High Serum Homocysteine Levels in Young Male Schizophrenic and Schizoaffective Patients With Tardive Parkinsonism and/or Tardive Dyskinesia

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Background: The pathogenesis of neuroleptic-induced tardive movement disorders (TMD), including tardive parkinsonism and tardive dyskinesia (TD), has not yet been established. An elevated serum level of total homocysteine has been implicated as a risk factor for various neuropathologic states and some movement disorders. The aim of our study was to determine whether there is an association between serum total homocysteine level and the presence of TMD among schizophrenic and schizoaffective patients.

Method: This study was conducted in Be'er Sheva Mental Health Center from August 2002 to May 2004. Fifty-eight patients with schizophrenia or schizoaffective disorder (DSM-IV) and TMD for at least 1 year (38 men, 20 women; age range, 28–73 years) were compared to a control group of 188 patients with DSM-IV–diagnosed schizophrenia or schizoaffective disorder without TMD (123 men, 65 women; age range, 19–66 years) regarding serum total homocysteine levels.

Results: Men with TMD (demonstrating tardive parkinsonism and/or TD) had significantly higher mean serum total homocysteine levels compared to sex- and age group–matched controls. The difference between groups was almost entirely attributable to the homocysteine levels of young male patients (age group, 19–40 years old) with TMD.

Conclusion: High serum total homocysteine level may constitute a risk factor for certain variants of TMD, especially in young schizophrenic or schizoaffective male patients. Further prospective studies are needed to clarify these findings.

(J Clin Psychiatry 2005;66:1558–1563)

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The authors report no financial affiliations or other relationships relevant to the subject of this article.

The authors thank Tzvi Dwolatzky, M.D., of Be'er Sheva Mental Health Center for editorial assistance.

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Tardive dyskinesia (TD) is a chronic movement disorder that frequently appears in those receiving psychotropic agents. This condition constitutes a substantial problem in long-term antipsychotic therapy and may lead to various clinical consequences including noncompliance with treatment and an interruption in the patient-physician therapeutic alliance. Tardive dyskinesia consists of a group of delayed-onset abnormal involuntary movements and refers to a wide range of motor disturbances. Hence, a more appropriate term would be *neuroleptic-induced tardive subsyndromes*,[1–8] or *neuroleptic-induced tardive movement disorders* (TMD). It has recently been suggested that a distinction be made between classic TD (orobuccal-lingual-facial syndrome) and other forms of TMD such as tardive akathisia, tardive dystonia, tardive parkinsonian symptoms, tardive tremor, and tardive tics.[1–8] This distinction is based on data suggesting a varying profile of risk factors, clinical presentation, epidemiology, and treatment response for different forms of TMD.[2,4,6,7]

The pathophysiology of TMD is not well understood, and various theories suggest the involvement of dopaminergic neuronal pathways.[4,9] However, involvement of noradrenergic, GABAergic, cholinergic, serotonergic, and peptidergic pathways has also been reported.[4,10] More recently, excessive lipid peroxidation induced by free radicals has been suggested to play an important role in TMD.[11]

Homocysteine is a neurotoxic amino acid generated via methionine metabolism.[12–14] Homocysteine may be rapidly taken up by neurons via a specific membrane transporter.[15] Elevated plasma total homocysteine levels were reported in several neuropsychiatric disorders including Alzheimer's disease, major depression, and schizophrenia, and such high levels were suggested to constitute a risk factor in Alzheimer's disease and possibly depression and schizophrenia.[16–18] High homocysteine levels were also found in movement disorders, including dystonia and Parkinson's disease,[19–21] and recently homocysteine was reported to exacerbate oxidative stress, mitochondrial dysfunction, and apoptosis in human dopaminergic cells, with these effects being ameliorated by administration of antioxidants.[22]

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Normal serum homocysteine level is maintained by remethylation to methionine by enzymes that require folic acid and vitamin B_{12} and by catabolism to cysteine by the vitamin B_6–dependent enzyme cystathionine β-synthase (CβS).[23] In general, folate and vitamin B_{12} are more effective than vitamin B_6 in reducing plasma homocysteine levels unless the transsulfuration pathway metabolizing homocysteine via CβS is impaired. In this regard, it is of note that pharmacologic doses of vitamin B_6 were reported to have beneficial effects in different movement disorders including TD, neuroleptic-induced parkinsonism, and lithium-induced tremor.[24–26]

The above-described association between homocysteine and dopaminergic pathways, in addition to the finding of high levels of this toxic amino acid in certain movement disorders, suggests that a study of total homocysteine levels in patients suffering from TMD has clinical validity.

