

## Homocysteine and cognitive functions in bipolar depression

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### Summary

**Aim.** The aim of the study was to evaluate a relationship between concentrations of homocysteine (HCY), vitamin B12 and folic acid and disturbances of cognitive functions during acute episode of bipolar depression.

**Methods.** 116 patients were studied (93 women, 23 men), aged 20-78 (mean 51±13) years during acute episode of bipolar depression. Depression was evaluated by the 17-item Hamilton's Depression Rating Scale (HDRS). The following tests measuring cognitive functions were applied: Trail Making Test, Wisconsin Card Sorting Test, Stroop Test and Wechsler Adult Intelligence Scale-Revised. In all patients, the measurements of serum homocysteine, vitamin B12 and folic acid were carried out.

**Results.** Hyperhomocystemia (HCY >15 µM/l) was detected in 41 patients (35%), more frequently in men (52%) than in women (31%). Patients with hyperhomocysteinemia achieved worse results in sub-tests of WAIS-R (Verbal comprehension, perceptual organization). In men, negative correlation was found between HCY concentration and number of errors in Stroop Test, and WCST (total errors and non-perseverative errors). In women with bipolar disorder, type II, negative correlation between HCY concentration and time of Stroop Test, and between vitamin B12 concentration and number of errors in Stroop Test, were demonstrated. In the whole group and in men, there was positive correlation between higher folic acid concentration and the number of errors in Stroop Test.

**Conclusions.** The results obtained show higher HCY concentration in considerable proportion of patients with bipolar depression, especially in men. They also confirm a connection between high homocysteine concentration and worse performance in some neuropsychological tests. Such relationship was more marked in men.

**Key words:** bipolar disorder, cognitive functions, homocysteine

## Introduction

During acute episode of depression, cognitive dysfunctions such as: impairment of general intellectual ability, memory, learning, and verbal fluency appear [1-4]. Depressive patients also show visual-spatial and motor functions disorders, connected with perception and visual differentiation, visual-motor coordination, as well as visual memory and psychomotor speed [5, 6].

Research comparing neuropsychological aspects of bipolar and unipolar depression demonstrated worse results in these tests obtained by bipolar patients in non-verbal part of Wechler Tests, both parts of Stroop Test, verbal fluency test and Trail Making Test [4]. Merriam et al. [7] noticed significantly worse results in the Wisconsin Card Sorting Test (WCST) in 79 depressive patients in comparison with healthy people. Martinez-Aran et al. [3] obtained results showing a persistence of some cognitive disorders in bipolar patients during remission period. Sackheim and Steif [8] found marked disorders in working memory and executive functions both during manic and depressive episodes. It was also shown that the degree of intensity of those disturbances is connected with worse prognosis about the illness' course. [9, 10].

Increase of serum homocysteine concentration (HCY) as well as decrease of folic acid and vitamin B<sub>12</sub> concentration constitute the risk factor for development of depression and also for its more severe course. It was shown that hyperhomocysteinemia may appears in over a half of depressed patients [11, 12]. In our own studies, we have shown a considerable frequency of hyperhomocysteinemia, especially in men, during depression in the course of mood disorders, and a reduction of this frequency after treatment. We have also confirmed a relationship between higher concentration of HCY and lower level of vitamin B<sub>12</sub> and folic acid during depression episode. [13, 14]

A connection between increase of HCY level and impairment of cognitive functions has been mainly demonstrated in the elderly subjects. Prins et al. [15] showed a correlation between increased homocysteine concentration and worse results on psychomotor tests in healthy people. In other studies, the deficits in information processing in elderly depressives [16, 17] and global impairment on neuropsychological tests in people with increased homocysteine level were found also in the context of dementia symptoms [15, 18-21]. Polish researchers indicated that people in whom mild cognitive impairment converts into dementia have higher intensity of depression and higher initial homocysteine concentration, in comparison with those not converting into dementia [22]. Recent studies also pointed at a connection between both depression and increased HCY level and impaired cognitive functions in elderly people [23, 24].

Alexopoulos et al. [25] obtained opposed results: they found a positive effect of higher homocysteine level on verbal information processing. According to these authors, homocysteine working agonistically on glutamatergic transmission in damaged synapses, can improve linguistic deficits and increase information processing in elderly depressive patients.

