Correlations Between Atherosclerosis and Stroke –Can We Predict It?

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Abstract

Although, atherosclerosis is a risk factor for stroke, there are many questions about this relationship. Stroke remains the major cause of disability and death, and atherosclerosis is responsible for 15-20 % of strokes. Moreover, atherosclerosis is not likely to play a direct role in cardioembolic infarction, intracerebral and subarachnoid hemorrhage. This study aimed to elucidate how the presence of carotid atherosclerosis influenced the occurance of stroke and also how it interacted with other risk factors for stroke. Is it possible to make predicttions about it?

Keywords: atherosclerosis, plaque, stenosis, stroke, prediction of, reccurence

INTRODUCTION

Atherosclerosis is a progressive disease, characterised by hardening walls of arteries (intimale plaques with a soft part (athere) and a hard one (sclerosis) and it is a systemic inflammatory disease [1]. Atherosclerosis is not a new issue, Sandison, a paleontologist of XX century found evidence of athrosclerosis in egyptien mummies. Another paleontologist found that atherosclerosis of ancient egyptiens had the same evolution as in our days. In XVII century, the degeneration of aorta and main arteries was known but the physiopathology of the process was unknown. In 1815 Hodgson, who was a surgeon, published an important vascular monography, and he sustained the inflammation as the main cause of atherosclerosis. In the late XIX century, the inflammatory theory of atherosclerosis was abandoned and a new conception arised (THE DEGENERATION THEORY). The modern era of atherosclerosis has begun in 1908 when the Russian scientist Ignatovski induced atherosclerosis in rabitts with a diet based on milk and egg yolks. In the late XX century, the interes about atherosclerosis had a major impact due to burden of cardiovascular disease. The cardiovascular disease remains

the leader of our diseases and death causes. [2] Atherosclerosis and its complications are the major cause of death and disability due to myocardial infarction and stroke, so around 35-40 % of causes of death in the world are produced by atherosclerosis.

VASCULARIZATION

This includes the anterior cervical arterial system i.e. the common carotid artery (CCA) its related branches (internal and external) and pathologies, in addition to the previously considered posterior circulation, i.e. the vertebrobasilar arterial system (VBA).

Internal Carotid Artery

Knowledge of the anterior system is important because:

1. The internal carotid artery (ICA) provides the most significant proportion of blood to the brain.
2. Pathological changes of the ICA leading to stenosis are very common.
3. Blood flow in the ICA is known to be influenced by movement of the neck.
4. The ICA is commonly implicated in ischaemic stroke

The two ICA's carry around 80% of the blood flow to the brain compared to the 20% via the posterior system. It is primarily increased flow through the ICA and the presence of an intact circle of Willis, which helps maintain brain perfusion in the presence of vascular compromise in other parts of the system (i.e. vertebral arteries).

External Carotid Artery (ECA)

The ECA is a major artery of the cranio-cervical region. It arises from the common carotid artery at a bifurcation point around the C3 level (upper thyroid cartilage). It eventually forms the occipital artery and terminates in the maxillary artery and superficial temporal artery. THE ROLE of the external carotid artery in the pathogenesis of some intracranial ischemic events has been reported. The external carotid artery does not contribute to cerebroretinal perfusion, but when the homolateral internal carotid is obstructed, collateral supply from the external carotid may become important. In this situation, pathological changes in the external carotid artery may have ischemic consequences in the cerebrum or retina through embolic or hemodynamic mechanisms. [3]

GENERAL VIEW

Stroke incidence is declining in many developed country, largely as a result of better control of high blood pression, and the increased education of the patients worldwide. [4]. Despite all of this, Stroke remains the third cause of death in USA and Europe and the leading cause of disability.

In 2012, Stroke was second cause of death in Romania, after ischemic heart disease (17.8% of all deaths), and this situation is the same since 2000. [5] Strokes are two major types – haemorage (cerebral haemorhage and subarahnoidian haemorhage (15 %) and ischaemia (85 %). [6)]

- large artery atherosclerosis

- cardioembolism

- small artery disease

- other determined etiologies

- undetermined etiology

Atherosclerosis of major cervical arteries is an established risk factor of ischemic stroke. On the other hand, ischemic stroke patient has a higher likelihood of having carotid atherosclerosis and stenosis. Ischemic strokes occurring in the anterior circulation are the most common of all ischemic strokes, accounting for approximately 70% of all cases. They are caused most commonly by occlusion of one of the major intracranial arteries or of the small single perforator (penetrator) arteries. [7]

Stroke is a heterogeneous disease that comprises several subtypes with different etiologies. Because atherosclerosis is a precursor of atherothrombotic infarction (AI), carotid atherosclerosis is a reasonable risk factor for this stroke subtype. This rationale is reinforced by an association between carotid and major cerebral artery atherosclerosis.

