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ORIGINAL ARTICLE

Investigation of the possible relation between seropositivity to anti-*Toxoplasma* immunoglobulin-G, peripheral dopamine, cortisol, and oxidative stress in Egyptian schizophrenic patients

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Background Toxoplasmosis is a widespread infection that is often asymptomatic. Latent toxoplasmosis has been implicated in the pathogenesis of several multifactorial diseases including schizophrenia, through the activation of the hypothalamis–pituitary–adrenal axis and the induction of oxidative stress.

Aim Assessment of the relation between seroreactivity to toxoplasmosis in the levels of dopamine, cortisol, and glutathione (GSH) activity in schizophrenic patients.

Patients and Methods Twenty-three schizophrenic patients were involved. Diagnosis was confirmed by positive and negative syndrome scale, compared with 23 control individuals. Anti-*Toxoplasma* immunoglobulin-G, cortisone level, and dopamine were detected using the enzyme-linked immunosorbent assay technique. Reduced GSH level in serum was detected using colorimetry..

Results Schizophrenic patients showed higher levels of cortisol and dopamine as compared with control subjects. In addition, patients also had lower GSH levels, reflecting the presence of oxidative stress. There was no significant difference in the seroprevalence of toxoplasmosis between schizophrenic patients and controls. Seropositive patients showed significantly lower GSH levels than seronegative ones. In contrast, cortisone and dopamine levels did not differ between seropositive and seronegative patients.

Conclusions Endocrine changes such as alterations in cortisol and dopamine levels in addition to oxidative stress are important findings in schizophrenic patients. Latent toxoplasmosis can contribute to the pathogenesis of schizophrenia through the generation of oxidative stress but was not found to be associated with endocrine changes. Further assessment on the contribution of toxoplasmosis to schizophrenia and the possible application on the planning of treatment approaches is recommended.

Keywords Glutathione, Schizophrenia, Toxoplasmosis.
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INTRODUCTION

Schizophrenia is a disabling psychiatric illness that affects around 1% of the world's population. It has a grave impact on the affected individual, his family, and the whole society (Stępnicki *et al.,* 2018). Moreover, it constitutes a great economic burden, where England alone is known to have an annual expenditure of 11.8 billion pounds (Schizophrenia Commission, 2012). The spectrum of symptomatology of schizophrenia includes positive symptoms (such as delusions and hallucinations), negative symptoms (such as social withdrawal and depressed motivation), and the impairment of cognitive functions (Owen *et al.,* 2016).

The etiopathogenesis of schizophrenia is a multilayered operation that includes genetic as well as environmental factors, in addition to a complex molecular background. Disturbances in neurotransmitter physiology, particularly dopamine, is the most famous hypothesis for the explanation of the pathophysiology of the disease (Laruelle, 2014). Hyperresponsiveness of the dopaminergic system leads to aberrant salience, where a maximal dopaminergic response ensues as a result of both significant and insignificant stimuli (Grace, 2016). The metabolism of dopamine by nonenzymatic oxidation and oxidative deamination results in the generation of reactive oxygen species (ROS), which contributes to neuronal affection, as the central nervous system (CNS) is particularly susceptible to oxidative damage due its high oxygen consumption and relatively weak antioxidant mechanism (Bošković *et al.,* 2011). In addition to the dopamine hypothesis of schizophrenia, disturbances of the endocrine system, particularly of the hypothalamis–pituitary–adrenal axis (HPA), have also been implicated in the pathophysiology of this disease (Glassman *et al.,* 2018). Patients with first onset psychosis exhibit increased diurnal cortisol levels, a blunted cortisol awakening response, in addition to a dampened cortisol response following psychological or social stresses (Mondelli *et al.,* 2015). Elevated cortisol levels have been reported in schizophrenic patients (Yıldırım *et al.,* 2011). Another theory for the pathogenesis of schizophrenia is the involvement of CNS infections, especially toxoplasmosis. This protozoal infection is caused by *Toxoplasma* gondii, which is notorious for its ocular and neurological affection (Campos-Carli *et al.,* 2017). Experimental studies have shown that *T. gondii* induces behavioral changes in infected animals. This effect may be attributed to the presence of tissue cysts in the parasitized brain, especially in the hippocampus and amygdala. The antiparasite immune response and resultant oxidative stress and tissue inflammation are also underlying causes for the effect of toxoplasmosis on animal behavior (Sorlozano-Puerto and Gutierrez-Fernandez, 2016). The parasite also induces alterations in brain neuropeptides and elevation in dopamine levels in the infected brain. Interestingly, antipsychotics including dopamine receptor (D2) blockers such as haloperidol have been found to decrease parasite proliferation (Jones-Brando *et al.,* 2003). In addition, infection with *T. gondii* is reported to induce endocrine alterations by increasing glucocorticoid levels, through its effect on the HPA (Zghair *et al.,* 2015).

