Stenosis of Carotid Arteries Induced by Homocysteine

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Abstract

In the present study, the relationship between increased homocysteine serum level (HHcy) and carotid atherosclerosis, was evaluated. Atherosclerotic plaques can involve supra-aortic trunk (SAT), especially common carotid artery (CCA) and internal carotid artery (ICA). Their disruption can cause thrombo-embolic mechanisms able to induce a reduced intracerebral perfusion, evolving in some intracerebral acute accidents, as amaurosis fugax, TIA, minor stroke or stable stroke.

Therapeutically, vitamins-B supplementation may reduce carotid plaques-formation and their progression in patients with HHcy. Calcification and stabilization of these plaques can be obtained with statins-use. Carotid endarterectomy also reduces the incidence of cerebral acute events. But, previous large trials have demonstrate that vitamins-B supplementation is unable to prevent brain events in patients that already suffered of these (secondary prevention).

In conclusion, several uncertainties exist too about the treatment of these patients and about the exact link existing among HHcy, carotid plaques and cerebral accidents.

Keywords: Homocysteine; carotid-artery atherosclerosis; TIA; ischemic stroke

Introduction

Atherosclerosis is a hardening of the arteries-walls due to atheromatous plaques that can result in coronary artery disease, ischemic stroke and peripheral arterial disease [1-4]. Among these, carotid arteries may be involved [5,6]. It must be added that, thrombo-embolic events originating from disruption of atherosclerotic carotid branches can often induce acute intracerebral vascular accidents [7-10].

Anatomically, three branches arise from the superior border of aortic arch: brachiocephalic trunk (BCT), left common carotid artery (CCA) and left subclavian artery carotid (SCA). In turn, BCT partes into right CCA and right SCA. At carotid bifurcation, CCA divides oneself in two branches: extracranial (ECA) and intracranial carotid artery (ICA) (Figure 1). ECA provides blood flow supply to the scalp, face and neck, while ICA supplies blood to the brain [11].

Atherosclerotic process can cause stenosis/occlusion of carotid’s walls (in particular of CCA or ICA) through the plaques’ formation. The possible disruption of these could bring on disturbed intracranial arterial hemodynamics due to an artery-to-artery embolism or chronic hypoperfusion, with possible cerebrovascular acute events [12].

According to Mannheim carotid intima-media thickness (IMT) consensus, IMT</=1.0 mm was defined as thickening (Figure 2). On the contrary, IMT>/=1.5 mm or above the lumen was defined as a plaque (Figure 3) [13]. Carotid stenosis was defined as greater than 50% luminal narrowing, according to the criteria described by North American Symptomatic Carotid Endarterectomy Trial (NASCET) [14]. Finally, carotid occlusion was diagnosed if a carotid branch was completely obstructed (Figure 4).

It must be added that carotid stenosis or obstruction has been reported frequently associated with retinal vein obstrucive
A previous study also reports that more than 30% of patients with ischemic stroke exhibited significant coronary artery stenosis, even without cardiac symptoms [16].

Both stenosis or occlusion can be often associated with cigarette smoking, arterial hypertension, diabetes mellitus or dyslipidemia or other risk factors, such as hyperhomocysteinemia (Hcy), (Table 1) [17].

The role and the mechanisms through an increase Hcy plasma level can induce arteries carotid plaques and possible cerebrovascular events are illustrated in this review [18-24].

**Homocysteine**

Hcy is an essential amino acid derived from the conversion of Methionine to Cysteine. It is metabolized via two pathways: remethylation and trans-sulfuration. In the former, Hcy is re-converted to Methionine by a process requiring Methyltetrahydrofolate (derived from folic acid) and vitamin B$_{12}$ as cofactors. On the contrary, when Methionine is in excess, Hcy metabolism is directed to the transsulfuration pathway, where it is sulfo-conjugated to cysteine by cystationine-B-synthase, having vitamin B$_{6}$ as a cofactor [25].

**Carotid atherosclerosis**

Several studies shown that HHcy promote atherosclerosis through increased oxidative stress, impaired endothelial function, and induction of thrombosis [26-28]. But, HHcy can induce atherosclerotic process through a reduction of HDL-lipoproteins too, for inhibition of Apo-lipoprotein-A (Apo-A) [29-32]. In addition, some inflammatory events, as expression of adhesion molecules, recruitment of leukocytes, migration of monocyte can also contribute to atherosclerotic process [33]. In her turn, carotid atherosclerotic plaques can disrupt and cause thrombo-embolic events able to induce cerebrovascular accidents [34]. Approximately 20%-30% of stable ischemic strokes are due to plaque-rupture of extracranial carotid branches, while the disruption of intracranial carotid plaques account for 5%-10% of all vascular ischemic brain-events [35].

