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EPIDEMIOLOGY OF FEVER OF UNKNOWN ORIGIN (FUO) AT IMBABA FEVER HOSPITAL, GIZA GOVERNORATE, EGYPT

By

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Abstract

Fever of unknown origin (FUO) is caused by various diseases, and infections were the most frequent causes of FUO. The progress of the diagnostic techniques may have changed the breakdown of diseases causing FUO. This prospective study aimed to explore the clinical spectrum of fevers of undetermined origin (FUO) among adult patients treated at the Imbaba Fever Hospital from June 2018 to May 2019.

All Egyptian patients who met the FUO criteria and were hospitalized during this period were followed up until they were diagnosed. They were 350 of whom186 females (53.1%) and 164 males (46.9%), with ages ranged from 18 to 82 years (32.77±14.4). The commonest FUO cause was infections (72%), followed by autoimmune diseases (20%), malignancies accounted (2%) of the total with the diagnosis unknown in 4.6%. Brucellosis and pneumonia were considered major causes of infections.

Keywords: Patients, FUO, Infections, Brucellosis, Autoimmune diseases.

Introduction

Fever is among the most prevalent symptoms in the clinical setting. Most fever is either self-limiting or with a definite underlying etiology. If fever remains persistent and undiagnosed, it is termed fever of unknown origin or FUO (High *et al,* 2009).

Petersdorf and Beeson (1961) defined the criteria for FUO as follows: fever of more than 3 weeks' duration, temperature >38.3 on multiple occasions, and an unclear diagnosis a week of the patient evaluation. Feikin *et al.* (2011) reported that fever is a common reason for seeking healthcare in low- and middle-income countries, among patients with febrile illness required admission case fatality ratios were high that exceeded 20%. Yamanouchi *et al*. (2014) added that inf-ections were the commonest FUO cause. Prasad *et al.* (2015) reported a wide range of pathogens associated with severe febrile illness and highlight the substantial information gaps regarding the geographic distribution and role of common pathogens, and that high quality severe febrile illness etiology was comprehensive with respect to pathogens and geographically representative. Beresford and Gosbell (2016) reported that FUO is a syndrome that has tested clinicians' ability to diagnose affected patients. It's a term that refers to a group of unrelated medical diseases that share the symptom of persistent unexplained fever despite investigations.

Diagnostic techniques as imaging, serological, and genetic analyses were improved as an important diagnostic techniques (Stojanov and Kastner, 2005). But, despite advance in diagnostic tools, particularly imaging modalities, some studies continue to show an increased undetected FUO% (Mourad *et al*, 2003). The progress of these diagnostic techniques changed the FUO diseases causing, and periodic fever diseases such as the familial Mediterranean fever (FMF) became the more common diagnostic disease detection (Watanabe *et al*, 2019).

This study aimed to analyze the clinical spectrum of FUO among Egyptian patients admitted to Imbaba Fever Hospital and to describe unclassified FUO patients in terms of demographic and clinical presentation, investigations, and diagnosis.

Materials and Methods

Study participants: They were 350 patients admitted with prolonged febrile illness in

Imbaba Fever Hospital from June 2018 to May 2019. Patients were checked for their eligibility for the study, if presented with the following criteria: age >18 years old, fever >38.3°C on multiple occasions, lasted > 3 weeks without obvious source, and at least a week for hospital investigation. The patients with short febrile illness < 2 weeks, post-surgical fever, HIV-related FUO, neutropenic FUO, or nosocomial FUO were excluded.

Study design: This clinical study exhibited descriptive suspected features. They were subjected to the following: 1- History taking with special stress on past history (D.M, HTN, B.A, COPD), family history (autoimmune disease, FMF), drug history especially (antibiotics, antipyretics and immunosuppressive drugs) more than six months travel history, social history, sexual history, toxic manifestations, and fever grade, pattern, and duration. A thorough clinical examination was done including general, abdominal, chest, heart auscultation, and nervous system examination.

Full laboratory investigations were requested for, CBC, liver profile, renal profile, ESR, CRP, widal agglutination test the presence of typhoid and paratyphoid fever, (Abdel Wahab *et al,* 1996) and *Brucella* agglutination test. Some patients underwent more investigations as urine, stool and blood three successi-ve cultures, sputum culture, CMV-IgM, EBV-IgM, Quantiferon-TB Gold, ascitic fluid analysis, autoimmune profile, the MEFV genotyping, cerebrospinal fluid examination, and pathergy test.

Imaging investigations: Chest X-ray & abdominal ultrasound were requested, and sometimes if needed C.T. for abdomen, pelvis, and chest and Echocardiography in cases suspected with infective endocarditis.

Ethical consideration: The study was approved by the Research Ethical Committee, Faculty of Medicine, Ain Shams University, which when with Helsinki rules (2000).

