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Vulnerable carotid plaque - Vulnerable patient

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Liapis CD

ABSTRACT

Carotid artery plaques are one of the main causes of cerebrovascular events. Several imaging techniques have been used to identify the high-risk plaque, among which ultrasound is the most widely available. It is increasingly recognized that echolucent and heterogeneous carotid plaques on ultrasound in patients with high-grade carotid stenosis are associated with an increased risk for stroke. The expression of several local and systemic factors may influence plaque stability. Additionally, established and emerging risk factors are associated with a higher risk of stroke. It is also relevant that the carotid plaque may mirror clinically relevant atherosclerosis elsewhere in the vascular bed. We need to consider all these factors to assess the overall risk of the patient with an unstable carotid plaque and ultimately identify the "vulnerable plaque" in the "vulnerable patient". This will help patient surveillance and evaluation of the aggressive medical treatment in high-risk patients. Identifying the unstable carotid plaque in high-risk patients will also improve selection criteria for vascular intervention (surgery/angioplasty) and increase cost-effectiveness.

Key words: *instable carotid plaque, high-risk patients.*

INTRODUCTION

I am very grateful to the Young Vascular Surgeons in Training for electing me as an Honorary Member of their Association, following on from the election last year of Hans O Myhre, first President of ESVS (European Society for Vascular Surgery). I have been involved in training for many years and this recognition by the European Vascular Surgeons in Training is indeed rewarding, although I have to say there are many European vascular surgeons who deserve this much more than I do. The title of my lecture: Vulnerable Carotid Plaque - Vulnerable Patient has been the focal point of my research together with collaborators to whom I am extremely grateful.

President of the European Society for Vascular Surgery

Stroke is a major cause of morbidity and mortality worldwide, with considerable clinical, social and economic implications. Internal carotid artery stenosis is one of the main causes of focal cerebral ischaemia.

WHAT IS THE VULNERABLE CAROTID PLAQUE?

The high-risk carotid plaque is characterized by advanced histological lesions with a large lipid core, a thin fibrous cap and often ulceration, lumen thrombosis and intraplaque haemorrhage[1]. A large number of abundant inflammatory cells, mostly macrophages and T cells, are usually detected in the cap of unstable plaques with smaller number of smooth muscle cells and less collagen than stable plaques. The likelihood of plaque rupture is a balance between the tensile strength of the plaque and the stress exerted on it.

What causes a silent atherosclerotic lesion to rupture? Activated macrophages, T cells and mast cells produce several types of molecules -inflammatory cytokines, proteases, coagulation factors, radicals and vasoactive molecules- that can destabilize lesions; two types of proteases seem to play a key role in plaque activation: matrix metalloproteinases (MMPs) and cysteine proteases. All these molecules inhibit the formation of stable fibrous cap, attack collagen in the cap and initiate thrombus formation. These reactions can conceivably induce the activation and rupture of plaque, thrombosis and ischaemia[2].

It has been shown that accumulation of macrophages, T cells and mast cells in the fibrous cap was correlated with plaque ulceration, lumen thrombosis, emboli frequency as detected by Transcranial Doppler (TCD) and cortical symptoms in the carotid circulation.

HOW CAN WE CURRENTLY IDENTIFY THE VULNERABLE PLAQUE?

Several imaging methods, in addition to ultrasound, have been used to identify the high-risk carotid plaque; all have their limitations.

Digital subtraction angiography (DSA) is considered as the "gold standard" for the evaluation of the morphology of the carotid artery lumen. A strong association between histology and carotid angiographic plaque surface morphology has been demonstrated; surface morphology (ulceration and irregularity) predicted not only stroke but also acute coronary events. Furthermore, ulceration or irregularity was associated with the presence of cap rupture, intraplaque haemorrhage, large lipid core, reduced fibrous tissue and plaque instability. However, DSA is not suitable to assess plaque texture. DSA is an invasive procedure that requires a contrast medium and ionising radiation. Furthermore, it is more expensive than ultrasound and carries a small risk of stroke, renal failure and allergic reactions.

