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ORIGINAL ARTICLE

Postural Control in Patients After a Recent Vestibular Neuritis with Hyperhomocysteinemia

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Abstract To assess the possible role of hyperhomocysteinemia (HyHcy) in delaying recovery after acute vestibular neuritis. In our retrospective study, 90 subjects were evaluated within 7 days from the beginning of an acute vertigo. All subjects had high plasma levels of homocysteine (Hcy). 46 patients were treated with homocysteine lowering therapy and betahistine for 1 month, while 44 subjects received only betahistine. Subjective symptoms were evaluated with the Dizziness Handicap Inventory (DHI) questionnaire, administered 7 days after the beginning of vertigo and again after 1 month. Moreover, postural control performed at 1 month' control was studied with static stabilometry in a subgroup of 21 non-treated and 20 treated patients. DHI total score decreased significantly more in the subgroup of subjects treated with homocysteine lowering therapy. Moreover, posturographic data were significantly increased in non-treated compared with treated subjects. Our data support the possibility of a role of HyHcy in preventing recovery after a recent vestibular neuritis. A microvascular disorder or the neurotoxic effect of HyHcy have been considered as possible causal factors. Although not conclusive, our data are not inconsistent with the hypothesis of a poorer adaptation in patients with untreated HyHcy.

Keywords Vestibular neuritis · Vestibular adaptation · Hyperhomocysteinemia · Static stabilometry

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Introduction

Hyperhomocysteinemia (HyHcy) is a condition characterized by high levels of homocysteine (Hcy) in the blood; levels higher than 15 μmol/l of Hcy in the blood are clinically defined as hyperhomocysteinemia [1]. High plasma levels of homocysteine may result from the interaction between genetic and dietary conditions.

Among the genetic factors, hyperhomocysteinemia has been demonstrated in individuals with mutation of methylenetetrahydrofolate reductase (MTHFR), particularly in the homozygous condition [2]; in the normal population, the frequency of the mutation rises from 1 % in Africa and Southeast Asia to 30 % in Europe and America [3].

Often, an improved regime of Vitamin B12 and folic acid is helpful to correct the levels of homocysteine, particularly in subjects with a smooth genetic predisposition to the condition (heterozygous condition), and high plasma levels of Hcy may arise solely from an insufficient intake of these vitamins [4].

High plasma levels of Hcy have been demonstrated to be a risk factor in various disease conditions, including neural tube defects, cardiovascular and neural disorders [5, 6]. In particular, HyHcy has been demonstrated to be an independent risk factor for cardiovascular-related mortality and patients with lower plasma levels of 12 μmol/l Hcy presented higher survival rates after an acute coronary syndrome [7, 8]. Moreover, HyHcy is also an independent risk factor for ischemic stroke [9].

More recently, HyHcy has been correlated with the possibility of developing dementia and Alzheimer's disease. Although inconclusive, other studies have proposed that arterial endothelial damage may be the pathophysiological mechanism [10]; an interesting finding is that, when

treating patients having HyHcy with folic acid and vitamins B6 and B12, the function of the blood–brain barrier was improved [11].

Recent studies have focused on the possibility that HyHcy as well as low serum folate may be a risk factor for sudden sensorineural hearing loss, and impaired cochlear perfusion has been proposed to be the causal factor [12, 13]. Moreover, acute peripheral vertigo may be correlated with high plasma levels of homocysteine and a case with symptoms mimicking Ménière's disease and HyHcy which caused a left internal jugular vein thrombosis has been reported [14, 15].

The clinical recovery from acute vestibular neuritis, a condition in which a viral etiology is commonly accepted, is called adaptation and is primarily related to central nervous system reprogramming of eye movements and postural responses [16].

So far, nothing has been published on a possible role of HyHcy in preventing adaptation. In our study, we wanted to assess whether high plasma levels of homocysteine may play a role in delaying mechanisms related to vestibular adaptation.

Materials and Methods

In this retrospective study, we included data from 90 patients evaluated in the ICP Poliambulatory, and San Raffaele Hospital between January 2005 and June 2008. The mean age of our sample was 57.5 ± 13 years; 37 were male and 53 were female.

The inclusion criteria were as follows: a recent rotational vertiginous episode with autonomic symptoms lasting for several days without cochlear symptoms; clinical evaluation made by a senior otologist within 7 days from the beginning of symptoms, and showing a horizontal spontaneous nystagmus in the dark with a positive head impulse test. All patients performed caloric tests according to Fitzgerald–Hallpike after a week from the onset of vertigo and were included when unilateral weakness was higher than 50 %. All included patients performed a central nervous system MRI which resulted negative.

The patients were included if the examiner had the possibility to assess homocysteine plasma levels in a few days and whether HyHcy was demonstrated (when plasma levels exceeded 15 μmol/l). In all patients, the final diagnosis was that of recent vestibular neuritis.

