SHORT COMMUNICATION

Hyperhomocysteinemia and retinal vascular changes in patients with epilepsy

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Received 14 December 2007; received in revised form 7 April 2008; accepted 13 April 2008

KEYWORDS
Homocysteine; Atherosclerosis; Retinopathy

Summary  The possible occurrence of asymptomatic retinal vascular damage was investigated in 87 hyperhomocysteinemic (plasma total homocysteine >13 μmol/L) adult epileptic patients (46 M, 41 F; age 34.2 ± 7.5 years; mean plasma homocysteine levels 29.8 ± 15.4 μmol/L; duration of epilepsy 11.5 ± 2.4 years) with no other risk factors for atherosclerosis. Plasma total homocysteine (t-Hcy) levels were assayed by high performance liquid chromatography. Retina vascular status was assessed by fundus oculi ophthalmoscopy performed in blind conditions by two skilled ophthalmologists and compared with that obtained from 102 randomly chosen epileptic patients and 94 healthy subjects, matched for age and sex, showing normal t-Hcy levels. No retina abnormality was detected in any of the subjects belonging to the three groups. Based on these results, we conclude that epileptic patients with mild to intermediate hyperhomocysteinemia are not at risk to develop retinal vascular disease.

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Introduction

Literature data support the view that patients with epilepsy exhibit an increased risk for atherosclerosis, including heart disease and stroke (Cleary et al., 2004; Elliott et al., 2007; Hamed et al., 2007). Among the various variables analyzed, total increased homocysteinemia (hyper-tHcy) levels have been indicated as an independent risk factor for the above-mentioned vascular diseases (Elliott et al., 2007; Hamed et al., 2007). This is in line with a large amount of studies performed in nonepileptic patients (Spence, 2007).

Retinal vascular occlusive disease has also been associated with hyper-tHcy and a recent meta-analysis including all case-control studies has drawn the conclusion that a lowering dietary therapy with folate and B12 vitamin supplementation should be considered for affected persons (Cahill et al., 2003).

Retinal arteries share common anatomic and functional properties with small cerebral arteries and it has been proven that their damage may reflect a concomitant cerebrovascular disease (Mitchell et al., 2005). Notably, unlike cerebral circulation, the retinal vascular system is easily accessible for clinical assessment. In particular, retinal photographic examination may provide a unique method for investigating subclinical microangiopathy (Wong, 2004).

It is well-known that a condition of moderate to intermediate hyper-tHcy (i.e., tHcy <100 μmol/L), is quite common (10–40%) in patients with epilepsy, mainly due to the interference between chronic medication with enzyme-inducing (EI), folate-depleting antiepileptic drugs (AEDs), and to the effect of polymorphisms in the methylenetetrahydrofolate reductase gene (MTHFR), encoding for a key enzyme in the conversion of Hcy to methionine (Belcastro et al., 2007).

The present study aimed to explore through retinal photographic examination the possible occurrence of asymptomatic retinal microangiopathy in a population of epileptic patients exhibiting hyper-tHcy. Early knowledge of the retinal vascular status might allow a prompt initiation of therapy as well as to prevent stroke and other vascular diseases in these patients.