Carotid plaques consist of lipid core, with infiltration of inflammatory cells covered with fibrous cap. Its consistency can be stable or instable. This last is characterized by a thin cap with a large lipid core, active inflammation, accumulation of macrophages and platelets’ aggregation (36). On the contrary, stable plaques are calcified and less inflamed. Obviously, the calcification is a marker of stability, while the calcium lack favours the instability. Functionally, this last can break, inducing thrombo-embolization in the vessels-brain [37,38].

**Neurological sequences**

Neurological findings caused by rupture of symptomatic carotid plaques are numerous in relation to site interested, duration of ischemia and brain-vessels involved. These can be: amaurosis fugax, TIA, minor stroke and stable stroke.

Amaurosis fugax is a focal neurological deficit, characterized by a painless temporary loss of vision in one or both eyes.
Stroke subtypes of ischemic stroke in relation to etiology

Table 1: The most common risk factors for atherosclerosis.

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Other risk factors</th>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Advanced age</td>
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<tr>
<td>Dyslipidemia</td>
<td>Obesity</td>
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Table 2: Leading symptoms can be present in TIA (temporarily) and in ischemic stroke (permanently).

Main symptoms in TIA and ischemic stroke

*Sudden weakness of an arm/leg on one side of the body;
*Sudden paralysis of a limb (superior and/or inferior) on one side of the body;
*Temporary loss of vision or blurred vision;
*Temporary loss of vision or blurred vision;
*Inability to speak clearly or slurred-spech.

Table 3: Stroke subtypes of ischemic stroke in relation to etiology related to the TOAST criteria.

TOAST subtypes of ischemic stroke

1) Ischemic stroke by large-artery atherosclerosis;
2) Ischemic stroke by small-artery atherosclerosis;
3) Stroke of cardioembolic or embolic source;
4) Stroke of other determined etiology;
5) Stroke of undetermined etiology.

Therapy

A study by Hodis et al. demonstrated that high-dose of vitamin B supplementation reduces carotid intima-media thickness and its progression in HHcy-patients [45]. In addition, the use of B-vitamin complex (B<sub>6</sub> + folic) resulted positively associated with reduction of carotid plaque progression [46]. On the contrary, Jacobs and coworkers suggested that low dietary intake of vitamin B<sub>6</sub> is associated with increased risk of ischemic stroke [47]. However, the large prospective Vitamin Stroke Prevention (VISP) trial did not show a benefit with treatment with B<sub>6</sub> of folate in prevent recurrent stroke [48]. Neither VITATOPS (VITamins TO Prevent Study) supports the vitamins B supplementation for secondary prevention of TIA or stroke or other events [49].

Referring to the surgical treatment of carotid plaques to prevent their increased vulnerability, the North American Symptomatic Carotid Endarterectomy (NASCET) demonstrated that carotid endarterectomy significantly reduces the risk of neurological acute events due to the disruption of these [14]. The European Carotid Surgery Trial (ECST) also showed a significant benefit for high-grade of carotid stenosis [50].

With reference to the lipid deposition in the carotid plaques and their following growth and disruption, it must be added that statin therapy is believed to stabilize carotid plaques and has been shown to decrease their lipid content [51]. Zhao et al. also found that lipid-lowering therapy was not only significantly associated with lower lipid content of plaque, but also with a tendency for increased calcium in treated human carotid arteries [52]. Finally, for secondary prevention of focal or global neurological deficits due to the disruption of carotid plaques, the antiplatelet drugs seem to be useful [53].

In conclusion, the uncertainties for therapeutic treatment of these patients and for secondary prevention of intracerebral acute events further studies are requested. These need also to better define the exact link existing among HHcy, carotid plaques and cerebral accidents.

References


Obscured vision can be due to the papilledema and may last few seconds up to 1-5 minutes [39]. Minor stroke is defined as mild and non-disabling reduction/loss of some neurological functions, with incomplete regression of the symptoms [40].

TIA is a sudden and temporary loss of blood flow to an area of the brain, usually lasting a few minutes to 1 hour. Symptoms disappear within 24 hours with complete recovery [41]. Stable stroke occurs when a blood clot blocks a blood flow in an artery and interrupts blood flow to the brain region supplied by that artery [42]. Ischemic stroke secondary to carotid plaques rupture is about 20% of all ischemic strokes.

Contrarily to TIA, stable stroke is characterized from a persistence of the symptoms. The main symptoms that can characterize both cases are reported in table (Table 2). As aforesaid, all cerebral acute events caused by the plaques’ fragments, are consequent to the alteration of local hemodynamic conditions, due to an arterio-arteriolar thrombo-embolism [43]. Therefore, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [44], these same are included in third group of this pathogenic criteria (Table 3).


49. VITATOPS Trial Study Group: B vitamins in patients with recent transient ischemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomized, double-blind, parallel, placebo-controlled trial. Lancet Neurol. 2010; 9, 855-865

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