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SEROPREVALENCE OF *TOXOPLASMA GONDII* IN SCHIZOPHRENIC PATIENTS VERSUS HEALTHY INDIVIDUALS AND ITS POSSIBLE IMPACT ON HUMAN SERUM DOPAMINE LEVEL

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Abstract

Several studies demonstrated a high seroprevalence of *Toxoplasma gondii* in schizophrenic patients than healthy individuals. This case control study determined the serprevalence of *T. gondii* among schizophrenic patients and healthy individuals at Kafrelsheikh University Hospitals and to estimate its effect on serum dopamine level. *T. gondii* IgG was detected in 52.2% &23.9% of schizophrenic patients and healthy individuals respectively with significance (*P* value = 0.005). Serum dopamine level was higher in schizophrenic patients than healthy individuals with statistical significance (*P* = <0.001) and also higher in *T. gondii* IgG positive than *T. gondii* IgG negative patients with statistical significance (*P* = <0.001).

Key words: *Toxoplasma gondii*, Schizophrenic Non-schizophrenic, Dopamine level

Introduction

Toxoplasmosis is an infectious disease caused by a parasitic protozoan *Toxoplasma gondii* that affected about one third of world population (Flegr *et al,* 2014). It infects all species of mammals and numerous species of warm-blooded animals, but, human incidence varied according to demographic, hygienic and human factors (Jones *et al,* 2014).

Many health disorders and diseases were correlated with toxoplasmosis (Fuglewicz *et al,* 2017). A persistent dormant toxoplasmasis was involved in many neuro-psychiatric symptoms (Henriquez *et al,* 2009). They reported higher incidence of chronic toxoplasmosis in patients suffered from various psychiatric disorders (Torrey *et al,* 2007).

Schizophrenia is a severe psychiatric disorder affected about 1% of population as the 9th most common cause of disability worldwide (Torrey *et al,* 2012). It is manifested by the hallucinations, delusions, disturbances in thinking & communication and main substances responsible for such symptoms were dopamine, serotonin, GABA, and glutamate (Ali *et al,* 2020). The clinical picture onset typically occurred between the late teens and early 30s, with the peak incidence occurring in males in the early to mid-twenties, and in females in the late twenties (Ferri, 2019). Schizophrenia is characterized by continuous or relapsing episodes of psychosis (Owen *et al,* 2016). It was described as a neurodevelopmental feature without precise boundary, or a cause, developed from gene-environment interactions with involved vulnerability factors (Davis *et al,* 2016), or environmental infectious agent factors (Fuglewicz *et al,* 2017). One cause in the schizophrenia context was *T. gondii* (Xiao *et al,* 2018). Exposure to pet cats during infancy and childhood was associated with altered rates of psychiatric disorders development as schizophrenia and bipolar disorder in later life (Yolken *et al*, 2019). Several mechanisms by *T. gondii* achieved this behavioral in the host, as influencing the neurotransmitters levels in the intermediate hosts' brain (Elsheikha *et al,* 2016), by increasing dopamine release in neurons, probably by self-expression of genes encoding enzyme responsible for dopamine synthesis (McFarland *et al,* 2018). Toxoplasmosis altered glutamate signaling in brain (David *et al,* 2016). Also, the immunological pathway was another possible mechanism when pro-inflammatory cytokines associated with toxoplasmosis induced apoptosis that led to neurodegeneration (Sutterland

et al, 2020). Such mechanisms have important role in psychotic disorders, as neurotransmitters and immunological disturbances attributed to psychosis and schizophrenia pathophysiology (Al-Diwani *et al,* 2019).

Diagnosis of toxoplasmosis depends on serological tests as ELISA that detected *T. gondii*-specific IgG & IgM antibodies. An IgG titer cannot differentiate recent from past infection but may be considered as a confirmation for exposure to the infection while IgM antibodies were detected earlier than IgG antibodies and decrease faster, but they didn't indicate acute infection as they could remain for years after acute infection without clinical value (Ekici *et al,* 2021).

This study aimed at serological diagnosis of toxoplasmosis in relation to schizophrenia and estimation of its effect on human serum dopamine level.

Materials and Methods

Study design and population: A cross-sectional study was conducted on 92 individuals; 46 patients aged 19-45 schizophrenia diagnosed and followed-up at outpatient clinic of Neuropyschiatry Department, Kafrelsheikh University Hospitals all over the year 2020 (case group) and cross-matched 46 healthy individuals without schizophrenia were included as a control group. A pre-designed questionnaire was used to collect demographic and clinical data of all subjects.

