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SERO-PREVALENCE OF ANTI- *TOXOPLASMA GONDII* ANTIBODIES AMONG PATIENTS WITH NEUROPSYCHIATRIC DISORDERS: EPILEPSY AND DEPRESSION

By
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Abstract

Toxoplasma gondii infection is concerned to have an association with epilepsy and depression either as a cause or a potential risk factor for their occurrence. Nevertheless, there has been long-standing interest in investigating this possible association, the evidence for such relationship is yet not conclusive. The current study correlated between *T. gondii* infection and Neuropsychiatric disorders: epilepsy and depression, through serological valuation of anti-*Toxoplasma* immunoglobulin (Ig) G antibodies. In the current study, 112 patients suffered from epilepsy (72 cryptogenic and 40 non-cryptogenic), 118 had depression and 60 healthy volunteers that had no history of any neuropsychiatric disorders in their first degree relatives were enrolled. Full history taking, complete physical examination, cranial magnetic resonance imaging (MRI), scalp electroencephalography (EEG), a structured questionnaire and *T. gondii* specific IgG antibody ELISA were performed to all groups. The results showed that the anti-*Toxoplasma* IgG antibodies were detected among cases with cryptogenic epilepsy 34.7% (25 out of 72 cases), non-cryptogenic epilepsy 2.5% (1 out of 40) and depression 20.3% (24 out of 118) groups compared to healthy control group (11.7%). There were significant associations between *T. gondii* seropositivity of epilepsy and depression groups in age, residence, contact with pets and social class compared to control healthy group ($p<0.05$). Youth and adults had the highest sero-*T. gondii* infection especially male in rural areas with low social class.

Keywords: Toxoplasmosis; Epilepsy; Depression; Seropositivity, ELISA, IgG.

Introduction

Toxoplasma gondii is a neurotropic intracellular protozoan, causes toxoplasmosis (Hamidinejat *et al,* 2010). It is worldwide and influences about 33% of the total population (Fekadu *et al,* 2010). Despite the fact that cats are its definitive host, human infection is often by ingestion of oocyst in water, or through tissue cyst in under cooked or raw meat. Contact with felines, feline defecation and soil have been included with transmission of the disease to humans (Guo *et al,* 2015). Toxoplasmosis varies across the world, in sub-Saharan Africa high rates of infection were reported (Negash *et al,* 2007). In Egypt, Wishahi (1972) reported neurological manifestations in congenital toxoplasmic children. Saleh *et al*. (2014) reported *T. gondii* infection among childbearing age females and Abdel Aaty and El-Sheemy (2016) stated that prevalence of *T. gondii* infection was increasing particularly in individuals with psychological illness. Also, In Jordan, Obaidat *et al.* (2015) *T. gondii* infection in female university students was high and most women become infected before marriage and Morsy *et al*. (1978) reported Toxoplasma positivity in a royal institute for mentally retarded children. During chronic infection, cysts of toxoplasmosis are located in numerous anatomical sites including the brain. *T. gondii* genome is known to contain 2 fragrant amino corrosive hydroxylases that could specifically influence dopamine as well as serotonin biosynthesis, that been associated with behavior and mood changes in individuals (Henriquez *et al,* 2009). Exposure to *T. gondii* was essential to develop neuropsychiatric and behavioral disorders (Fabiani *et al,* 2013). Correlation between toxoplasmosis and epilepsy was reported (Ngoungou *et al,* 2015).

Epilepsy is a chronic neurological disorder that influences almost 70 million individuals

of all ages around the world (Kariuki *et al,* 2015). Two types of epilepsy are known: idiopathic epilepsy with unknown cause; 60% (Scheffer *et al,* 2016) and the secondary type epilepsy from cerebral lesions due to hypoxic, traumatic, or infections (Schmidt and Sillanpää, 2016). Cryptogenic epilepsy is defined as epilepsy syndrome for which the cause is unknown, but an underlying brain disease is supposed and *T. gondii* infection should be excluded (El-Tantawy *et al,* 2013).

