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CAN HUMAN TOXOPLASMOSIS BE WITHIN THE DIFFERENTIAL DIAGNOSIS OF FEVER OF UNKNOWN ORIGIN: A CROSS-SECTIONAL STUDY

By

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Abstract

More than 200 diseases can be represented in differential diagnosis of fever of unknown origin (FUO). The mainstay for the proper diagnosis of FUO took right path for the correct investigations. Globally, *Toxoplasma gondii* infection persists lifelong within the affected host organs in the dormant bradyzoites form. Once the host immunity decreases, it can be converted back to the activate tachyzoite form that attach the host cells. The aim of our study is to estimate the frequency of toxoplasmosis in patients with fever of unknown origin, concerning the etiology. A cross-sectional study was done from November 2017 to May 2018, including 140 patients chosen with FUO (100 males &40 females), recruited from Port Said Fever Hospital/ Egypt. Their ages ranged between 16 and 70 years old. Patients were subjected to comprehensive history taking, laboratory investigations, clinical and radiologic examination. Detection of anti-*Toxoplasma* IgM&IgG antibodies was done by the Electrochemiluminescence immunoassay. Patients had fever with known origin proved by investigations, were excluded from the study. The results showed that 7.1% of the FUO cases were serologically positive for *Toxoplasma* IgG. Of them, 80% were females and 20% were males. About 70% of *Toxopl-asma*-IgG positive cases were represented with fever for 3weeks, and 30% were represented with fever for more than 3weeks. The 70% of the target group had cervical lymphadenopathy and all of them had hepatosplenomegaly. Moreover, all cases were eating fast food.

Key words: Patients, Fever of unknown origin Toxoplasmosis, Lymphadenopathy

Introduction

When fever is continuously persistent for three weeks and evading any diagnosis, it is termed as fever of unknown origin. After many years of the unique description of FUO, it remains a serious challenge for clinicians (Mir *et al*, 2014). Designing the correct strategy for FUO diagnosis was tricky due to altering field that obliges a frequent updating consistent with the variation of its causes and reasons (Vanderschueren *et al,* 2003). In spite of the progress in diagnostic facilities, it was a complex question about, which are conflicting opinions (Knockaert *et al,* 2003). The FUO causes were demarcated as infections, tumors, non-infectious inflammatory diseases and miscellaneous. In developing countries, FUO cause was infectious but in developed countries the commonest were non-infectious inflammation (Natio *et al,* 2019). Apart from the initial tests contrast computed tomography or magnetic resonance imaging were used (Gafter-Gvili *et al*, 2014). More invasive examinations including, lumbar puncture, pleural, pericardial or ascitic fluid analysis, lymph node or bone marrow aspiration, and liver biopsy may be done, if indicated by the examination, lab or imaging test.

Toxoplasma gondii that causes toxoplasmosis is a worldwide disease (Rouatbi *et al,* 2019). Man is infected either congenitally or acquired. Congenital transmission occurs during acute toxoplasmosis in a seronegative mother when tachyzoites present in blood might cross the placenta and infect the fetus (Jones *et al*, 2009). The prevalence varies geographically according to primary *Toxoplasma* infection in women risk of childbearing age (McAuley, 2008). Infection is mainly acquired by ingestion of food or water that is contaminated with oocysts shed by

cats or by eating undercooked or raw meat containing tissue cysts. Infection acquired during pregnancy may cause severe damage to fetus (Montoya and Liesenfeld, 2004). Also, acquired nosocomial toxoplasmosis infection was reported (Saleh *et al,* 2016) with blood transfusion and needle-stick injury (Abdel-Motagaly *et al,* 2017). In Egypt, prevalence of *T. gondii*-antibodies was reported among chickens and pigeons (Rifaat *et al,* 1969), camels (Hilali *et al*, 1998), rabbits (Harfoush and Tahoon, 2010), and different edible animals (Fereiga *et al*, 2016), as well as in pet & stray animals (Khalid *et al,* 1982), and domestic and wild rodents (Morsy *et al,* 1987). Besides, *T. gondii* antibodies were reported in Egyptian children with fever (Wishahy *et al,* 1971a) in Egyptian blood donors (Elsheikha *et al*, 2009). Only 10-20% of toxoplasmosis cases in adults and children are symptomatic, but acute was often asymptomatic in healthy adults (Dubey and Jones, 2008). Symptoms may manifest as influenza-like: swollen lymph nodes, headaches, fever, and fatigue, or muscle aches and pains that last for a month or more. People with weakened immune systems were likely to experience headache, confusion, poor coordination, seizures; lung problems resemble tuberculosis or *Pneumocystis* pneumonia (a common opportunistic infection in AIDS people), or blurred vision caused by severe retina inflammation (Weiss and Dubey, 2009).