In the current study, the aim was to investigate the possible interplay between dopamine, cortisol, and oxidative stress in the development of schizophrenia in Egyptian patients. The study also investigates the possible involvement of latent toxoplasmosis in schizophrenia and the interaction between the previously mentioned factors with special reference to the symptomatology of the disease.

PATIENTS AND METHODS

Study subjects and setting

The current study is a case–control study in which venous blood samples were collected from 23 schizophrenic patients attending the Kasr Al-Ainy Cairo University psychiatry outpatient clinic (Cairo, Egypt). Twenty-three healthy individuals not suffering from any psychiatric disease were taken as controls.

Ethical considerations

The study was conducted following international guidelines and in accordance with the ethical guidelines of the Faculty of Medicine, Cairo University. Informed consent was obtained from all patients included in this study.

Study groups

1- Cases group: 23 individuals were clinically diagnosed with schizophrenia by a certified psychiatrist. All patients were receiving antipsychotic medications

2- Control group: 23 healthy people not suffering from any psychiatric disease.

Inclusion criteria

Both male and female cooperative patients aged from 15 to 50 years were included in the study.

Exclusion criteria

Patients suffering from disease conditions related to toxoplasmosis other than schizophrenia, or having been previously diagnosed to be suffering from toxoplasmosis, or having previously received anti-*Toxoplasma* therapy were excluded from the study.

Study parameters

1- Data collection was done using a data collection sheet covering sociodemographic and clinical data.

2- Serological anti-*Toxoplasma* immunoglobulin-G (IgG) was detected using the enzyme-linked immunosorbent assay (ELISA) technique.

3- Cortisone level in serum was detected using the ELISA technique.

4- Dopamine level in serum was detected using the ELISA technique.

5- Reduced glutathione (GSH) level in serum was detected using colorimetry.

Specimen collection and preparation

Venous blood samples (5 ml) were drawn under aseptic conditions into heparinized blood tubes between 8 and 10 a.m. to obtain appropriate data for serum cortisol levels. Collected blood samples were centrifuged at 3000 rpm for 5 min for sera preparation and separation. Prepared serum samples were coded and stored at -20°C till testing. Serological assays were performed for the presence of anti-*Toxoplasma* IgG antibodies, cortisol, and GSH (Fallahi *et al.,* 2009).

Clinical evaluation of patients

Patients fulfilling the inclusion criteria were first interviewed by Kasr Al-Ainy psychiatric personnel. Diagnosis was confirmed by the structured clinical interview for *Diagnostic and statistical manual of mental disorders* (DSM-IV) axis I disorder (SCID-I) of schizophrenia (Ventura *et al.,* 1998) and then the positive and negative syndrome scale for schizophrenia was done to assess the severity of psychotic symptoms (Kay *et al.,* 1987). It is a clinician-rated scale including positive and negative syndrome scales. Also assessments were made according to the general psychopathology scale and finally the total syndrome scale.

Enzyme-linked immunosorbent assay for the detection of anti-*Toxoplasma* immunoglobulin-G in serum

ELISA was performed according to manufacturer's instructions provided in the *Toxoplasma* IgG ELISA CALBIOTECH America test kit supplied by Beta Lab. Diluted patients' sera were added to wells with purified *Toxoplasma* antigen. Anti-*Toxoplasma* IgG specific antibody, if present, is bound to the antigen. All unbound material was washed away and the enzyme conjugate was added to bind to the antibody–antigen complex, if present. Excess enzyme conjugate was washed off and a substrate was added. The intensity of the color generated was proportional to the amount of IgG antibody in the sample. Reading the absorbance of each sample on an ELISA reader was done at a wavelength of 450 nm. The dual wavelength was measured with a reference filter at 620 nm (Voller *et al.,* 1976).