The etiology of psychiatric disorders is mostly unknown. Infections are potential risk factors for psychiatric disorders especially *T. gondii* (Al-Hussainya *et al,* 2015). Depression is a public psychiatric disorder that is accompanying with significant morbidity and mortality. The prevalence of depression is high in individuals with *T. gondii* infection (Chu Hsu *et al,* 2014). Depression is a mood changes described by changes in state of mind, loss of interest, cognitive function, pleasure, rest, appetite, or energy level and suicide attempts (Arling *et al,* 2009). A case of depression with *T. gondii* seropositive who responded only to antidepressant treatment after treatment of *T. gondii* was reported (Kar and Misra, 2004). Also, Alvarado-Esquivel *et al.* (2016) reported an association between *T. gondii* exposure and depression especially in young age individuals.

Toxoplasmosis primarily controlled by cell mediated immunity (Denkers and Gazzinelli, 1998), although humoral immune response plays a significant role (Dupont *et al,* 2012). In human, IgG is the main antibody class produced in humoral response to toxoplasmosis and the diagnosis based on ELISA (Cañedo-Solares *et al,* 2008).

There was limited number of studies with insufficient data that discuss the correlation between toxoplasmosis and neuropsychiatric disorders. More and better studies are needed to determine the real impact of this parasite on the occurrence of such disorders.

There is no precise report on anti-*Toxoplasma* antibodies in epileptic and depressed patients in Zagazig city, Egypt. So, the current study aimed to correlate between toxoplasmosis and neuropsychiatric disorders: epilepsy and depression, through serological valuation of anti-*T. gondii* IgG antibodies.

Subjects, Materials and Methods

Study design and Data collection: The present case control seroprevelance study included 112 epileptic, 118 depressed patients and 60 healthy volunteer control group; aged between 2-46 years of both sexes, were admitted to Neurology and Psychiatry Outpatient Clinics of Zagazig University Hospitals, from June 2015 to September 2016. Epilepsy, depression and control groups were subjected to full history taking and complete physical examination.

The epileptic cases were selected from those attending the Neurology Outpatient Clinics of Zagazig University Hospitals, and diagnosed according to the International League against Epilepsy (ILAE) 2016 classification (Scheffer *et al,* 2016). They were classified into Group1 (G1) composed of 72 cryptogenic epileptic patients presented with recurrent epileptic fits with unknown etiology. They had no past history of head trauma, brain surgery, previous meningitis, encephalitis; with normal brain magnetic resonance imaging (MRI) and normal electroencephalography (EEG) without family history of epilepsy. Group2 (G2) composed of 40 epileptic patients presented with recurrent epileptic fits with known causes such as head trauma, family history of epilepsy, brain surgery, previous encephalitis or meningitis.

While, depressed cases were selected from those attending the Psychiatry Outpatient Clinics of Zagazig University Hospitals, and diagnosed by psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, (DSM V) criteria for depression (American Psychiatric Association 2013). The control group was composed of 60 healthy volunteers that had no family history of epilepsy, depression, mood disor-

der or other mental disorders with matched and similar socio-economic and environmental conditions to patient groups.

A structured questionnaire was used to evaluate risk factors in all groups, which included; age, sex, residence, contact with pets, contact with soil, pattern of meat consumption, and social class. Anti-*Toxoplasma gondii* immunoglobulin G (IgG) antibodies were assessed in the sera of all groups in the laboratory of medical Parasitology department, Faculty of Medicine, Zagazig University.

Serum collection and serological assay: Five ml venous blood samples were taken from cases and control groups under sterile condition, and centrifuged at 2000 rpm for 10 min; the serum was separated and kept at -80°C until investigation.

Anti-*T. gondii* IgG antibodies were measured in sera of all groups using commercially available quantitative ELISA kit (DRG International, Inc., Mountainside, New Jersey, USA). The test was performed according to manufacturer's instructions.

Ethics statement: The study was approved by the Ethical Committee of Faculty of Medicine, Zagazig University. The purpose and procedures were explained to all participants, and a written informed consent was obtained from all cases. Parents provided informed consent on behalf of all children.

Statistical analysis: Data were analyzed using SPSS version 16 software (SPSS Inc., Chicago, Illinois, USA). Definite data were presented as frequencies (number and percentages). Chi-square test (χ^2) was used to test significance. The $P<0.05$ was considered significant.

