

Highlighting the Role of Infections in the Etiology of Fever of Unknown Origin Pointing out Toxoplasmosis; in Port Said Governorate

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Background and study aim: Fever of unknown origin (FUO) is a state of febrile illness for more than three weeks, with a body temperature greater than 38.3 °C on several occasions and uncertain diagnosis. Conditions blamed for FUO were categorized as infectious diseases, non-infectious inflammatory diseases, neoplasms along with miscellaneous causes. This study aims to identify the infectious causes of FUO counting the parasitic causes in Port-Said Fever Hospital/ Egypt.

Patients and Methods: 341 patients admitted to Port-Said Fever Hospital/ Egypt during the period from November 2017 till May 2018 complaining of prolonged fever ≥ 3 weeks, without a definite diagnosis, were included in this study. Complete history taking and clinical data including pattern, duration and degree of temperature, in addition to other co-morbidities, radiological examination, laboratory investigations, and clinical evaluation were reported for each patient.

Results: The majority of affected cases were adult males, lived in urban areas, and were in contact with animals.

Luncheon and beef were the commonest types of consumed food among the studied population. The uppermost detected infection was tuberculosis (17%) followed by typhoid and Brucella infection (11.7% for each), toxoplasmosis and hepatitis were detected in 2.9% and 1.8% respectively. After investigations, 5.9% of the studied group had hepatosplenomegaly and 77.4% of them presented with lymphocytosis. Clinically, 78.9% of patients had lymphadenopathy and 1.8% had jaundice. Additionally, 75.4% of cases presented with an intermittent fever while 24.6% with continuous fever. Approximately 57.2% of them had fever for three weeks and the majority of patients had fever $\geq 39^{\circ}\text{C}$.

Conclusion: Tuberculosis, typhoid fever, and brucellosis signified the major identified infectious causes for FUO in Port Said governorate/Egypt. Toxoplasmosis can be represented as one of FUO infectious causes. Patients with toxoplasmosis either presented with lymphadenopathy or not, all of them had hepatosplenomegaly, high CRP, leucocytosis, and eosinophilia.

INTRODUCTION

Fever of unknown origin (FUO), or fever lacking a definite cause, is an exciting clinical challenge that is omnipresent [1]. Temperature going upwards 38.3°C on numerous occasions for 3 weeks or more without definitive diagnosis, is defined as fever of unknown origin

(FUO) [2]. The difficulty in diagnosing several cases of FUO may be due to the a wide range of the factors that can influence its final diagnosis [3]. Many scholars identified over 200 conditions to be responsible for FUO [4], they categorize them as infectious diseases, non-infectious inflammatory diseases, neoplasms, and miscellaneous causes

[5]. Various concerns can influence the diagnosis of FUO. Geographic distribution, demographic data, socioeconomic level, the outlook of clinicians as well as the difference in investigation funds between developed and developing countries may possibly of a great significance [3]. Infectious diseases remain the main cause of FUO particularly in developing countries [6]. Aiming to shed light on the contributing aspects that influence the clinical spectrum of FUO, we carried out this research.

Toxoplasmosis; is a universal, food borne parasitic infection with inconstant symptoms and signs [7]. *Toxoplasma gondii* is an obligate intracellular parasite that can invade and replicate within all nucleated cells of warm blooded animals and humans [8]. It has a complex life cycle with various stages fluctuating between replicating (tachyzoites) and quiescent (bradyzoites) forms [9]. Within the intermediate hosts' cell, the parasite initially replicates as tachyzoites, with an intense increase in number and spread to different body tissues. After a potent immune response, it differentiates to dormant bradyzoites within tissue cysts resides in neurons and skeletal muscle cells [10]. Human infection with *Toxoplasma gondii* occurs via eating raw or undercooked meat or drinking contaminated water [11], contaminated garden vegetables with oocysts shed by cats, in addition to the congenital infection when a mother is infected early during pregnancy [12]. The serological prevalence of toxoplasmosis, mostly reflecting subclinical chronic infections, is extremely variable. Approximately 25% of the world's population may be chronically infected with *T. gondii* [13]. In healthy grown-ups, *Toxoplasma* induces a quite mild infection, with a raised temperature, muscle weakness, and enlarged lymph nodes. FUO and weakness in the upper legs are among the presenting symptoms in acute toxoplasmosis, which can occur in immune-competent individuals [14]. Acute infection usually resolves quickly, leaving the individual with chronic, subclinical infection [15].

