

The role of homocysteine in the pathogenesis of migraine.

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Abstract

There are recent evidences that homocysteine may be involved as a risk factor for cerebral infarction. An association between migraine and hypercoagulopathic states has also been observed. Besides, there is a probable connection between oxidative stress, homocysteine and cerebral ischaemia. The aim of our work was to evaluate, in a set of subjects with migraine, the plasmatic levels of copper, iron, folate, vitamin B12 and homocysteine. Besides, in hyperhomocysteinemic patients we gave an additional therapy of folate and vitamin B12 to evaluate their efficacy. One hundred and fifty patients (of which 112 were women), with mean age 37.4 years (SD 16.8), suffering from migraine with aura (26) and without aura (124) (International Headache Society, 2004 criteria) were studied. Fifty patients out of them, with basal hyperhomocysteinemia, were treated with vitamin B12 and folate for 60 days. We found basal blood hyperhomocysteine in 24% of the patients (55% with migraine plus aura and 45% with migraine minus aura), having blood levels of folate and vitamin B12 lower than normal while copper and iron levels were within the normal range. Anova test done during the follow-up, to compare migraine indices of treated subjects with those of controls as well as their respective basal values, showed significant ($P<0.05$) differences in treated patients, in whom basal blood homocysteine levels were decreased to 40%. Our data indicate that the administration of folates and vitamin B12 is able to produce a reduction of the migraine index and plasma levels of homocysteine. Therefore, homocysteine, probably by a modification of vasoactive endothelial factors (especially NO and thrombomoduline), could play an important role in migraine.

Keywords: Migraine, homocysteine, vitamin B12, folates

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Introduction

Vascular damage may be induced by high levels of plasma homocysteine [1-6]. Hyperhomocysteinemia induces an increase of the factors XII, V and prothrombin activation [7] while it is able to reduce the activation of protein C [8]. Another important aspect is the effect of the homocysteine on the endothelial production of nitric oxide [9]. Generally, the circulating homocysteine reacts with nitric oxide producing s-nitroso-homocysteine, which prevents the auto-oxidation of homocysteine and therefore the generation of free radicals. When the level of homocysteine is elevated, the available quantity of NO gets saturated and the homocysteine in excess causes endothelial damage [10].

Migraine is a neuro-vascular syndrome characterised by attacks of headache associated with photophobia,

phonophobia, nausea and vomiting. Migraine occurs in about 18% of women and 6% of men, regardless of race or geographical location [11,12].

Although the exact aetiology of migraine headaches is unknown, several theories have been proposed. The vascular theory, as proposed in 1938 by Graham and Wolff [13], attributes migraines to an initial intracranial arterial vasoconstriction resulting in reduced blood flow to the visual cortex, followed by a period of extra-cranial vasodilation. Modern imaging techniques have shown that during a common migraine attack there are in fact only minor changes in cerebral blood flow, and the proposed initial vasoconstrictive phase may actually last much longer than the aura [14]. It has also been hypothesised that migraine sufferers have an inherent vasomotor instability and are more susceptible to the vasodilatory effects of certain physical and chemical agents. This point of view has been reinforced by the observation that

organic nitrates, which are capable of delivering nitric oxide, trigger migraine attacks in migraineurs, at low doses, ineffective in normal subjects [15].

Moskowitz's theory, which involves the trigeminovascular complex, links the aura and the headache of migraine [16-19]. According to this theory, the trigeminovascular neurons release substance P and other neurotransmitters in response to various triggers. Substance P is associated with vasodilation, mast cell degranulation, increase in vascular permeability and edema of the meninges. All together these events configure the phenomenon called neurogenic inflammation. Excessive trigeminal discharge and neurovascular inflammation of meninges ensues in migraine headache.

Numerous studies were focused on the link between hypercoagulation and migraine. In this respect, it was reported that homocysteine might be considered a clear predisposing factor for thrombosis, an increased risk of stroke and cardiovascular events [20-24].

The vascular damage seems to be related to an increase in the oxidative stress, which in turn, through direct and indirect mechanisms, would lead to vascular damage [25]. Also, the production of endothelial nitric oxide, involved in the genesis of the migraine, may be related to the possible relationship between oxidative stress and high plasma level of homocysteine [26].

Considering that few studies have considered the plasma level of homocysteine in the patients with migraine [27-28], we have studied subjects with migraine evaluating their plasmatic levels of copper, iron, folates, vitamin B12 and homocysteine and then, we have correlated the results with a possible new physiopathologic mechanism.

