Disrupted Antioxidant Enzyme Activity and Elevated Lipid Peroxidation Products in Schizophrenic Patients With Tardive Dyskinesia

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Background: Free radical–mediated pathology has been implicated in the development of tardive dyskinesia (TD). Antioxidant defense system alterations and increased lipid peroxidation have been postulated as a possible mechanism for neuronal damage associated with TD. However, the relationship between antioxidant enzymes, lipid peroxidation products, and the severity of TD symptoms has not been determined within a single patient group.

Method: Plasma levels of malondialdehyde (MDA), a marker of lipid peroxidation, superoxide dismutase, glutathione peroxidase, and catalase were examined in 80 patients with schizophrenia (DSM-IV criteria) and TD (Schooler-Kane criteria) and 45 schizophrenia patients without TD. Results were compared to those of 50 age-, sex-, and smoking status–matched controls. Tardive dyskinesia severity was assessed using the Abnormal Involuntary Movement Scale, and patient psychopathology was assessed using the Positive and Negative Syndrome Scale.

Results: Patients with TD had lower plasma superoxide dismutase, glutathione peroxidase, and catalase levels but higher MDA levels than those without TD. In the patients with TD, MDA levels were positively correlated with Abnormal Involuntary Movement Scale total score and with Positive and Negative Syndrome Scale negative subscore. Superoxide dismutase and catalase activities were inversely correlated with MDA levels.

Conclusions: Our data support the hypothesis that oxidative stress is involved in the pathophysiology of TD. These data also suggest a relationship between oxidative stress and the severity of dyskinesia in TD patients. Increased lipid peroxidation may likely be a result of decreased endogenous antioxidant enzyme activities in TD.

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Tardive dyskinesia (TD) is a movement disorder that occurs in 20% to 40% of patients treated chronically with neuroleptic drugs.[1] Although much research has focused on TD, its pathophysiology remains unclear. It has been conjectured that neuroleptic drugs—by blocking dopamine receptors—cause compensatory increases in the turnover and metabolism of dopamine, which leads to increased formation of free radicals.[2,3] This imbalance between free radical metabolism and the antioxidant defense system results in increased oxidative stress and may be involved in the development of TD.[4,5]

There are several lines of evidence supporting the free radical hypothesis of TD. For example, studies have shown increased membrane lipid peroxidation and impairment in antioxidant enzyme activity in animals treated with antipsychotic medication.[6] Elkashef and Wyatt[4] reported that rats with vacuous chewing movements, a widely accepted animal model of TD, had significantly higher thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation, in the striatum. More recently, preclinical studies by Naidu et al.[7,8] showed that chronic haloperidol treatment associated with vacuous chewing movements increases lipid peroxidation and decreases superoxide dismutase (SOD), glutathione, and catalase levels. They blocked this effect using melatonin, an effective antioxidant, and quercetin, a bioflavonoid with strong antioxidant properties. These data strongly

suggest that oxidative stress may be involved in the development of haloperidol-induced dyskinetic movements in an animal model.[7,8]

Clinical studies also support the notion that free radicals may play a role in TD. Elevated levels of lipid peroxidation are found in the cerebrospinal fluid (CSF) of patients with TD.[9] Increased lipid peroxidation in both CSF and plasma is significantly correlated with the severity of TD.[9–11] SOD has also been found to be lower in both erythrocytes and CSF in patients with TD,[12,13] and decreased SOD levels are significantly correlated with dyskinetic movements in TD patients.[14] One study also found a significant association between a functional genetic polymorphism (Ala-9Val) of manganese-SOD enzyme and TD,[15] although a later study did not replicate this finding.[16] Indirect evidence for the involvement of oxidative stress in the pathogenesis of TD is provided by a number of controlled therapeutic trials showing positive results with vitamin E and other antioxidants.[17–20]

Antioxidant enzymes are known to act via several different biochemical pathways. For example, SOD turns superoxide anion into H_2O_2, catalase detoxifies H_2O_2, and glutathione peroxidase (GSH-Px) catalyzes the breakdown of H_2O_2 and lipid hydroperoxides into nontoxic products.[5] Therefore, effective antioxidant protection may be provided by the cooperative and sequential actions of these 3 critical enzymes. To our knowledge, however, no study has evaluated these 3 enzymes simultaneously in the same group of TD patients. The purpose of the present study, therefore, was to determine plasma activities of these antioxidant enzymes and lipid peroxidation. In addition, we sought to explore relationships among these oxidative parameters, psychopathologic symptoms, and the severity of TD symptoms in schizophrenic patients with this movement disorder.