Magnetic resonance angiography (MRA) demonstrates the physiology of blood flow with high sensitivity. Contrast enhanced MRA is much faster and accurate than conventional MRA. Multi-sequence, high-resolution MR imaging can accurately quantify the relative thickness of fibrous cap and lipid core. Multicontrast MR imaging can distinguish advanced lesions from early and intermediate atherosclerotic plaque and can detect intraplaque haemorrhage, ulceration, calcification and thrombosis. However, MRA remains an expensive method that is not widely available. Several meta-analyses compared the diagnostic value of ultrasound and MRA with DSA for the diagnosis of carotid stenosis. Overall MRA had a pooled sensitivity of 95% and a specificity of 90% in detecting severe stenosis (70-99%). The corresponding numbers for ultrasound were 86% and 87% respectively.

Helical computed tomographic angiography provides useful information on the degree and extent of carotid stenosis, as well as the presence of atherosclerotic plaques and their composition. However, it uses ionising radiation and is not widely available.

Other techniques have also been developed, such as xenon-blood-flow, positron emission tomography (PET), acetazolamide-enhanced single photon emission computed tomography (SPECT), TCD. These methods can assess cerebral blood flow. PET scanning can also assess metabolism and brain function. Other imaging techniques, such as intravascular thermography, optical coherence tomography and elastography have been used to detect atherosclerotic lesion composition. These techniques are expensive and not widely available.

High-resolution duplex ultrasound scanning is the most widely available investigative tool. It is a non-invasive, safe, real-time, reproducible and relatively inexpensive modality that facilitates the study of the lumen and atherosclerotic plaque, both morphologically and haemodynamically.

Ultrasound facilitates the accurate measurement of the degree of carotid stenosis and the classification of the plaque to different types according to its echodensity. Several visual plaque classifications have been proposed; the most widely used consists of five types from completely

echolucent (type 1) to uniformly echogenic (type 4) and calcified plaques with acoustic shadow (type 5). Furthermore, computer-guided assessment of the overall brightness of the plaque was used to quantitate echodensity more objectively. This includes the measurement of the median of the frequency distribution of grey values of the pixels within the plaque [grey scale median (GSM); scale 0 - 255; 0 = black and 255 = white]. More objectively, the type of plaque and GSM can be calculated following standardisation (normalisation) using blood and adventitia as reference points. Thus, images captured using different instrument settings, scanners, operators and peripherals can be compared. Moreover, computer assisted methods of plaque characterisation using digital image processing can provide measurements of texture to evaluate heterogeneity of the plaque.

Several studies have demonstrated that the high-risk plaque is typically characterized on ultrasound by high degree of stenosis, ulceration and intraplaque haemorrhage; it is echolucent with heterogeneous texture and irregular borders. It is interesting that echolucent plaques (low GSM) are associated with larger necrotic core volume and with increased macrophage density of the carotid specimen (analysis of variance, p = 0.02).

WHY SHOULD WE IDENTIFY THE VULNERABLE CAROTID PLAQUE?

It is crucial to detect the vulnerable carotid plaque, since this:

a) is associated with cerebrovascular events,

b) predicts atherosclerosis elsewhere in the vascular bed,

c) can help improving the selection of optimal management, and,

d) it may also help with patient surveillance.

VULNERABLE PLAQUE IS ASSOCIATED WITH CEREBROVASCULAR EVENTS

Plaque echodensity and surface characteristics have prognostic implications. In particular, plaque ulceration and/or intraplaque haemorrhage seem to be associated with an increased risk of cerebral embolism. Furthermore, hypoechoic (echolucent) plaques are associated with silent infarcts on computed tomography brain scans in asymptomatic patients (p = 0.003). Additionally, emboli counted on TCD in the middle cerebral artery were more frequent in the presence of low GSM (after image normalisation) of the ipsilateral carotid plaque but not in the presence of a high degree of stenosis alone.