Results

Of 112 epilepsy cases 72 were cryptogenic epilepsy with normal neuroradiologic findings (MRI & CT) and 40 non-cryptogenic epilepsy were with abnormal neuroradiology findings. The epilepsy and controls were quite similar regarding most of sociodemographic characteristics (age, sex, eating under cook-ed meat, social class) ($p>0.05$), but with significant difference between epileptic and controls as to residence, pets contact and soil contact ($p<0.05$). In 118 cases of depression no significant difference was between depression and controls regarding sex, reside-nce, soil contact, eating under cooked meat ($p>0.05$), but with significant difference in age, pets contact, social class ($p<0.05$) (Tab. 1).

There was significant difference between epilepsy and controls in *T. gondii* seropositive; 26/112 (23.2%) & 7/60 (11.7%) respectively ($p<0.05$), without significant difference between depression and control groups 24/118 (20.3%) and 7(11.7%) respectively ($p>0.05$). There was significant difference between cryptogenic and control groups as to seropositivity 25/72 (34.7%) and 7/60 (11.7%) respectively ($P<0.05$). Insignificant difference was between non-cryptogenic and controls 1/40 (2.5%) & 7/60 (11.7%) respectively ($P>0.05$), with significant difference between cryptogenic and non-cryptogenic groups ($P<0.05$) (Tab. 2). There were significant differences between epilepsy, depression and controls regarding *T. gondii* seropositive rates in age, residence, contact with pets and social class ($p<0.05$), while no significant difference between the three studied groups in sex ($p>0,05$) (Tab. 3).

Discussion

No doubt, epilepsy is an important health problem in the developing countries. Cryptogenic epilepsy is an epilepsy syndrome for which the etiologies are hidden or occult (Moshé *et al*, 2015). In cryptogenic epilepsy, persons were more susceptible to parasitosis and/or intrinsic immunologic alterations that led to epilepsy (Zibaei *et al*, 2011).

In the current study, there was significant age difference between epilepsy, depression and control groups with highest prevalence in (17- ≥31ys) and (2- ≥16ys) age groups in cryptogenic and non-cryptogenic groups 52.8% & 62.5% respectively.

Table 1: Sociodemographic characteristics in all groups.

Frequency / Feature	Epilepsy G		Depression G	Control G	χ^2	P-value
	Cryptogenic G1=72	Non-Cryptogenic G2=40	N=118	N=60		
Age: 2- ≥16y	27(37.5%)	25(62.5%)	8(32.2%)	28(46.7%)		
17- ≥31y	38(52.8%)	12(30%)	72(61%)	30(50%)		
32-46y	7(9.7%)	3(7.5%)	38(32.2%)	2(3.3%)	65.97	<0.0001[a]
Female	44(61.1%)	29(72.5%)	73(61.9%)	33(55%)		
Male	28(38.9%)	11(27.5%)	45(38.1%)	27(45%)	1.71	0.43
Residence: Rural	57(79.2%)	27(67.5%)	62(52.5%)	34(56.7%)		
Urban	15(20.8%)	13(32.5%)	56(47.5%)	26(43.3%)	13.25	<0.001[a]
Contact with pets						
Yes	63(87.5%)	38(95%)	92(78%)	46(76.7%)	9.1	<0.012[a]
No	9(12.5%)	2(5%)	26(22%)	14(23.3%)		
Eating under cooked meat						
Yes	19(26.4%)	24(60%)	55(46.6%)	22(36.7%)	2.29	0.68
no	53(73.6%)	16(40%)	63(53.4%)	38(63.3%)		
Contact with soil						
Yes	38(52.8%)	22(55%)	72(61%)	48(80%)	11.68	0.02[a]
No	34(47.2%)	18(45%)	46(39%)	12(20%)		
Social class						
Low	53(73.6%)	30(75%)	84(71.2%)	14(23.3%)	66.31	<0.0001[a]
Moderate	16(22.2%)	9(22.5%)	22(18.6%)	44(73.3%)		
High	3(4.2%)	1(2.5%)	12(10.2%)	2(3.3%)		

[a]Significant differences between 3 groups (χ^2 test).