Exclusion criteria were:

- Previous episodes of vertigo or imbalance.
- Presence of comorbidities for neurological or psychiatric disorders (in particular, migraine and anxiety disorders).
- Therapies with drugs active on the central nervous system, except betahistine, in the last 30 days before inclusion.
- Significant visual or orthopedic disorders.

Assessment of subjective symptoms was made with a Dizziness Handicap Inventory (DHI) questionnaire [17]. Proposed by Jacobson and Newman, the 25-item self-administered questionnaire has been demonstrated to be useful in the evaluation of balance disorders as perceived by the patient. For each question, the score for the answer 'yes' is 4 points, 2 for the answer 'sometimes' and 0 for 'no'. The total score scale ranges from 0 (no handicap) to 100 (severely handicapped). Patients were asked to complete the DHI questionnaire on day 7 after the beginning of vertigo and then 1 month after the first evaluation. On that occasion, a second blood withdrawal was performed to assess homocysteine plasma levels.

46 patients were treated with a homocysteine lowering therapy [including folic acid (1 mg/day), vitamin B12 (400 μg/day) and vitamin B6 (10 mg/day)] from the first evaluation for 1 month, while in 44 cases, the examiner only suggested dietary measures. All 90 patients received a therapy with 48 mg betahistine per day for 1 month and were told to perform their daily activities.

Moreover on a sample of 20 treated and 21 not-treated patients from S Raffaele Hospital, static stabilometry (posturography) was performed at 1 month control. This gives information on the ability to integrate multiple inputs that contribute to the control of posture.

Stabilometry was performed with an Amplaid SveP platform with 10 Hz frequency of signal acquisition. The recordings were carried out in a quiet room. The standard test battery included the following measurements:

- Eyes opened (EO)
- Eyes closed (EC)
- Eyes opened while standing on 10-cm thick rubber foam (EOF)
- Eyes closed while standing on 10-cm thick rubber foam (ECF).

For each condition, we recorded the following parameters:

- Length of body sway (L), expressed in millimeters, defined as the sum of the path lengths of the center of pressure (COP).
- Surface of body sway (S), expressed in mm^2, represented by the confidence ellipse containing 90 % of the sample position.

For the value of length (L), the quotients EO/EC (Q1), EOF/ECF (Q2), and EO/ECF (Q3) were also calculated; the first two quotients underline the importance of visual

Table 1 Demographic data, values of homocysteine plasma levels (expressed in μmol/l) and DHI total score at the first control and after 1 month in the group of patients receiving lowering therapy for HyHcy and in the sample of not treated patients

	Treated patients ($n = 46$)	Not-treated patients ($n = 44$)	p Value
Age	58.5 ± 13.8	56.3 ± 12.4	≥0.05
Sex	18/46 males (39 %)	19/44 males (43 %)	≥0.05
Homocysteine before	29.9 ± 6	29.5 ± 7.8	0.51
Homocysteine after	17.4 ± 4.3	28 ± 8	≤0.05
DHI before	37 ± 8.7	33.8 ± 8.7	
DHI after	22.8 ± 7.9	30 ± 9.6	≤0.01

cues in balance control (with and without the proprioceptive variable), the third considers a complementary measure of unmasked vestibular function without vision and proprioception.

Demographic data are summarized in Table 1. No statistical significance was detected between groups for age and sex.

Statistical Analyses

Continuously distributed variables are described by mean and standard deviation. The significance of any difference between groups was evaluated by the t test for independent samples and analysis of variance (ANOVA) for repeated measures. Nominal data were compared with the Chi squared test. Since values of homocysteine in the subgroups demonstrated to have a bimodal distribution, a Mann–Whitney test has been performed.

Results and Analysis

The group of patients treated with vitamins had lower plasma levels of homocysteine at 1 month control and DHI was significantly lower than in the group of patients only receiving dietary suggestions, although treated patients exhibited higher values for DHI total score at the control 7 days after the beginning of vertigo (37 ± 8.7 and 33.8 ± 8.7 respectively; $t = 3.15$, $p = 0.03$). On the other hand, no difference was detected between groups for homocysteine plasma levels at the first control (29.9 ± 6 and 29.5 ± 7.8).

Treated patients had a significantly decreased DHI total score (37 ± 8.7 before and 22.8 ± 7.9 after, $p \leq 0.05$) while not-treated subjects did not (33.8 ± 8.7 before and 30 ± 9.6 after, $p = 0.06$).

Only treated patients showed decreased homocysteine plasma levels.

Demographic data, homocysteine plasma levels, results of DHI questionnaire and statistics are summarized in Table 1. Stabilometric findings and quotients are summarized in Tables 2 and 3.

Discussion

A reduction in DHI total score was present in both groups treated with betahistine, underlying the physiological mechanisms related to adaptation after an acute loss of vestibular function. Our study demonstrated a significant reduction, particularly in subjects treated with homocysteine lowering therapy. The DHI questionnaire is a validated instrument to assess self-perceived dizziness and disequilibrium, and is a reliable measure of recovery after rehabilitation for vestibular neuritis [18, 19].