Materials and Methods

One hundred and fifty patients (of which 112 were women), with mean age 37.4 years (SD 16.8), suffering from migraine with aura (26) and without aura (124) (International Headache Society, 2004 criteria) were studied. Fifty patients out of them, with basal hyperhomocysteinemia, were treated with vitamin B12 and folate for 60 days. The patients were observed in the Headache Center of the San Luca Hospital (Vallo della Lucania, SA) for two years (2003-2004) [29].

The patients were submitted to a complete clinical (general and neurologic) instrumental evaluation and plasmatic level of iron (Fe), copper (Cu), vitamin B12, folates and basal homocysteine were evaluated. HPLC

was used to determine the plasma level of homocysteine and the above parameters were so evaluated: Normal range < 15 $\mu\text{mol/L}$

Light increase 15-30 $\mu\text{mol/L}$

Intermediary increase 30-100 $\mu\text{mol/L}$

Marked increase >100 $\mu\text{mol/L}$

Statistical Analysis

ANOVA test was performed during the follow-up, in order to compare migraine indexes of treated subjects with those of controls and the respective basal values in both groups. Significance was assumed at $P < 0.05$.

Results

The patients studied suffered from migraine, 10 with aura (10.5%), 85 without aura (89.13%).

The plasma concentration of homocysteine in the migraine patients was 12.02 $\mu\text{mol/L}$ (SD=9.95) whereas in the control group it was 7.45 $\mu\text{mol/L}$ (SD=3.2) ($P < 0.001$) (Table 1).

In the migraine patients only 28 patients (29.16%) showed basal values of hyperhomocysteinemia higher than 15 $\mu\text{mol/L}$.

In the control group the plasma concentration of folates was 6.2 pg/ml (SD=1,8) and of vitamin B12 was 422.6 pg/ml (SD=52.8), while in the migraine patients the plasma concentration of folates was 6.3 pg/ml (SD=9,7) and of vitamin B12 was 353 pg/ml (SD =184).

The plasma concentration of copper in the control group was 101.2 mg/dl (SD=23.5) and iron was 71.71 $\mu\text{g/dl}$ (SD=32.57), while in the migraine patients the value of copper was 194.14 mg/l (SD=223.9) and of the iron was 69.97 $\mu\text{g/dl}$ (SD=32.57).

The administration of folates and B12 vitamin was able to produce a reduction of the migraine index and plasma levels of homocysteine (from 14.07 $\mu\text{mol/L}$ to 7.52 $\mu\text{mol/L}$; $P < 0.001$).

Figure 1 shows a typical tracing of normal values of homocysteine in a patient without migraine whereas figure 2 shows that increased levels of homocysteine in a migraine patient.

The plasma concentrations of B12 vitamin, folates and copper in the hyperhomocysteinemia patients (reported in Tab I) were significantly reduced for B12 vitamin and folates and increased for iron and copper when compared to normal-hyperhomocysteinemia patients subgroups and control patients.

Table I. Value B12 vitamin, folates, copper and iron in patients subgroups and controls

	Hyperhomocysteinemia groups		Normal-homocysteinemia groups		Controls	
	Plasmatic Concentration	% < normal value	Plasmatic Concentration	% < normal value	Plasmatic Concentration	% < normal value
Vitamin B12	339.76 pg/ml (DS=125.48)	17.85	469.8 pg/ml (DS=203.15)	6.6	422.6 pg/ml (DS=52.8)	18.5
Folate	4.3 ng/ml (DS=1.56)	22.72	6,3 ng/ml (DS=1.38)	0	6.2 ng/ml (DS= 1.8)	25.5
	Plasmatic Concentration	% > normal value	Plasmatic Concentration	% > normal value	Plasmatic Concentration	% > normal value
Copper	166 µg/ml (DS= 148)	87.5	99.8 µg/ml	0	101.2 mg/dl (DS=23.5)	0
Iron	95.83 ng/ml (DS= 40.20)	83.33	59 ng/ml	0	76.8 µg/dl (DS=168.2)	0