Written informed consent was obtained from all the included patients.

Statistical analysis: Data were analyzed by using Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean±standard deviation (SD), and were expressed as frequency and percentage. Chi-square (X2) test of significance was used to compare proportions between two qualitative parameters, and Mann Whitney test. P-value less than 0.05 were considered significant.

Results

FUO patients: Diabetes mellitus was the commonest cause of morbidity. Fever pat-tern was intermittent in 69.7%, relapsing in 28.9%, and remittent in 1.4%. A total of 95.4% were diagnosed. Infectious disorders were the most common etiology of FUO, followed by autoimmune diseases and malignancies. Fever caused by brucellosis was in 132 patients (39.5%), pneumonia in 39 patients where the chest X-ray and CT chest of all patients revealed segmental infiltrates compatible with bronchopneumonia, and in 35 of them tuberculosis was confirmed. There were 13 pulmonary tuberculosis cases and 22 extra-pulmonary tuberculosis cases, included TB peritonitis (11 cases), TB meningitis (2 cases), TB lymphadenitis (7 cases), and Potts disease (2 cases). In 14 patients, a recurrent urinary tract infection was diagnosed of whom nine patients had infective endocarditis.

Typhoid fever was in five patients, rheumatic fever in two, ovarian abscess in two, and one for each of mastitis, and syphilis. Adult-onset still disease was in 25 patients, but SLE, and rheumatoid arthritis were confirmed in 24 & 10 patients, respectively. Seven patients have malignancies. Fever was caused by non-Hodgkin lymphoma in three cases. Bronchogenic carcinoma was detected in the fourth patient, renal tumor in another and gastric carcinoma and lymphocytic leukemia in the sixth and seventh cases, respectively. These were ten pulmonary sarcoidosis, five Behcet's disease or Behcet's syndrome and four FMF proved by the MEFV gene.

The FUO median duration was seven days (range, 3-210 d), the median overall follow-

up after admission was 45 days (range, 30-270 d), 88.6% were improved and 11.4% were referred. FUO patients were clinically ranged between diagnosed and undiagnosed cases, without significant differences in history or in physical examination data except for temperature and chest abnormalities. Diagnosed FUO patients had a significant high temperature, and chest abnormalities.

Laboratory examinations showed high significant differences in lymphocyte & neutrophil count, serum albumin, C- reactive protein, ESR, *Brucella* titer, and blood culture between FUO diagnosed and undiagnosed ones. Fate (58.4%) was in FUO diagnosed patients compared to 87.5% of undiagnosed ones. Median overall follow-up after admission in diagnosed FUO patients was 45 days (30-270 days) and 30 days (30-90 days) in undiagnosed FUO ones.

Details were given in tables (1, 2, 3, 4, 5 & 6) and figure (1)

Table 1: Demographic data of 350 patients.

Variations		No.	%
Age (years)	Mean ±SD	32.77 ± 14.41	
	Range	18- 82	
Sex	Female	186	53.1%
	Male	164	46.9%
Occupation	Housewife	131	37.4%
	Student	94	26.9%
	Retired	1	0.3%
	Workers (124 or 35.4%): Employees	27	7.7%
	: Manual workers	97	27.7%
Residence	Rural	185	52.9%
	Urban	165	47.1%
Marital status	Single	113	32.3%
	Married	236	67.4%
	Widow	1	0.3%

Table2: Diagnosis of cases.

Final Diagnosis	No.	%
Undiagnosed	16	4.6%
Diagnosed	334	95.4%
Infection	240	72%
Autoimmune	68	20%
Malignancy	7	2%
Others	19	6%

Table 3: Fever duration and fate

Fate		Total
Duration (days)	Median(IQR)	7 (6-9)
	Range	3- 210
Discharge	Improved	310 (88.6%)
	Referred	40 (11.4%)
Follow up	No	141 (40.3%)
	Yes	209 (59.7%)
Follow up (days)	Median(IQR)	45 (45- 90)
	Range	30 -270

*IQR, interquartile range; SD, standard deviation.

Table 4: Comparison between diagnosed and undiagnosed cases as to laboratory findings.

Laboratory findings		Undiagnosed (N= 16)	Diagnosed (N= 334)	Test value	P-value	Sig.
Lymphocytes	Mean ± SD	0.38 ± 0.16	0.29 ± 0.15	2.371•	0.018	S
	Range	0.15 – 0.79	0.05 – 0.87			
Neutrophil	Mean ± SD	0.46 ± 0.12	0.56 ± 0.18	-2.193•	0.029	S
	Range	0.17 – 0.75	0.03 – 0.9			
Serum albumin	Mean ± SD	4.39 ± 0.43	4.06 ± 0.37	3.507•	0.001	HS
	Range	3.4 – 5	2.6 – 5.5			
ESR	Median(IQR)	26.5(15 – 41.5)	60(36 – 95)	-3.336‡	0.001	HS
	Range	5 – 130	5 – 150			

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS); •: Independent t-test; ‡: Mann Whitney test.

