Elevated Plasma Total Homocysteine and Vascular Disease About Seventy-Two Cases

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Abstract
Elevated plasma total homocysteine is considered as a risk factor for occlusive cardiovascular disease. However, some observations have raised questions about elevated plasma total homocysteine as a risk factor. Also, it is considered as a risk factor for venous thromboembolism, but other authors deny this harmful effect of homocysteine.

Introduction
Cardiovascular disease is a major cause of mortality worldwide [1-3]. While high blood pressure, high cholesterol, type 2 diabetes, obesity and smoking are known risk factors, epidemiological data collected during the last thirty years suggest that other biological factors may be associated with increased cardiovascular risk [1-3]. Of these, one is increasing interest in moderate hyperhomocysteinemia (HH), numerous studies attempt to clarify the relationship moderate HH, and cardiovascular disease and thromboembolism [1-4].

Patients and Methods
We report a retrospective study performed on 72 cases of patients with HH and discuss the potential profile associated vascular diseases. Inclusion criteria were patients collected in Department of Internal Medicine of Sahlioul Hospital, Sousse, Tunisia; age superior to 16 years old; homocysteine level greater than 15 µmol/l and method used for measurement of plasma homocysteine levels was “immunologic dosage by fluorescence polarization (FPIA)" made in the laboratory of the same hospital. Exclusion criteria were patients taking medications, which could have influenced plasma homocysteine levels.

Results
They were 48 men and 24 women. The average age was 65 years and 3 months with extremes of 22 and 99 years. The main circumstances of the discovery of HH were either part of a thrombophilia (27 cases) or in the assessment of cardiovascular risk factors (44 cases), including three cases of diffuse atherosclerosis early either as part of a megaloblastic anemia vitamin B 12 (1 case). HH was moderate (between homocysteine levels from 15 to 30 µmol/l) in 55 cases, it was of intermediate grade in 23 cases. It was isolated in 9 cases.

The causes were selected multiple nutritional deficiencies including vitamin B12 deficiency in 14 cases and folate deficiency in 2, diabetes type 1 and 2 was implicated in 32 cases, kidney failure dans11 cases, hypothyroidism in 3 cases and an iatrogenic cause (methotrexate) was found in 2 cases. The HH1 was undetermined in 8 cases. The events were selected from the HH: deep vein thrombosis (DVT) in 13 cases, superfical venous thrombosis (SVT) in a case of recurrent ischemic stroke in 3 cases, acute ischemia of the toes in one case, atherosclerotic stenosis of the renal artery in one case and a coronary syndrome in 16 cases. In addition, several studies describe an association between HH and moderate cardiotoxicity during following clinical practices. In our study, the HH1 was asymptomatic in 37 cases. The cardiovascular risk factors were associated with the HH type 2 diabetes in 29 cases, diabetes type 1 in 3 cases, hypertension in 38 cases, 7 cases of hypercholesterolemia, hyper triglyceridaemia in 22 cases and smoking in 23 cases. It was isolated in 9 cases.

The therapeutic management of HH was based on folic acid alone in 27 cases or in combination with vitamin B12 in 9 cases. Six patients were started on vitamin B12 alone. Thirty patients have not yet received treatment. The homocysteine control, performed in patients who received folic acid, was normal. In patients who received vitamin B 12, homocysteine control was normal in 3 cases, still high in one case and not yet controlled in the other two.