Hyperhomocysteinemia groups	Normal-homocysteinemia groups
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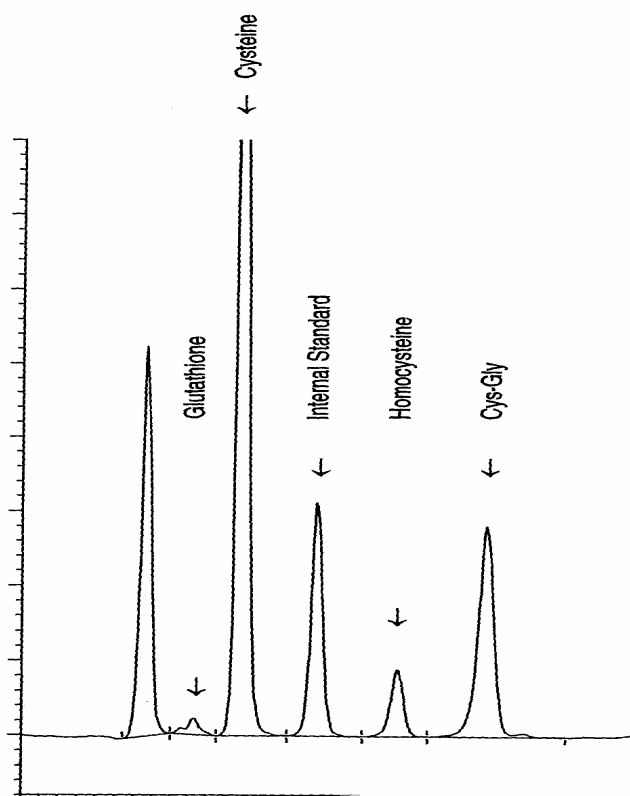


Figure 1: Typical tracing showing normal values of homocysteine in control patients without migraine

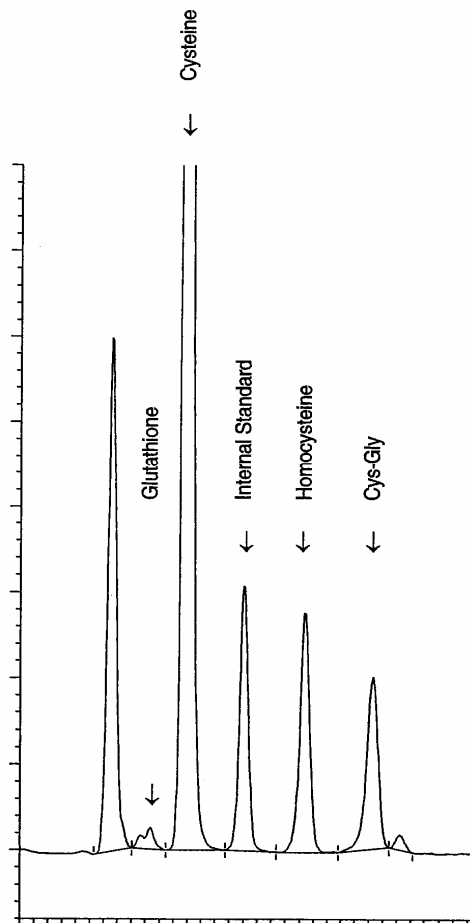


Figure 2.. Typical tracing showing increased values of homocysteine in patients with migraine

Discussion

In our study, we found an increase in plasma homocysteine level higher than 15 $\mu\text{mol/L}$ in 29.16% of patients with migraine. Also, in the hyperhomocysteinemia group, we found that the levels of vitamin B12 and folates were significantly reduced (17.85% and 22.72% respectively). Furthermore, the administration of folates and vitamin B12 was able to produce a reduction of the migraine index and plasma levels of homocysteine (from 14.07 $\mu\text{mol/L}$ to 7.52 $\mu\text{mol/L}$; $P < 0.001$). Given the above results, our study shows a strong relationship between migraine, hyperhomocysteinemia and reduced levels of folates and vitamin B12 suggesting a possible involvement of vitamin B12 and folates in the

development of migraine pathology. The ability of folates and vitamin B12 to reduce the migraine as well as plasma level of homocysteine may support our hypothesis.

This is the first study showing a possible relationship between hyperhomocysteinemia and migraine, which is probably, also related to a reduction in vitamin B12 and folates.

Although the pathogenic mechanisms underlying the hyperhomocysteine-induced migraine are still unknown, some hypothesis should be considered.

Hyperhomocysteinemia may induce an increase in production of homocysteic acid [30]: this compound is a cytotoxin [30,31] acting as an endogenous agonist of