A prospective study on FUO was carried out in the Department of Internal Medicine, SKIMS, Kashmir; India and declared that infections produced by protozoa represented about 7.5% of cases (Mir *et al*, 2014). The seroprevalence of toxoplasmosis is widely varied from 6.1% to 74.5% along different regions of the world (Sakikawa *et al,* 2012). Lymphadenitis is the frequent symptom, any node may be infected, and the deep cervical nodes are mainly involved. The infected node is usually tender. Lymphadenopathy may be accompanied by fever, malaise, fatigue, muscle pains, rash, sore throat, and headache (Dubey, 1996). The fever of unknown origin and the weakness in the upper legs were reported among presented symptoms of acute toxoplasmosis in immune-competent individuals (Mentink *et al,* 2017).

Patients and Methodology

The present research was a cross-sectional study between November 2017 and May 2018, on patients attending Port-Said Fever Hospital MOH, under the supervision of the Tropical Medicine Department, Faculty of Medicine, Zagazig University, Egypt. The patients were 140 chosen with FUO (100 males &40 females), with ages ranged between 16 & 70 years.

Inclusion and exclusion criteria: Cases were chosen suffered from pro-longed fever for three weeks or more with unknown origin and with or without lymph node enlargement, or splenomegaly. But, patients with a diagnosed fever were excluded.

All patients were subjected to: 1- Personal and medical history: name, age, sex, eating habits: fast foods, sausage or luncheon (raw and under cocked meat kind), dealing with animals, as well as previous hospital admission with FUO (continuous, or intermittent, or relapsing), antibiotics treatment, history of pregnancy, chemotherapy or steroids treatment, diabetes mellitus and hypertension. 2- Clinical examination: checking vital signs, chest and abdominal examination, eye examination for jaundice, any abnormal body swelling or lymph node. 3- Radiologic Investigations: Chest X-ray, abdominal and pelvic ultrasonography (US) and CT imaging were done. 4- Laboratory investigation: a- Stool and urine analysis were performed, b- Hematological assessment including complete blood count (CBC) using automated cell counters (CELL-DYN 1700), erythrocyte sedimentation rate (ESR) and blood film examination were done., c- Biochemical assessment was done including liver function tests (ALT, AST, serum albumin, serum bilirubin), renal function tests by HITACHI 912 automatic analyzer (Roche Diagnostics GmbH. Sandhofer Str. Mannheim, D-68298 Germany) and random blood sugar as well.

Serological assessment: 1- Sera HCV antibody using an anti-HCV enzyme immunoassay kit for qualitative determination of antibodies to hepatitis C virus (anti-HCV) in human serum or plasma samples using ELISA kits (Diasorin S.p.A. 13040 Saluggi, Vercelli, Italy). Same kit was used for qualitative determination of hepatitis B surface antigen (HBs-Ag) in human sera. Antibody (HAV) IgM was done by radioimmunoassay.

2- Thyroid function tests, anti-nuclear antibody (ANA) and anti-double-strand DNA (anti-ds-DNA) for systemic lupus erythematosus (SLE) were done using Electrochemiluminescence practicing Cobas e411 (Roche Diagnostic GmbH, SandhoferStrasse 116, D-68305 Marnheim, Germany).

3- C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels were measured.

4- Widal test, *Brucella* agglutination titer test, and TB skin test were carried out.

5- Anti-*Toxoplasma* IgM & IgG antibodies were assessed by electrochemiluminescence immunoassay using Cobas e411 (Roche Diagnostic GmbH, Sandhofer/Strasse 116, D-68305 Marnheim, Germany) according to manufacturer's instructions. Both Cobas® Toxo-IgG & IgM assays contained a soluble form of recombinant native-like folded; immunodominant surface antigen1 protein (SAG1 or p30) showed an elevated reactivity. Application of a voltage to electrodes induced electrochem-iluminescence reaction & resulting light emission was measured by photomultiplier (Marquette and Blum 2008).

Ethical Considerations: The study was carried out in compliance with the Helsinki De claration. An informed consent was taken from each patient and the study aim was explained to patients. No harm was caused to patients as blood samples were routinely collected from patients. The study approval was obtained from the Institutional Review Board (IRB) Unit, Faculty of Medicine, Zagazig University, Egypt (no. 4056).

Statistical analysis**:** Data were collected, tabulated and analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous data were conveyed as M±SD and the median (range). Categorized data were expressed as a number (percentage).