Table 5: Comparison between diagnosed and undiagnosed cases as to CRP, *Brucella* and blood culture

Variations		Undiagnosed		Diagnosed		Test value*	P-value	Sig.
		No.	%	No.	%			
C reactive protein	Negative	12	75.0%	28	8.4%	66.939	0.000	HS
	Positive	4	25.0%	306	91.6%			
Brucella titer	Negative	16	100.0%	203	61%	9.787	0.002	HS
	Positive	0	0.0%	132	39.5%			
Blood culture	Not done	0	0.0%	263	78.7%	64.737	0.000	HS
	Negative	16	100.0%	56	16.8%			
	Staphococcus aureus	0	0.0%	1	0.3%			
	Streptococcus viridins	0	0.0%	8	2.4%			
	Salmonella spp	0	0.0%	5	1.5%			
	MRSA	0	0.0%	1	0.3%			

P-value< 0.01: highly significant (HS); *Chi-square test.

Table 6: Comparison between diagnosed and undiagnosed patients as to fate.

Fate		Undiagnosed (N= 16)	Diagnosed (N=334)	Test value	P-value	Sig.
Duration (days)	Median(IQR)	6 (5 - 7)	7 (6 - 9)	-1.707‡	0.088	NS
	Range	5 -10	3 - 210			
Discharge	Improved	16 (100.0%)	294 (88.0%)	2.163*	0.141	NS
	Referred	0 (0.0%)	40 (12.0%)			
Follow up	No	2 (12.5%)	139 (41.6%)	5.381*	0.020	S
	Yes	14 (87.5%)	195 (58.4%)			
Follow up (days)	Median(IQR)	30 (30 - 30)	45 (45 - 90)	-6.345‡	0.000	HS
	Range	30 - 90	30 - 270			

P-value >0.05= Non significant (NS); P <0.05= Significant (S); P < 0.01=highly significant (HS),
*Chi-square test; ‡: Mann Whitney test.

Discussion

The FUO is one of the most difficult aspects from clinical practice, with wrong indicative symptoms (Mourad *et al*, 2003). The causes of FUO were classified as infectious diseases, malignancies, collagen diseases, and others (Yamanishi *et al*, 2007). Fever of unknown origin (FUO) was originally characterized in 1961 by Petersdorf and Beeson as a disease condition of temperature exceeding 38.3°C on at least three occasions over a period of at least three weeks, without diagnosis made despite one week of inpatient investigation. However, as underlying diseaases were often reported for classical FUO, these presentations may not be considered to be of unknown origin. Rather, the etiology of prolonged fever may resolve, or not resolve. The definition of fever with unresolved cause (true FUO) is difficult, as it is a moving target, given the constant advancement of imaging and biomarker analysis. Therefore, the prevalence of the fever with unresolved cause (FUO) is unknown and such a case of prolonged fever, which initially has presented as the classical FUO (Unger *et al,* 2016).

In the present study, infectious etiology was found to be the major cause of FUO accounted for 72% followed by autoimmune diseases 20%, and finally malignancies 2%.

Meanwhile, the present undiagnosed etiology represented 4.6% of cases despite the emergence of new diagnostic tools. Kabapy *et al* (2016) in an Egyptian hospital-based study (2009-2010), reported 959 patients suffered from FUO. They added that clinical and epidemiological criteria showed that the infectious diseases were the commonest (63.4%), followed by autoimmune diseases (30.3%) and malignancies (0.9%), while the undiagnosed (3.2%). But, Liu *et al* (2016) in Japan reported that the FUO infectious diseases were 33.9% cases, followed by the collagen diseases (25.1%), lastly neoplasms (21.1%), and that adult-onset still's disease was the most common collagen cause of FUO, but unidentified causes were 19.8%.

Besides, the present results as compared with the 374 patients with FUO conducted by Montasser *et al* (2015) in Egypt showed that infections continue to be the leading cause of FUO (69.7 vs. 66.3%), but the undiagnosed cases dropped from 7.8% to 4.6%. The lower proportion of undiagnosed cases of FUO may be due to advances in diagnostic technologies. The present study showed

that collagen diseases were the cause of fever in 20% as compared to 7.2% reported by Montasser *et al* (2015) among the diagnosed with collagen diseases. Also, more or less in agreement with the present data, Rozik *et al* (2011) in Embaba Fever Hospital, Giza reported that infectious were commonest causes of FUO (57%), then neoplasms (18.5%) and collagen diseases (13%). They added that the miscellaneous diseases were diagnosed in (7%), while (4.5%) were undiagnosed, but in the present study the relative increase in infectious causes and decrease in neoplasms might be due to patients' young ages.