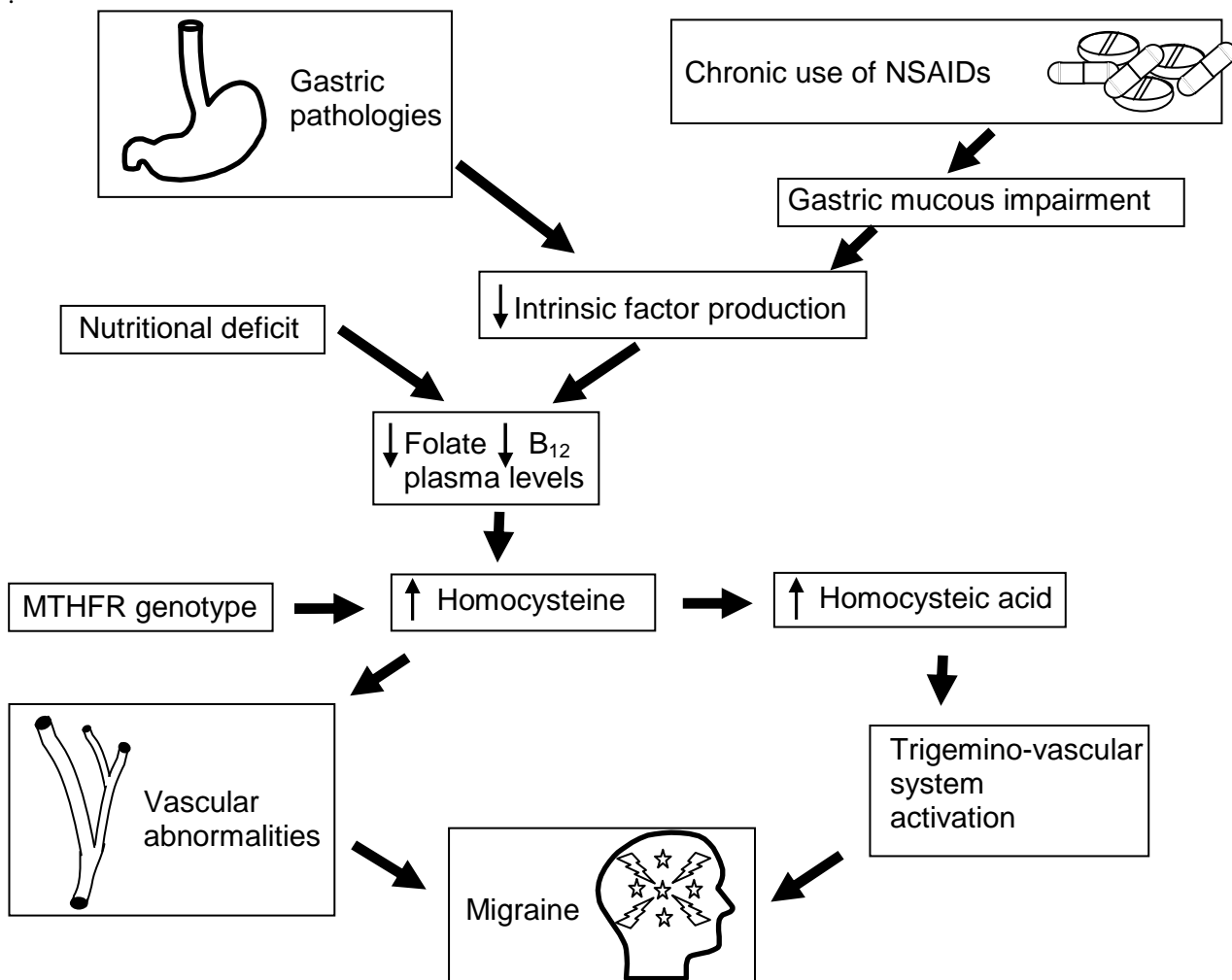


Figure 3. Role of vitamin B12 & folate in the pathogenesis of migraine. Gastric pathologies and/or the chronic use of anti-inflammatory drugs (NSAIDs) in patients with migraine prevent the production of intrinsic factor with a reduction of the absorption of vitamin B12. The nutritional deficits can also contribute to the deficiency of vitamin B12. The plasma levels of B12 and/or mutations of gene MTHFR can lead to hyperhomocysteinemia. Elevated levels of homocysteic acid derived from hyperhomocysteinemia could activate the trigemino-vascular system, and promote the attacks of migraine.

receptor N-methyl-aspartame (NMDA) thus developing migraine [32-38].

High plasma levels of homocysteic acid were found in the patients with migraine (both with and without aura) while in the patients with tension headache the levels were similar to the controls [39]. Figure 3 shows the possible role of homocysteic acid in the pathogenesis of migraine due to its effects on the trigemino-vascular system. Stimulation of the trigeminal innervation may induce vasodilatation and the release of neuropeptides [40]. The homocysteic acid increases the cellular inflammation of the trigeminal [41]. Therefore, high levels of homocysteic acid, related to the hyperhomocysteinemia, could induce the activation of the trigemino-vascular system, predisposing patients to attacks of migraine or increasing the gravity of the illness. Given the above scheme, in our study, the ability of vitamin B12 and folate to reduce hyperhomocysteinemia and migraine may be related to the resulting block of homocysteic acid as well as blocking of activation of the trigemino-vascular system.

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