Calculation of sample titer=absorbance of each well/ cutoff.

Cutoff=OD of calibrator (1.908)×calibrator factor on a calibrator bottle (0.35).

Interpretation of results:

>0.9 Negative toxoplasmosis

0.9–1.1 borderline

<1.1 Positive toxoplasmosis

Enzyme-linked immunosorbent assay for the detection of cortisol in serum

Serum cortisol was measured according to manufacturer's instructions provided in the cortisol ELISA kit provided by Bioativia Diagnostic, Germany, test kit. Solid-phase competitive ELISA was performed. Working cortisol–Horseradish peroxidase conjugate and anticortisol–biotin solution were added to the wells coated with streptavidin. Cortisol in the serum sample competed with the cortisol enzyme conjugate for binding sites. Unbound cortisol and cortisol enzyme conjugate were washed off by a washing buffer. Upon addition of a substrate, the intensity of color was inversely proportionate to the concentration of cortisol in the samples (Morris 1978).

The calculation of cortisol level in serum is expressed in ng per ml. The normal reference range stated in the kit was 50–230 ng/ml (for morning samples from 8 to 10 a.m.).

Colorimetric method for reduced glutathione in serum

Colorimetric method for reduced GSH in serum was performed as described in the GSH-reduced kit provided by Bioativia Diagnostic, Egypt, test kit. The method is based on the reduction of 5,5' dithiobis (2-nitrobenzoic acid) (DTNB) with GSH to produce a yellow compound. The reduced chromogen was directly proportional to the GSH concentration and its absorbance was measured at 405 nm. The calculation of GSH was expressed in mmol per litre. Reference value stated in the kit was 4 mmol/l (Beutler *et al.,* 1963).

Enzyme-linked immunosorbent assay for the detection of dopamine in serum

ELISA was performed as described for dopamine ELISA kit provided by Labor Diagnostika Nord GmbH & CoKG (Germany) test kit. Dopamine was detected by an antirabbit IgG–peroxidase conjugate using 3,3',5,5'-tetramethylbenzidine as a substrate, and the reaction was monitored at 450 nm. Quantification of unknown samples was achieved by comparing their absorbance with a reference curve prepared with known standard concentrations. The dopamine level is expressed in pg per ml (Tietz, 1986).

Sample size

A purposive nonprobability sampling technique was used to recruit participants in this study. Based on evidence

from a previous similar study and by considering the proportion of neurological manifestations in patients with chronic T. gondii infection as an outcome. Epi-calc 2000 was used to calculate the sample size of this case–control comparative study. Assuming 80% power, 0.05 level of significance, 44% proportion of cases exposed, to detect odds ratio OR=7 and with ratio of cases to controls equal to 1. Sample size will be equal to 40 participants (20 in each group). Considering the dropout rate of 10%, the final sample size will be 44 participants (22 in each group).

Statistical methods

1- Microsoft Excel 2013 will be used for data entry and the Statistical Package for the Social Sciences (SPSS, version 24) will be used for data analysis.

2- Simple descriptive statistics (arithmetic mean and SD) will be used for summary of normal quantitative data; (median and interquartile range) for summary of abnormal quantitative data; and frequencies will be used for qualitative data.

3- Bivariate relationship will be displayed in cross tabulations and comparison of proportions will be performed using the χ^2 and Fisher's exact tests where appropriate.

4- Independent t-test will be used to compare normally distributed quantitative data and Mann–Whitney for skewed data.

5- *P* value will be calculated to assess statistical significance. A value less than 0.05 will be considered statistically significant.

RESULTS

Clinical evaluation of patients

The current study included 23 cases and 23 control subjects. The mean age among the study group was 29.2±8.3 years with a mean duration of disease of 4.87±3.891. Mean age of onset of disease was 24.13±7.71. In the control group, the mean age was 21.7±5.2 years. The age difference between both groups was statistically significant (*P*=0.003). The minimum age recorded among the cases group was 16 years and the maximum 45 years. Controls had a minimum age of 15 years and a maximum of 35 years. Table 1 summarizes a comparison between the sex, occupational status, marital status, and history of raising pets in both cases and control groups.

