Maternal Toxoplasmosis: *Risk factor for Schizophrenia and its Disabling Effect on Maternal Quality of Life*

Fawzy N, Saber M

Department of Psychiatry, Zagazig University, Sharkia, Egypt.

ABSTRACT

Background: Recent studies have linked schizophrenia with perinatal exposure to many viruses and with postnatal exposure to viral and bacterial agents causing meningitis and encephalitis. The largest number of studies linking an infectious agent to schizophrenia, however, has involved *Toxoplasma gondii*. **Objective:** to determine the relation between maternal toxoplasmosis, risk of schizophrenia in the offspring and the maternal quality of life. **Subjects and methods:** The recruited sample includes 94 mothers of schizophrenic patients, and 89 mothers of normal off spring The recruited sample was classified into two groups, mothers of Schizophrenic patients (group I), Hospital visitors (group II). All participants were subjected to Serological assays for *Toxoplasma* antibody, and quality of life assessed by the Short Form (36) Health Survey. **Results:** The prevalence rate of sero-positive (IgG) cases was 58.5%, 5.6% respectively in group I and II, also the prevalence rate of sero-positive (IgM) cases was 5.4%, 4.5% respectively in group I and II. There is a high significant difference between means of (IgG) of both groups. **Conclusion:** This study demonstrated that elevated maternal IgG antibody to *Toxoplasma* is associated with increased risk of schizophrenia and decreased quality of life.

Key words: Maternal Toxoplasmosis, Toxoplasma gondii, Schizophrenia, Egypt.

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INTRODUCTION

In 1896, the Journal Scientific American published an editorial entitled "Is Insanity Due to a Microbe?" thereby initiating interest in a possible infectious etiology of schizophrenia[1]. Interest in the hypothesis was widespread in the early years of the 20th century, and then waned until the closing years of the century. Recent studies have linked schizophrenia with perinatal exposure to viruses such as influenza A virus, rubella virus, herpes simplex virus type and polioviruses[2] and with postnatal exposure to viral and bacterial agents causing meningitis and encephalitis. The largest number of studies linking an infectious agent to schizophrenia, however, has involved *Toxoplasma gondii*[3].

Several maternal infections have been associated with an elevated risk of schizophrenia in offspring[4].

Evidence suggests that infections known to cause congenital CNS anomalies in humans, including rubella, herpes simplex, polio, and varicella-zoster virus[5], might be related to the risk of schizophrenia. Toxoplasmosis is also associated with mal development of the CNS, and ecological

data have led to the suggestion that this organism might be involved in the etiology of schizophrenia. Therefore, serological methods used to investigate whether maternal exposure to toxoplasmosis is associated with an increased risk of schizophrenia in adult offspring[6].

Toxoplasma gondii the cause of toxoplasmosis is intracellular parasite; when primary infection occurs during pregnancy the offspring has a markedly increased risk of CNS congenital abnormalities, including microcephaly, hydrocephalus, mental retardation, convulsions, cerebral calcifications, and chorioretinitis[7].

Delayed neurologic sequel, including lower IQ, retarded psychomotor development, and sensorineural deafness, have also been demonstrated in subjects who were exposed in utero, even among those with subclinical infection during the neonatal period[8]. However, increased IgG titers to *Toxoplasma* have been associated with both severe and slight neuropsychiatric abnormalities[9].

Detection of *Toxoplasma* includes direct detection of the parasite, immunoassays for serum immunoglobulin (IgM) antibody, and elevation of maternal IgG antibody to *Toxoplasma*. In addition, elevation of *Toxoplasma* IgG may reflect primary active or reactivated infection; IgM antibody is a specific indicator of recent infection. Increased IgG may persist for years in subjects with dormant infection[8].

Toxoplasma gondii, coccidian protozoa of the apicomplexa family, was first described in 1908. In 1939, it was linked to a congenital syndrome that includes deafness, retinal damage, seizures, mental retardation, and intracranial calcifications[9]. Postnatal transmission may produce lymphadenopathy and nonspecific symptoms of infection, but most cases are thought to be asymptomatic.