METHOD

Subjects

All patients satisfied DSM-IV[21] criteria for schizophrenia. Psychiatric diagnosis was made by consensus of 2 experienced clinical psychiatrists, using the Structured Clinical Interview for DSM-IV. Tardive dyskinesia was diagnosed using the criteria of Schooler and Kane.[22] The patients with TD (N = 80) and those without TD (N = 45) were selected from among the inpatients of Beijing Hui-Long-Guan Hospital, a Beijing City–owned psychiatric hospital. All patients were of the chronic type and were chronically institutionalized, with a mean ± SD hospitalization duration of 9.9 ± 7.2 years. The study was conducted from July 2004 to July 2005.

Since admission, all patients received dietetically balanced hospital meals (daily energy intake for men, 2500 kcal; for women, 2200 kcal), which were occasionally supplemented by gifts (usually fruit); patients had the opportunity for an hour of physical exercise every day. All patients adhered to a low-monoamine, alcohol-free, and caffeine-restricted diet. All patients had no access to alcohol or illegal drugs since admission. They had been receiving stable doses of oral neuroleptic medications for at least 12 months. The medications that patients had been taking were clozapine (34 TD vs. 21 non-TD); risperidone (18 TD vs. 11 non-TD); haloperidol (11 TD vs. 6 non-TD); chlorpromazine (5 TD vs. 3 non-TD); perphenazine, fluphenazine, or trifluoperazine (4 TD vs. 2 non-TD); or others (8 TD vs. 2 non-TD). In addition, 37 patients received anticholinergic drugs (25 TD vs. 12 non-TD). Medication was similar between the groups. Antidepressants and mood stabilizers were not used by this patient population. The detailed medication information was obtained from clinical records.

Fifty age- and gender-matched healthy controls were recruited from the local community through advertisements and from within the Beijing Hui-Long-Guan Hospital. We excluded subjects with previous exposure to antipsychotic agents, substance abuse during the preceding 6 months, systemic medical illness requiring treatment, and neurologic disorders. Psychiatric disorders were ruled out among controls by psychiatric evaluation conducted by a psychiatrist. Control subjects also reported a negative history of psychiatric illness in their first-degree relatives. All healthy controls were on a low-monoamine, alcohol-free, and caffeine-restricted diet for 2 weeks preceding the blood draw. Both patients and normal subjects had similar socioeconomic status and dietary patterns. The smoking status of each subject was ascertained by questionnaire at the time of each blood draw.

A complete medical history was obtained, a physical examination was performed, and laboratory tests were conducted on patients and control subjects. All patients were without additional neurologic disease and without other physical diseases. Since high rates of smoking are reported in schizophrenic patients,[23] normal controls were chosen to closely match the patients on the number of cigarettes smoked per day and the time course of smoking. Smoking history and demographic data are shown in Table 1.

All subjects gave signed, informed consent to participate in the study, which was approved by the Institutional Review Board, the Institute of Mental Health, Peking University (Beijing, China).