Table 2:Anti-*Toxoplasma* (IgG) seropositive rates in all groups

T. gondii	Epilepsy group				Depression group		Control group		χ^2	P-value
	Cryptogenic		Non-Cryptogenic							
	n= 72	(%)	n= 40	(%)	n= 118	(%)	n=60	(%)	3.36[a]	0.19[a]
Seropositive	25	34.7%	1	2.5%	24	20.3%	7	11.7%	20.58[b]	<0.0001[b]
									9.47[c]	0.008[c]
Seronegative	47	65.3%	39	97.5%	94	79.7%	53	88.3%	18.84[d]	<0.0001[d]

[a]χ^2 test to compare between 3 groups, [b]χ^2 test to compare between 2 types of epilepsy and control groups, [c]χ^2 test to compare between cryptogenic and control groups, [d]χ^2 test to compare between cryptogenic and non-cryptogenic groups.

Table 3. Anti-*Toxoplasma* (IgG) seropositive rates regarding sociodemograpgic characteristics in all sgroups.

Frequency / Feature	Epilepsy G	Depression G	Control G	χ^2	P- value
	+ve *T. gondii* N=26	+ve *T. gondii* N=24	+ve *T. gondii* N=7		
Age					
2- ≥16y	6(23.1%)	1(4.2%)	4(57.1%)		
17- ≥31y	18(69.2%)	14(58.3%)	2(28.6%)	15.22	0.004[a]
32-46y	2(7.7%)	9(37.5%)	1(14.3%)		
female	10(38.5%)	6(25%)	5(71.4%)		
male	16(61.5%)	18(75%)	2(28.6%)	5.07	0.28
Residence					
Rural	23(88.5%)	20(83.3%)	3(42.9%)	7.55	0.023[a]
Urban	3(8.67%)	4(16.7%)	4(57%)		
Contact with pets					
Yes	22(84.6%)	21(87.5%)	3(42.9%)	7.41[a]	0.025[a]
No	4(15.4%)	3(12.5%)	4(57%)		
Social class					
Low	20(76.9%)	18(75%)	2(28.6%)	7.09	0.029[a]
Moderate	5(19.2%)	4(16.7%)	4(57.1%)		
High	1(3.8%)	2(8.3%)	1(14.3%)		

[a]Significant difference between 3 groups (χ^2 test).

. The data agreed with Yazar *et al.* (2003) who reported a mean age of 37.82±16.64ys among the cryptogenic epilepsy patients, 35.78±13.53ys in known epileptic cases and 34.02±13.85ys among healthy volunteers. Also, Zibaei et al. (2011) recorded that there were significantly more students among the epileptic patients. Currently, there are in-complete and sometimes inadequate results about the association of *T. gondii* infection

and depression. In the present study, depression was common (61%) in young age group (17- ≥31ys) similar to cryptogenic epilepsy. These results agreed with Alvarado-Esquivel *et al*. (2016).

Sex differences with epilepsy were not clear. There was broad agreement between studies that females have an apparent lower incidence of epilepsy and motiveless seizures than males. In this study, epilepsy was slightly higher in females (61.1% of cryptogenic and 72.5% of non-cryptogenic epilepsy) vs 38.9% of cryptogenic and 27.5% of non-cryptogenic epileptic males. The results were similar to Eraky *et al.* (2016) who reported that epilepsy was slightly higher in females (52.5% of cryptogenic and 53.3% of non-cryptogenic epilepsy) vs 47.5% of cryptogenic & 46.7% of non-cryptogenic epileptic males. This is not consistent with the fact that epilepsy is 1 to 2.4 times more common in men than in women (Sander, 2003). Also, Akyol *et al.* (2007) reported 46 women and 54 men were epileptic.

Likewise, depression similar to cryptogenic epilepsy where females was slightly higher 61.9% than 38.1% male vs (55% female and 45% male) in controls. Arling *et al.* (2009) reported that male 76 (64%) were more exposed to depression which result in suicide attempts than female 60 (61%) compared to healthy individuals 26 (67%).