Other social and clinical data of cases are presented in Table 2.

Serum levels of dopamine, cortisol, and reduced glutathione

In comparison to healthy controls, schizophrenic patients were found to have significantly higher levels of dopamine (*P*<0.00001), cortisol (*P*<0.00099), and lower levels of reduced GSH (*P*<0.000092), reflecting higher oxidative stress (Table 3).

Assessment of seroreactivity to toxoplasmosis and anti-*Toxoplasma* immunoglobulin-G titer

Toxoplasma titer among seropositive patients was found to be 2.32±0.59 and 2.68±0.51 in controls. The two values were not found to be significantly different (*P*=0.197). The anti-*Toxoplasma* titer in seronegative cases was 0.189±0.117 as compared with 0.420±0.268 in controls. In addition, there was no significant difference between the number of seropositive and seronegative individuals in the cases and control groups (Table 4).

Relation between seroreactivity to toxoplasmosis and different study parameters

Seroreactivity to toxoplasmosis did not influence most evaluated study parameters. However, reduced GSH levels were found to be significantly lower in seropositive schizophrenic patients (*P*=0.045). Also, the general symptom scale was significantly higher in seronegative patients (0.025) (Table 5).

Correlation studies revealed a significantly negative correlation between anti-*Toxoplasma* titer and serum cortisol, on one hand, and GSH levels on the other hand (*P*<0.001) (Table 6).

Table 1: Comparison between sex, occupational status, marital status, and history of raising pets in both cases and control groups:

	Study groups			
Social data	**Cases**	**Control**	**Total number of study participants**	***P* value**
Sex				
Male	12	5	17	0.134
Female	11	18	29	
Occupational status				
Unemployed	16	9	25	0.617
Employed	7	14	21	
Marital status				
Unmarried	17	18	35	0.0143*
Married	6	5	11	
Pets				
None	19	20	49	0.001*
Present	4	3	7	

*Statistical significance at *P* less than 0.05.

DISCUSSION

Schizophrenia is a multifactorial disorder that results from different pathologies. Disturbances in neurotransmitter physiology, particularly dopamine, are the most recognized etiological factors in the development of schizophrenia.

Regarding the relation of *Toxoplasma* and schizophrenia, our study revealed that there was no

Table 2: Social and clinical data of cases:

Sample parameter	*n* (%)
Sex	
Male	12(52.2)
Female	11(47.8)
Education	
None	7(30.4)
Basic	8(34.8)
Middle	6(26.1)
High	2(8.7)
Occupation	
None	16(69.6)
Present	7(30.4)
Marital status	
Unmarried	17(73.9)
Married	6(26.1)
Residence	
Urban	12(52.2)
Rural	11(47.8)
Pets	
Absent	19(82.6)
Present	4(17.4)
Electroconvulsive therapy	
Not received	9(39.1)
Received	14(60.9)
Medical H/O	
Absent	22(95.7)
Present	1(4.3)
Substance abuse H/O	
Absent	22(95.7)
Present	1(4.3)
Family H/O of psychosis	
Absent	16(69.6)
Present	7(30.4)
Family H/O of mood	
Absent	18(78.3)
Present	5(21.7)
Anti-Toxoplasma IgG	
Seronegative	15(65.2)
Seropositive	8(34.8)

IgG, immunoglobulin-G.

significant difference between the number of seropositive and seronegative individuals in the cases and control groups (P=0.076).

However, in Assiut University Hospitals in a study on 53 patients with schizophrenia, 57 patients with bipolar disorder, and 50 healthy volunteers were recruited and showed different results from our study. It detected anti-*Toxoplasma* IgG antibodies by indirect-ELISA showing

Table 3: Comparison between biochemical parameters between patients and controls:

	Cases		Controls		
Biochemical parameters	**Mean**	**SD**	**Mean**	**SD**	***P* value**
Dopamine (pg/ml)	51.73	0.41	41.87	0.34	<0.00001[a]
Cortisol (ng/ml)	210.63	144.11	101.27	35.995	<0.00099[a]
GSH (mmol/l)	2.4	1.07	4.05	1.48	<0.000092[a]

One-way analysis of variance. [a]Statistical significance at P less than 0.05.

