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ORIGINAL PAPER

Homocysteine and cognition in first-episode psychosis patients

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Abstract In the last years, there has been growing evidence linking elevated homocysteine levels with cognitive dysfunction in several neurological and neuropsychiatric diseases. The aim of the present study was to investigate the potential relationship between elevated homocysteine levels and cognitive deficits in first-episode psychosis patients. Plasma levels and cognitive performance of 139 patients and 99 healthy volunteers were compared. Patients were classified as elevated homocysteine (>90 percentile for controls) and normal and compared on 22 cognitive outcome measures grouped into cognitive domains known to be impaired in schizophrenia. Patients had a statistically significant increase in plasmatic homocysteine levels. In addition, they presented with significantly increased cognitive deficits. However, no relationship between homocysteine levels and cognitive impairment was detected. These results suggest the need for further studies to clarify the role of homocysteine in the etiology and prognosis of psychosis.

Keywords Homocysteine · Cognition · Psychosis · Schizophrenia

Introduction

Cognitive deficits are already present at the first break of schizophrenia [18]. Most schizophrenic patients have cognitive deficits, and these deficits account for much of their functional impairment in the real world [17]. However, little is known about brain pathophysiological mechanisms related to these cognitive impairments, and pharmacological treatments have limited efficacy against cognitive deficits [8]. The investigation of biological substrates of cognitive symptoms in schizophrenia is a timely topic of research.

Homocysteine (Hcy) is a non-protein neurotoxic amino acid that has been proposed as an independent risk factor for schizophrenia through developmental effects on brain structure and function [4]. Increased total plasma Hcy levels have been associated with cognitive dysfunction in a wide array of neurological and psychiatric disorders [46]. A substantial body of literature confirms the association between elevated plasmatic Hcy levels and cognitive deficits in Alzheimer's disease [32], Parkinson disease [26], multiple sclerosis [39], bipolar disorder [10] and schizophrenia [23]. On the contrary, some of the previous studies

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have failed to observe this association between plasma Hcy levels and cognitive dysfunction in psychiatric disorders [9, 14]. We still do not have convincing evidence regarding the relationship between Hcy and cognitive impairment in schizophrenia.

Discrepant results may be due to the heterogeneity of patient samples or differences in factors affecting Hcy levels. The assessment of Hcy levels requires the measurement of known confounding variables [29]. Deficiency in either folate or vitamin B_{12} leads to an increase in total serum Hcy concentrations, so it is important to consider if elevated Hcy levels may reflect vitamin B_{12} or folate deficiency. Hcy levels rise progressively with age, and elevated Hcy levels in the elderly may contribute to age-related neurodegeneration [11]. Gender also has to be taken into account given the higher incidence of elevated Hcy levels reported in male schizophrenic patients [22]. In addition, increased Hcy levels could be caused by smoking, renal function, lack of exercise or poor diet [23].

The aim of our study was to explore whether elevated levels of plasma Hcy are associated with cognitive impairments, in a large sample of patients with first-episode non-affective psychosis. We hypothesize that first-episode patients might have higher Hcy levels and that increased total plasma Hcy levels would be associated with cognitive deficits found in this population. We took into account confounding factors such as age, gender, smoking, serum folate and vitamin B_{12} levels that might affect Hcy plasma levels.

Methods

Subjects

The patient group consisted of 139 (age range 16–60, 64 females) medication naïve subjects included in the first-episode psychosis program of Cantabria, Spain, (PAFIP) from January 2005 to December 2010 who met inclusion criteria for PAFIP [33]. The patients were screened for demographic and clinical characteristics such as age, education, age of illness onset, duration of untreated psychosis (DUP) and symptoms of psychosis that were assessed by means of the Scale for the Assessment of Negative symptoms (SANS) [1] and the Scale for the Assessment of Positive symptoms (SAPS) [2]. A group of 99 healthy volunteers (40 females, age range 15–50 years) were initially recruited from the community through advertisements. They had no current or past history of psychiatric, neurological or general medical illnesses, including substance abuse and significant loss of consciousness, as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH). The study was approved by the Marqués de Valdecilla University Hospital review board, and written informed consent was obtained from all subjects after complete description of the study. FEP and HC underwent the same laboratory and neuropsychological testing procedures.