PATIENTS AND METHODS

Study design:

Our cross-sectional study incorporated 341 patients admitted to Port-Said Fever Hospital/ Egypt during the period from November 2017 till

May 2018 supervised by the Tropical Medicine Department, Faculty of Medicine, Zagazig University/ Egypt.

Patients:

The current study comprised of 341 patients complaining of fever, including 231 males and 110 females, with an age range of 16 - 70 years. Patients fulfilled the inclusion criteria (prolonged fever \geq 3 weeks, without definite origin, with /without lymph node enlargement or splenomegaly) were included in our study, while patients with the diagnosed cause of fever were excluded.

Data collection:

All patients were subjected to complete history taking (age, sex, residence, animal contact, dealing with soil and type of consumed food). Clinical data included (previous hospital admission, pattern, duration, and degree of temperature, in addition to other co-morbidity e.g hypertension, diabetes, renal/ hepatic disease, abortion, medications).

Clinical evaluation & radiological examination:

All patients were examined for vital signs, temperature, pallor or jaundice, chest and abdominal examination, abnormal body swellings, lymph node enlargement, and lower limb edema then subjected to radiological imaging including chest X-ray, abdominal and pelvic ultrasound (US) in Port-Said Fever Hospital/ Egypt.

Laboratory investigations:

The following laboratory investigations were carried out:

- Complete blood picture (CBC), CRP, Liver function tests, kidney function tests, thyroid function tests, blood sugar, stool and urine analysis.
- Detection of serum hepatitis A (HAV) IgM by radioimmunoassay.
- Hepatitis C (HCV) antibodies and hepatitis B surface antigen (HBs Ag) were detected using an enzyme immunoassay for the qualitative determination of antibodies in human serum / plasma samples by ELISA kits (Diasorin S.p.A. 13040 Saluggia (VERCELLI, Italy).
- Widal test, brucella agglutination test and tuberculin test as well.
- Specific markers as the anti-nuclear antibody (ANA) and anti- double-strand DNA (anti-ds-

DNA) for systemic lupus erythematosus (SLE) were detected in serum using Electrochemiluminescence practicing Cobas e411 (Roche Diagnostic GmbH, Sandhofer Strasse 116, D-68305 Marnheim, Germany).

- Assessment of Anti-*Toxoplasma* IgM & IgG antibodies using the Electrochem-

iluminescence immunoassay using Cobas e411 (RocheDiagnostic GmbH, SandhoferStrasse 116, D-68305 Marnheim, Germany) guided by the manufacturer's guidelines.

RESULTS

Table (1): Demographic data of the studied population.

	No. (n = 341)	%
Age		
Adolescent	35	10.3%
Adult	306	89.7%
Sex		
Male	231	67.7%
Female	110	32.3%
Residence		
Urban	325	95.3%
Rural	16	4.7%
Contact with animals		
Yes	18	5.3%
No	323	94.7%
Dealing with soil		
Yes	9	2.6%
No	332	97.4%