The definitive hosts of this organism are cats and other felines. Transmission of *T. gondii* to humans may come about through ingestion or inhalation of oocysts shed by infected cats into litter boxes, gardens, sandboxes, or other children's play areas. Organism may also be transmitted through the ingestion of tissue cysts by the eating of undercooked meat containing tissue cysts from sheep, goats, or other animals that have been infected from cats[7].

The availability of serological assays has allowed the testing of exposure to *T. gondii* in large numbers of individuals. Studies using these assays have indicated that *Toxoplasma* infection is widespread and varies in geographic regions and among individuals with different demographic characteristics[10].

Given *T. gondii*'s neurotropism and association with congenital brain dysfunction, there has been long-standing interest in investigating a possible association between exposure to this organism and the development of severe psychiatric disorders[8]. The first study of *T. gondii* antibodies in psychiatric patients was published in 1953 by Kozar in Poland. Since that time, 41 additional published and unpublished studies have been identified by the authors and were subjected to a meta-analysis directed at defining the association between *Toxoplasma* exposure and the risk of schizophrenia[8].

SUBJECTS AND METHODS

Subjects: Participants were classified into two groups:

Group I: Include 94 mothers of schizophrenic patients randomly selected when they accompanied their sons during their follow-up in psychiatric outpatient of Zagazig university hospital. The included mothers have no age limits, all occupational, social and educational classes, alternatively the exclusive criteria were mothers with general medical diseases, past history of psychiatric disorders in her family.

Group II: Include 89 mothers of Zagazig University Hospital visitors in the study as control subjects with normal mental and physical offspring; they should match the study group as regards the inclusive and exclusive criteria.

This study was done between March 2008 to November 2008; and all subjects gave a written consent.

Methods:

Psychiatric assessment: Mental state examination of participants was done according to DSM-IV TR criteria, a semi Structured Psychiatric Interview was introduced to all subjects. The collection of information concerning socio-demographic characteristics, treatment and social support was done using the Patients Follow-up Schedule (PFS) in psychiatric outpatient clinic and history of illness from mothers. Assessment of quality of life for group I and II was done using Short Form (36) Health Survey (SF-36), the most widely used instrument to assess health related quality of life. It consists of eight domains (physical function, role function physical, role function emotional, social function, mental health, general health, vitality and pain). The domain scores are rated, so that higher values indicate better health (range 0–100). Its reliability and validity is rather high. The SF-36 items are summarized in two weighted summary scales: mental domain summary and physical domain summary[11].

Serological assays: for *Toxoplasma* antibody to participants. Blood samples were collected by vienopuncture and centrifuged to separate their sera, which preserved at -20°C then examined later for presence of anti *Toxoplasma* seropositivity, The preserved sera of these cases were tested to monitor the level IgG and IgM using ELISA technique, and results monitoring by optical density (O.D), where the cut off value is 0.3 O.D.

The Virulent strain of *Toxoplasma gondii,* strains are maintained in laboratory by repeated sub passage in Swiss albino mice. *Toxoplasma* antigen was prepared using *T. gondii* trophozoites from the peritoneal exudate of mice infected three days earlier with the RH strain. The protein concentration of *Toxoplasma* antigen was estimated using BCA[12].

Statistical analysis:

It was done by using SPSS program version 14, to examine the correlation between varying levels of Ig and other variables by chi- square (x2) test.

$$\alpha = \sum \frac{(0-E)^2}{E} \quad where \sum = summation$$

O=observed value, E= Expected value

Comparison between the means of SF-36 scores and the means of IgG and IgM was calculated in both groups.

RESULTS

The prevalence rate of sero-positive (IgG) cases was 58.5%, 5.6% respectively in group I and II. The prevalence rate of sero-positive (IgM) cases was 5.4% and 4.5% respectively in group I and II.