There are two types of ischemic stroke caused by blood clots, narrowing of blood vessels to the brain caused by atherosclerosis or other particles. The first type is called atherothrombotic stroke is the most common stroke. It occurs when a blood clot forms on an atherosclerotic plaque within a blood vessel in the brain and blocks blood flow to that part of the brain.

The second type is called cerebral embolism occurs when a wandering clot or some other particle, called an embolus, is carried by the bloodstream until it lodges in an artery leading to or in the brain and blocks the flow of blood. The embolism could be due to a piece of clot or plaque that broke off from an atherosclerotic plaque. However, most embolic strokes are due to blood clots that form in persons with atrial fibrillation and enter the bloodstream. [8]

Lacunar infarction (LI) is most often the result of lipohyalinosis, fibrinoid necrosis, or microatheroma in intracerebral small arteries, diluting the significance of carotid atherosclerosis for this stroke subtype. Moreover, atherosclerosis is not likely to play a direct role in cardioembolic infarction (CE), intracerebral hemorrhage, and subarachnoid hemorrhage. Nevertheless, associations between carotid atherosclerosis and the specific stroke subtypes have not been established. [9]

Stroke and computer tomography exam:

Atherothrombotic Infarction was defined as infarction presumably due to intracranial major artery occlusion with MRI evidence of a large infarction (15 mm) in areas such as the cortex, semioval center, or watershed area.

Lacunar stroke is the stroke when the patient had to have an CT scan after the events that demonstrated a small (<15 mm) deep infarction in the territories supplied by the perforating branches of major cerebral arteries

RISK FACTORS

In many respects stroke is a preventable disorder. Prevention is the target of a variety of programs to reduce risk factors for stroke. The aim of primary prevention is to reduce the risk of stroke in asymptomatic people. Hypertension, carotid artery stenosis, atrial fibrillation and certain other cardiac conditions, cigarette smoking, diabetes mellitus, dislypidemia, sickle cell disease, poor diet, physical inactivity, and obesity are well-established risk factors for ischemic stroke. Less well-established risk factors include alcohol and drug abuse, the metabolic syndrome, oral contraceptive use, sleep-disordered breathing, migraine, hyperhomocysteinemia, elevated lipoprotein(a), elevated lipoprotein-associated phospholipase, inflammation, infection, and hypercoagulability. The greatest stroke risk, however, occurs in those with previous transient ischemic attack or previous stroke.

For these patients, risk factor reduction for secondary prevention is essential. Secondary vascular risk has been shown to decrease with treatment of hypertension, hyperlipidemia, and the institution of antiplatelet drug treatment, or surgery, if necessary (endarterectomy or stenting) [10]

Globally, hypertension is the most significant risk factor for stroke, both ischemic and hemorrhagic. Elevation in blood pressure plays a big role in the development of vascular disease, including coronary heart disease, ventricular failure, atherosclerosis of the aorta, and cerebral arteries, as well as small vessel occlusion. Treating blood pressure considerably reduces coronary and stroke risk.

Risk Factors of Atherosclerosis [11]:

- High blood cholesterol

- High blood pressure

- Smoking

- Diabetes

- Obesity

- Physical inactivity

GENDER

It is well-documented that the incidence of stroke is higher in men than in women in all age classes, and women are, on average, several years older than men when they suffer their first stroke. The prevalence of stroke is higher among men up to the age of approximately 80 years, after which it becomes higher in women. A majority of studies indicate that the case-fatality rate is higher in female than in male stroke patients; there is also some evidence, relatively weak, indicating a better functional outcome in men.

AGE

The chance of having a stroke approximately doubles for each decade of life after age 55. While stroke is common among the elderly, a lot of people under 65 also have strokes. Nearly three-quarters of all strokes occur in people over the age of 65. The risk of having a stroke more than doubles each decade after the age of 55. Strokes can and do occur at ANY age. Nearly one fourth of strokes occur in people under the age of 65.

Ultrasound in ischemic stroke [12]

Carotid stenosis is usually diagnosed by color flowduplex ultrasound scan of the carotid arteries in the neck. This involves no radiation, no needles and no contrast agents that may cause allergic reactions. This test has moderate sensitivity and specificity, and yields many false-positive results.

Typically duplex ultrasound scan is the only investigation required for decision making in carotid stenosis as it is widely available and rapidly performed. However, further imaging can be required if the stenosis is not near the bifurcation of the carotid artery.

One of several different imaging modalities, such as angiogram, computed tomographyangiogram (CTA) or magnetic resonance imaging angiogram (MRA) may be useful. Each imaging modality has its advantages and disadvantages. Magnetic resonance angiography and CT angiography with contrast is contraindicated in patients with renal insufficiency, catheter angiography has a 0.5% to 1.0% risk of stroke, MI, arterial injury or retoperitoneal bleeding. The investigation chosen will depend on the clinical question and the imaging expertise, experience and equipment available. [13]

Screening for carotid stenosis? NO!