Table 4: Comparison between seroreactivity among patients and controls:

Study groups	Cases [*n* (%)]	Control [n (%)]	χ^2	*P* value
Seropositive	15(65.2)	14(60.9)	0.0933	0.76
Seronegative	8(34.8)	9(39.1)		
Total	23(100)	23(100)		

a relationship between T. gondii infection and psychiatric disorders. The seropositivity rate, among patients with schizophrenia (50.9%) and patients with bipolar disorders (52.6%), was significantly higher than the control group (30%) (P=0.031 and 0.018, respectively) (13).

In this study, peripheral dopamine levels in schizophrenic patients was compared with dopamine levels of controls and was found to be significantly higher. Changes in the turnover of biogenic amines including dopamine are implicated in the disease pathophysiology. Evaluation of the disturbances in chemical imbalance in monoamine metabolism can be in part achieved by monitoring their level and that of their amino acid precursors in peripheral blood (De Luca *et al.,* 2008). Rao *et al.,* (1992) assessed the peripheral level of dopamine and some amino acids including tyrosine, the precursor of dopamine, in schizophrenic patients as compared with controls. Cases showed statistically higher dopamine and lower tyrosine levels, reflecting the contribution of disturbances in tyrosine availability to dopamine imbalance and the development of schizophrenia. Dopamine does not cross the blood–brain barrier; therefore, dopamine detected in the serum is of peripheral origin. It is synthesized by peripheral sympathetic neurons, and is transported inside platelets to its various sites of action. In addition to its regulatory effect on the peripheral nervous system, dopamine is also an important regulator of the immune system, angiogenesis, and wound repair (Arreola *et al.,* 2016; Vaughn *et al.,* 2017). Moreover, dopamine plays an important role in the generation of oxidative stress (Meiser *et al.,* 2013).

Hormonal disturbances, especially of the HPA axis, have also been implicated in the pathophysiology of this disease (Glassman *et al.,* 2018). In the current study, serum cortisol levels were significantly higher in schizophrenic

Table 5: Study parameters in relation to seroreactivity to toxoplasmosis:

Group descriptive						
Study parameters	**Serology of Toxoplasma**	***N***	**Mean**	**SD**	***F* value**	***P* value**
Age	Negative	15	26.53	7.060	5.24	0.051
	Positive	8	34.13	8.509		
Duration of illness	Negative	15	4.53	3.335	0.31	0.631
	Positive	8	5.50	4.957		
PS scale (7-49)	Negative	15	20.93	7.545	0.9	0.296
	Positive	8	23.75	4.979		
NS scale (7-49)	Negative	15	18.93	10.498	0.52	0.460
	Positive	8	15.75	9.114		
GS scale (16-112)	Negative	15	28.20	8.108	3.43	0.025[a]
	Positive	8	22.75	2.053		
TS (total scale)	Negative	15	68.07	15.664	0.81	0.352
	Positive	8	62.25	12.848		
Cortisol	Negative	15	195.25	159.200	0.48	0.453
	Positive	8	239.45	114.543		
GSH	Negative	15	2.70	1.115	3.67	0.045[a]
	Positive	8	1.85	0.771		
Dopamine	Negative	15	51.70	0.269	0.21	0.725
	Positive	8	51.78	0.608		

One-way analysis of variance. [a]Significant at *P* less than 0.05.

Table 6: Correlation between anti-Toxoplasma immunoglobulin-G titer, cortisol, reduced glutathione, and dopamine levels:

Correlation matrix				
	Anti-*Toxoplasma* IgG titer	**Cortisol**	**GSH**	**Dopamine**
Anti-*Toxoplasma* IgG titer				
Pearson's *r*	–			
P value	–			
Cortisol				
Pearson's *r*	0.234	–		
P value	0.282	–		
GSH				
Pearson's *r*	−0.450	−0.781	–	
P value	0.031	<0.001	–	
Dopamine				
Pearson's *r*	0.161	0.089	−0.019	–
P value	0.462	0.685	0.932	–

GSH, glutathione; IgG, immunoglobulin-G.

