes-Stovin syndrome (variant of Behçet's disease)
Intermediate-vessel arteritis
Polyarteritis nodosa
Kawasaki disease
Eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss syndrome)
Granulomatosis with polyangiitis (also known as Wegener's granulomatosis)
Small-vessel arteritis
Immunoglobulin A deposition vasculitis (formerly known as Henoch-Schönlein purpura)
Microscopic polyangiitis (also called microscopic polyarteritis)
Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) Wegener
Eosinophilic granulomatosis with polyangiitis (formerly referred to as Churg-Strauss syndrome)
Arteritis with varying manifestations in terms of the size of the constricted arteries
Cogan syndrome (a very rare form of interstitial keratitis associated with audio-vestibular involvement with progressive hearing loss up to complete deafness within the first 2 years of life)
Behçet's disease
Arteritis associated with systemic diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren's syndrome
Antiphospholipid antibody syndrome
Scleroderma
Other forms
Resulting from infections
Resulting from drugs and narcotics
Paraneoplastic
Actin
Anderson Fabry disease

antitumour treatment but also after it. It is well known, in fact, how different, modern biological therapies can favour the appearance and/or increase the progression of vascular damage, with localization that can be coronary, peripheral, or cerebral.[18]

Inflammatory pathologies involving large, medium, and small vessels

All forms of vasculitis can cause organ ischaemia. As is known, vasculitis that can cause strokes can have an infectious or neoplastic origin, but above all, they are immune-mediated.[19] Very rare, but at the same time, well known for its exclusive neurological localization, is primary angiitis of the central nervous system, a rare form of primary vasculitis, with an incidence that does not appear to exceed 2–3 cases per million people per year. This vasculitis—which can also be of paediatric relevance—affects the medium and small calibre vessels of both the brain and the spinal cord and can result in ischaemic stroke in 6–7 cases out of 10 affected patients. In addition to this pathology, which in its primary form with exclusive neurological localization, is known by the term PACNS (primary angiitis of the central nervous system), other forms of vasculitis can cause ischaemic stroke (*Table 1*).

Conclusions

Cryptogenic stroke is far from rare and must be diagnosed, without hiding behind diagnoses that may seem easier and more credible because they are more common. In this perspective, if on the one hand it is desirable that the prevention of cryptogenic stroke is of a primary type, it appears to be mandatory that we do not resign ourselves to the absence of a diagnosis and that we always try to investigate more deeply and identify the origin that lies behind the term cryptogenic or cryptogenetic.

Only in this way, in fact, will it be possible to obtain the effective reduction of this type of neurological disease, which frequently affects—with even disabling outcomes—the younger population.

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Disclaimer

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