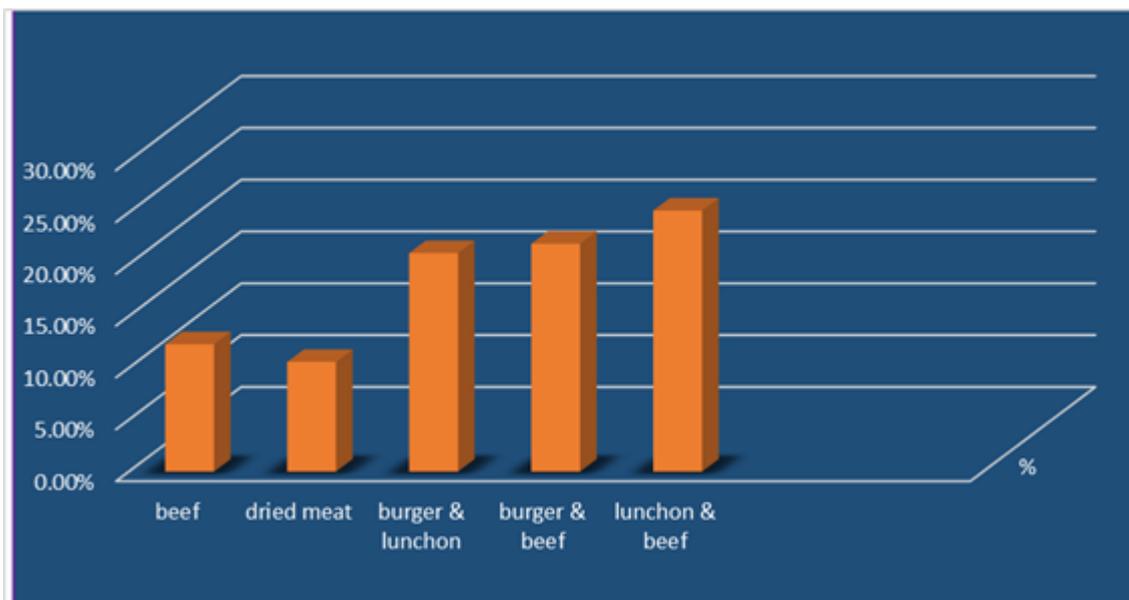
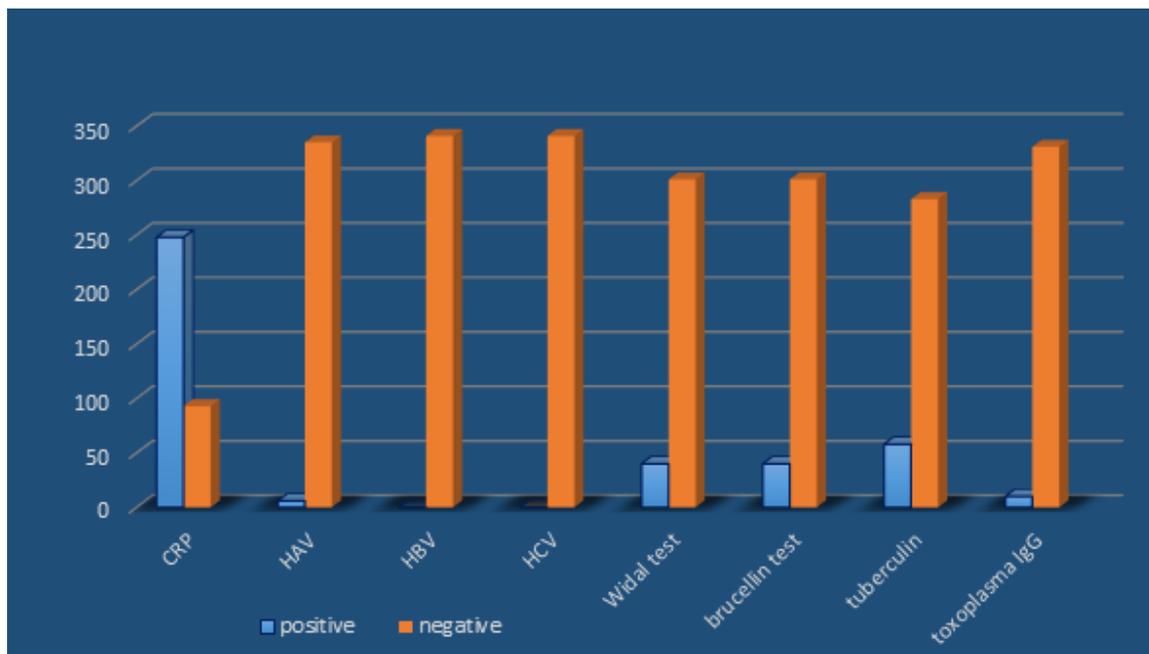


Fig. (1): Bar chart showing different types of consumed food among the studied population.