Stabilometric findings are in accordance with the DHI questionnaire, since not-treated patients presented higher values of body sway than treated subjects and their balance control rely more on visual cues.

Several factors have been demonstrated to influence vestibular adaptation, including preexisting postural deficits, central nervous system and anxiety disorders [20]. Our preliminary data are not inconsistent with the hypothesis that high plasma levels of homocysteine may delay vestibular adaptation.

These findings may be explained by considering the different effects of higher homocysteine plasma levels. Above all, hyperhomocysteinemia has been identified as an independent risk factor for vascular diseases [21]; it is thus possible that homocysteine may be associated with poorer vestibular adaptation because of an influence on cerebral microvasculature.

On the other hand, homocysteine has been shown to be a potent neurotoxin and elevated plasma levels are correlated with multiple neurological and degenerative disorders such as Alzheimer's disease [22].

Prolonged exposure to homocysteine provokes a significant increase in neuronal apoptotic cell death in vitro, dependent on activation of the *N*-methyl-D-aspartate (NMDA) glutamate receptor, leading to excessive Ca^{2+} influx and reactive oxygen generation. Moreover, homocysteine potentiates glutamate excitotoxicity and β-amyloid (Aβ) toxicity, and could induce apoptosis by damaging DNA [23]. It should be noted that NMDA receptors have been demonstrated in medial vestibular nucleus neurons

Table 2 Stabilometric findings in the group of subjects not-treated and treated for HyHcy

	Not-treated ($n = 21$)	Treated ($n = 20$)	Statistical analyses p Value
Length of body sway; eyes open	312 ± 141	275 ± 83	0.30
Length of body sway; eyes closed	668 ± 195	481 ± 129	0.001
Length of body sway; eyes open; standing on rubber foam	422 ± 128	320 ± 95	0.005
Length of body sway; eyes closed; standing on rubber foam	884 ± 128	580 ± 110	0.002
Surface of body sway; eyes open	321 ± 148	200 ± 86	0.01
Surface of body sway; eyes closed	630 ± 120	472 ± 176	0.01
Surface of body sway; eyes open; standing on rubber foam	466 ± 120	310 ± 100	0.006
Surface of body sway; eyes closed; standing on rubber foam	830 ± 180	540 ± 1222	0.001

Table 3 Quotients between values of length of body sway in patients with residual dizziness and controls

	Not-treated ($n = 21$)	Treated ($n = 20$)	Statistical analyses p Value
Q1 (L eo/L ec)	0.48 ± 0.10	0.58 ± 0.14	0.001
Q2 (L eof/L ecf)	0.47 ± 0.12	0.59 ± 0.11	0.001
Q3 (L eo/L ecf)	0.36 ± 0.11	0.46 ± 0.12	0.001

and a bath application of NMDA agonists in vitro provokes an increase in neural spontaneous discharge [24].

Other studies have demonstrated that high plasma levels of homocysteine are associated with poorer neurobehavioral test performance in the elderly; subjects with HyHcy perform worst in all cognitive domains but were strongest in the domains related to simple motor and psychomotor speed and eye-hand coordination [25]; on the other hand, controversial results have been obtained on a possible reduction in spatial learning and other cognitive tasks in rats with diet-induced HyHcy [26, 27].

Finally, HyHcy has been associated with depression and partially with anxiety and these findings do not correlate with the age of subjects; moreover, HyHcy has been correlated with the possibility of chronicization of emotional disorders in a sample of male adults [28, 29].

Since DHI questionnaire assess self perceived symptoms and posturography above all integrations of different cues in balance control, our results should be confirmed by other studies based on more conclusive tests, including dynamic stabilometry and Dynamic Gait Index. If confirmed, our preliminary study nonetheless underline some difficulties in postural recovery, possibly related with HyHcy and these findings may be linked to different mechanisms.

Since NMDA receptors are thought to play an important role in vestibular compensation after unilateral vestibular deafferentation, a poorer postural control may be related to a dysfunction of the glutamatergic system in vestibular nuclei [30, 31]. Neurotoxicity provoked by HyHcy, delaying cognitive processes playing an important role in the early stages of recovery after an acute vestibular loss, may be the causal factor of our findings [32].

Finally, since a bidirectional correlation has been demonstrated between anxiety and vertigo, underlining possible common neural pathways, emotional factors may be hypothesized to play a role in a poorer postural control [33, 34].

Conclusions

Our study is based on retrospective data and should be confirmed by other studies. Nonetheless it underlines a possible role of HyHcy in delaying adaptation after a vestibular neuritis. Since assessment of plasma levels of homocysteine is a simple and not expensive exam, we would suggest to perform it routinely in all subjects after a vestibular disorder.

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