Discussion
Homocysteine is a sulfur amino acid that is involved in cellular metabolism of methionine. The normal plasma homocysteine levels are between 5 and 15 µmol/l. Physiologically, they increase with age and are usually higher in males. Among female subjects, homocysteine rises significantly after menopause. Diverses pathologies may increase, to a varying degree of plasma homocysteine. This is essentially genetic diseases (involving key enzymes of its metabolism) and/or nutritional deficiencies [5,6]. HH of genetic origin is most severe. The main one
follows a cystathionine-synthetase deficiency resulting in a blockage of the trans-sulfuration with, upstream accumulation of homocysteine, leading to HH and homocystinuria. In the homozygous form of this hereditary disease, homocysteine levels are generally higher than 100 μmol/l. Its evolution is characterized by early onset of stroke. Patients heterozygous for the mutation usually have homocysteine levels between 20 and 40 μmol/l, and are also predisposed to develop vascular macro-angiopathic early. The other mutation is that of gene 5, 10-methylene tetrahydrofolate reductase, resulting in the formation of a variant enzyme with reduced activity, thereby limiting the path of partially remethylation with, as a result, a degree of mild HH or intermediate. A mostly moderate hyperhomocysteinemia may result from a deficiency of folate or other cofactors, such as vitamins B6 and/or B12 [5-7]. Kidney failure is another frequent cause of an increase in homocysteine, which can then be up to three or four times the normal values [5-6]. Several authors have considered logical that HH secondary to renal failure may contribute to the development of atherosclerotic lesions commonly encountered in this context [8]. HH has been associated with other diseases such as hyperthyroidism, pernicious anemia and certain proliferative diseases [5,6]. Several drugs have been implicated in its genesis especially those that interfere with folate metabolism [5,6]. Finally, homocysteine tends to rise moderately in smokers and in cases of chronic alcohol and/or coffee.

In our series, the causes were many: nutritional deficiencies including vitamin B12 and/or folate deficiency, diabetes type 1 and 2, kidney failure, hypothyroidism and iatrogenic (methotrexate).

The HH was undetermined in 8 cases. Numerous experimental data, clinical and epidemiological evidence that increased plasma level of homocysteine is considered a risk factor independent of cardiovascular ischemic [9,10]. Indeed, under normal conditions, the vascular endothelium plays an important role in the prevention of atherosclerosis by producing nitric oxide (NO). Homocysteine causes endothelial cell damage and proliferation of smooth muscle cells of blood vessel walls, that it hinders the release of NO and thus inhibits the vascular relaxation [11]. Homocysteine has many other actions on the cardiovascular system: modification of the extracellular matrix and lipoprotein oxidation. It initiates the production of tumor necrosis factor-alpha (TNF-α) and many cellular signals involved in the inflammatory process: it binds to lipoproteins, thereby increasing their ability to bind to fibrin, potentiating the risk of atherogenesis [12].

Homocysteine inhibits the expression and activity of thrombomodulin on the surface of endothelial cells, which allows the activation of protein C, powerful natural anticoagulants, and inhibits the binding of antithrombin III to membrane heparin sulphates [13]. The first clinical observations which an opportunity to discuss a link between hyperhomocysteinemia and cardiovascular disease in young adults with hereditary hyperhomocystinurie [14]. These patients have plasma levels of homocysteine very high and have frequently early thromboembolic stroke or atheromatous, it’s actually Mc Cully [14] who was the first to suggest the hypothesis of a relationship between the excess homocysteine and atherosclerosis. Since then, many epidemiological studies have confirmed this postulated original. In our study, recurrent ischemic strokes were observed in 3 cases, atherosclerotic stenosis of the renal artery in one case and a coronary syndrome in 16 cases.

A meta-analysis of 72 studies of MTHFR (gene for methylenetetrahydrofolate reductase) and 20 prospective studies showed that homocysteine increased 5 μmol/l of homocysteine is associated with increased ischemic heart disease of 42% + and stroke (stroke) of + 59% and a decrease 3 μmol/l of homocysteine is associated with a reduction of ischemic heart disease -16% and stroke-24% [15].