Table (2): The ultrasonography, chest X-ray and blood picture among the studied group

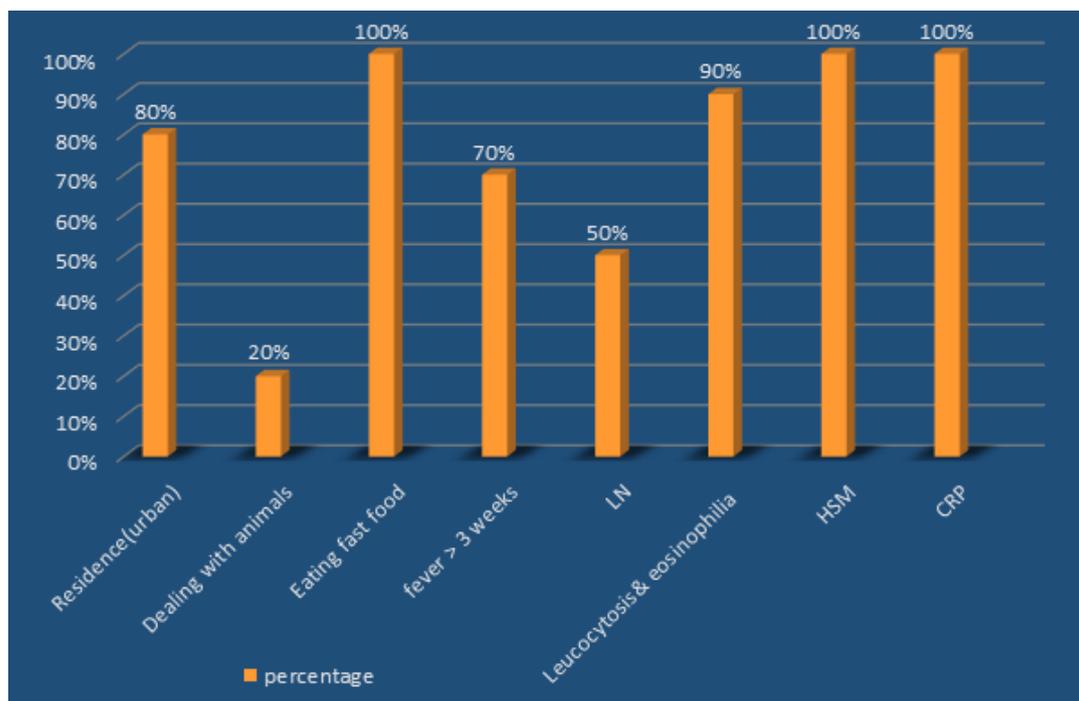
	No. (n=341)	%
US (HSM)		
+ve cases	20	5.9%
-ve cases	321	94.1%
Chest X-ray finding		
+ve X-ray finding	25	7.3%
Free chest	316	92.7%
Blood picture		
normal	16	4.7%
leucocytosis & eosinophilia	61	17.9%
lymphocytosis	264	77.4%

**Fig. (2):** Bar chart showing lab finding among the studied group.**Table (3):** Characteristics of fever among the studied group.

	N0 (n= 341)	%
Pattern of fever		
Continuous	84	24.6%
Intermittent	157	46%
relapsing	100	29.3%
Duration of fever		
3-4 weeks	195	57.2%
≥ 4 weeks	146	42.8%
Temperature rising		
38- 39°C	10	2.9%
39-40°C	205	60.1%
>40°C	126	37.0%

Table (4): Clinical presentations & examinations within the studied group.

	No. (n=341)	%
LN		
Enlarged	269	78.9%
Normal size	72	22.1
Jaundice		
Yes	6	1.8%
no	335	98.2%
treatment with antibiotics		
Yes	257	75.4%
no	84	24.6%

**Fig. (4):** Bar chart shows demography, types of consumed food, clinical presentation and investigations among only toxoplasmosis cases.

DISCUSSION

FUO is a state of febrile illness for more than three weeks, with a body temperature greater than 38.3°C on several occasions and uncertain diagnosis [16]. The foremost causes are the infectious, the neoplastic, and rheumatic. The diagnosis is based on good clinical history, the physical examination of these patients, and the proper investigations [1].