Laboratory assessments

Blood samples were assessed for Hcy, serum vitamin B_{12} and serum folate. To minimize the effects of diet and technique, patients' and healthy volunteers' blood samples were obtained during fasting between 8:00 and 10:00 a.m. by the same personnel, in the same setting. Vitamin B_{12} and serum folate levels were measured by automated methods on an Advia Centaur (SIEMENS). Plasma Hcy levels were measured by means of immunonephelometry in a Nephelometer Analyzer II (SIEMENS) using the reagents manufactured by SIEMENS. Reproducibility of intra-assay and interassay was <5 and $<7\%$, respectively.

Neuropsychological assessment

The neuropsychological evaluation was performed 12 weeks after recruitment, as this time is considered optimal for patients' stabilization [16]. All participants, FEP and healthy volunteers, completed the test in the following standardized sequence (scores considered in brackets): 1—the Rey Auditory Verbal Learning Test (RAVLT) [38] (trials 1–5, list recall and list recognition discrimination subscore); 2—WAIS-III digit symbol subtest [47] (standard total score); 3—Grooved Pegboard Test [24] (time to complete with dominant hand); 4—The Zoo Map Test [12] (first and second conditions); 5—Tower of London Test (ToL) [42] (total correct and total moves score); 6—Rey Complex Figure (RCF) [31] (copy figure and delayed recall); 7—Trail Making Test (TMT) [36] (trails A and B); 8—WAIS-III digits forward and backward subtests [47] (standard total score); 9—WAIS-III letter-number sequencing subtest [47] (standard total score); 10—WAIS-III vocabulary subtest that was used as measure of premorbid IQ [47] (standard total score); 11—Stroop Test [15] (color-word); 12—letter (FAS) [43] and semantic (animal) [5] fluency tests; 14—Eyes Task [3] (total correct score); 15—Continuous Performance Test (CPT) [6] (reaction time and discrimination subscores). The evaluation required approximately 2 h and was carried out in the same day by the same neuropsychologist R.A.-A. and E.G.-R.

This test was grouped in the following cognitive domains consistently shown to be impaired in schizophrenia [28]: information processing speed, motor dexterity, working memory, verbal learning, visuospatial abilities, delayed memory, attention, executive function and theory of mind.

Hypothesis testing

Statistical analyses addressed the following predictions: (1) In FEP patients, Hcy plasma levels will be increased relative to healthy comparison subjects. (2) Patients will be impaired on neuropsychological measures when compared with healthy volunteers. (3) Among patients, those with elevated Hcy plasma levels will perform worse on neurocognitive tests.

Parametric χ^2 and t-tests were used to compare the patients and healthy volunteers on demographic, clinical and laboratory variables. To test the first hypothesis, ANCOVAs were performed considering plasma Hcy level as the dependent variable and group (patients vs. controls) as the independent variable, and controlled for age, sex, serum folate, vitamin B_{12} and smoking as indicated. ANCOVAs were used to test the second hypothesis, using performance on test as the dependent variable and controlled for age, sex and education. In order to test the third hypothesis, and based on previous literature [45], patients were categorized into two groups using the cutoff level of >90 percentile (>14.85 μmol/L): patients with normal Hcy (≤14.85 μmol/L) and patients with elevated Hcy levels (>14.85 μmol/L). Moreover, in clinical milieu, similar cutoff Hcy plasma level (>15 μmol/L) is utilized to define elevated Hcy levels. ANCOVAs adjusted by confounding variables were used to compare each of the items in the neuropsychological test battery in the two Hcy groups. Post hoc analyses were performed on all main effects (Bonferroni corrected $p < 0.05$).

The Statistical Package for Social Science, version 19.0 (SPSS Inc., Chicago, IL), was used for statistical analyses. All statistical tests were two-tailed, and significance was determined at the 0.05 level.