Epidemiological studies suggested an association between helminth infection and epilepsy, mainly in the poorer areas of the world (Wagner and Newton, 2009). In the present study, 75% of epileptic groups existed in rural areas and 25% in urban areas. This agreed of Eraky *et al*. (2016) who reported 64.3% & 35.7% of epileptic groups were in rural and urban areas respectively. But, El-Tantawy *et al.* (2013) reported no significance between epilepsy and residence.

In the present study, depression was slightly higher in rural areas (52.5%) than in urban ones (47.5%). This agreed with Alvarado-Esquivel *et al*. (2006) who reportted that most psychiatric inpatients belonged to a lower socio-economic level and had lower housing conditions than the healthy populations. The present findings showed significant difference between the three groups regarding contact with soil and social class with high prevalence of epilepsy and depression in low social class. Also, there was significant difference between epilepsy, depression and controls regarding contact with pets (90.2%, 78% & 76.7% respectively), which indicated that contact with pets might be a risk factor for epilepsy. These results agreed with El-Tantawy *et al*. (2013) who reported (40.9% & 31.7%) regarding contact with pets between epileptic and controls respectively. There was significant difference between the three groups regarding soil contact and social class with high prevalence of epilepsy and depression in low social class. But, there was insignificant difference between the three studied groups regarding eating under cooked meat

In the present study, there was a significant correlation of toxoplasmosis and cryptogenic epilepsy, as 34.7% of cryptogenic group were seropositive compared to 11.7% of controls. Thus, latent toxoplasmosis may be an underlying cause for cryptogenic epilepsy (Zibaei *et al*, 2011). Moreover, Eraky *et al*. (2016) reported 20% of epileptic cryptogenic group were seropositive compared to 10% of controls. The difference in the prevalence from ours might be explained by a difference in the prevalence found in the general population in each studied city.

This association can be explained by either presence of dormant *T. gondii* cysts that can cause epileptic foci. Some tissue cysts may rupture and cause marked inflammation which trigger microglial formation that may represent the 'tombstones' of *T. gondii* cysts and end to scarring (Frenkel and Escajadillo, 1987). Patient with cryptogenic epilepsy could be more vulnerable than others to such infections for reasons distinct to epilepsy, or due to intrinsic immunologic differences that predispose them to epilepsy (Stommel *et al*, 2001). Akyol *et al*. (2007) reported that no

relationship was reported between cryptogenic epilepsy and *T. gondii* IgG seropositivity. Cerebral toxoplasmosis has been reported to cause seizures in about 25% of infected cases (Senanayake and Roman, 1991) by producing diffuse encephalitis or localized lesions (Neto and Bittencourt, 1996).

On the other hand, there was no significant correlation of *T. gondii* infection and non-cryptogenic epilepsy (2.5%) compared to controls (11.7%). This result agreed with Eraky et al. (2016). There was a significant correlation of toxoplasmosis and depression, as (20.3%) of depression group had anti-*T. gondii* antibodies compared to 11.7% of controls. Significant associations between *Toxoplasma* seropositivity and depression with total mood disturbance score were reported (Duffy *et al*, 2015). Prenatal depression was associated with higher anti-*T. gondii* antibodies titers in infected women (Groër *et al*, 2011). Individuals suffering from depression had a significantly higher seroprevalence of toxoplasmosis than control cases without depression (Alvarado-Esquivel et al, 2016). All preceding studies supported the possible role of toxoplasmosis in depression. This correlation could be explained by that *T. gondii* was associated with manufacture of interferon-gamma (INF-γ) and initiation of cerebrum indoleamine 2, 3-dioxygenase, which changes tryptophan to kynurenine and makes it inaccessible for serotonin amalgamation. Besides, serotonin turnover to its main metabolite, 5-hydroxyindoleacetic acid, was likewise improved at reactivation phase, consequently, improved tryptophan catabolic shunt and serotonin turnover, plus, hyperdopaminergic state in brain (Mahmoud *et al*, 2016). On the other hand, Sutterland et al. (2015) did not find a significant association of anti-*T. gondii* IgG antibodies and depression in a meta-analysis