Clinical Measures

The severity of tardive dyskinesia was assessed on the day of the blood sampling by the same experienced investigator, who was blinded to the biochemical measures of the patients, using the Abnormal Involuntary Movement Scale (AIMS).[24] The patients' psychopathology was assessed using the Positive and Negative Syndrome

Table 1. Demographics of Patients With Tardive Dyskinesia (TD) and Without TD and Normal Control Subjects[a,b]

Characteristic	Patients With TD (N = 80)	Patients Without TD (N = 45)	Normal Controls (N = 50)
Sex, N, male/female	58/22	35/10	36/14
Age, y	48.6 ± 6.8	47.8 ± 5.2	45.9 ± 5.2
Duration of illness, y	24.6 ± 9.1	21.6 ± 7.3	NA
Age at onset, y	24.7 ± 6.1	25.6 ± 6.8	NA
Daily antipsychotic dose, mg (chlorpromazine equivalents)	377 ± 238	392 ± 267	NA
No. of hospitalizations	3.9 ± 2.6	3.9 ± 2.4	NA
Hospitalization duration, y	10.4 ± 7.6	9.4 ± 6.8	NA
Duration of treatment with neuroleptic medications, y	22.1 ± 7.6	19.2 ± 6.5	NA
PANSS score			
Positive symptoms	15.7 ± 5.7	15.0 ± 6.8	
Negative symptoms	25.3 ± 5.1	23.6 ± 6.0	
General psychopathology	34.0 ± 6.6	31.9 ± 9.2	
Total	74.9 ± 12.4	70.5 ± 17.1	
Smokers, N (%)	58 (73)	32 (71)	35 (70)
Smoked cigarettes daily	14.1 ± 9.7	13.9 ± 9.1	12.9 ± 6.5
Subtype of schizophrenia, N			
Paranoid type	29	16	
Disorganized type	16	10	
Undifferentiated type	11	8	
Residual type	24	11	

[a]Data are reported as mean ± SD unless otherwise indicated.
[b]No difference was noted among groups on any characteristic by χ^2 and analysis of variance.
Abbreviations: NA = not applicable, PANSS = Positive and Negative Syndrome Scale.

Scale (PANSS),[25] which was administered by 2 psychiatrists, who had simultaneously attended a training session in the use of the PANSS before the start of the study. After training, a correlation coefficient greater than 0.8 was maintained for the PANSS total score by repeated assessments.

Blood Sampling

Fasting venous blood from forearm vein was collected into tubes containing ethylenediaminetetraacetic acid (EDTA). Plasma samples from healthy controls and patients with schizophrenia were all collected between 7 and 9 a.m. The plasma was separated, aliquoted, and stored at –70°C before use. Antioxidant enzymes and lipid peroxidation products were determined by a technician blind to the diagnostic status of subjects. The identity of the subjects was indicated by a code number maintained by the investigator and revealed only when all biochemical analysis was completed.

Determination of Antioxidant Enzymes

SOD activity measurement. Determination of plasma total SOD activity[26] was performed using a standard assay involving spectrophotometric determination of the inhibition of superoxide-induced formation of nitrite from hydroxylamine, as described by Oyanagui.[27] Xanthine-xanthine oxidase provided the superoxide source. One unit is defined as the amount of SOD that inhibits 50% of nitrite formation under the assay conditions. Activity is expressed as units per milliliter plasma (U/mL). The inter-assay and intra-assay coefficients of variation (CVs) for SOD activity were 4.1% (N = 8) and 3.2% (N = 8), respectively.

GSH-Px activity measurement. GSH-Px activity was measured by a method developed by Paglia and Valentine.[28] The enzymatic reaction was initiated by adding H_2O_2 to the reaction mixture containing reduced glutathione, reduced nicotinamide adenine dinucleotide phosphate, and glutathione reductase. The change in the absorbance at 340 nm was monitored by a spectrophotometer. One unit of GSH-Px is defined as micromoles of nicotinamide adenine dinucleotide phosphate oxidized per minute. Activity is expressed as units per milliliter plasma volume. The intra-assay and interassay CVs were 4.8% (N = 6) and 5.7% (N = 6), respectively.

Catalase activity measurement. Catalase activity was assayed by the method of Aebi[29] that is based on the decomposition of hydrogen peroxide by catalase. Catalase catalyzes the transformation of hydrogen peroxide to water and oxygen. Catalase activity was determined by monitoring the decreased absorbance spectrophotometrically at 240 nm due to degradation of hydrogen peroxide. One unit of catalase was defined as the amount of enzyme that decomposes 1 μmol H_2O_2/min under specific conditions. Catalase activity is expressed as U/mL. The intra-assay and interassay CVs were 4.5% (N = 5) and 5.9% (N = 5), respectively.