Several studies showed that hypoechoic (echolucent) plaques in patients with high-grade carotid stenosis are associated with a greater risk of cerebrovascular events (stroke, transient ischaemic attack, amaurosis fugax). Echolucent plaques are also associated with progression of carotid stenosis (p = 0.02)[3]. In asymptomatic adults (≥65 years) the risk of incident stroke was associated with hypoechoic plaque [relative risk (RR) = 2.78; 95% confidence interval (CI) = 1.36-5.69] and carotid stenosis of 50-100% (RR = 3.08; 95% CI = 1.28-7.41). Furthermore, the Tromsø study showed that patients with echolucent plaques have an increased risk of ischaemic cerebrovascular events independently of the degree of stenosis (adjusted RR for all cerebrovascular events = 4.6, 95% CI = 1.1-18.9)[4].

VULNERABLE PLAQUE PREDICTS ATHEROSCLEROSIS ELSEWHERE IN THE VASCULAR BED

The presence of echolucent carotid plaques in patients with stable coronary heart disease (CHD) predicts future coronary events independently of other risk factors [odds ratio (OR) = 7.0, 95% CI = 2.3-21.4; p <0.001][5,6].

In patients who electively underwent abdominal aortic aneurysm repair, carotid stenosis ≥50% and echolucent plaques were independent predictors of increased vascular mortality [hazard ratio (HR) = 3.61 for stenosis (p = 0.01); HR = 3.83 for echolucency (p = 0.03)] and morbidity [HR = 4.04 for stenosis (p = 0.0007); HR = 2.82 for echolucency (p = 0.008)][7].

Carotid plaques and peripheral arterial disease (PAD) commonly coexist. In CHD patients carotid atherosclerosis and PAD are not only highly prevalent but also strongly associated, being independent predictors of each other.

Additionally, aortic arch atherosclerosis, a potential source of embolic strokes, commonly coexists with carotid plaques.

Vascular and renal disease may also progress in parallel. Even modest reductions in glomerular filtration rate are independently associated with a higher prevalence of vascular disease[8].

These findings support the concept that atherosclerosis is a generalized disease and carotid atherosclerosis mirrors vascular disease elsewhere.

VULNERABLE PLAQUE AND SELECTION OF OPTIMAL MANAGEMENT

This includes the best medical treatment and the selection of the proper carotid intervention (endarterectomy or angioplasty and stenting).

Best medical treatment

Best medical treatment has evolved over the years and it is always applicable in high-risk patients. New drugs have been added to our armoury and new guidelines have set more aggressive treatment targets, for example, for hypertension and dyslipidaemia. Several studies demonstrated that aggressive treatment of the modifiable risk factors significantly reduces the risk of vascular events. The use of antiplatelet agents is also beneficial in stroke prevention. It has been estimated that a comprehensive control of four vascular risk factors (hypertension, hyperlipidaemia, high serum homocysteine levels and platelet function) may reduce CHD events by about 88% and stroke by 80%, at least partly through stabilization of atherosclerotic plaques[9].

Furthermore, it is relevant that a comprehensive monitoring of the high-risk carotid plaque could facilitate the evaluation of the effectiveness of aggressive medical treatment in high-risk patients.

Carotid endarterectomy

Several trials demonstrated that endarterectomy is beneficial in selected patients. This was confirmed for symptomatic patients with severe internal carotid artery stenosis of ≥70%, or even moderate stenosis (50-69%) and in asymptomatic patients with stenosis of ≥80% (according to the European Carotid Surgery Trial criteria).

Carotid angioplasty and stenting (CAS)

Carotid angioplasty and stenting (CAS) is a less invasive, alternative technique for the treatment of severe carotid stenosis, especially in patients with significant comorbidities. The wide use of cerebral protection devices decreased the risk of distal embolisation during the procedure. However, there is some debate regarding endarterectomy and CAS. It has been suggested that carotid plaque morphology may play an important role in selecting the optimal carotid intervention procedure. Thus, the ICAROS (Imaging: Carotid Angioplasty and Risk of Stroke) study showed that echolucent plaques, with GSM less than 25, are high-risk for cerebral complication during CAS procedures ($p = 0.002$) and therefore should undergo surgery rather than CAS[10].