The U.S. Preventive Services Task Force (USPSTF) recommends against screening for carotid artery stenosis in those without symptoms

Ultrasound is widely, available, non invasive method having numerous advantages: bedside use, low cost, fast and repeatability. Development of ultrasound technology has allowed for a noninvasive evaluation of atherosclerosis in the

carotid arteries. The initial manifestation is characterized by a subtle increase in vascular intima-media thickness (IMT), whose progression leads to plaque formation and vascular narrowing. Because advanced carotid stenosis often impairs cerebral blood flow and becomes the nest for emboli, carotid ultrasound examination is most often performed for the diagnosis and risk assessment of stroke. With the use of ultrasound, studies have shown that carotid stenosis 70% increases the incidence of future stroke, whereas the risk is limited when the stenosis is 60%. Thus, carotid stenosis, as the result of advanced atherosclerosis, is a well-defined risk factor for stroke. In addition to such advanced lesions, earlier carotid atherosclerosis, without direct threat to the brain, has been linked to an elevated risk for stroke. The linkage is supported by an association between carotid and systemic atherosclerosis. [9]

Carotid ultrasound can provide the following information:

1.　IMT (intima-media thickness) - prospective studies have demonstrates that pathological IMT vales result in a high risk of myocardial infarction and stroke, so this is a marker of future vascular events as a reflector of systemic atherosclerosis, increased carotid artery IMT has been associated with a higher risk for stroke. In the Rotterdam Study and the Cardiovascular Health Study, 7 each 1 SD change in IMT increased the incidence of future stroke by approximately 30%, independent of traditional cardiovascular risk factors.
2.　plaques – location, size, number, surface, echogenicity – plaques with irregular surface and /or soft plaques present a higher embolic risk. Existence of carotid artery plaques was associated with transient ischemic attack (TIA), and the enlargement increased the risk for future neurological events. Plaque is dangerous not only because of its stenotic effects, but also because it may rupture or dissect at the atherosclerotic wall, showering debris into the bloodstream, leading to multiple embolic cerebral infarcts downstream of the plaque. The ruptured, ulcerated plaque can also be a source of thrombus formation in that the anticoagulant properties of the endothelial surface are locally disrupted.
3.　carotid stenoses and occlusions

Carotid stenosis is common especially in patients with vascular risk factors or with coexistent pathology of coronary or peripheral arteries. Since many decades the classification between symptomatic (that lead to a stroke) and asymptomatic carotid stenosis (not associate with stroke) has dominated the management of affected patients. This distinction corresponds to the design and results of previous clinical trials on surgical versus medical treatment.

Severe stenosis caused by plaques alters blood flow characteristic and turbulence replaces laminar flow when the degree of stenosis exceeds about 70 %. The most common sites for symptomatic atherosclerosis are the bifurcations of common carotid arteries followed in frequency by aortic arch, the proximal subclavian arteries and the vertebral origin.

Carotid bifurcation is susceptible to develop atherosclerotic lesions and stenosis, and the stenosis could be estimated by morphological, hemodynamic assessment or both (duplex technique). Most studies consider carotid stenosis of 60 % or greater to be clinically important.

The following stenosis criteria are respected: [14]

<50% stenoses –peak systolic velocity <125cm/sec, ICA /CCA<2.0)

50-69% stenoses –peak systolic velocity :125-130 cm /s, ICA/cca 2.0-4.0)

>70% stenoses-peak systolic velocity >230cm/sec, ICA/CCA>4.0)

The risk of ischemic stroke distal to an atherothrombotic carotid stenoses increases proportionately to the severity of carotid stenosis [15]

Carotid stenosis >70% increase the incidence of future stroke, whereas the risk is limited when stenosis is <60% [16]

In the European Trial of symptomatic patients undergoing surgery, the investigators took the opportunity to examine the risks of stroke in the opposite carotid artery, that was not causing symptoms. In this study, 2,295 patients were followed

for 4.5 years. In patients with the most severe narrowing, only 5.7% (5-6 in every 100) of patients suffered a stroke over 3 years. There were only 9 fatal strokes in 2,295 patients over 3 years.