Studying the demographic data of the studied population in this work presented in the table (1), we observed that the majority of affected cases were adults. Almost two-thirds of the studied participants were males. The majority of them lived in urban areas, and at most 5% of them had contact with animals. Furthermore, only 9

patients were dealing with soil. Santana et al. [17] emphasized that elderly patients constituted the most represented among FUO cases. Others proved that females are generally more frequently affected than males, as females have increased immune reactivity, resulting in resistance to infectious and some non-infectious diseases. However, it is possible that this pronounced immune reactivity makes women more prone to developing autoimmune diseases [18]. Contact with animals or birds is important risk factors for acquiring infections that may cause FUO [19].

The majority of our cases lived in urban areas, this may be as a result of urbanization and the general increase of quality and duration of life

that may lead to the detection of some feverish patients who would not receive medical care in a rural area.

Concerning types of consumed food among the studied population (figure 1), luncheon and beef were the commonest type of consumed food followed by a burger and beef (25.2% and 22% respectively) and the least consumed type was dried meat (10.6%). We suppose that this kind of food may contribute to *Salmonella* or *Toxoplasma* infection, which are common with poor sanitation in developing countries.

Owing to high costs, no specific investigational flow protocol for the diagnosis of FUI in Egypt is followed. Only initial investigations are done, together with the history and clinical findings that may guide the diagnosis [20].

Fever of unknown origin remains a difficult diagnostic challenge because over 200 disorders are in the differential diagnosis [21]. The diagnostic procedure is divided into multiple stages. The first includes ESR, C-reactive protein, complete blood count, renal and liver function tests, creatine phosphokinase, lactate dehydrogenase, ferritin, serum electrophoresis, antinuclear antibodies, rheumatoid factors, urine analysis, blood and urine cultures, radiography of chest, pelvi-abdominal ultrasonography were included as well. The second requires more specific radiological, serological, and microbiological tests. More invasive techniques are used, as bone marrow aspiration, liver biopsy, scintigraphy, or emission tomography, in addition to molecular tools [22]. The diagnostic work-up in Taiwan [23] begins with schedule hematological and biochemical and radiological investigations for all patients. In Saudi Arabia [24], a single diagnostic work-up is performed for all FUI cases involving the majority of mentioned investigations. The variability in diagnostic work-up give you an idea about the lack of integrated approach and strategy for handling the FUI cases. Despite considerable development in the imaging, serological, and immune-histopathological investigations, the task of diagnosis is often difficult and cannot be achieved in up to 50% of the cases [25].

Lab findings among the studied group in the present work (Figure 2) revealed that about 72.7% of the studied participants had positive CRP. The number of +ve CRP detected cases were more than the number of infectious diseases

included in this work disclosed that there were some patients suffering from other infections, collagen or tissue destructing disorders not investigated in our study. The uppermost detected infection in our work was tuberculosis (17%) followed by *Salmonella* and *Brucella* infections (11.7% for each). Furthermore, toxoplasmosis and hepatitis were detected in 2.9% and 1.8% respectively. A study done by Lamiaa et al. [26] revealed that bacterial infection was on the top of FUI causes, as 50% of patients had bacterial infections: salmonellosis in 15.6% of patients, brucellosis in 11.1% of patients, tuberculosis peritonitis in 10% patients, pyelonephritis in 7.7% of patients, pyogenic liver abscesses in 3.3% patients, and tuberculosis lymphadenitis in 2.2% of patients. Moreover, Mir et al. [27] enrolled 91 patients with classical pyrexia unknown origin (PUO), infections were the most common cause (44%) of PUO, followed by malignancies (12%), and connective tissue disorders (12%).

Investigations among the studied group (table 2) disclosed that 5.9% of the studied group had hepatosplenomegaly detected by the US. Almost 77.4% of them presented with lymphocytosis. We cannot exclude the possibility that the false-positive tuberculin test may have accounted for some of the TB cases in persons with normal CXRs, as Pepper et al. [28] accounted that the most important finding in their study was the high rate of normal chest X-ray (CXR) among persons with culture-confirmed Pulmonary TB (PTB). Also, renal failure patients are known to be associated with an increased frequency of atypical radiographic presentations of PTB, including normal CXR [29]. However, DNA fingerprinting must be performed when laboratory cross-contamination was suspected, false-positive tests or cultures were therefore unlikely. Almost 77.4% of patients in the present study presented with lymphocytosis. Similar to our findings Lamiaa et al. [26] found that 28 (31.12%) out of 90 patients had leukocytosis, whereas leucopenia was presented in 12 (13.33%) patients. Also, 22 (24.4%) patients had hepatosplenomegaly. Isolated hepatomegaly could signify Q fever, typhoid/enteric fever and brucellosis. Isolated splenomegaly could be a clue for miliary TB, Epstein-Barr virus, and cytomegalovirus [21].