There are also studies conducted in elderly subjects concerning a relationship between lowered vitamin B<sub>12</sub> concentration and impairment of cognitive functions,

especially during depressive episode [26-28] Hankey et al. [29] used vitamin B<sub>12</sub> to lower HCY level in patients after brain stroke. Despite a reduction of this aminoacid they did not observe an improvement of cognitive functions.

In the last years, several papers concerning relation between hyperhomocysteinemia and cognitive dysfunctions in patients with mood disorders and schizophrenia, including also younger people, appeared. Osher et al. [30] described, in patients with bipolar disorder during euthymic period, greater worsening of cognitive function in people with higher HCY concentration in comparison to patients with normal HCY level. Also Dittmann et al. [31, 32], among bipolar patients during euthymic period, showed increased homocysteine level in those with impaired cognitive functions in comparison to patients without such impairment. Whereas Levine et al. [33] observed an improvement in neurocognitive functioning in schizophrenic patients after lowering homocysteine level.

### **Aim**

The aim of this study was to evaluate a relationship between concentrations of homocysteine (HCY), vitamin B<sub>12</sub> and folic acid and disturbances of cognitive functions during acute episode of bipolar depression.

### **Methods**

#### Patients studied

The study included 116 patients (93 men, 23 women), aged 20-78 (mean 51±13) years, during acute episode of bipolar depression (bipolar, type I – 37 persons, bipolar, type II – 79 persons). All subjects were hospitalized at Department of Adult Psychiatry, Poznan University of Medical Sciences. The mean duration of illness was 8 years (±5), and the mean duration of depressive episode was 4.6 months (±1.8). No illnesses that may influence cognitive functions were diagnosed among participating patients.

#### Assessment of depression

For the assessment of depression, the 17-item Hamilton Depression Rating Scale (HDRS) was used. Initial intensity of depression symptoms in whole group of patients on this scale was 19±2.9 points.

#### Assessment of cognitive functions

The following neurocognitive tests were used.

- The Trail Making Test (TMT). Part A of the test measures psychomotor speed. The results of part B reflect the ability to shift strategy and assess executive function and visuospatial working memory [34];

- The Wisconsin Card Sorting Test – WCST, which evaluates working memory and executive functions. The assessment included total number errors, perseverative errors and non-perseverative errors [35];
- The Stroop Test (Color-Word Interference Test). This test measures verbal working memory and executive functions. It consists of two parts. The first assesses a speed of reading colors' names and the second consists in naming the color in which the word is printed. However, the color of the printed word is different from the color described by the word [36];
- The Wechsler Adult Intelligence Scale – Revised (WAIS-R).

It enables the assessment of three aspects of intellectual abilities:

- verbal comprehension – level of knowledge acquired during education process, ability to define ideas, understand social norms and ability to create abstract ideas,
- Perceptual organization- visual-motor coordination, ability to visual synthesis and analysis, ability to notice significant deficiencies in perceptual material,
- memory and resistance to distractors – capacity of short-term memory, working memory efficiency, concentration ability.

#### Laboratory measures

In all patients biochemical tests were performed including measurement of serum homocysteine, folic acid and vitamin B<sub>12</sub>.

For the assessment of homocysteine, the analysed plasma thiol compound (Homocysteine, Fluka, Germany) was diluted with water at 2:1 ratio and reduced using 1% TCEP (Tris-(2-carboxyethyl)-phosphin-hydro-chloride, Applichem, Germany) at 1:9 ratio. Subsequently, the samples were deproteinized using 1M HClO<sub>4</sub> (at 2:1 ratio) and applied to the HPLC system. The samples were injected to the HPLC system (P580A; Dionex, Germany) coupled to an electrochemical detector (CoulArray 5600, ESA, USA). The analysis was performed in Termo Hypersil BDS C18 column (250 mm × 4.6 mm × 5 μm, Germany) in isocratic conditions, using the mobile phase of 0.15 M phosphate buffer, pH 2.9, supplemented with 12.5%-17% acetonitrile for estimation of HCY [37].