Results

The results showed that *Toxoplasma* IgG level ranged from 0.09 to 1527 with a mean value of 51.71 and about 7.1% of *Toxoplasma* infection patients (Tab. 1). *Toxoplasma*IgM among ranged from 0.1 to 0.4 with a mean value of 0.08(col) (Tab. 2), with significance ($P<0.05$) positive correlation between IgG & IgM levels (Tab. 3). *Toxoplasma*-IgG & IgM levels in infected cases and control showed high significance increase in IgG & IgM levels among *Toxoplasma* patients compared to control (Tab. 4).

The demographic data, a highly significance ($P<0.01$) increase was in *Toxoplasma* infection females but without significance differences in age between patients and control (Tab. 5).

Handling the history, clinical examination and presentation, the target groups of toxoplasmosis were free from any chronic diseases, while the rest of cases showed 2 cases with hypertension and type 1 diabetes, 2 cases with renal disease and 2 cases had abortion. The clinical examination showed about 70% of the target group had cervical lymphadenopathy, whereas 50% of the other cases with lymphadenopathy. Also, 70% of patients with fever for 3 weeks, but 30% of them had fever for more than 3 weeks, without significance differences (Tab. 6). All toxoplasmosis cases ate fast food, 16.7% ate beef and 11.5% uncooked meat (Fig. 1).

Lab examinations showed that toxoplasmosis patients had normal liver and kidney function tests, but CBC showed abnormal eosinophilia. Imaging findings particularly ultrasonography proved hepatosplenomegaly in all toxoplasmosis cases (Tab. 7).

The details were given in tables (1, 2, 3, 4, 5, 6 & 7) and figure (1).

Table 1: Toxoplasma prevalence and level of IgG among groups

Variable	(n=140)
IgG: (IU/ml)	51.71± 233.56
Median	0.55
Range	0.09 - 1527
Toxoplasma: (By IgG)	
-ve N(%)	130 (92.9%)
+ve N(%)	10 (7.1%)

IgG normal value: <1 IU/ml non-reactive, 1 - <3 IU/ml intermediate, ≥ 3 IU/ml reactive

Table 2: *Toxoplasma* IgM level among groups:

IgM: (Col)	(n=140)
Mean ± SD	0.08 ± 0.07
Median	0.06
Range	0.1 – 0.4

IgM normal value: <0.08 Col non-reactive, 0.8 - <1 Col intermediate, ≥ 1 Col reactive

Table 3: *Toxoplasma* IgG & IgM levels among groups:

Variable	IgM (col) (n=140)	
	r	P
IgG: (IU/ml)	0.34	0.04*

r: Spearman correlation coefficient, *: Significant (P<0.05)

Table 4: Comparison between cases with or without *Toxoplasm*a with reference to IgG&IgM levels:

Variable	No *Toxoplasma* (n=130)	*Toxoplasma* (n=10)	MW	P
IgM: (Col)	0.07 ± 0.07	0.14 ± 0.07		
Median	0.06	0.10	3.55	<0.001
Range	0.01 – 0.4	0.09 – 0.27		**
IgG: (IU/ml)	0.50 ± 0.27	717.46 ± 558.73		
Median	0.49	380.2	5.26	<0.001
Range	0.09 – 0.99	357.6 - 1572		**

**Highly significant (P<0.01), IgM normal value: <0.08 Col non-reactive, 0.8 - <1 Col intermediate, ≥ 1 Col reactive IgG normal value: <1 IU/ml non-reactive, 1 - <3 IU/ml intermediate, ≥ 3 IU/ml reactive

Table 5: Comparison between cases with or without *Toxoplasm*a with reference to demographic data:

Variable	No *Toxoplasma* (n=130)	*Toxoplasma* (n=10)	MW	P
Age : (years)	23.36±13.52	22.6±5.36	0.21	0.84
Median	24.5	21		NS
Range	16 63	16- 58		
Female	40 (30.8%)	8 (805)		
Male	90 (69.2%)	2 (205)	(χ^2)9.99	0.002**

NS: Non significant (P>0.05) **: Highly significant (P<0.01)

Table 6: Comparison between cases with or without *Toxoplasm*a regarding history, examination and presentation:

Variable	No *Toxoplasma* (n=130)		*Toxoplasma* (n=10)			
	No	%	No	%	χ^2	P
Past history: *Toxoplasma* -ve	124	95.4	10	100	0.32	0.85
Toxoplasma +ve	6	4.6	0	0		NS
HPT + DM	2	1.5				
Renal disease	2	1.5				
Abortion	2	1.5				
Examination: Free	65	50	3	30	1.49	0.22
Cervical lymphadenopathy	65	50	7	70		NS
Presentation: Fever for 3 weeks	62	47.7	7	70	1.85	0.17
Fever more than 3 weeks	68	52.3	3	30		NS

χ^2:Chi square test NS: Non significant (P>0.05)

Table 7: Imaging findings of studied cross-section (N=141).