Determination of Lipid Peroxidation

Lipid peroxidation levels were monitored by determining the end product of lipid peroxidation malondialdehyde (MDA) by the thiobarbituric acid method.[30] Plasma MDA values were calculated using the extinction coefficient of MDA-thiobarbituric acid complex at 532 nm. MDA results are expressed as nmol/mL.

Statistical Analysis

Statistical analyses were performed by the use of 1-way analysis of variance. Post hoc tests were conducted to determine the difference between groups, followed by Fisher least significant difference test. When significance was found in analysis of variance, the effects of sex, age, illness course, age at onset, dose of drug (in chlorpromazine equivalents), and duration of antipsychotic treatment, as well as PANSS total score and its subscores, were tested by adding these variables to the analysis model as covariates. Correlation between variables was studied using Pearson product moment correlations. Bonferroni corrections were applied to each test to adjust for multiple testing. In addition, the t tests were used to compare age, age at onset, duration of illness, age at first antipsychotic treatment, period of antipsychotic treat-

Table 2. Activities of Plasma Antioxidant Enzymes and MDA Levels in Schizophrenia Patients With and Without Tardive Dyskinesia (TD) and Normal Control Subjects[a]

Substance	Patients With TD (N = 80)	Patients Without TD (N = 45)	Normal Controls (N = 50)	F	df	p
SOD, U/mL	80.6 ± 23.3†	88.9 ± 21.1*	97.2 ± 10.9	9.78	2,165	< .001
GSH-Px, U/mL	104.5 ± 27.9†	117.1 ± 35.1*	142.7 ± 31.0	21.11	2,166	< .001
Catalase, U/mL	2.0 ± 1.9‡	4.2 ± 4.9	2.7 ± 2.4	6.57	2,166	.002
MDA, nmol/mL	12.6 ± 7.5†	7.3 ± 6.5*§	2.6 ± 1.9	39.65	2,166	< .001

[a]Data are reported as mean ± SD.
*p < .01 vs. normal controls after Bonferroni correction.
†p < .001 vs. normal controls after Bonferroni correction.
‡p < .01, patients with vs. without TD after Bonferroni correction.
§p < .001, patients with vs. without TD after Bonferroni correction.
Abbreviations: GSH-Px = glutathione peroxidase, MDA = malondialdehyde, SOD = superoxide dismutase.

ment, lifetime antipsychotic dose, and current antipsychotic dose, as well as PANSS total score and subscores, between groups. Two-tailed significance values were used, and significance levels were set at .05.

RESULTS

Demographic Data

There was no significant difference in age or gender between the groups (see Table 1). Sex, age at onset of psychosis, and hospitalization did not significantly correlate with AIMS total score in the TD patient group. However, there was a significant correlation between the duration of illness and AIMS total score (r = 0.23, N = 80, p = .02). This significant correlation might be in part due to the longer neuroleptic medication periods associated with longer duration of illness, because there was also a significant correlation between the duration of neuroleptic medication treatment and AIMS total score (r = 0.28, N = 80, p = .01). AIMS total score was significantly correlated with PANSS negative subscore (r = 0.24, N = 80, p = .02) and marginally associated with PANSS total score (r = 0.19, N = 80, p = .06). However, all of them did not pass through Bonferroni test. In addition, the mean ± SD length of time the patients had TD was 14.2 ± 7.8 years. All of them developed TD after taking neuroleptic medications; none had TD before taking medications. There was no significant correlation between the duration of TD and any indices. Additionally, no significant correlation was noted between neuroleptic dose (chlorpromazine equivalents) or the duration of taking neuroleptic medications and any parameter related to oxidative stress.