To the best of our knowledge, this is the first study to evaluate serum total homocysteine levels in schizophrenic and schizoaffective patients suffering from TMD.

METHOD

This study was conducted in Be'er Sheva Mental Health Center from August 2002 to May 2004. The following inclusion criteria were determined: (1) male and female patients, older than 18 years; (2) DSM-IV diagnosis of schizophrenia or schizoaffective disorder; (3) diagnosis of TMD as confirmed by 2 specialists in psychiatry experienced in the assessment and treatment of movement disorders. Neuroleptic-induced tardive akathisia, tardive tremor, and tardive parkinsonism were diagnosed according to DSM-IV research criteria for these acute disorders; however, the duration of signs and symptoms had to be at least 1 year; (4) signs and symptoms of TMD had to have developed while the patient was taking a neuroleptic medication or within a period of 4 weeks after withdrawal in the case of oral medications or 8 weeks for depot compounds; and (5) exposure to neuroleptic medication for at least 3 months prior to the appearance of signs and symptoms of TMD.

Exclusion criteria included (1) concurrent medical illnesses including cardiovascular, endocrine, renal, hepatic, and neurologic diseases or a family history of hereditary movement disorders; (2) vitamin supplementation that may have influenced serum total homocysteine levels (namely folic acid, vitamin B_{12}, vitamin B_6); (3) evidence of substance or alcohol abuse; and (4) eating disorders, malnutrition, gastrointestinal absorption disorders, or any other form of avitaminosis. These criteria were added in order to exclude other possible causes of either raised plasma homocysteine levels or non–drug-induced movement disorders.

The study was approved by the institutional review board of Ben Gurion University. All patients provided their written informed consent after receiving a detailed explanation regarding the study.

Table 1. Demographic Data of TMD Patients and Non-TMD Controls

Characteristic	TMD Group (N = 58)	Non-TMD Control Group (N = 188)
Sex		
Female, N	20	65
Male, N	38	123
Male:female ratio	1.90	1.89
Age, y		
Mean ± SD	46.9 ± 10.3	41.4 ± 10.1*
Range	28–73	19–66
Smoking status, N (%)		
Female smokers	14 (70)	13 (20)
Male smokers	35 (92)	98 (80)
CPZ-equivalent treatment, mg/d		
Mean ± SD	404 ± 203	430 ± 222
Range	200–900	50–800
Severity of TMD		
CGI score		
Mean ± SD	4.1 ± 0.86	…
Range	3–6	…
ESRS[a] subscale score, mean ± SD		
Parkinsonism	7.8 ± 6.7	…
Dyskinesia	7.2 ± 6.9	…
TMD subgroup, N (%)		
Tardive parkinsonism	30 (51.7)	…
Tardive dyskinesia	11 (19.0)	…
Tardive parkinsonism and tardive dyskinesia	17 (29.3)	…

[a]The ESRS was used to assess a sample of 29 (50%) of 58 TMD patients.
*p = .001.
Abbreviations: CGI = Clinical Global Impressions scale, CPZ = chlorpromazine, ESRS = Extrapyramidal Symptom Rating Scale, TD = tardive dyskinesia, TMD = neuroleptic-induced tardive movement disorders. Symbol: … = not applicable.

Fifty-eight schizophrenic and schizoaffective patients suffering from TMD for 1 to 10 years (mean = 5.2 years, SD = 4.2) were enrolled. The severity of TMD was assessed by the Clinical Global Impressions scale (CGI)[27] in all TMD patients and the Extrapyramidal Symptom Rating Scale (ESRS)[28] in 29 (50%) of 58 TMD patients. All patients with TMD were divided into one of 3 subgroups: (1) tardive parkinsonism (including patients with tardive akathisia, tardive parkinsonian symptoms, and tardive tremor), (2) tardive dyskinesia, or (3) combination of tardive parkinsonism and TD (Table 1). There was a significant age difference between TMD patients and control schizophrenic and schizoaffective disorder patients without TMD (mean ± SD = 46.9 ± 10 vs. 41.4 ± 10 years, respectively; $t = -3.578$, $p = .001$). The male-to-female ratio was similar (1.9) in both groups (Table 1), as were smoking status and chlorpromazine treatment dosage equivalent.