Results

Metabolic differences between FEP patients and healthy volunteers

We observed that patients had statistically significant ($p < 0.001$) elevated plasma Hcy levels compared with healthy volunteers (mean (SD) = 13.64 (7.13) μmol/L in patients vs. 11.09 (2.99) μmol/L in healthy volunteers). The concentrations of serum folate and vitamin B_{12} did not differ between groups, but the presence of smokers is higher in male patient group (66.6 vs. 37.9%). (See Table 1). The ANCOVA analyses showed the significant association between Hcy level and group ($F = 50.83$; $p < 0.001$; adjusted R squared = 0.188) supporting Hypothesis 1. Hcy plasma level was significantly associated with sex ($F = 4.19$; $p = 0.04$) and serum folate level ($F = 9.94$; $p = 0.002$). No significant associations between Hcy levels and age ($p = 0.75$), vitamin B_{12} ($p = 0.36$) and smoking status ($p = 0.1$) were observed (Table 2).

Table 1 Demographic, clinical and laboratory characteristics of FEP patients and healthy volunteers

	Patients ($N = 139$)		Healthy volunteers ($N = 99$)		p
	Mean	SD	Mean	SD	
Age (years)	32.09	10.83	26.97	6.1	<0.001*
Sex (female)	46%		41%		0.5
Education (years)	10.22	3.54	11.3	2.77	0.009*
Age of illness onset (years)	30.96	10.44	–	–	–
DUP (months)	14.79	34.13	–	–	–
SAPS	14.31	4.46	–	–	–
SANS	6.65	6.13	–	–	–
Hcy (μmol/L)	13.64	7.13	11.09	2.99	<0.001*
Male	15.15	8.61	12.38	3.05	0.01*
Female	11.84	4.51	9.56	1.86	0.001*
Folate (ng/mL)	7.76	3.87	7.11	3.86	0.21
Male	7.33	4.18	6.36	2.45	0.11
Female	8.9	4.71	8.3	5.35	0.55
Vitamin B_{12} (pmol/L)	437.15	177.13	432.88	160.57	0.84
Male	423.16	171.29	426.22	146.8	0.91
Female	513.29	508.39	447	180.24	0.44
Smoking (yes)	57.6%		43.9%		0.06
Male	66.6%		37.9%		0.004*
Female	46.9%		52.5%		0.4

DUP duration of untreated psychosis, *SAPS* Scale for the Assessment of Positive symptoms, *SANS* Scale for the Assessment of Negative symptoms, *Hcy* homocysteine

*$p < 0.05$

Table 2 Demographic, clinical and laboratory characteristics of the patients with elevated and normal Hcy levels

	Patients ($N = 31$) with elevated Hcy		Patients ($N = 108$) with normal Hcy		
	Mean	SD	Mean	SD	p
Age (years)	29.29	9.74	32.9	11.03	0.1
Sex (female)	32.25%		50%		0.1
Education (years)	9.1	2.98	10.54	3.63	0.04*
Age of illness onset (years)	29.04	9.91	31.49	10.57	0.26
DUP (months)	7.96	12.22	16.71	37.92	0.04*
SAPS	13.8	4.46	14.45	4.38	0.47
SANS	6.53	6.34	6.68	6.1	0.9
Hcy (μmol/L)	22.85	10.18	11	2.21	<0.001*
Male	24.23	11.61	11.6	2.16	<0.001*
Female	19.56	5.66	10.39	2.11	<0.001*
Folate (ng/mL)	5.38	2.02	8.43	4	<0.001*
Male	5.26	1.94	7.71	3.18	0.002*
Female	5.61	2.26	9.08	4.6	0.023*
Vitamin B_{12} (pmol/L)	379.13	213.3	453.81	162.64	0.03*
Male	379.24	216.05	436.83	153.36	0.376
Female	341.1	213.42	470.78	171.17	0.038*
Smoking (yes)	61.3%		56.5%		0.63
Male	66.7%		66.7%		1
Female	50%		46.3%		0.829

DUP duration of untreated psychosis, *SAPS* Scale for the Assessment of Positive symptoms, *SANS* Scale for the Assessment of Negative symptoms, *Hcy* homocysteine