Antioxidant Enzymes and Lipid Peroxidation Product Levels in Schizophrenic Patients With and Without Tardive Dyskinesia Versus Normal Control Subjects

There was a significant difference in SOD among the patients with TD and without TD and normal controls (F = 9.78, df = 2,165; p = .000). Post hoc tests showed that the patients with TD had a trend toward lower levels of SOD than the patients without TD (p = .056, Bonferroni test: p = .17). Both the patients with and without TD had lower levels of SOD than normal controls (respectively, p = .000, p = .003; Bonferroni test: p = .000, p = .008) (Table 2).

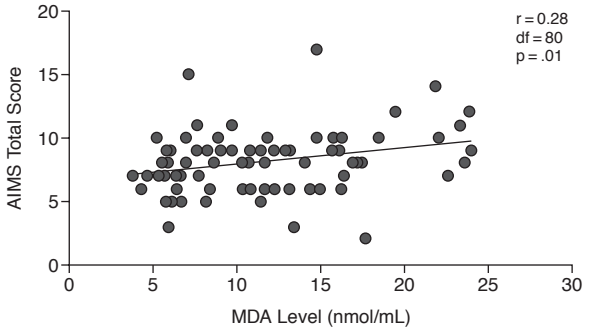
There was a significant difference in GSH-Px among the patients with TD and without TD and normal controls (F = 21.11, df = 2,166; p = .000). Post hoc tests showed that the patients with TD had lower levels of GSH-Px than the patients without TD (p = .022, Bonferroni test: p = .07). Both the patients with and without TD had lower levels of GSH-Px than normal controls (respectively, p = .000, p = .000; Bonferroni test: p = .000, p = .001) (Table 2).

There was a significant difference in catalase among the patients with TD and without TD and normal controls (F = 6.57, df = 2,166; p = .002). Post hoc tests showed that the patients with TD had lower levels of catalase than the patients without TD (p = .000, Bonferroni test: p = .001). The patients without TD had higher levels of catalase than normal controls (p = .027, Bonferroni test: p = .08) (Table 2).

There was a significant difference in MDA among the patients with TD and without TD and normal controls (F = 39.65, df = 2,166; p = .000). Post hoc tests showed that the patients with TD had higher levels of MDA than the patients without TD (p = .000, Bonferroni test: p = .000). Both the patients with and without TD had higher levels of MDA than normal controls (respectively, p = .000, p = .001; Bonferroni test: p = .000, p = .002) (Table 2).

Since there was a relationship between PANSS negative symptom subscore and AIMS total score, PANSS negative symptom subscore was added as a potentially confounding covariate to the main model. The results showed that covarying for negative symptoms did not eliminate the findings in antioxidant enzymes and MDA levels between TD and non-TD patients, although the p values were elevated (data not shown). In addition, when sex, age, illness course, age at onset, dose of drug, duration of antipsychotic treatment, hospitaliza-

Figure 1. Correlation Between Plasma MDA Levels and AIMS Total Score in Schizophrenic Patients With Tardive Dyskinesia



Abbreviations: AIMS = Abnormal Involuntary Movement Scale, MDA = malondialdehyde.

tion times, and duration of hospitalization were individually added as either potentially confounding covariate terms or factors to the main model, there was still a significant TD effect (data not shown).

Relation Between Antioxidant Enzymes and MDA Levels

SOD and catalase activities were inversely correlated with MDA levels in patients with TD (SOD: $r = -0.22$, $N = 80$, $p = .02$; catalase: $r = -0.21$, $N = 80$, $p = .03$). SOD was positively correlated with catalase ($r = 0.29$, $N = 45$, $p = .052$) and marginally with GSH-Px ($r = 0.24$, $N = 45$, $p = .07$) in the patients without TD. All of them, however, did not pass through Bonferroni test. No significant correlation among antioxidant enzymes and MDA was observed in normal controls (all $p > .05$).