Table (1 and 2) represent statistically significant increase number of widowed or divorced mothers who lived in bad home atmosphere in the group with positive IgG and IgM groups compared with the group with negative IgG and IgM.

Table (3 and 4) represent statistically significant increase number of mothers lived in urban area with positive IgG and IgM compared with the group with negative IgG and IgM.

Table (1): Comparison between the percentage of positive and negative IgG in Group I according to socio-demographic data.

	Variable	+ve IgG (%)	-ve IgG (%)	x^2	P value
Residence:	Rural	46-48.9%	33-35.1%	0.016	0.898
	Urban	9-9.6%	6-6.4%		
Occupation	Employed	17-18.1%	9-9.6%	0.700	0.403
	Unemployed	38-40.4%	30-31.9%		
Marital state:	Married	42-44.7%	37-39.3%	5.83	0.015*
	single	13-13.8%	2-2.2%		
Home atmosphere:	Good	35-45.7%	35-33.0%	8.18	0.004*
	Bad	20-12.8%	4-8.5%		
Number diseased sons	one patient More than one patient	40-42.6% 15-15.9%	30-31.9% 9-9.6%	0.21	0.645
Prognosis of sons illness	Good Bad	42-44.7% 13-13.8%	27-28.7% 12-12.8%	0. 59	0.440
Compliance to ttt	compatible incompatible	39-41.5% 16-17%	29-32.1% 10-9.4%	0.14	0.712
Prevalence of antibodies		55-58.5%	39-41.5%		

Table (2): Comparison between the percentage of positive and negative IgM in Group I according to socio demographic data.

	Variable	+ve IgM (%)	-ve IgM (%)	x^2	P value
Residence:	Rural	4-4.3%	75-79.8%	0.06	0.79
	Urban	1-1.1%	14-14.8%		
Marital state:	Married	2-2.2%	77-81.9%	7.64	0.005*
	Single	3-3.2%	12-12.7%		
Home atmosphere:	Good	1-4.3%	69-73.4%	8.24	0.004*
	Bad	4-1.1%	20-21.2%		
Occupation	Employed	1-1.1%	25-26.6%	0.155	0.695
	Unemployed	4-4.3%	64-68.0%		
Number diseased sons	One patient More than one patient	4-4.3% 1-1.1%	66-70.2% 23-24.4%	0.08	0.771
Prognosis of sons illness	Good Bad	3-3.2% 2-2.2%	66-70.2% 23-24.4%	0. 49	0.481
Compliance to ttt	Compatible Incompatible	3-3.2% 2-2.2%	65-69.1% 24-25.5%	0.40	0.52
Prevalence of antibodies		5-5.4%	89-94.6%		

Table (3): Comparison between the percentage of positive and negative IgG in Group II according to socio–demographic data.

	Variable	+ve IgG (%)	-ve IgG (%)	x^2	P value
Occupation	Employed	1-1.1%	28-31.5%	0.382	0.537
	Unemployed	4-4.5%	56-62.9%		
Residence:	Rural	2-2.2%	68-76.2%	4.71	0.029*
	Urban	3-3.4%	16-18.2%		
Marital state:	Married	4-4.5%	66-74.2%	0.01	0.939
	Single	1-1.1%	18-20.2%		
Education	Highly education	1-1.1%	19-21.3%	0.02	0.89
	Lower education	4-4.5%	65-73.1%		
Home atmosphere:	Good	3-3.4%	67-75.3%	1.098	0.295
	Bad	2-2.2%	17-19.1%		
Prevalence of antibodies		5-5.6%	84-94.4%		

Table (4): Comparison between the percentage of positive and negative IgM in Group II according to socio-demographic data.