In the current study, epilepsy and depression demonstrated that *T. gondii* seropositivity was more common in males (61.5%, 75%) than in females (38.5%, 25.5%) respectively, males were more frequently infected than females in most endemic areas (Kaiser *et al,* 2013), especially those from rural (88.5%) areas, which matched with El-Tantawy *et al.* (2013). But, Zibaei *et al.* (2011) did not find significant difference between seroprevalence of *T. gondii* in rural compared to urban areas. This is consistent with what Akyol *et al.* (2007), who reported that population from urban and rural area were equally exposed to *T. gondii*. Besides, Alvarado-Esquivel *et al.* (2016) found that sexes had no difference in sero-prevalence in depressed patients. In epilepsy and depression high seropositive rate for *T. gondii* was in low social class (76.9%, 75%) respectively similar to El-Tantawy *et al.* (2013) and common in young age group (17-≥31y) (69.2%, 58.3%) respectively. Also, Zibaei *et al.* (2011) reported that toxoplasmosis was more frequently among youth and adults due to more frequent contact and consumption of contaminated food and poor hygiene. The gradual increase in seroprevalence related to age showed that soil exposure has the major role in the childhood years (Jones *et al*, 2001), besides, an important risk factor associated with toxoplasmosis was contact with cats and dogs, in which there was significant association between toxoplasmosis and positive history of contact with animals (84.6%, 87.5%) respectively mostly cats and dogs. These results were nearly agreed with Eraky *et al*. (2016) and Alvarado-Esquivel *et al*. (2016).

Conclusion

The outcome data proved that toxoplasmosis should be considered as a potential cause for neuropsychiatric disorders: cryptogenic epilepsy and depression that results from central nervous system infection. Thus, recommendations with endorsing health education to prevent such infection together with recording children and young adults for toxoplasmosis that could help early treatment therefore, decreasing the incidence of neuropsychiatric disorders. Youth and adults had the highest seroprevalence of *T. gondii* infection that associated with such disorders

especially male residing in rural areas with low social class.

Undoubtedly, health education about toxoplasmosis should be tailored to women of childbearing age may help to prevent its complications.

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References

AbdelAaty, H, El-Sheemy, H, 2016: Current state of toxoplasmosis in Egypt: a systematic review. PROSPERO: CRD42016036539 Available from at http://www.crd.york.ac.uk/PROSPERO/ display_record.asp?IDCRD42016036539.

Akyol, A, Bicerol, B, Ertug, S, Ertabaklar, H, Kiylioglu, N, 2007: Epilepsy and seropositivity rates of *Toxocara canis* and *Toxoplasma gondii*. Seizure 16:233-7.

Al-Hussainya, NH, Al-saedib, AM, Al-lehaiib, JH, Al-lehaibib, YA, Al-Sehlib, YM, *et al*,, 2015: Serological evidences link toxoplasmosis with schizophrenia and major depression disorder. J. Microsc. Ultrastruct. 3, 3:148-53.

Alvarado-Esquivel, C, Alanis-Quiñones, OP, Arreola-Valenzuela, MA, Rodríguez-Briones, A, Piedra-Nevarez, LJ, *et al*, 2006: Seroepidemiology of *Toxoplasma gondii* infection in psychiatric inpatients in a northern Mexican city. BMC Infect. Dis. 6: 178-88.

Alvarado-Esquivel, C, Sánchez-Anguiano, L F, Hernández-Tinoco, J, Segovia, L O, Torres, YE, *et al*, 2016: *Toxoplasma gondii* infection and depression: A case-control seroprevalence study. Euro J. Microbiol. Immunol. 6, 2:85-9.

American Psychiatric Association 2013: Diagnostic & Statistical Manual of Mental Disorders Text-Revision DSM-V-TR (5th ed). Washington, DC: American Psychiatric Association. Doi: 101176/appi.book.978. ISBN:0-89042-555-8.

Arling, TA, Yolken, RH, Lapidus, M, Langenberg, P, Dickerson, FB, *et al*, 2009: *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. J. Nerv. Ment. Dis. 197, 12:905-8.