Relation Between Tardive Dyskinesia Presentations and Psychopathologic Measures and Antioxidant Enzymes and MDA Levels

MDA levels were positively correlated with AIMS total score in patients with TD ($r = 0.28$, $N = 80$, $p = .01$) (Figure 1) and with PANSS negative subscore ($r = 0.31$, $N = 80$, $p = .006$). However, since there was a relationship between negative symptoms and MDA, as shown, we further examined whether covarying for negative symptoms would eliminate the TD finding. The result showed a trend toward significant correlation between MDA levels and AIMS total score ($r = 0.22$, $p = .06$). Similarly, after covarying for AIMS total score, there was still a positive correlation between MDA levels and PANSS negative subscore, with a less significant p value ($r = 0.25$, $p = .03$). No relationship between psychopathologic measures and PANSS total score or subscores and antioxidant enzymes and MDA levels was found in patients without TD (all $p > .05$).

DISCUSSION

The main findings of this study are as follows. (1) Patients with TD had significantly decreased plasma SOD, GSH-Px, and catalase activity and increased levels of MDA compared to those without TD; however, the results of SOD and GSH-Px did not reach significance with the Bonferroni test. (2) MDA was negatively correlated with SOD and catalase activities in patients with TD. (3) MDA levels were positively correlated with the AIMS total score and the PANSS negative subscore in patients with TD. However, the findings must be regarded as preliminary because of the relatively small sample size and marginal associations between MDA and AIMS total score with $r = 0.28$. (4) Covarying for negative symptoms did not eliminate the TD finding with MDA, but the p value was less significant. To our knowledge, this is the first large study designed to evaluate both antioxidant metabolizing systems and evidence of free radical–induced pathology in patients with TD. Because antioxidant enzymes are critical in the detoxification of free radicals, attenuated activity of these antioxidant enzymes may contribute to oxidative stress and increase oxyradical-mediated cellular injury in TD. Hence, our results indicate that a free radical mechanism may play an important role in the pathophysiology of TD. Furthermore, our finding of decreased antioxidant enzymes and increased lipid peroxidation in patients with TD provides further evidence for the free radical hypothesis.[5,31]

Our finding of decreased levels of SOD in patients with TD is in agreement with previous studies.[12–14] To our knowledge, this is the first report of a comparison of plasma GSH-Px and catalase in patients with and without TD. However, animal studies have shown that neuroleptic treatment is associated with impaired activities of antioxidant enzymes and increased membrane lipid peroxidation.[6] For example, antipsychotic-induced vacuous chewing movements in rats have significantly higher TBARS in striatum[4] and significantly lower antioxidant enzymes such as SOD and catalase.[7,8] Thus, dysregulation of protective mechanisms that act to neutralize harmful oxidative free radicals may contribute toward TD. Indeed, our finding of reduced SOD, GSH-Px, and catalase and increased MDA levels in human schizophrenia patients with TD is in agreement with these preclinical studies.

As mentioned previously, SOD dismutates superoxide radicals to form hydrogen peroxide, which in turn is decomposed to water and oxygen by GSH-Px and catalase, thereby preventing the formation of hydroxyl radicals.[32,33] Therefore, these enzymes act cooperatively at different sites in the metabolic pathway to counteract free radicals. Failure of this antioxidant defense system may lead to an oxidative damage and initiation of lipid peroxidation. Indeed, decreased levels of antioxidant defense enzymes in the present study indicate increased oxidative stress in

patients with TD. In addition, SOD is protective against glutamate-induced neuronal degeneration,[34] which is thought to be relevant to the pathophysiology of TD.[13] Moreover, GSH-Px is a key antioxidant enzyme catalyzing the reduction of peroxides to protect against oxidative tissue damage. Therefore, it is possible that chronic and sustained deficiency of antioxidant enzymes could render subjects more vulnerable to free radical damage, lipid membrane peroxidation, and ultimately TD. Certainly, if free radicals play a role in the development of TD, patients with a lower antioxidant defense system would be more likely to develop TD.[35] We also found a significant negative relationship between MDA and SOD or catalase activities in patients with TD, suggesting that there may be an etiologic relationship between the decreased antioxidant enzymes and increased lipid peroxidation. That is, increased lipid peroxidation in TD was most likely a result of decreased endogenous antioxidant enzymes. The present study, therefore, provides evidence that reduced antioxidant enzymes may be one mechanism whereby lipid peroxidation is increased in patients with TD.