The seemingly clinical stable symptomatic 50–99% carotid stenosis patients without additional ipsilateral events have a high risk of recurrent stroke. [17]

OCCLUSION OF THE INTERNAL CAROTID artery has aroused clinical interest as a result of the appreciation of the poor correlation which has been demonstrated to exist between the angiographic find ings and the associated neurological symptoms. The number of patients with significant strokes after the occlusion of an internal carotid artery are less impressive than initially suspected, with only 27% having severe complicated strokes and 73% being asymptomatic or experiencing only transient or mild focal neurological disorders. Occlusion of the internal carotid artery may, however, be associated with transient or fixed neurological symptoms after the occurrence of the occlusion, and the evidence strongly suggests that such symptoms are frequently related to embolic disease originating from the external carotid artery or the proximal blind stump of the internal carotid artery. This concept is in direct conflict with the opinion of Gomensoro et al. that "when a lesion progressed to complete thrombosis, there was no long er any possibility for emboli to pass into the distal circulation." [18] In the current era of intensive medical therapy, carotid artery disease rarely progresses to occlusion and, when it does, patients' risk of ipsilateral stroke is very low, according to an observational study published online September 21, 2015, ahead of print in *JAMA Neurology*.

Common carotid artery (CCA) occlusion is a rare cause of cerebrovascular events. The prevalence is approximately 0.24–5% in stroke patients.

In contrast to the large amount of data in the literature about internal carotid artery occlusion, there is little information regarding the incidence, clinical presentation, ultrasound findings, haemodynamics, causes, and treatment of common carotid artery occlusion (CCAO).

CCA occlusion is generally associated with occlusion of the distal vessels (internal carotid artery (ICAs) and external carotid artery (ECA)). In some cases, blood flow in the ICA and ECA is maintained by collateral circulation via extracranial branches through the retrograde external carotid artery. [19]

ATHEROSCLEROTIC PLAQUES CLASSIFICATION

Atherosclerotic plaques are characterised by intimal thickening from the progressive accumulation of lipids, together with cellular and molecular components such as smooth cells, lipid filled macrophages, monocites, T and B lymphocytes, erythrocytes and platelets [1]

Histologic studies of human vessels provided by AHA committee on vascular lesions to divide plaques into 6 stages I to VI, based of plaque composition and morphology.

Gray –Weale classification (1988) combined the two aspects of echogenity and omogenity, and there are described 4 types of plaques: [20]

-type 1 –hipoechogenous plaque with intact fibrous cap

-type 2 –mixed type but more hipoechogenous (less than 25 % of hiperechogenity)

-type 3 –mixed type but more hyperechogenous (less than 25 % of hipoechogenity)

-type 4 –hyperechogenous plaque

Usualy, both for symptomatic and asymptomatic patients, the hipoechogeneous plaques seems to be more instable as the hiperechogenous type [20]

Calcification is absent in the normal vessel wall and is one of the process involved in the development of atherosclerosis [1]

Inflamation is a key element of atherosclerotic plaque vulnerability. Fibrous plaque cap inflammation is more likely to occur in non-calcified plaques. Calcifications plaque is a mark of stability. Symptomatic plaques are more inflamed and less calcified than asymptomatic ones. Quantifying plaques morphology and potential thromboembolic danger are markers of severity of atherosclerosis other than the stenosis measurements. [21]

Duplex Ultrasonography to Evaluate Asymptomatic Patients with Known or Suspected Carotid Stenosis [22]

Class I 1. In asymptomatic patients with known or suspected carotid stenosis, duplex ultrasonography, performed by a qualified technologist in a certified laboratory, is recommended as the initial test to detect hemodynamically significant carotid stenosis. (Level of Evidence: C) Class IIa 1. It is reasonable to • perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. (Level of Evidence: C) • repeat duplex ultrasonography annually, by a qualified technologist in a certified laboratory, to assess progression or regression of disease and response to therapy in patients with previous atherosclerotic stenosis greater than 50%. Once stability is established over an extended period or candidacy for intervention has changed, longer intervals or termination of surveillance may be appropriate. (Level of Evidence: C) 9 Class IIb 1. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered • in asymptomatic patients with symptomatic peripheral arterial disease, coronary artery disease or atherosclerotic aortic aneurysm. (Level of Evidence: C) • to detect carotid stenosis in asymptomatic patients without evidence of atherosclerosis who have greater than or equal to 2 of the following: hypertension, hyperlipidemia, tobacco smoking, or family history of atherosclerosis before age 60 in a first degree relative or ischemic stroke. (Level of Evidence: C) It is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (Level of Evidence: C) 10 Class III: 1. Carotid duplex ultrasonography is not recommended No Benefit • for routine screening of asymptomatic patients who have no risk factors for atherosclerosis. (Level of Evidence: C) • for routine evaluation of patients with neurological or psychiatric disorders unrelated to focal cerebral ischemia. (Level of Evidence: C) • for patients without risk factors for atherosclerotic carotid disease and no disease on initial vascular testing. (Level of Evidence: C)

CONCLUSIONS

Although several large randomized trials tried to establish a direct relationship between atherosclerosis and stroke, we do not have all the answers regarding this connection. Atherosclerosis and stroke remain the enemies of our century; future studies are needed to clarify aspects of these disorders.

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