Further randomised trials are needed to resolve this issue.

VULNERABLE PLAQUE AND PATIENT SURVEILLANCE

Echolucent plaques were found to be associated with an increased risk of progression of carotid stenosis ($p = 0.02$). There is also evidence supporting that echomorphological and histological features of plaques belonging to either symptomatic or asymptomatic patients may change with time. Furthermore, echolucent plaques are associated with an increased risk of restenosis after carotid intervention when compared with echogenic plaques ($p < 0.001$). It follows that high-risk carotid plaques should be monitored on a regular basis; ultrasound is currently the most widely used method for that[11].

BIOCHEMICAL AND HAEMATOLOGICAL PREDICTORS

Several established and emerging risk factors are associated with a higher risk of cerebrovascular events. Established modifiable risk factors include hypertension, dyslipidaemia, smoking, diabetes mellitus, cardiovascular disease and alcohol abuse. The role of emerging risk factors is also increasingly recognised; these include: C-reactive protein (CRP), homocysteine, lipoprotein (a), fibrinogen, creatinine, uric acid, white blood cells, neutrophils and monocytes. There are probably other relevant risk factors that remain unknown. It is therefore crucial to evaluate the overall risk of patients when a high-risk plaque is identified and treat them aggressively according to the current knowledge. Several identification systems are available to estimate the risk of a patient for a future vascular event. These are based on computer calculation (e.g. Framingham or PROCAM risk calculation), or on tabular methods (e.g. the Sheffield tables and the General Rule to Enable Atheroma Treatment).

However, there is limited research evaluating the association between carotid plaque echolucency and biochemical and haematological variables[12].

Low circulating levels of high density lipoprotein cholesterol (HDL-C) were independently associated with an increased risk of the presence of echolucent, rupture-prone plaques and a higher risk of stroke.

Our group suggested that echolucent plaques were

significantly and independently associated with low HDL-C and high levels of malondialdehyde and high sensitivity CRP after multivariate analysis.

In addition to high sensitivity CRP levels, higher interleukin (IL)-6 levels may predict severity of atherosclerosis and appear to be associated with lower echodensity of carotid plaques, suggesting a link between inflammation and potential risk of plaques.

Furthermore, the circulating levels of intercellular cell-adhesion molecule-1 (cICAM-1) or P-selectin (cP-selectin) are related to real measurements of plaque formation in the carotid arteries, independently of conventional risk factors. It is interesting that marked elevation of cP-selectin occurs when carotid atherosclerosis becomes advanced, while the elevation of cICAM-1 is gradual[13].

Further research is needed to identify those blood markers which are associated with carotid plaque instability.

However, it seems that there are specific plaque characteristics interacting with blood variables that reflect an increased risk of vascular events. In other words, unfavourable plaque features ("vulnerable plaque") together with the presence of other (biochemical and haematological) risk factors contribute to create the "vulnerable patient".

LOCAL FACTORS MAY INFLUENCE CAROTID PLAQUE STABILITY

Inflammation is involved in the development and progression of atherosclerosis. A variety of proinflammatory and proteolytic cytokines are expressed in the plaque and may modulate extracellular matrix remodelling, cell proliferation and cell death. Elevated expression/activity of several MMPs, the main physiological regulators of the extracellular matrix, especially MMP-9, have been identified within lipid-rich carotid plaques and are implicated in the evolution, rupture and instability of plaques. Oxidative stress also plays a role in atherosclerosis.