patients as related to controls. Research results on the level of cortisol in schizophrenic patients are inconsistent. In a study by Muck-Seler *et al.,* (2004), plasma cortisol levels were evaluated in patients suffering from schizophrenia or bipolar depression and were found to be significantly higher in both patient groups as compared with healthy controls. A study by White *et al.,* (2014) investigated the basal morning cortisol level in 85 schizophrenic patients, while there was no significant difference in cortisol levels between patients and controls. Patients within the study group suffering from deficit syndrome schizophrenia had higher morning plasma cortisol levels. Deficit syndrome schizophrenia is characterized by the dominance of primary negative syndrome. In our study, there was no significant correlation between negative or positive symptoms. We found, however, a significantly negative correlation between serum cortisol and reduced GSH levels. Glucocorticoids are known to stimulate carbohydrate and lipid metabolism, thus leading to the generation of ROS which lead to cellular damage, including that of neuronal cells (Spiers *et al.,* 2015).

Chronic CNS infections such as toxoplasmosis are also involved in the etiopathogenesis of schizophrenia, as infection per se results in oxidative stress and neuroendocrine alterations (Sorlozano-Puerto and Gutierrez-Fernandez, 2016). In a study by Lindgren *et al.,* (2018) including the whole adult Finnish population, seropositivity to toxoplasmosis was found to be significantly higher in individuals suffering from psychotic-like symptoms. The association of seropositivity with diagnosed psychotic disorders, however, did not reach statistical significance. The authors thus concluded that toxoplasmosis could be considered as a risk factor for the development of psychosis. In a study including 6,367 individuals, Flegr and Horáček (2020) explored the

association of toxoplasmosis with mental disorders through an online questionnaire. Schizophrenia was the second most common disorder to be associated with schizophrenia after autism. Other disorders included attention-deficit hyperactivity disorder, obsessive compulsive disorder, antisocial personality disorder, learning disabilities, and anxiety disorder. El Mouhawess *et al.,* (2020) reported a significant association between seropositivity to anti-*Toxoplasma* IgM and IgG and schizophrenia. They investigated the possible role of matrix metallopeptidase 9 (MMP9) gene polymorphism and the etiopathogenesis of schizophrenia in seropositive patients and found that seropositive schizophrenic patients displayed mutated MMP9 alleles. MMP9 has an important function in neuroinflammation. In a study by Campos-Carli *et al.,* (2017) , on the other hand, the level of anti-*Toxoplasma* IgG and IgM did not differ between schizophrenic patients and healthy controls. They also found that seropositivity to toxoplasmosis did not affect the severity or the type of schizophrenia symptoms. These results are similar to the present study, where no significant difference between anti-*Toxoplasma* IgG levels between patients and controls was found. However, serum-reduced GSH levels were found to be significantly lower in seropositive schizophrenic patients as compared with seronegative ones. In a study by Bahrami *et al.,* (2016), *T. gondii*-infected rats displayed increased oxidative stress levels and decreased antioxidant capacity on day 7 after infection. ROS are generated by macrophages as a defense mechanism against toxoplasmosis. Imbalance of the oxidant/antioxidant mechanisms are well-recognized factors (Rubesa *et al.,* 2011) of schizophrenia and may result from injuries to membrane phospholipids. In the present study, lower GSH levels were found in the cases group as compared with control subjects, which reflects its consumption as an antioxidant in the face of increased oxidative burden. Gunes *et al.,* (2017) investigated the total antioxidant level and oxidative stress index in schizophrenic patients. Oxidative stress was significantly higher in cases as compared with control subjects. Interestingly, patients receiving atypical antipsychotics had lower oxidative stress than those receiving typical antipsychotics or combined antipsychotic regimen.

CONCLUSION

Understanding the pathophysiology of schizophrenia remains a challenging task, as it involves several crossing pathophysiological pathways including neuroendocrine and immunological mechanisms. The exploration of the role of neurotransmitters, particularly dopamine, in the pathogenesis of schizophrenia has formed a basis for the tailoring of antischizophrenic drug therapy. As this disease is a consequence of a complex interplay of several etiological factors, the investigation of these factors could add to potential therapeutic possibilities. In addition to elevated dopamine levels, elevated cortisol levels and decreased GSH levels were found in schizophrenic patients as compared with controls. Though toxoplasmosis per se was not found to be a risk factor for schizophrenia, it might be a contributing factor by the generation of oxidative stress.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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