Relationships of MDA levels, TD severity, and psychopathology were examined between schizophrenic patients with and without TD. Our results show an increase in the plasma levels of MDA and a significant positive correlation of plasma MDA levels with AIMS total score, severity of TD symptoms, and PANSS negative subscore in TD patients. In line with the present study, Lohr et al.[9] found a significantly higher level of lipid peroxidation products including TBARS and conjugated dienes in the CSF of schizophrenic patients with TD compared with those without TD. They also demonstrated a positive correlation between conjugated dienes and total scores on the AIMS. Peet et al.[10] also reported a positive relationship between plasma TBARS and the severity of dyskinetic movements. In addition, Brown et al.[11] showed a positive correlation between AIMS score and TBARS in patients with TD. Taken together, these studies further demonstrate that increased indices of free radical activity in TD and the degree of peroxidation are related to TD severity, suggesting that free radicals may, at least in part, contribute toward the development of TD.

However, it is worth mentioning that there may be an interrelationship between negative symptoms, increased free radical activities, and TD severity, because we found a significantly positive correlation between MDA and both AIMS total score and PANSS negative subscore. Moreover, there was a significantly positive correlation between AIMS total and PANSS negative subscore. On the other hand, covarying for negative symptoms did not eliminate the TD findings, or vice versa, suggesting that the negative symptom finding is not separate from the TD finding.

Previous studies have shown that the negative symptoms of schizophrenia may be a risk factor for the early development of tardive dyskinesia, suggesting that these schizophrenic symptoms increase the risk of developing this condition.[36] This means that negative symptoms may be a proxy of a severe pathologic process that also indicates a vulnerability to movement disorders. We speculate that, taken together, the synergistic effects of negative symptoms and the elevated lipid peroxidation caused by increased free radical activities may be involved in the development of TD. However, the underlying mechanisms deserve further investigation.

As seen in the present study, patients with and without TD have lower oxidative enzymes and higher lipid peroxides compared with normal controls. However, alteration in these oxidative parameters was greater in patients with TD compared to those without TD. Why some individuals eventually develop TD is unknown. Two likely factors may partially explain this phenomenon: (1) antipsychotic drug treatment and (2) the illness itself. As cited above, numerous reports indicate that chronic neuroleptic treatment is associated with impaired antioxidant enzymes and increased membrane lipid peroxidation.[4,7,8] In the present study, patients with and without TD had been on long-term neuroleptic treatment that decreased oxidative markers and perhaps contributed toward the development of TD in some patients. However, neuroleptic treatment cannot completely explain the difference in antioxidant enzymes in all patients and normal controls. Indeed, we did not find a correlation between the dose in chlorpromazine equivalents or the duration of treatment with drugs and the levels of antioxidant enzymes and MDA. Moreover, patients with and without TD had similar antipsychotic drug treatment profiles and demographics, but a significant difference in antioxidant enzymes and lipid peroxides. Thus, vulnerability to the development of TD may be related more to the underlying disease than to the drug per se. The changes in the activities of these antioxidant enzymes studied in TD patients seem to be independent of antipsychotic treatment and may reflect the pathophysiologic process of the disease.

In summary, our data indicate that an impaired antioxidant defense system and increased peroxidation may be integral to the development of TD. These results provide support for the free radical hypothesis of tardive dyskinesia.[5,31] In addition, our data suggest that the reduced antioxidant enzymes lead to increased lipid peroxidation product levels in the plasma of patients with TD, suggesting that decreased antioxidant enzymes render subjects more vulnerable to free radical damage. Moreover, increased lipid peroxidation is associated with the severity of dyskinetic movement in TD. The exact mechanism(s) underlying the ability of chronic antipsychotic treatment to decrease antioxidant enzymes and produce TD in some patients but not others are still unknown. Further research is required to help determine factors that may explain this vulnerability.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), risperidone (Risperdal), trifluoperazine (Stelazine and others).

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