*$p < 0.05$

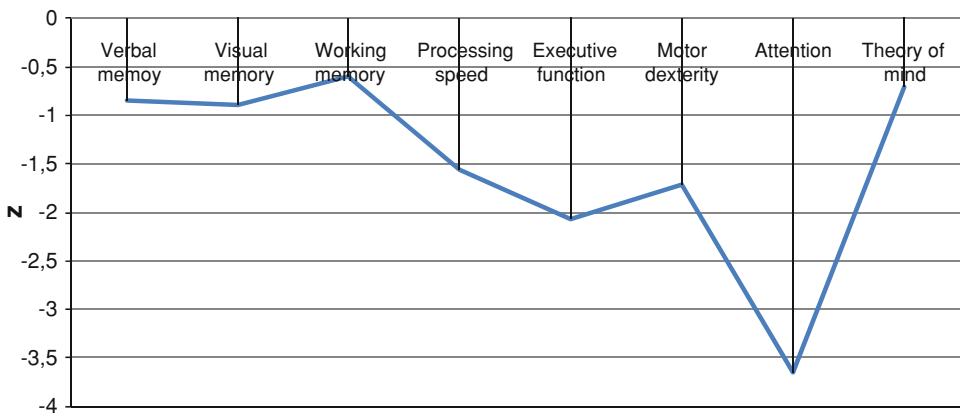

Fig. 1 Comparison of FEP patients and healthy volunteers on cognitive domains

Neurocognitive differences between FEP patients and healthy volunteers

Consistent with Hypothesis 2, patients showed significantly worse cognitive performance compared with healthy volunteers. In most of the cognitive tests $p < 0.001$, with the exception of the Rey Complex Figure copy ($p = 0.81$); WAIS-III vocabulary subtest ($p = 0.04$), Rey Auditory Verbal Learning Test recognition ($p = 0.05$), Zoo Map Test, first ($p = 0.004$) and second ($p = 0.003$) conditions and ToL total corrects moves score ($p = 0.006$) did not survive Bonferroni correction ($p < 0.002$). (See Fig. 1; Table available as supplementary material).

Neurocognitive differences between Hcy groups

When groups of patients with normal and elevated Hcy levels were compared, we did not find significant differences in cognitive functioning adjusting for age, sex and education, with the exception of WAIS-III digit symbol subtest (normal Hcy = 50.56 (16.37) vs. elevated Hcy = 55.23 (15.19); $p = 0.03$). However, this difference did not survive Bonferroni correction. The results of cognitive performance in the two groups are summarized in Table 3. In repeating analyses after additional adjustment for serum folate, vitamin B_{12} and smoking status, the relationships between Hcy levels and cognitive performance remained overall unaltered. No other

Table 3 Relationship between Hcy and cognition in FEP patients with normal (≤14.85 μmol/L) vs. elevated (>14.85 πmol/L) Hcy levels

	Patients ($N = 108$) with normal Hcy		Patients ($N = 31$) with elevated Hcy			
	Mean	SD	Mean	SD	F	p
Cognitive domain						
Pre-morbid IQ						
WAIS-III vocabulary raw score	37.8	9.37	36.5	8,23	0.18	0.66
Information processing speed						
WAIS-III digit symbol raw score	50.56	16.37	55.23	15.9	4.94	0.03*
TMT-A (sec)	52.84	21.57	53.07	17.61	0.03	0.86
CPT reaction time msec	542.03	70.32	552.45	73.04	0.8	0.37
Motor dexterity						
Grooved Pegboard dominant hand (sec)	75.22	23.63	75.9	19.75	0.1	0.75
Working memory						
WAIS-III letter-number sequencing raw score	8.15	2.84	7.93	3.04	0.07	0.8
WAIS-III digits forward raw score	8.56	2.23	8.10	2.02	0.51	0.47
Verbal learning						
RAVLT trials 1-5	42.56	10.62	42.5	10.74	0.47	0.49
Visuospatial abilities						
Rey figure copy	33.22	4.26	33.86	2.2	1.41	0.23
Delayed memory						
RAVLT list recall	7.51	3.19	7.73	3.25	0.71	0.4
RAVLT list recognition discrimination subscore	0.96	0.04	0.97	0.03	1.36	0.24
Rey figure recall	16.82	6.92	18.95	8.29	2.85	0.09
Attention						
CPT discrimination subscore	0.94	0.08	0.95	0.05	0.75	0.38
Executive function						
TMT-B (sec)	122.41	68.05	111.4	52.65	1.58	0.21
Stroop color-word	35.1	9.71	35.5	12.35	0.6	0.44
Zoo Map (first condition)	3.88	2.96	3.62	3.44	0.44	0.5
Zoo Map (second condition)	6.33	2.16	6.93	1.58	1.21	0.27
ToL total correct score	3.58	2.3	3.41	2.32	0.1	0.74
ToL total move score	43.83	20.68	40.83	20.1	0.89	0.34
Phonemic fluency FAS total score	29.48	10.08	26.3	7.99	0.2	0.65
Semantic fluency animals total score	15.93	4.03	16.57	3.58	2.9	0.09
Theory of mind						
Eyes Task total correct	20.96	4.78	20.41	4.8	0.05	0.82