Numerous studies have shown an abnormal increase in homocysteine after methionine overload in the coronary [16], and/or in patients with peripheral arterial disease (PAD) [17]. The work of Clarke et al. [17] demonstrated that the relative risk of coronary heart disease is 20 times higher than normal when there is excess homocysteine. Boushey et al. [18] conducted a meta-analysis including all studies relating to the association between HH and cardiovascular pathology and published until June 1994. From seventeen studies, it was estimated that an increase in total homocysteine by 5 mmol/l is an increasing risk of coronary disease in men by 1.6 and 1.8 in women. A meta-analysis of same authors [18] of eleven studies on the relationship between HH and cerebrovascular disease had found an increased cardiovascular risk of 1.9 for both sexes when homocysteine increases 5μmol/l. Finally, from three studies, Boushey et al. [18] have calculated that the risk of developing peripheral vascular disease was 6.8 times higher for an increase in homocysteine of 5 μmol/l. Data from the study United British Provident Association Prospective Study [2] showed that the mean homocysteine was higher in patients who died following a stroke than in matched healthy subjects (13.1 vs. 11.8 μmol/l). Souissi et al. also showed that plasma homocysteine levels and the prevalence of HH were significantly (p<0.001) higher in coronary patients (16.3 ± 7.9 and 29%) than controls (12.6 ± 4.0 and 10%) and that this association persisted after adjustment for major cardiovascular risk factors [19]. Moreover, several studies have reported a positive relationship between higher moderate HH and cardiovascular disease among subjects with pre-existing conditions such as kidney failure [20], coronary artery disease [21], peripheral vascular disorders [22], a diabetes [23], lupus erythematosus [24] or venous thromboembolism [25]. Several other studies supported this positive relationship between HH and chronic arterial disease. In practice, Taylor et al. showed that the risk of cardiovascular death increased by nearly 6% when homocysteine level increased by 1 μmol/l [22]. Elevated homocysteine levels of 5 μmol/l appears to increase coronary risk in the same way that an increase in serum cholesterol of 20 mg/dl [18]. Similarly, the prognostic value of homocysteine in coronary artery disease has been highlighted by several studies. The homocysteine has emerged as a powerful predictor of mortality in patients with angiographically proven coronary artery disease [21]. Moderate HH is frequently objectified in diabetics type 1 or type 2. She is best described when there is a preclinical or clinical nephropathy, and/or when plasma levels of folate are reduced [7,26].

In our study, we identified three HH with type 1 diabetes and 29 HH with type 2 diabetics. The association of HH (measured fasting or after methionine load) to a macro-angiopathic pathology was found by several authors. This is particularly the case in the study of Buysschaert et al. [27] who found a macro-angiopathy (in term cerebral, coronary and/or localized to the lower limb arteries) in 70% of a cohort of type 2 diabetics. The association of HH (measured fasting or after methionine load) to a macro-angiopathic pathology was found by several authors. This is particularly the case in the study of Buysschaert et al. [27] who found a macro-angiopathy (in term cerebral, coronary and/or localized to the lower limb arteries) in 70% of a cohort of type 2 diabetics. The association of HH (measured fasting or after methionine load) to a macro-angiopathic pathology was found by several authors. This is particularly the case in the study of Buysschaert et al. [27] who found a macro-angiopathy (in term cerebral, coronary and/or localized to the lower limb arteries) in 70% of a cohort of type 2 diabetics.
individuals with plasma homocysteine concentrations highest did not show an increased risk of developing a cardiovascular morbidity event. Therefore, the hypothesis that moderate HH is an independent risk factor for cardiovascular disease remains the subject of controversy [9, 10]; thereby creating a reserve to use in the interpretation of previous results [6-34]. The authors of these works consider contradictory, on the basis of several prospective analyses, the HH could be more an indicator of macro-angiopathy and/or consequence of atherosclerosis, rather than an etiological factor. Several reports of the Physicians Health Study [1] showed no significant relationship between homocysteine and myocardial infarction: subjects with myocardial infarction (n=271) had an initial homocysteine little different matched healthy subjects but the difference was significant because of the large number of subjects (11.1 versus 10.5 μmol/l). In the Tromso Health Study [35], the difference between cancer patients and healthy subjects was also low: the average homocysteine was 12.7 ± 4.7 mmol/l in patients and 11.3 ± 3.7 mmol/l in control subjects.