One hundred eighty-eight schizophrenic and schizoaffective patients without any signs or symptoms of TMD served as a control group (Table 1). This group, described elsewhere by Applebaum et al.,[29] was enrolled and exam-

Table 2. Serum Total Homocysteine Levels in Schizophrenic Versus Schizoaffective Control Patients by Age and Sex

	Schizophrenic Patients (N = 105)						Schizoaffective Patients (N = 83)					
	Male Homocysteine Level (μmol/L)			Female Homocysteine Level (μmol/L)			Male Homocysteine Level (μmol/L)			Female Homocysteine Level (μmol/L)		
Age, y	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
19–40	54	14.3	9.6	18	12.3	6.6	23	13.1	4.0	18	12.1	6.7
41–73	16	13.2	3.3	17	12.6	7.9	30	13.9	6.7	12	11.6	4.1

Table 3. Serum Total Homocysteine Levels in Neuroleptic-Induced Tardive Movement Disorders (TMD) Group Versus Non-TMD Control Group by Age and Sex

	TMD Group (N = 58)						Non-TMD Control Group (N = 188)					
	Male Homocysteine Level (μmol/L)			Female Homocysteine Level (μmol/L)			Male Homocysteine Level (μmol/L)			Female Homocysteine Level (μmol/L)		
Age, y	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
19–40	14	29.7[a]	24.3	2	13.7	6.6	77	13.9[a]	8.3	36	12.2	6.5
41–73	24	15.7	8.0	17	8.4	2.5	46	13.6	5.7	29	12.2	6.5

[a]The difference in total homocysteine levels between TMD and non-TMD patients was significant only in the young male group: t = –2.323, df = 26.532, 95% CI = –18.2 to –1.12, p = .028.

ined at the same time period as the TMD group. Exclusion criteria for these patients were identical to those of the TMD group.

All TMD and non-TMD patients were treated with antipsychotic medications in a variety of clinical settings, including acute inpatient units, chronic inpatient wards, and community care in hostels. The TMD and non-TMD control patients received a mean antipsychotic dose of 404 mg/day versus 430 mg/day of chlorpromazine equivalent, respectively (range = 200–900 mg/day vs. 50–800 mg/day, respectively) (Table 1). With regard to smoking, which is reported to affect TMD and serum homocysteine levels,[30–33] 92% of men and 70% of women with TMD were smokers. An estimation of smoking rates in non-TMD schizophrenic and schizoaffective patients in our sample, based on the findings of Stahl et al.,[34] who reported rates of smoking in a sample of schizophrenic inpatients in the Be'er Sheva Mental Health Center, is 80% for men and about 20% for women.

Morning fasting blood samples were taken from all TMD and non-TMD control patients. Serum was separated from whole blood by centrifugation at 4°C and then stored at –20°C. Total homocysteine levels were assayed by high-performance liquid chromatography with monobromobimane—a modification to the assay reported by Araki and Sako.[35] Central 95% reference range of serum total homocysteine levels in the Israeli population according to this method is 5.0 to 15.0 μmol/L.[18]

Statistical Analysis

Data were analyzed using SPSS, version 6.0 for Windows (SPSS, Inc.; Chicago, Ill.). We performed 1-way analysis of covariance with age, sex, and diagnosis (schizophrenia vs. schizoaffective disorder) as covariates to test the effect of TMD on homocysteine levels. Since age and sex were shown to have significant influence on homocysteine levels both previously[36] and in the current study, we present data on TMD and non-TMD patients separately for men and women and for the different age groups. We used a regression model to explore the predictive value of different baseline variables on homocysteine levels among patients with TMD. Finally, Student independent t test was used where appropriate.

RESULTS

A regression analysis model showed that age groups, sex, and the existence of TMD, but not diagnosis (schizophrenia vs. schizoaffective disorder), were significantly correlated to total homocysteine levels (t = 7.679, p = .00001). A 1-way analysis of covariance with age groups, sex, and diagnosis as covariates was performed. The effect of TMD on total homocysteine levels was significant (F = 6.012, p = .015). Since diagnosis (schizophrenia vs. schizoaffective disorder) did not influence the total homocysteine levels, the analysis was combined for schizophrenia and schizoaffective patients.

Table 2 presents mean ± SD serum homocysteine levels for schizophrenia patients versus schizoaffective control patients according to age group and sex. Table 3 presents mean ± SD serum homocysteine levels for TMD patients versus non-TMD patients according to age group and sex. As can be seen in Table 3, the difference in total homocysteine levels between TMD and non-TMD patients was significant only in the young male group.