Patients and methods

This prospective, multicentre, case-control, single-blind (observer–ophthalmologist) study, was conducted from January 2006 to March 2007 at the outpatient epilepsy centres of Messina, Napoli and Perugia Universities, Italy. The study was approved by the local ethics committees and informed consent was obtained from all the participants. Epileptic patients were consecutively recruited according to the following inclusion criteria: (a) firm diagnosis of epilepsy, (b) stable therapy with AEDs levels and the regular attendance to the Centre; (c) no use of vitamins or other drugs other than AEDs; (f) no evidence for any condition known to affect the cardiovascular system, including, for example, routine laboratory blood tests, hypertension, diabetes, renal diseases, etc.; (g) no evidence for any condition, apart from epilepsy, known to be associated with hyper-tHcy (i.e., cancer, malabsorption disorders, inborn errors of Hcy, cobalamin or folate metabolism, use of tobacco products, chronic alcohol consumption, vegetarianism). Retina findings observed in this population were compared with those of a group of randomly chosen epileptic patients and healthy volunteers, matched for age and sex, exhibiting normal values of tHcy. Blood samples were collected after an overnight fast, cooled on ice immediately, and centrifuged at 4°C. Plasma t-Hcy levels were assessed as previously described in detail (Belcastro et al., 2007). Hyper-tHcy was defined as tHcy levels ≥13 μmol/L. Retinal vascular status was assessed by a fundus oculi ophthalmoscopy performed in blind conditions by two skilled ophthalmologists (C.J.T., R.R.) who independently examined the images. After pupil dilation with tropicamide 1%, patients underwent fundus indirect biomicroscopy with a standard 90 or 78 diopter lens and fundus photography (infrared and red-free) to appreciate the thickness of retinal vessels (measured directly by the computer’s software-Heidelberg HRA fluorescein angiograph). In order to detect the possible early signs of a mild vascular retinopathy (Michaelson, 1980; Mitchell et al., 2005), the following parameters were investigated: (a) retinal arterial signs such as generalized and focal arterial narrowing; (b) arterial wall opacification; (c) arteriovenous nipping; (d) flame-shaped or blot-shaped haemorrhages; (e) cotton-wool spots; (f) hard exudates.

Statistics were computed using STATISTICA version 6 (U.S.A.). Continuous variables (age, etc.) were evaluated by a Student’s t-test and analysis of variance (one-way ANOVA) followed by a Dunnett’s post hoc test. Categorical variables (sex, etc.) were analyzed by a χ²-square test. A p value <0.05 was considered to be statistically significant. Agreement between the existence or absence of retinal abnormalities was analyzed by using unweighted kappa (κ) for categorical data (i.e., the measure of observers’ agreement corrected for chance), where κ = 0 and κ = 1 define the presence and the absence of retinal abnormalities, respectively.

Results

Overall, 322 out of 775 consecutive epileptic patients screened at the three centres fulfilled the inclusion criteria and underwent further investigation. Eighty-seven (27%; 46 M, 41 F; mean age 34.2 ± 7.5 years) of them exhibited elevated tHcy levels, with mean value of 29.8 ± 15.4 μmol/L (61 (70.1%) patients with moderate (13–30 μmol/L) hyper-tHcy (mean values 22.5 ± 6.5 μmol/L), 26 (29.9%) with intermediate (30–100 μmol/L) hyper-tHcy (mean values 46.3 ± 14.8 μmol/L)).

The retina photographic images of these patients were compared with those obtained from additional 102 epileptic patients (55 M, 47 F; mean age 32.1 ± 10.7 years) and 94 healthy subjects (50 M, 44 F; mean age 33.1 ± 8.8 years) showing normal tHcy values. There was a normal distribution of the data and no statistically significant difference was observed between the characteristics of subjects belonging to the three groups, with exclusion of tHcy levels (Table 1).

After the accurate inspection of the retinal photograph images, no abnormalities were identified in any of the subjects belonging to each of the three groups. There was an agreement of 100% (κ = 1) on the presence or absence of retinal changes between both ophthalmologists.

Discussion

Over the last two decades, the medical literature has been flooded with articles indicating that hyper-tHcy is a risk factor for vascular and thrombotic disease, including retinal vascular occlusion (Cahill et al., 2003; Spence, 2007).
Hyper-Hcy and retinopathy in epileptic patients