Work plan: Serum samples were collected from each participant (case and control) and subjected to: 1- Anti-*Toxoplasma* IgG antibodies detection by using Nova-Lisa *Toxoplasma* IgG-ELISA (Nova Tec-Immundiagnostica GmbH, D-63128 Dietzenbach, Germany). Results were interpreted and reactive when IgG index was at > 35IU/ml, equivocal at 30 -35IU/ml and non-reactive at < 30 IU/ml. 3- Anti-*Toxoplasma* IgM antibodies detection by IgM-capture ELISA (DRG® *Toxoplasma* IgM, TORCH, EIA1799, DRG International, Inc., USA). Results were interpreted as negative when IgM index at < 0.9, equivocal at 0.9 to 1.0, while positive if IgM index was at > or equal to 1.0. 3- Human serum Dopamine level was detected by using human dopamine ELISA kit (DRG® Dopamine EIA-4161, DRG® International, Inc., USA) according to manufacturer's protocol. Solution absorbance in wells was read within 10minutes by a microplate reader set to 450nm and a reference wave-length between 620nm & 650nm. Plasma concentration samples were divided by 60.

Statistical analysis: Data were coded and entered using statistical package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized as mean, standard deviation, median, minimum, & maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done by non-parametric Mann-Whitney test (Chan, 2003a). For comparing categorical data, Chi square (χ^2) test was used. Exact test was used instead when the expected frequency was less than 5 (Chan, 2003b). *P*-less than 0.05 were considered significant.

Results

This cross-sectional study was done on 92 subjects divided into two groups: schizophrenic group (46 patients) and healthy individuals group (46 individuals). Schizophrenic group was 36 males & 10 females with mean age of 30.9+/-8.9, and healthy ones were 34 males and 12 females with mean age of 30.7+/-7.9. Cat exposure was high in schizophrenic patients (19.6%) than healthy ones (6.5%) without significance ($P = 0.063$), but raw meat consumption was a risk factor with high level in schizophrenic patients (54.3%) than healthy ones (6.5%) with significance ($P < 0.001$).

Psychotic disorders among patients and controls were behavioral and personality changes, increased activity, hallucinations and suicidal attempts were significance among schizophrenia ones.

T. gondii IgM was 10.9% & 17.4% in schizophrenic patients and healthy ones respectively without significance, *T. gondii* IgG was 52.2% & 23.9% in schizophrenic patie-

nts and healthy ones respectively with significance between schizophrenia and IgG positive ones (*P* 0.005), but no significant was between schizophrenia & IgM positivity (*P* 0.369). Dopamine mean level was higher in schizophrenic patients (89.15+/-18.73) than healthy ones (32.30+/-20.39) and the relation between schizophrenia and serum dopamine level was significant (*P* <0.001). Dopamine serum levels were paralleled in *T. gondii* IgG positive and *T. gondii* IgG negative patients and showed higher level in *T. gondii* IgG positive (92.32+/-20.61) than *T. gondii* IgG negative (41.33+/-26.06) with statistical significance (*P* <0.001).

Details were given in tables (1, 2, & 3).

Table 1: Demographic and clinical data of population

			Schizophrenic group		Healthy group		P value
			Count	%	Count	%	
Age		Mean age +/- SD	30.9 +/- 8.9		30.7 +/- 7.9		0.953
		Minimum	16		16		
		Maximum	45		45		
Sex		Male	36	78.3%	34	73.9%	0.625
		Female	10	21.7%	12	26.1%	
Contact with cats		yes	9	19.6%	3	6.5%	0.063
		no	37	80.4%	43	93.5%	
Consumption of raw meat		yes	25	54.3%	3	6.5%	< 0.001
		no	21	45.7%	43	93.5%	
Psychotic disorders	Behavioral changes	yes	46	100.0%	0	0.0%	< 0.001
		no	0	0.0%	46	100.0%	
	Personality changes	yes	46	100.0%	0	0.0%	< 0.001
		no	0	0.0%	46	100.0%	
	Increased activity	yes	46	100.0%	0	0.0%	< 0.001
		no	0	0.0%	46	100.0%	
	Hallucinations	yes	46	100.0%	0	0.0%	< 0.001
		no	0	0.0%	46	100.0%	
	Suicidal attempts	yes	8	17.4%	0	0.0%	0.006
		no	38	82.6%	46	100.0%	
T. gondii	IgM	Positive	5	10.9%	8	17.4%	0.369
		Negative	41	89.1%	38	82.6%	
	IgG	Positive	24	52.2%	11	23.9%	0.005
		Negative	22	47.8%	35	76.1%	
Dopamine		yes	37	80.4%	30	65.2%	0.101
		no	9	19.6%	16	34.8%	

Table 2: Relation of schizophrenia and serum dopamine level

Dopamine	Schizophrenic patients				Healthy individuals				P value
	M±SD	Median	Minimum	Maximum	M±SD	Median	Minimum	Maximum	
pg/ml	89.15 ±18.73	88.50	60.00	120.00	32.30±20.39	24.00	11.00	84.00	<0.001

Table 3: Relation of *T. gondii* IgG positivity and serum dopamine level

Dopamine	IgG positive				IgG negative				P value
	M±SD	Median	Minimum	Maximum	M±SD	Median	Minimum	Maximum	
pg/ml	92.31±20.61	97.00	55.00	120.00	41.33±26.06	26.00	11.00	90.00	<0.001

Discussion

One of the main associations between toxoplasmosis and development of psychiatric disorders was schizophrenia (Fekadu *et al,* 2010).