Cañedo-Solares, I, Galván-Ramírez, M de L, Luna, H, Rodríguez Pérez, LR, Ortiz-Alegría, LB, *et al*, 2008: Congenital toxoplasmosis: specific IgG subclasses in mother/newborn pairs. Pediatr. Infect. Dis. J. 27:469-74.

Chu Hsu, P, Groer, M, Beckie, T, 2014: New findings: depression, suicide, and *Toxoplasma gondii* infection. J. Am. Assoc. Nurse Pract. 26, 11:629-37.

Denkers, EY, Gazzinelli RT, 1998: Regulation and function of T-cell-mediated immunity during *Toxoplasma gondii* infection. Clin. Microbiol. Rev.11:569-88.

Duffy, AR, Beckie, TM, Brenner, L, Beckstead, J, Seyfang, A, *et al*, 2015: Relationship between *Toxoplasma gondii* and mood disturbance in women veterans. Mil. Med. 180, 6:621-5.

Dupont, CD, Christian, DA, Hunter, CA, 2012: Immune response and immunopathology during toxoplasmosis. Semin Immunopathol. 34: 793-813.

El-Tantawy, NL, El-Nahas, HA, Salem, DA, Salem, NA, Hasaneen, BM, 2013: Seroprevalence of *Toxoplasma gondii* and *Toxocara* spp. in children with cryptogenic epilepsy. Am. J. Infect. Dis. Microbiol. 1:92-5.

Eraky, MA, Abdel-Hady, S, Abdallah, KF, 2016: Seropositivity of *Toxoplasma gondii* and *Toxocara* spp. in children with cryptogenic epilepsy, Benha, Egypt. Korean J. Parasitol. 54, 3: 335-8.

Fabiani, S, Pinto, B, Bruschi, F, 2013: Toxoplasmosis and neuropsychiatric diseases: can serological studies establish a clear relationship? Neurol. Sci. 34:417-25.

Fekadu A, Shibre, T, Cleare, AJ, 2010: Toxoplasmosis as a cause for behavior disorders – overview of evidence and mechanisms. Folia Parasitol. 57, 2:105-13.

Frenkel, JK, Escajadillo, A, 1987: Cyst rupture as a pathogenic mechanism of toxoplasmic encephalitis. Am. J. Trop. Med. Hyg. 36:517-22.

Groër, MW, Yolken, RH, Xiao, JC, Beckstead, JW, Fuchs, D, Mohapatra, SS, Seyfang, A, Postolache, TT, 2011: Prenatal depression and anxiety in *Toxoplasma gondii*-positive women. Am. J. Obstet. Gynecol. 204, 5:433.e1-7

Guo, M, Dubey, JP, Hill, D, Buchanan, RL, Gamble, HR, *et al*, 2015: Prevalence and risk factors for *Toxoplasma gondii* infection in meat animals and meat products destined for human consumption. J. Food Prot. 78:457-76.

Hamidinejat, H, Ghorbanpoor, M, Hosseini, H, Alavi, SM, Nabavi, L, *et al*, 2010: *Toxoplasma gondii* infection in first-episode and inpatient individuals with schizophrenia. Int. J. Infect. Dis. 14: e978–81.

Henriquez, SA, Brett, R, Alexander, J, Pratt, J, Roberts, CW, 2009: Neuropsychiatric dis-

ease and *Toxoplasma gondii* infection. Neuroimmunomodulation\ 16, 2:122-33.

Jones, LJ, Kruszon-Moran, D, Wilson, M, McGuillan, G, Navin, T, *et al*, 2001: *Toxoplasma gondii* infection in the United States: seroprevalence and risk factors. Am. J. Epidemiol. 154:357-65.

Kaiser, C, Pion, SD, Boussinesq, M, 2013: Case-control studies on the relationship between onchocerciasis and epilepsy: systematic review and meta-analysis. PLoS. Negl. Trop. Dis. 7: e2147.

Kar, N, Misra, B, 2004: *Toxoplasma* seropositivity and depression: a case report. BMC Psych. 4, 1:23.

Kariuki, SM, Chengo, E, Ibinda, F, Odhiambo, R, Etyang, A, *et al*, 2015: Burden, causes, and outcomes of people with epilepsy admitted to a rural hospital in Kenya. Epilepsia 56.4:577-84.