Table 1 Details of the three investigated groups

<table>
<thead>
<tr>
<th>Population (no. of subjects)</th>
<th>Age (years)</th>
<th>Gender (M/F)</th>
<th>Seizure type (no. of patients)</th>
<th>Epilepsy duration (years)</th>
<th>AEDs (n)</th>
<th>tHcy levels (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-Hcy group (87)</td>
<td>3.4 ± 7.5</td>
<td>46/41</td>
<td>PS (63) PS + SG (21) PGS (3)</td>
<td>11.5 ± 2.4</td>
<td>CBZ (5)</td>
<td>29.8 ± 15.4*</td>
</tr>
<tr>
<td>Normal-tHcy group (102)</td>
<td>3.2 ± 7.0</td>
<td>55/47</td>
<td>PS (69) PS + SG (25) PGS (8)</td>
<td>12.2 ± 3.9</td>
<td>PB (21)</td>
<td>9.1 ± 3.4</td>
</tr>
<tr>
<td>Control group (94)</td>
<td>3.3 ± 8.8</td>
<td>50/44</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>7.8 ± 2.3</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.D. AEDs = antiepileptic drugs; PS = partial seizures; SG = secondary generalization; PGS = primary generalized seizures; CBZ: carbamazepine; PB: phenobarbital; PHT: phenytoin; VPA: valproate; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; TPM: topiramate. For details of statistical analysis see the text.

However, contrasting results derive from the different studies, and firm conclusions have not yet been achieved. Thus, it is still unanswered the question whether or not hyper-tHcy is a mere biochemical marker of atherogenesis or a clear causative factor (Hankey, 2007).

The results of our study show that a condition of hyper-tHcy <100 μmol/L is not associated with vascular retinal damage in epileptic patients, according to the data from independent studies which failed to find an association between hyper-tHcy and retinal vascular occlusion in nonepileptic patients (Di Crecchio et al., 2004; Pinna et al., 2006). The discrepancy between these findings and those deriving from the above quoted meta-analysis by Cahill and coworkers might have different explanations (Cahill et al., 2003). First, our population and that investigated by Di Crecchio et al. (2004), for instance, included subjects younger than 50 years, while in most of the studies considered in the meta-analysis (Cahill et al., 2003) patients had a mean age greater than 65 years. It is also well-known that older populations generally have a lower degree of collaboration, higher degree of media opacities, and smaller pupil size (Soto-Pedre et al., 2003). It is therefore possible that advanced age plays a crucial role in the facilitation of the detrimental effects of hyper-tHcy. In addition, other possible variables include the degree of hyper-tHcy, the exposition time and, for the epileptic patients, the disease itself as well as its duration, and the effect of the antiepileptic therapy. Notably, a recent fine study showed an association between the latter three parameters and the average carotid intima-media thickness in epileptic subjects, leading to the conclusion that these patients show an increased vulnerability to develop subclinical atherosclerosis (Hamed et al., 2007). In the latter study, however, mean plasma tHcy levels were remarkably higher than those observed in our patients (50.37 vs. 29.8 μmol/L).

Our study has some limitations. The assessment of retinal vascular status relied on the accurate visual inspection of retinal images performed in blind conditions by skilled ophthalmologists. However, we acknowledge that refinement of digital retinal image analysis may lead to a greater degree of automation and may ultimately give more valuable information regarding an individual’s potential risk of cerebrovascular disease (Tobin et al., 2007).

In conclusion, our findings suggest that adult hyperhomocysteinemic epileptic patients do not show increased risk to develop retinal microangiopathy damage. A complex interplay among different factors, including genetic/ethnic differences in vascular disease predisposition, and methodological differences between the different studies could explain the contradictory data observed in the literature (Hankey, 2007). Large, prospective, specifically designed, ongoing studies will provide further data and should eventually establish also whether dietary therapy with folate and B12 vitamin supplementation may prevent vascular diseases in subjects with increased tHcy levels (B-Vitamin Treatment Trialists’ Collaboration, 2006).

References


Please cite this article in press as: Belcastro, V., et al., Hyperhomocysteinemia and retinal vascular changes in patients with epilepsy, Epilepsy Res. (2008), doi:10.1016/j.eplepsyres.2008.04.008