	Variable	+ve IgM (%)	-ve IgM (%)	x^2	P value
Occupation	Employed	0-0.0%	29-32.6%		
	Unemployed	4-4.5%	56-62.9%	2.024	0.155
Residence:	Rural	1-1.1%	69-77.6%	7.18	0.007*
	Urban	3-3.4%	16-17.9%		
Marital state:	Married	2-2.25%	68-76.4%	0.059	0.808
	Single	2-2.25%	17-19.1%		
Education :	Highly education	1-1.1%	19-21.3%	0.02	0.901
	Lower education	3-3.4%	66-74.2%		
Home atmosphere:	Good	1-1.1%	67-75.2%	1.137	0.286
	Bad	3-3.4%	18-20.3%		
Prevalence of antibodies		4-4.5%	85-95.5%		

Table (5): Comparison between means of immunoglobulns in groups

Variable	no	mean	St.d	T.test	P value
IgG (group I)	94	0.4001	0.20234	0.00	0.000**
IgG (group II)	89	0.2141	0.07562		
IgM (group I)	94	0.1330	0.07623	0.462	0.061
IgM (group II)	89	0.1022	0.08404		

*p-value<0.05 is statistically significant **p-value<0.001 is statistically highly significan

Table (5) represents highly significant difference between means of IgG of group I and group II. However, these results represent insignificant difference between means of IgM in group I and group II.

Table (6) represents higher scores in physical domain summary especially in role-physical, bodily pain and general health than mental domain summary in SF-36. Therefore group I represent low quality of life than group II in total SF-36 score. Also statistical methods represent a significant difference between physical domain of quality of life in both groups as measured by the mean SF-36 for each group

Table (6): Comparison between means of Quality of life in group I and group II

SF-36 Health Survey measure	Group I	Group II	P-Value
Aggregate mental domain	**40.1**	**41.2**	**0.57**
Vitality	66.6	65.4	0.77
Social function	52.0	56.2	0.54
Role-emotion	43.6	42.6	0.67
Mental health	64.4	73.2	<0.01*
Aggregate physical domain	**52.0**	**56.9**	**<0.01***
Physical functioning	48.0	60.6	<0.01*
Role-physical	74.1	88.6	<0.01*
Bodily pain	77.5	91.6	<0.01*
General health	76.1	82.8	0.02*

DISCUSSION

Conventional mental practice largely ignores the possibility of parasitic disease. There are several reasons for this: First, when a disease is never diagnosed, it is easy to assume that it does not exist. Second, parasites are often overlooked, and spending one's day studying microscopic sample of stool specimens probably does not attract many laboratory personnel[13].

In the current study, the prevalence rate of IgG seropositive is 58% and the prevalence rate of IgM seropositive is 5.4% between mothers of Schizophrenic patients. This is in associations with previous results which gave associations between prenatal exposure to other infectious agents and the risk of schizophrenia[4, 13]. Nevertheless another study proposed that there is no association between antibody to Toxoplasma and the risk of schizophrenia[8].

An Egyptian study proposed that acute infection can produce psychotic symptoms similar to those displayed by persons with schizophrenia[14]. Conversely to the current study results showed that chronic infection is a risk for schizophrenia. In a previous study, an enzyme immunoassay (ElISA) was applied to measure the level of *Toxoplasma* IgG antibodies in serum samples from 75 patients of schizophrenia and 85 matched controls, where percentage of positive sera for *Toxoplasma* IgG antibodies was significantly higher in schizophrenic cases than controls (80% vs. 52.9% respectively). These results may be explained by the small sample size and the chance of misdiagnosis due to absence of qualified psychiatrist who gave accurate diagnosis of the schizophrenic cases. Furthermore, quantified IgG antibody was used by solid-phase enzyme immunoassay rather than by ELISA technique[4, 7, 13].

The sera in the current study had been frozen for over 30 days, decreasing the possibility that storage for this period of time may have altered the *Toxoplasma* antibody levels. However, this factor appears unlikely to have had a significant impact on study results for several reasons. First, *Toxoplasma* antibody levels are generally stable in frozen stored sera. Second, the seroprevalence of toxoplasmosis in comparison subjects was 58%, not similar to the 17.5% seroprevalence found in a large previous studies of toxoplasmosis in reproductive-age women in the United States although the period of frozen was similar[15].