Additionally, several molecules have been implicated in the atherosclerotic process and in plaque instability. For example, vascular endothelial growth factor (VEGF), vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), P-selectin, endothelin-1, platelet-activating factor (PAF), nuclear factor-kappaB (NF-kB), tumour necrosis factors (TNFs), ILs, leukotactin (LKN)-1.

However, less is known about protective mechanisms. For example, IL-10 (a potent anti-inflammatory cytokine) seems to inhibit monocyte-endothelial cell interactions, while the tissue inhibitors of MMPs (TIMPs) counterbalance MMP activity. Our group demonstrated for the first time that the expression of metallothioneins (MTs, antioxidant proteins) is higher in symptomatic than in asymptomatic plaques. It is interesting that MT expression was mainly related to carotid plaque echodensity rather than the presence of symptoms; echolucent plaques were expressing MT to a greater extent whether or not they belonged to symptomatic or asymptomatic patients, when compared to echogenic plaques. This could represent a response to injury, aiming to protect cells from further DNA damage and apoptosis. We speculate that MT expression is a gradual process that occurs in "vulnerable plaques" and increases as plaques become more unstable. In that case, the occurrence of the event could represent a failure of the protective action of MTs[14].

The expression of local factors, such as those mentioned above, as well as local infection (e.g. Chlamydia pneumoniae) may influence carotid plaque stability. In this case they may not only represent predictors/markers of the atherosclerotic process but also potential future therapeutic targets.

THE FUTURE LOOKS PROMISING

New possibilities are under investigation for early and accurate detection of the unstable atherosclerotic carotid plaque. New developments in ultrasound equipment include the use of echocontrast agents and novel applications of three- and four-dimensional ultrasound. Recent technical developments in MR imaging technology, such as dedicated surface coils, the introduction of 3.0-T high-field systems and parallel imaging, the use of ultrasmall superparamagnetic iron oxide, as well as developments in the field of molecular imaging, such as contrast agents targeted to specific plaque constituents, are likely to lead to the necessary improvements in accurately identifying and characterizing the high-risk plaques. Furthermore, the development of optical coherence tomography (an intravascular imaging technique that provides cross-sectional images of the tissue) will enable the accurate detection of lipid cores, thin caps and macrophages and high-resolution visualisation of atherosclerotic plaque morphology.

These developments will provide both enhanced information on disease progression, as well as new insights into pathophysiological mechanisms of carotid plaque embolisation and they will ultimately lead to more widespread application of this technology in the clinical practice.

Furthermore, new therapeutic techniques, e.g. percutaneous endoluminal arterial cryoenergy, may improve the current treatment approach and they may become potential methods of stabilizing the vulnerable plaque.

Ideally in the future we will be able to evaluate the overall risk score of the patient taking into account a combination of specific plaque characteristics, blood markers and concomitant vascular disease, in order to identify a subgroup of patients at increased risk for stroke, more effectively than other methods used so far.

CONCLUSIONS

It is important to unravel the characteristics of the high-risk carotid plaque and focus on plaque stabilization and regression. Apart from the degree of stenosis, we need to consider plaque morphology to evaluate the high-risk carotid plaque. Additionally, we need to modify established and emerging risk factors that may affect the risk of plaque rupture and are associated with a higher risk of vascular events. These factors together with a comprehensive imaging assessment may help patient surveillance (ipsilateral and contralateral side). This could facilitate the evaluation of the effectiveness of aggressive medical treatment and implement a more cost-effective therapeutic strategy by improving patient selection criteria for any vascular intervention (endarterectomy/angioplasty). For example, a subgroup of patients with high-grade stenosis may carry a low risk of stroke. If correctly identified, they will be spared an unnecessary, potentially dangerous and expensive intervention. In contrast, a subgroup of asymptomatic or symptomatic patients with lower-grade stenosis may be at an increased risk of stroke and would benefit from intervention.

Additionally, we should bear in mind that the presence of carotid atherosclerosis may mirror clinically relevant atherosclerosis elsewhere in the vascular bed.