In the present study, schizophrenia patients showed a higher *T. gondii* antibodies level to than in controls. This agreed with El-Sayed *et al.* (2012) who found that toxoplasmosis patients developed psychotic symptoms as delusions and hallucinations-like those of schizophrenia, with elevated dopamine levels in experimentally infected animals and schizophrenic patients. *T. gondii* seroprevalence of up to 85% was among tropic populations in the developing countries (Hernández-Cortazar *et al,* 2015; Nayeri *et al,* 2020).

In Egypt, Wishahy *et al.* (1975) reported congenital toxoplasmosis in children with some neurological manifestations. Rifaat *et al.* (1975) reported infantile toxoplasmosis & some neurological disorders. Rifaat *et al.*

(1981) reported *T. gondii* seropositivity in stray cats. Mabrouk and Dahawi (1991) found that 42 meningoencephalitis patients with negative C.S.F. cultures for commonest pathogenic showed 10/42 (26%) positive IIFA *Toxoplasma* IgG antibodies. They added that clinical presentation & C.S.F changes with high antibody titers incriminated toxoplasmosis to be the etiologic agent. Al-Kappany *et al.* (2010) reported that high prevalence of *T. gondii* in feral cats indicated a high oocysts environmental contamination. Saleh *et al.* (2014) found *T. gondii* infection among childbearing age females. Abdel Rahman *et al.* (2016) found protozoa parasites as *T. gondii, Babesia* species and *Plassmodium falciparum* in patients with aseptic meningitis. Abbas *et al.* (2020) reported that toxoplasmosis was highly prevalent in man and animals from rural Egypt where life circumstances favor for *T. gondii* transmission.

In the present study, high *T. gondii* IgG positivity (52.2%) was in schizophrenic patients than in controls (23.9%). This agreed with Ali *et al.* (2020) who reported higher *T. gondii* seroprevalence in Egyptian Schizophrenic patients (55.6%) than healthy persons (28.9%). Mortensen *et al.* (2007) in Denmark reported that early exposure to several infectious agents was associated with later schizophrenia development. They added that the causal linking mechanisms were the present speculative but with possible direct effects of maternal *T. gondii* IgG on the developing CNS of the offspring

Dogruman *et al.* (2009) in Turkey found a rate of 47.7% and 21.6% in schizophrenic patients and healthy persons, respectively, and added that *T. gondii* played a role in pathogenesis of some schizophrenia patients. Morsy *et al.* (1978) in Jordan found that congenital toxoplasmosis was the main cause among mentally retarded children. Tanyüksel *et al.* (2010) in Turkey reported *T. gondii* sero-positivity was 43.8% in schizophrenic patients and 32.5% in healthy ones. Yagmur *et al.* (2010) in Turkey detected toxoplasmaosis as cause of attempted suicide (41%) versus (28%) in control ones. But, Arling *et al.* (2009) in USA neither found significant relation between *T. gondii* seropositivity or the suicide attempt status, number of prior suicide attempts, nor recurrent diagnosed mood disorder. They added that although preliminary and bearing replication, this was the first report, to their knowledge, of an association between attempting suicide and toxoplasmasis infection.

In the present study, *T. gondii* IgM didn't show significantly different between 10.9% & 8.7% in the schizophrenic patients and healthy ones, respectively. No doubt, IgM is the marker of infection, which became negative within 4-12 weeks, and thus no schizophrenia significance. Also, Hamidinejat *et al.* (2010) in Iran didn't find associations between immune status ratio values and the schizophrenia risk, but Juanah *et al.* (2013) in Malaysia found a marked relationship between toxoplasmosis and schizophrenia.

The schizophrenic patients with toxoplasmosis showed different serum dopamine levels (Flegr *et al,* 2003). Also, the increased dopamine levels in the seropositive schizophrenic cases compared to seronegative schizophrenic cases was accountable for the behavioral changes (Mahmoudvand *et al,* 2015). Ali *et al.* (2020) reported that the behavioral changes in the *T. gondii* seropositive patients were related to increase in the serum dopamine level. This neurotransmitter played the noteworthy role in schizophrenia (Hodková *et al,* 2007). Prandovszky *et al.* (2011) found that serum dopamine increase levels to risk deterioration of schizophrenia.

Conclusion

The outcome data may suggest an association between toxoplasmosis infection and schizophrenia.

Nevertheless, efforts must be directed to toxoplasmosis prevention by the health education and arising awareness of its risk factors as to the stray and/or pet cats, eating habits especially of raw vegetables and fruits, hand-washing and hygienic behavior.

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they neither have interest nor received fund.

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