Imaging findings	No.	%
Plain X-ray chest Normal	140	100%
Plain X-ray chest Abnormal	0	0%
Ultrasonography Enlarged fatty liver	10	7.1%
Ultrasonography Splenomegaly	46	32.8%

Discussion

Fever of unknown origin is a mystifying medical risky problem. It is announced as a fever more than 38.30°C for at least three weeks, lacking diagnosis even with appropriate investigations (Bleeker-Rovers *et al*,

2009). Long ago many diseases caused FUO counting infections, neoplasms, connective tissue diseases, miscellaneous disorders, and undiagnosed illnesses (Mackowiak and Durack, 2010).

Human toxoplasmosis is a global zoonotic infectious disease. *Toxoplasma* infection may alter the host cell function even in the absence of invasion (Koshy*et al*, 2012). Human toxoplasmosis may be clinically presented with atypical features such as FUO (Alavi and Alavi, 2016). The current study aimed to detect the frequency of toxoplasmosis in the cases represented by fever of unknown origin.

The present study included 140 patients with fever of unknown origin, with a range of 16-70 years old. Middle aged patients were the most represented among FUO cases. By using immunochemiluminescence assay, the results showed that 7.1% of them were serologically positive for *Toxoplasma* IgG. Comparable with the results that estimated 1.1 million USA inhabitants were *T. gondii* infected annually, and approximately 10.4% of the population gave seroprevalence linked to past exposure (Jones *et al*, 2018).

The present results showed an increased infection percentage (80%) among adult females. Also, about 52.2% of pregnant women in Menoufia Governorate/Egypt were seropositive for the anti-*Toxoplasma* IgG antibodies (Nassef *et al,* 2014). But, the seroprevalence of human toxoplasmosis reached up to 54% in diabetic patients compared with control normal (24%) in randomly selected from Al Hussein University Hospitals /Egypt (Hemida *et al*, 2018). Also, a sample of young Iranian females presented for premarital investigations, *T. gondii* sero-positivity was 15% (13% for IgG & 2% for IgM) by using ELISA (Alavi and Alavi, 2016). This variation might be due to the fact that the present study dealt with males and females. Besides, females are always in contact with sources of infection e.g. raw meat, home duty, marketing, farming (rural areas) as well as dealing with pet or domestic animals In the present study, cases that ate fast food (beef) showed 16.7% positive *Toxoplasma* IgG cases whereas, those ate them were ate under-cooked meat were 11.5%. This agreed with Abd El-Razik *et al.* (2014) who found that shawarma, menaced meat, luncheon, superficial pastrami, and boiled chickens were PCR positive but rusted meat and brain materials gave higher *T. gondii* ELISA antibodies. A case-control study indicated that the consumption of mutton/lamb meat was a highly significant risk factor for contracting *T. gondii*n fection in pregnant women (Fusco *et al*, 2007).

In the present study, FUO cases were admitted to the hospital, 50% had cervical lymphadenopathy, 70% had fever for 3 weeks, and 30% had fever for more than 3 weeks. Wishahy *et al.* (1971b) reported Egyptian children with mediastinal lymphadenopathy. Sathapatayavongs *et al.* (1983) reported that cervical lymph nodes were the commonest picture of toxoplasmosis, followed by axillary lymph nodes. The present result agreed with Nardone *et al.* (2006) who reported that about 80-90% of asymptomatic *Toxoplasma* patients had painless cervical lymphadenopathy. Besides, Abdullah and Hamza (2017) reported a case of submandibular and supraclavicular nodes with high titers of *Toxoplasma* IgG & IgM antibodies.,

In the present study, abdominal ultrasonography showed hepatosplenomegaly for cases with toxoplasmosis. Bossi and Bricaire (2004) found that some patients developed severe symptoms, including generalized lymphadenopathy, and hepato-splenomegaly. Atilla *et al*. (2015) foundd that toxoplasmosis must be considered in the patients with hepatitis or hepatomegaly.

Conclusion

Diagnosis of FUO must be evaluated in different communities, for underlining the main etiology among different them. This study reported a significant number of serologically positive cases (7.1%) for *Toxoplasma*-IgG. Adult males were the most rep-

resented among FUO cases, toxoplasmosis is common in females. This can clarify the importance of counting *Toxoplasma* infection within differential diagnosis of FUO, especially those with cervical lymphadenopathy. More attention is needed to fast food as a risk factor for *T. gondii* infection. The imminent research will be the genotyping of *Toxoplasma* parasite infecting the pregnant and immunosuppressed cases for demonstration of its genetic diversity.

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Fig. 1: Comparison between negative and positive anti-*Toxoplasma* IgG as regards eating fast