Univariate analysis of variance with age, gender and education as covariates

Hcy homocysteine, *IQ* intelligence quotient, *WAIS-III* Wechsler Adult Intelligence Scale III, *TMT-A* Trail Making Test A, *TMT-B* Trail Making Test B, *CPT* Continuous Performance Test, *RAVLT* Rey Auditory Verbal Learning Test, *ToL* Tower of London

*$p < 0.05$

variable reached significance for multiple regression analysis (data available as supplementary material). We found no neurocognitive performance differences between elevated and normal Hcy levels in FEP patients or healthy volunteers. Hypothesis 3 was not supported.

Metabolic and clinical differences between Hcy patient groups

Finally, when comparing Hcy patient groups, patients with elevated Hcy levels ($N = 31$) presented significantly lower serum folate levels as compared to patients with normal Hcy levels ($N = 108$) (5.38 (2.02) vs. 8.43 (4.12) ng/ml; $t = 3.85$, $p < 0.001$). Moreover, male patients with elevated Hcy levels ($N = 21$) but not females ($N = 10$) presented significantly higher serum folate levels ($p = 0.002$ vs. $p = 0.02$). Also the elevated Hcy group showed vitamin B_{12} deficits (453.81 (162.64) vs. 379.13 (213) pmol/L; $t = 2.09$, $p = 0.03$). Nevertheless, only women presented significant vitamin B_{12} deficits (male $p = 0.37$ vs. female $p = 0.03$). Smoking was similar in both groups ($p = 0.63$). Concerning clinical and demographic variables, patients

with elevated Hcy levels presented shorter DUP (7.96 (12.22) months vs. 16.71 (37.92) months; $t = 2$ $p = 0.04$). We found no symptom differences between patients with elevated and normal Hcy levels. (See Table 2).

Discussion

In the present study, we observed that (1) FEP patients, compared to healthy volunteers, have elevated plasma Hcy concentration; (2) FEP patients also have marked cognitive impairments; (3) however, our results here do not provide further support for an association between plasma Hcy levels and cognitive functioning in early phases of psychosis; (4) males with folate deficits, and females with folate and vitamin B_{12} deficits, may be considered risk factors for altered Hcy levels in FEP patients.

Plasma Hcy levels in FEP patients vs. healthy volunteers

Our findings of markedly elevated plasma levels of Hcy in FEP patients who had folate and vitamin B_{12} levels within normal limits at the early stages of the illness are in agreement with most of the previously reported results [20, 22, 25]. However, the pathogenic mechanism underlying these elevated Hcy levels in schizophrenia is not fully understood. It remains unclear whether higher plasma Hcy levels might be a cause or a consequence of psychosis. Petronijevic et al. [34] found a significant decrease in plasma Hcy levels, without changes in folate and vitamin B_{12} concentrations, in the remission phase of schizophrenia, which suggests an influence of Hcy metabolism in the pathogenetic process.

Neuropsychological functioning of FEP vs. healthy volunteers

FEP patients showed cognitive impairment in all areas of cognitive functioning assessed, except visuospatial abilities, independently of their age, sex and education level. Our results confirm previous findings revealing that cognitive dysfunction is present at the first break of schizophrenia [13], with some specific-domain particularities [37].