Using a regression model, total homocysteine levels among TMD patients were correlated to age and sex, but not to TMD type (tardive parkinsonism, TD, or both). Yet, this model showed that in a subgroup of 29 patients for whom we also collected data about TMD severity, the

ESRS measurements for tardive parkinsonism were correlated with total homocysteine levels ($t = 2.623$, $p = .024$).

DISCUSSION

Our results demonstrate high total homocysteine levels in men, especially in young male schizophrenic and schizoaffective patients with TMD exhibiting tardive parkinsonism and/or TD. With regard to women, no difference was found in those above the age of 40 years, whereas, for those aged 19 to 40 years, the number of women was too small to draw conclusions.

Interestingly, Goff et al.[37] recently studied 91 consecutive schizophrenia outpatients in an urban community mental health center and reported that homocysteine levels were positively correlated with extrapyramidal symptom severity as measured by the Simpson-Angus Scale, yet no correlation was found with the severity of TD as measured by the Abnormal Involuntary Movement Scale (AIMS).

The finding of high homocysteine levels in young male schizophrenic and schizoaffective patients with TMD warrants an explanation. Levine et al.[18] and Applebaum et al.[29] reported high plasma and serum total homocysteine levels in schizophrenic patients, mainly young and middle-aged male patients, suggesting that high serum homocysteine levels may constitute a risk factor for schizophrenia, as has been previously suggested for Alzheimer's disease.[16] The causes of such elevated homocysteine levels in individuals with schizophrenia are not yet clear. One possible explanation is the existence of low plasma folate and/or low plasma vitamin B_{12} levels in such individuals. In this regard, Stahl et al.[34] reported that, in a cohort of 258 schizophrenic hospitalized inpatients in the Be'er Sheva Mental Health Center, a multiple linear regression found that plasma folate and vitamin B_{12} levels explained 25% of the variance in homocysteine levels. Seventy-five percent and 15% of men ($N = 201$) had low plasma folate (> 3.7 ng/mL) and vitamin B_{12} (> 157 pg/mL) levels, respectively, whereas 65% and 12% of women ($N = 57$) showed low plasma folate and vitamin B_{12} levels, respectively. Lerner et al.[38] studying 224 newly admitted schizophrenic and schizoaffective patients to the Be'er Sheva Mental Health Center reported that 37% of the men ($N = 143$) and 17% of the women ($N = 81$) had low serum folate levels (> 3.1 ng/mL). Low serum vitamin B_{12} levels (> 223 pg/mL) were found in 28% of these men and 23% of the women. These data suggest that low folate and/or vitamin B_{12} levels may contribute to high homocysteine levels reported in schizophrenic and schizoaffective patients.

Another possible reason for high homocysteine levels in schizophrenic patients is smoking—reported to elevate homocysteine levels.[34] In this regard, there seems to be no substantial difference in smoking status between men with TMD and sex-matched controls in our study, as the data suggest that the majority of both groups were smokers ($\geq 80\%$). The high percentage of smokers seems to confirm data suggesting that smoking is 3 times more frequent in schizophrenic patients than in the general population.[39–41] On the other hand, more women with TMD smoked compared to corresponding controls. Such a difference may have theoretically contributed to higher homocysteine levels in women with TMD compared to women without TMD; however, no such difference was noticed (see Table 3). In this regard, evaluating the effect of smoking in these institutionalized patients and hostel residents is rather complex if one considers the possible effects of passive smoking. Future measurements of biological markers of nicotine abuse/dependence may be needed to study the effect of smoking on homocysteine levels in these groups. Other causes of high homocysteine levels in the study participants may consist of a variety of genetic and environmental causes that are beyond the scope of this article.[29]

Our sample mainly represents chronic middle-aged patients, all treated previously with typical neuroleptics that were later—due either to a lack of adequate clinical response or to the presence of adverse effects—switched to atypical neuroleptics or to a combination treatment of typical and/or atypical antipsychotics. The application of such a therapeutic strategy made it practically too complex to separate the effects of typical versus atypical neuroleptics on the development of TMD.

One may claim that differences as to the use of neuroleptics between the study groups may have contributed to the high homocysteine levels among young men with TMD compared with the levels among the corresponding men without TMD. We could not analyze this difference. However, in a group of 258 schizophrenic patients, Stahl et al.[34] could not find any effects of neuroleptics (typical or atypical) on homocysteine levels, nor has such an effect been reported in the literature.