The assay of folic acid and vitamin B<sub>12</sub> was performed by immunodiagnostic method using direct chemiluminescence procedure by ADVIA Centaur Folate and ADVIA Centaur VB12 tests.

#### Statistical methods

Statistical calculations were conducted using the package STATISTICA for Windows, version 10. Chi-square test, Student's t-tests and Pearson's correlation analysis were applied. For statistical analysis the level of significance  $p < 0.05$  was adopted.

The research was approved by the Bioethics Committee, Poznan University of Medical Science.

## Results

The intensity of depression measured by the Hamilton scale was significantly higher in men ( $20.6 \pm 1.7$  vs  $18.6 \pm 3.0$ ;  $p=0.003$ , Student's t-test).

In the studied group, the mean concentration of homocysteine was  $14 \pm 8.6$   $\mu\text{M/l}$ , vitamin B<sub>12</sub>:  $343 \pm 144$   $\text{pg/ml}$  and folic acid  $5.7 \pm 2.7$   $\text{ng/ml}$ . Hyperhomocysteinemia (HHCY) defined as concentration of HCY  $\geq 15$   $\mu\text{M/l}$ , was found in 41 patients (35%), decrease of folic acid concentration ( $\leq 5.0$   $\text{ng/ml}$ ) was observed in 54 patients (47%) and decrease of vitamin B<sub>12</sub> concentration ( $\leq 200$   $\text{pg/ml}$ ) in 14 patients (12%).

HHCY was more frequent in males (52%) than in female (31%), difference at the borderline statistical significance ( $p=0.059$ , chi-square test).

There were no statistical differences in performing any neuropsychological test between male and female group.

Table 1 presents a comparison of clinical, laboratory and neuropsychological data between group of patients with hyperhomocysteinemia and patients in whom HCY concentration was  $< 15$   $\mu\text{M/l}$ .

**Table 1. Comparison of clinical, laboratory and neuropsychological data between group of patients with hyperhomocysteinemia and patients in which HCY concentration was  $< 15$   $\mu\text{M/l}$ .**

	Hyperhomocysteinemia (-) N=75	Hyperhomocysteinemia (+) N=41	p
Duration of illness	$7.9 \pm 5.7$	$9.0 \pm 5.5$	0.305
Duration of depressive episode	$4.6 \pm 1.6$	$4.4 \pm 2.1$	0.513
HDRS	$18.9 \pm 2.9$	$19.1 \pm 2.9$	0.844
Age	$49.2 \pm 12.2$	$52.8 \pm 14.3$	0.154
Folic acid	$5.8 \pm 2.4$	$5.4 \pm 3.2$	0.446
Vitamin B12	$366.3 \pm 146.8$	$301.7 \pm 130.1$	0.020*
Stroop A time	$31.3 \pm 7.6$	$31.7 \pm 7.9$	0.824
Stroop A errors	$0.1 \pm 0.1$	$0.0 \pm 0.0$	0.462
Stroop B time	$62.9 \pm 17.4$	$67.3 \pm 17.1$	0.193
Stroop B errors	$1.3 \pm 2.0$	$1.3 \pm 1.4$	0.885
TMT A	$39.0 \pm 12.9$	$39.5 \pm 12.9$	0.870
TMT B	$79.1 \pm 27.4$	$90.1 \pm 53.1$	0.143
WAIS-VU	$109.1 \pm 15.4$	$102.1 \pm 13.2$	0.015*
WAIS-PO	$98.6 \pm 12.2$	$91.8 \pm 13.5$	0.007*
WAIS-MRD	$95.7 \pm 13.7$	$93.3 \pm 13.0$	0.355
WCST tot err	$33.1 \pm 17.3$	$33.8 \pm 15.1$	0.835

*table continued on the next page*

WCST pers err	17.6±12.7	18.5±11.4	0.710
WCST non pers	15.6±9.7	15.1±7.3	0.770

WAIS-VU – verbal understanding, WAIS-PO – perceptual organization, WAIS-MRD – memory and resistance to distractors, WCST tot err – number of total errors, WCST pers err – perseverative errors, WCST non pers – non-perseverative errors

\* Statistical significance

Patients with HHCY performed significantly worse on two sub-tests of WAIS-R, namely verbal comprehension, perceptual organization. Patients with HHCY also differed from the remaining ones by significantly lower vitamin B<sub>12</sub> concentration, while folic acid concentration did not show differences between both groups.