The results of group I (mothers of Schizophrenic patients) shows there is statistically significant increase in widowed and divorced mothers living in bad home atmosphere with positive IgG and IgM mothers compared with the group with negative IgG and IgM. Kruszon et al. proposed there is significant correlation between acute *toxoplasmosis* (IgM) and bad home atmosphere[16]. The prevalence of antibodies of *T. gondii* has been shown to be higher in individuals who are poorer and

who live in more disturbed households. Also another study proposed that the prevalence of schizophrenia is higher in individuals who are poorer and who live in more crowded houses, due to the decreased immunity in quarreling homes, which increase *toxoplasmosis* dormant infection, where a healthy immune system can keep this parasite in the cyst state[17]. Without a healthy immune system, this organism can run rampant[18].

The results of group II (mothers of normal offspring) showed statistically significant increase in mothers lived in urban area with positive IgG and IgM compared with the group with negative IgG and IgM. Although infection by the protozoan parasite, *Toxoplasma gondii* is widely prevalent in humans and animals throughout the world, transmission takes place mainly by ingestion of raw or undercooked meat that contains parasite cysts or by ingestion of oocysts excreted in cat feces, which can contaminate water and raw vegetables. Therefore the incidence of toxoplasmosis in urban areas can thus be related to environmental contamination with oocysts[19].

This result associated with one summary concluded that such studies have shown "no consistent pattern, with rural predominance in some and urban in others[20]. Almost all studies have reported that being born in, or having lived as a child in, an urban area, compared to a rural area, confers an increased risk of later being diagnosed with schizophrenia[21].

In contrast, some studies of antibodies to *T. gondii* have reported them to be more common in individuals in urban areas, but other studies have reported them to be more common in individuals in rural areas[20].

The results of the current study represent high significant difference between means of (IgG) of group I, and group II. These results explain that chronic infection as a risk factor for schizophrenia in group I rather than in group II. Nevertheless there is insignificant difference between means of (IgM) of both groups.

These results in association with the study which proposed that increased IgG titers to *Toxoplasma* have been associated with both severe and slight neuropsychiatric abnormalities[9]. However, elevation of *Toxoplasma* IgG may reflect primary active or reactivated infection; unlike IgM antibody, which is a specific indicator for recent infection. Increased IgG may persist for years in subjects with dormant infection[8].

The results of quality of life for, Group I and Group II represent a significant difference between physical domains of quality of life in both groups as measured by the mean SF-36 for each group. But there is insignificant difference between means of mental domain of quality of life in both groups. These results are due to the retarded psychomotor development, repeated abortion and sensorineural deafness developed after chronic Toxoplasmosis[8]. The social and economic impact of toxoplasmosis on public health is demonstrated by the loss of the quality of life caused by blindness, neurological disorders and death due to abortion or encephalitis[22-23]. Chronic Toxoplasmosis affect the subject activity, mental health, and physical health life in seropositive patients, However, recent studies associate *T. gondii* infection with personality shifts and increased likelihood of reduced intelligence or schizophrenia and these conditions reduce the quality of life of

individuals, and may cause a significant economic burden upon society[25]. Although these factors prove that quality of life is impaired by Toxoplasmosis but we can't rule out the role of schizophrenia patient on his mother's quality of life, this fact enhance researchers to do further studies to demonstrate this role.

CONCLUSION

This study demonstrates that elevated maternal IgG antibody to *Toxoplasma* is associated with increased risk of schizophrenia, and decreased quality of life.

RECOMMENDATIONS

In the future further studies are needed to assess toxoplasmosis and its correlation with other psychiatric disorder on large number of psychiatric patients, and assess the effect of chronic toxoplasmosis on neurotransmitters. Indeed, standard obstetric practice should included recommendations to pregnant women to minimize exposure to *Toxoplasma*, as a measure for prevention of schizophrenia.

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Address of Correspondence:
Fawzy N. Department of Psychiatry, Zagazig University, Sharkia, Egypt.
e-mail*:nagyfawzy2007@yahoo.com*