It is important to mention that besides its deleterious role, even controversial, on arterial vascular trunks, HH promotes the development of lesions and venous thromboembolism associated pathologies [36]. The literature data indicate that moderate HH was found with a frequency of 19 to 47% in arterial thrombosis [37,38] and 10 to 25% in venous thrombosis [36,38]. Thus, in our series, the HH was associated with deep vein thrombosis (DVT) in 13 cases, a superficial thrombosis vein (STV) in one case and arterial thrombosis in one case. A meta-analysis of available epidemiological studies seems to confirm the role of HH in the development of venous thromboembolism (VTE) [39]. In case-control studies collected, an increase of 5 μmol/l homocysteine was associated with an increased risk of VTE. The strength of this association was moderate, however: the odds ratio (OR) estimated in this study was 1.60 (confidence interval 95%: 1.10 to 2.34). HH was also a risk factor for recurrence in the cohort studies, with an even lower risk, estimate of 1.24 (confidence interval 95%: 1.01 to 1.59). Thus, HH is a minor risk factor for VTE (OR <2) [40].

The treatment of HH based on oral administration of folic acid alone or in combination with vitamin B6 and/or B12 [41,42]. The folic acid dose to be administered is between 1 to 5 mg/day. In our series, the therapeutic management of HH was based on folic acid alone in 27 cases or in combination with vitamin B12 in 9 cases. Six patients received vitamin B12 alone. Thirty patients have not yet received treatment. The homocysteine control, performed in patients who received folic acid, had returned to normal. In patients who received vitamin B12, homocysteine control was normal in 3 cases, still high in one case and not yet controlled in the other two.

Many randomized controlled trials showed a decrease in homocysteine levels in patients receiving folate orally at a dose of 1 mg/day, this decrease being more important than starting homocysteine was elevated and low folate levels [43]. Schneyder et al. [44] showed in a cohort of subjects, who underwent coronary angioplasty, that oral supplementation with folate reduces homocysteine levels compared to placebo and significantly reduced the occurrence of vascular restenosis (19.6% versus 37.6%). However, Den Heijer et al. [45] showed that vitamin supplementation (5 mg of folate, 0.4 g of vitamin B12 and 50 mg of vitamin B6 per day) does not decrease the risk of recurrent thromboembolism, or hyperhomocysteinemic patients, nor in patients with normal homocysteine level [45]. This lack of effect in secondary prevention of clinical risk has also been reported in arterial disease [46]. As for our daily practice in Tunisia, the homocysteine is essential as part of a thrombophilia, an assessment of cardiovascular risk factors. An etiological investigation was immediately initiated if biology shows HH. Treatment, based on folic acid, is most often prescribed. Thus, Znazen et al. [47] emphasize the need for homocysteine to determine the etiology of a veinus thrombosis, assess the risk of recurrence and define the duration of oral anticoagulation prophylaxis. However, many teams consider that HH is not associated with an increased risk of coronary artery disease, cerebrovascular disease and peripheral vascular and therefore homocysteine is not required by first intention. This leads us to conclude that HH is still a controversial issue and that the route is still long to finally reach an agreement.

Conclusion
In addition to traditional cardiovascular risk factors, excess homocysteine could be a risk factor in itself. It is therefore logical to consider prescribing, particularly in the presence of other predisposing factors, drug treatment simple, inexpensive, and especially since folic acid is particularly effective in normalizing the rates of pathological homocysteine. This could help to limit the degenerative macrovascular complications. HH could also be a risk factor for venous thromboembolism. However, it is reasonable to encourage the initiation of other prospective studies to support additional interventional definitively the merits of this particular attitude that many experimental data, clinical and epidemiological studies continue to clear homocysteine in vascular disease. It appears that only intervention trials, designed to study the effects of reducing homocysteine levels by vitamin supplementation on cardiovascular disease, could determine whether moderate HH is a simple indicator or risk factor cardiovascular authentic.

References