Correlation between HCY concentration and the performance on cognitive tests was observed mainly among male group. In this group, negative correlation was found between HCY concentration and number of errors in Stroop Test, part B ( $r=0.43$ ;  $p=0.020$ ), and WCST total errors ( $r=0.56$ ;  $p=0.003$ ) and non-perseverative errors ( $r=0.54$ ;  $p=0.004$ )

In the group of 62 women with bipolar disorder, type II, negative correlation between HCY concentration and time of Stroop Test, part B ( $r=0.28$ ;  $p=0.014$ ) and between vitamin B<sub>12</sub> concentration and number of errors in Stroop Test, part A ( $r=0.38$ ;  $p=0.001$ ), was demonstrated.

There was positive correlation between higher folic acid concentration and number of errors in Stroop Test, part B, in the whole group ( $r=0.20$ ;  $p=0.016$ ) and in men ( $p=0.44$ ;  $r=0.018$ ).

Worse results at perceptual organization at Wechsler's test ( $r=-0.22$ ;  $p=0.017$ ) and higher number of non-perseverative errors at the Wisconsin Card Sorting Test ( $r=0.22$ ;  $p=0.0019$ ) were observed in older patients.

Among patients suffering long term illness positive correlation with Trail Making Test part B performance was observed ( $r=0.21$ ;  $p=0.024$ ).

## Discussion

In this study, we found hyperhomocysteinemia, defined as HCY concentration higher than 15  $\mu\text{M/l}$  in a half of men and in one-third of women during acute episode of bipolar depression. Higher frequency of HHCY in bipolar men was also observed by Israeli researchers [38].

The most important finding of our study was to indicate that patients with higher HCY level achieved worse results in two sub-tests of WAIS-R, namely verbal comprehension and perceptual organization compared to patients with normal homocysteine level. Patients with increased HCY performed worse in the area of ability to create abstract definitions and to define terms, they had less capacity of long-term memory, as well as worse ability to visual synthesis and analysis, visual-motor coordination, ability to notice significant deficiencies in perceptive material, along with worse working memory.

In male group, along with higher frequency of hyperhomocysteinemia, there were also significant relationships between homocysteine level and worse results in performing other neuropsychological tests. This was especially the case for tasks connected with executive functions, measured by Stroop Test and the WCST. It confirms the results obtained by Osher et al. [38] pointing to relation between hyperhomocysteinemia and worse performance on Wisconsin test in male bipolar patients which, in contrast to ours, were in euthymic state.

Some studies performed in the elderly subjects showed association between vitamin B<sub>12</sub> level and impairment of cognitive functions in this group [26-28]. Such association was not found in euthymic bipolar patients [38]. In this study we found lower vitamin B<sub>12</sub> level in patients with HHCY. Also, a negative correlation between time for Stroop Test part A and serum vitamin B<sub>12</sub> was found in female patients with bipolar disorder type II. Recent study performed in our clinic showed a relationship between lower level of vitamin B<sub>12</sub> and lower efficiency of single ketamine infusion in patients with bipolar depression [39]. However, it is difficult to interpret a positive correlation between the number of errors in Stroop Test part B and concentration of folic acid observed in our study.

The strength of our research may be connected with a high number of participating patients with bipolar disorder, both I and II type. Whereas some limitations may be due to a lack of the results of neuropsychological tests performed during remission period which could establish whether relation between HHCY and cognitive functions depends on depression intensity. During treatment of depression some decrease, although in some cases statistically significant, of HCY concentration and reduction of a number of HHCY patients may be observed [14]. The results of Israeli researchers may be recalled here as they have also observed such phenomenon in euthymic bipolar patients [38].

## Conclusions

To sum up, the obtained results show higher HCY concentration in considerable proportion of patients with bipolar depression, especially in men. They also confirm a connection between high homocysteine concentration and worse performance on some neuropsychological tests. Such relationship is more marked in men.

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