Mahmoud, ME, Ihara, F, Fereig, RM, Nishimura, M, Nishikawa, Y, 2016: Induction of depression-related behaviors by reactivation of chronic *Toxoplasma gondii* infection in mice. Behav. Brain Res. 298, Pt B:125-33.

Morsy, TA, El Dasouqi, ST, Michael, SA, 1978: Toxoplasmin skin tests in mentally retarded children in Jordan. J. Egypt. Pub. Hlth. Assoc. 53, 1/2:87-90.

Moshé, SL, Perucca, E, Ryvlin, P, Tomson, T, 2015: Epilepsy: new advances. Lancet 385, 9971:884-98.

Negash, T, Tilahun, G, Medhin, G. 2007: Seroprevalence of *Toxoplasma gondii* in Nazareth Town, Ethiopia. Cent. Afr. J. Med. 53, 9/12:47-51.

Neto, MC, De Bittencourt, PRM, 1996: Infections and post-infective causes. In: Wallace S ed, Epilepsy in Children. Madras: Chapman & Hall.

Ngoungou, EB, Bhalla, D, Nzoghe, A, Dardé, ML, Preux PM, 2015: Toxoplasmosis and Epilepsy: Systematic review and meta-analysis. Plos Negl. Trop. Dis. http://dx.doi.org/10.1371/journal. pntd.0003525

Ngugi,AK, Bottomley, C, Kleinschmidt, I, Sander, JW, *et al*, 2010: Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia, 51, 5:883-90.

Obaidat. MM, Al-Sheyab, NA, Bani Salman, AE, Lafi, SQ, 2015: Seroepidemiology and risk factors of Toxoplasma gondii infection in undergraduate university female students in Jordan. Epidemiol. Infect. 143, 9:1898-903.

Saleh, AMA, Ali, HA, Ahmed, SAM, Hosny, S M, Morsy, TA, 2014: Screening of *Toxoplasma gondii* infection among childbearing age females and assessment of nurses' role in prevention and control of toxoplasmosis. J. Egypt. Soc. Parasitol.. 44, 2:329- 42

Sander, JW, 2003: The epidemiology of epilepsy revisited. Curr. Opin. Neurol. 16:165-70.

Scheffer, IE, French, J, Hirsch, E, Jain, S., Mathern, GW, *et al*, 2016: Classification of the epilepsies: New concepts for discussion and debate: Special report of the ILAE classification task force of the commission for classification and terminology. Epilepsia Open. 1, 1/2:37-44.

Schmidt, D, and Sillanpää, M, 2016: Prevention of Epilepsy: Issues and Innovations. Curr. Neurol. Neurosci. Teports. 16, 11:95-9.

Senanayake, N, Roman, GC, 1991: Aetiologic factors of epilepsy in the tropics. J. Trop. Geogr. Neurol. 1:69-80.

Stommel, EW, Seguin, R, Thadani, VM, Schwartzman, JD, Gilbert, K, *et al*, 2001: Cryptogenic epilepsy: an infectious etiology? Epilepsia 42:436-8.

Sutterland, AL, Fond, G, Kuin, A, Koeter, MW, Lutter, R, *et al*, 2015: Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and metaanalysis. Acta Psychiatr. Scand. 132:161-79.

Wagner, RG, Newton, CR, 2009: Do helminths cause epilepsy? Parasite Immunol. 31, 11:697-705.

Wishahy, AO, Rifaat, MA, Morsy, TA, El Naggar, BA, 1972: Toxoplasmosis in children with some neurological manifestations. J. Trop. Med. Hyg. 75, 12:255-6, London.

Yazar, S, Arman, F, Yalcin, S, Demirtas, F, Yaman, O, Sahin, I, 2003: Investigation of probable relationship between *Toxoplasma gondii* and cryptogenic epilepsy. Seizure 12, 2: 107-9.

Zibaei, M, Zamani, Z, Esfahani, AC, Anbari, K, Nazer, MR, 2011: *Toxoplasma* infection and epilepsy: A case-control study in Iran. Neurol. Asia. 16, 4:299-302.