The use of psychotropic medications, such as carbamazepine and valproic acid, has been suggested as leading to increased levels of plasma homocysteine.[42–45] However, no such effect was found in the study by Stahl et al.[34] performed in our center. Also, the proportion of patients treated with mood stabilizers was similar in both of the patient groups. Antidepressants and anticholinergic agents have not been reported in the literature to induce high plasma homocysteine levels.

Some other nonpsychotropic medications were also reported to affect homocysteine levels[21,46–51]; however, since the exclusion criteria excluded patients with hepatic, renal, cardiovascular, endocrinologic, or neurologic disorders, very few patients were treated with nonpsychotropic medications, and practically none of them was treated with a drug reported to increase homocysteine levels. Finally, none of the patients was treated with vitamin E or

other antioxidants reported to possibly alleviate certain TMD subsyndromes.

Our findings show that the mean serum total homocysteine level in schizophrenic and schizoaffective patients with TMD is approximately double that of schizophrenic and schizoaffective patients without TMD. This suggests that the higher serum total homocysteine levels in young schizophrenic (and probably schizoaffective) male patients may be associated with the existence of TMD. The reasons for these high homocysteine levels are not clear. There seems to be no substantial difference as to smoking status between TMD and control men as we can assume that the majority of both groups smoked. As we do not have data as to the difference in vitamin B status between the study groups, we cannot determine whether the difference in homocysteine levels between the study groups is related to differences in vitamin B status between the study groups. We do suggest, however, that, regardless of the causes underlying these high homocysteine levels in TMD patients compared with the controls, high homocysteine levels may constitute a risk factor for the development of TMD.

The mechanism by which homocysteine may affect neuroleptic-induced TMD may involve damage to dopaminergic neurons since homocysteine has been reported to exacerbate oxidative stress, mitochondrial dysfunction, and apoptosis in human dopaminergic cells, with these effects ameliorated by the administration of antioxidants. Such effects may also be mediated via other metabolites of homocysteine. Some authors suggested that oxidized forms of homocysteine, namely homocysteinesulfinic acid and homocysteic acid, strongly inhibit neuronal network activity at relatively low concentrations, whereas the deleterious effects of homocysteine on neuronal tissue were reported at relatively high concentrations.[12,13,52]

Since neuroleptics were reported to induce the formation of free radicals,[53] one may postulate that, by the induction of free radicals, neuroleptics may lead to the formation of oxidized forms of homocysteine, namely homocysteinesulfinic acid and homocysteic acid, which may strongly inhibit neuronal network activity in relatively low concentrations and ultimately lead to TMD.

Moreover, it was suggested that exposure of the endothelium to homocysteine induces the release of nitric oxide, a further excitotoxic compound. Such excitotoxins were suggested to play a role in the pathogenesis of tremor, akathisia, and dyskinesia in Parkinson's disease, since excitotoxins hypothetically alter the circuit of basal ganglia function and may lead to TMD.[13,54–56]

However, the possibility also exists that, in patients with TMD, the high serum total homocysteine levels may result from inadequate food consumption and the resulting vitamin B deficiencies. Inadequate food consumption is often due to difficulties with hand and mouth movements and inadequate masticatory and/or swallowing functions caused by the existence of abnormal movements related to the different variants of TMD. In the latter case, high homocysteine levels would be expected to be a sequela of TMD. Yet, both possibilities may exist, leading to a vicious cycle of homocysteine either inducing or aggravating TMD, thus leading to decreased food and vitamin B consumption and the resultant high homocysteine levels further aggravating TMD, and so on. Future longitudinal prospective studies are needed to determine the exact relationship between high serum homocysteine levels and TMD.

Our study has a number of limitations. First, the design used in this cross-sectional study made it practically too complex to study the effect of different neuroleptic drugs on serum homocysteine levels. Second, although the total sample recruited was rather large, the number of patients in certain age and sex subgroups (especially women aged 19–40 years) was relatively small. Finally, vitamin B and folic acid status was not analyzed.

Since neuroleptic treatment is used in many other patient populations, such as those suffering from bipolar disorder, mental retardation, dementia, or other neurologic diseases associated with severe behavioral disturbances or psychotic symptoms, our results may have wider implications. The described association between high serum homocysteine levels and TMD and the existence of a relatively simple homocysteine-reducing strategy with the use of vitamin B supplementation may have further clinical ramifications. Further prospective studies are necessary to clarify these findings.

Drug names: carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), lithium (Lithobid, Eskalith, and others), valproic acid (Depakene and others).

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