Relationship between Hcy and neuropsychological functioning in FEP patients

We failed to confirm previous findings showing that elevated plasma Hcy levels are a risk factor for cognitive impairments in neuropsychiatric disorders. On the contrary, it should be noted that patients with elevated Hcy levels have a better performance in task such as WAIS-III digit symbol, Rey figure recall, TMT-B and semantic fluency. Despite differences did not reach statistical significance, these findings were unexpected because previous investigations in chronic schizophrenic individuals have described a critical role of elevated Hcy levels in cognitive dysfunction [30]. One possible explanation of these conflicting findings is that previous studies have investigated older (Alzheimer's disease [AD]) and chronic populations. It has been described that Hcy might produce cognitive impairment in the elderly via an accumulative neurotoxic effect [11]. Dias et al. [9] suggest that increased Hcy level may play a role in the pathophysiology of neurocognitive deficits in bipolar disorder, with a greater impact among older patients or those with a delayed onset of illness. Additionally, Levine and colleagues [21] suggested that elevated plasma Hcy levels may cause central nervous system changes only when a damaged blood–brain barrier would allow the entry of elevated Hcy into the brain. Our similar neuropsychological findings in healthy volunteers with elevated and normal Hcy levels corroborated this suggestion. Therefore, it would be expected to observe a significant association between elevated Hcy levels and cognition in chronic schizophrenia samples but not in early-phase populations. We may suggest that cognitive functioning in schizophrenia patients with a shorter duration of the illness is not significantly determined by the potential morbid effect of elevated Hcy levels.

Hcy and related factors in FPE patients

In the present study, age had a smaller impact on Hcy levels, which may be explained by the absence of geriatric patients. As noted above, older age has been found to be associated with increased Hcy levels, particularly in AD. The largest study derived from the Framingham study [41] suggests that plasma Hcy levels >14 μmol/L almost double the risk for AD.

On the other hand, and interestingly, patients with elevated Hcy levels presented shorter DUP. We considered this finding difficult to explain based on previous literature, but interesting to further explore. However, it is beyond the scope of this study.

Concerning sex, increased plasma Hcy level has been reported in male schizophrenic patients [22]. Other authors [35] suggest that elevated Hcy level in females is an unspecific risk factor for organic brain disorders but not endogenous psychosis. In our study, we found that sex is associated with Hcy, so our findings support the hypothesis that increased Hcy levels affects male and female psychotic patients in a different way, which is interesting to explore at the first break of psychosis, although outcome gender differences are under debate [40].

Regarding factors that affect Hcy metabolism, in the present study, patients with elevated Hcy level, particularly

males, presented serum folate deficits without vitamin B_{12} deficits. On the contrary, females with elevated Hcy level present both serum folate and vitamin B_{12} deficits. Considering total plasma Hcy level is a sensitive measure of a functional serum folate deficiency [44], some authors [23] suggest that nutritional fortification with folic acid and vitamin B_{12} in schizophrenia, parallel to reduce Hcy levels, results in symptom reduction. Finally, and in accordance with previous studies, it should be noted that prevalence of smoking is significantly higher in male patients (66%) [19]. However, despite the knowledge of the relationship between smoking and Hcy levels, in the present study, we did not confirm this association.

Limitations in the study

Several limitations qualify our findings. First, it cannot be ruled out that our study is susceptible to other confounding factors, such as dietary and nutritional intake, overweight, sedentary life-style or some combination with smoking, which can interfere with Hcy metabolism [23, 29]. Second, common genetic polymorphisms of MTHFR have been associated with elevated Hcy levels in the general population [7] and with an increased risk for schizophrenia [27]. Finally, it is necessary to mention cross-sectional study design limitation. Given the presumed effects of Hcy levels on brain maturation and aging, the need of similar studies in FEP patients, even in at-risk populations, over the life span is warranted to determine the causes of elevated Hcy level, the association with genetics, and whether the elevation in Hcy level at disease onset determines some aspects of the disease process.

Conclusion

We found no evidence for a direct relationship between elevated Hcy levels and cognitive impairment in FEP patients. Nevertheless, our results indicate the need for further studies to clarify the role of Hcy in the etiology and prognosis of psychosis.

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Conflict of interest None.

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