Concerning the pattern of fever in our studied group, it was noticed that approximately, 46% of patients presented with intermittent fever, 24.6%

presented with continuous fever, and 29.3% presented with relapsing fever. Around 57.2% of them had fever lasted for three weeks and the majority of patients had fever $\geq 39^{\circ}\text{C}$ (table 3). Among patients who presented with intermittent fever, 10.1% of patients were diagnosed as salmonellosis, 10.1% of them as brucellosis, 9.5% of them as tuberculosis, 3.1% as toxoplasmosis, and the rest of patients diagnosis could not be reached.

Amidst the patients who presented with continuous fever, 9.5% of them were diagnosed as salmonellosis, 9.5% of them as brucellosis, 39.2% of them as tuberculosis, 5.9% of them as toxoplasmosis, and the rest of patients diagnosis could not be reached. In dispersion through patients who presented with relapsing fever, 16% of them were diagnosed as salmonellosis, 16% of them as brucellosis, 10% of them as tuberculosis and, the rest of patient's diagnosis could not be reached. Nonspecific presentations and the empirical antibiotic therapies may be the most common reasons for a delay in diagnosis or the undiagnosed cases. In agreement with our results, it was found that 58.3% of cases were presented with a continuous pattern of fever, while 16% presented with a remittent pattern, 23.2% showed intermittent fever, and 1.6% had a relapsing fever [29]. Also, Lamiaa et al. [26] found that patients who presented with continuous fever were due to salmonellosis, pyelonephritis, and cytomegalovirus, other patients were undiagnosed.

Clinical presentations and examinations of the studied group in the table (4), disclosed about 78.9% of patients with lymphadenopathy and 1.8% had jaundice. Besides, about 75.4% of patients received antibiotics. Under the same circumstances, it was accounted that lymphadenopathy is a useful key feature in the diagnosis of FUO, especially cervical lymphadenopathy [30]. FUO with lymphadenopathy must be considered as a separate entity, mostly represented by malignancies and granulomatosis due to infections or malignancy-related origin [31], in addition to toxoplasmosis [32]

In our research, the co-morbidities signified, 2.6% of patients with diabetes mellitus, 1.5% with hypertension, and 1.2% had the renal disorder.

Poring over demography, types of consumed food, clinical presentation, and investigations of

the only cases with toxoplasmosis (figure 3), fever among toxoplasmosis patients were more in adults living in urban areas and dealing with animals without difference between males & females. The most commonly consumed food was undercooked meat and Burger & luncheon. They were presented with a continuous or intermittent fever between $39\text{--}40^{\circ}\text{C}$. They either presented with lymphadenopathy or not, but all of them had hepatosplenomegaly and high CRP and leukocytosis & eosinophilia. In agreement with us, Cunha et al. [21] also stated that contact with animals in patients presented with FUO must raise the suspicion of toxoplasmosis, brucellosis, cat-scratch disease, and leptospirosis.

CONCLUSION

Tuberculosis, typhoid fever, and brucellosis were the main infectious causes in Port Said governorate/Egypt, afterward toxoplasmosis. Most of patients with toxoplasmosis were presented with lymphadenopathy, all of them had hepatosplenomegaly, high CRP, leucocytosis, and eosinophilia. Lymph node, bone marrow and liver biopsies are recommended in future studies beside, CT MRI and PET scan as more advanced investigations will help in declaring the definitive diagnosis of fever.

Ethical respects:

All participants were informed about the study, and written consent was obtained. An agreement of our study was obtained from the Institutional Review Board (IRB) Unit, Faculty of Medicine, Zagazig University, Egypt (no. 4056) meeting the requirements of the Helsinki Declaration.

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Conflicts of interest

There are no conflicts of interest.

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