In conclusion, it is very important to identify the vulnerable plaque; it is crucial to identify the "vulnerable plaque" in the "vulnerable patient".

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[1]Dept of Vascular Surgery, Faculty of Medicine, Imperial College London, UK
[2]Dept of Vascular Surgery, Medical School, University of Athens, Greece
[3]Dept of Clinical Biochemistry, (Vascular Disease Prevention Clinics), Royal Free and University College, Medical School, University of London, UK
[4]Dept of Forensic Medicine and Toxicology, Medical School, University of Athens, Greece
[5]Dept of Pathology, Medical School, University of Athens, Greece
[6]Laboratory of Experimental Surgery and Surgical Research, Medical School, University of Athens, Greece
[7]Laboratory of Histology Embryology, Medical School University of Athens, Greece
[8]Dept of Electrical and Electronic Engineering, Imperial College London, UK
[9]Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

ΠΕΡΙΛΗΨΗ

Ασταθής καρωτιδική πλάκα - Ευάλωτος ασθενής

EAVST (European Association of Vascular Surgeons in Training)
Τιμητική Ομιλία
18 Σεπτεμβρίου 2005, Ελσίνκι, Φιλανδία

Χ.Δ. Λιάπης

Πρόεδρος της Ευρωπαϊκής Εταιρείας Αγγειοχειρουργικής

Η καρωτιδική πλάκα είναι μια από τις κύριες αιτίες πρόκλησης αγγειακών εγκεφαλικών συμβαμάτων. Διάφορες απεικονιστικές τεχνικές έχουν χρησιμοποιηθεί για την αναγνώριση της ασταθούς, υψηλού κινδύνου πλάκας, μεταξύ των οποίων το υπερηχογράφημα είναι η πιο ευρέως διαδεδομένη. Συνεχώς αναγνωρίζεται ότι οι υποηχογενείς και ετερογενείς πλάκες που απαντούν σε ασθενείς με υψηλού βαθμού καρωτιδική στένωση συσχετίζονται με αυξημένο κίνδυνο για αγγειακά εγκεφαλικά επεισόδια.

Η έκφραση διαφόρων τοπικών και συστηματικών παραγόντων μπορεί να επηρεάζει τη σταθερότητα της πλάκας. Επιπλέον, καθιερωμένοι αλλά και νεότεροι παράγοντες κινδύνου σχετίζονται με αυξημένο κίνδυνο

για αγγειακά εγκεφαλικά επεισόδια. Είναι επίσης σημαντικό ότι η παρουσία καρωτιδικής αθηροσκλήρωσης μπορεί να αντανακλά την παρουσία αθηροσκλήρωσης σε άλλα σημεία του αρτηριακού δένδρου. Είναι απαραίτητο να λαμβάνονται υπόψη όλοι αυτοί οι παράγοντες για τον υπολογισμό του ολικού κινδύνου ενός ασθενή με ασταθή καρωτιδική πλάκα και τελικά για την αναγνώριση της «ευάλωτης καρωτιδικής πλάκας» στον «ευάλωτο ασθενή». Αυτό θα βοηθήσει στην καλύτερη παρακολούθηση των ασθενών και στην αξιολόγηση της αποτελεσματικότητας της επιθετικής συντηρητικής θεραπείας. Η αναγνώριση της ασταθούς καρωτιδικής πλάκας σε ασθενείς υψηλού κινδύνου θα βοηθήσει επίσης στη βελτίωση των κριτηρίων επιλογής αυτών που θα υποβληθούν σε καρωτιδική επέμβαση (ενδαρτηρεκτομή/αγγειοπλαστική) με αύξηση της αναλογίας κόστους/ωφέλειας.

Όροι ευρετηρίου: *ασταθής καρωτιδική πλάκα, ασθενείς υψηλού κινδύνου.*

Διεύθυνση αλληλογραφίας

Χρήστος Δ. Λιάπης
Ελληνική Αγγειοχειρουργική Εταιρεία
Μεσογείων 8Β
Αθήνα

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