Abroad, Barbado *et al.* (1992) in Spain compared the etiology and diagnostic methods in 2 series of patients with classic criteria of pyrexia of unknown origin during 1968-1981 & during 1982-1989. They found significant decrease in the infections cases and an increase in neoplasms and connective tissue disorders in the second series. The percentage of patients diagnosed by laparatomy was similar in both series but the diagnosis yield at laparotomy was greater in the second period. Pyrexia of unknown origin continues to be a condition which can defy clinical expertise in in spite of advances in diagnostic techniques. Moawad *et al.* (2010) in Saudi Arabia infectious diseases, especially TB were the leading etiology of FUO. They added that data didn't identify any predictor of certain FUO diagnoses except for older age and neoplastic etiology. True FUO patients generally did well. Reporting local experience is important in guiding clinicians about the epidemiologic patterns of the FUO in their regions. Hayakawa *et al*. (2012) in USA reported that the infections were identified as the commonest cause of FUO in the majority of reports, with the relative frequency ranged from 27% to 42%. Besides, Tanveer *et al.* (2014) reported that infections were the leading cause of FUO, followed by the collagen diseases. They added that the rheumatologic diseases were 12%.

But, the present results disagreed with El-Rooby (1959) who reported that 63% of the FUO cases remained undiagnosed. This may be explained by the less advanced laboratory and radiological techniques that led to 63% undiagnosed FUO cases. Also, Larson *et al* (1982) in USA reported that the FUO neoplastic diseases outnumbered infectious causes, and Raque *et al.* (2001) found that sacral neoplasms form a wide range of pathological entities including primary and metastatic as well as benign and malignant conditions.

In the present study, in infections brucellosis was the common disease diagnosed in 39.5% followed by atypical pneumonia at 11.6%. This agreed with Ali-Eldin *et al* (2011) who reported brucellosis and infective endocarditis as the commonest infectious FUO causes. But, the present study infective endocarditis cases were diagnosed in nine patients (2.6%). This disagreed with Montasser *et al* (2015) reported 22 brucellosis cases. Afifi *et al.* (2005) in Egypt found that by surveillance network identified typhoid fever and brucellosis as the main cause of acute febrile illness. Abdelbaset *et al.* (2018) added that brucellosis a common health problem must be suspected.

In the present study, tuberculosis (TB) cases were 10.4% and not a common cause of FUO among diagnosed cases. Abdelbaky *et al* (2011) in Egypt, Tanveer *et al* (2014) in India and Jafari *et al* (2018) in Iran reported that TB was the most prevalent FUO etiology. Zheng *et al* (2008) in China found a relatively high incidence of tuberculosis due to the overcrowded population, alcohol abuse, and HIV infection.

In the present study, there was no osteomyelitis case among diagnosed cases. Also, Jafari *et al* (2018) didn't find osteomyelitis cases, due to successful treatment in setting, along with early detection of local infections in clinics. Bleeker-Rovers *et al*. (2007) in USA reported that in developed countries, FUO patients diagnosed with infectious diseases decreased, but diagnosed with collagen disorders and malignancy increased.

In the present study, the FUO undiagnosed cases being decreased, but still a public health problem not only in Egypt, but also ab-

road. The percentage of the FUO cases that were undiagnosed was much lower than previous report of 13% in Egypt (Ali-Eldin *et al*, 2011), the global rates, even those reported in other studies in developed countries as 25.7% in France (Zenone, 2006), 50% in USA (Bleeker-Rovers *et al*, 2007), 16.7% in Iran (Alavi *et al*, 2011), and 27% in India (Tanveer *et al*, 2014). Undoubtedly, the universal advances in clinical, serological, immunological, and diagnostic radiology have the valuable diagnostic progress (David and Quinlan, 2022). Nevertheless, there were many unmet financial needs following a diagnosis of the FUO even in settings with universal health coverage. Health care professionals may only be able to fulfill these unmet needs through multispectral collaborateons catalyzed by strong political will (Kong *et al,* 2020).

In the present study, FUO patients were usually improved with symptomatic treatment and discharged as cured cases. However, Montasser *et al* (2015) found that the undiagnosed cases were 7.8%, and Kabapy *et al* (2016) reported the undiagnosed cases were 3.2%. Also, Tanveer *et al* (2014) in India reported that the undiagnosed cases were 23% since 80% the populations were close contact with in- and out-doors domestic animals putting them at risk for zoonotic infectious but only less than 10% of the FUO were due to brucellosis. Alzubaidy (2008) and Al-Fadhli *et al.* (2008) from the Middle East (areas with highest disease burden) reported a FUO rough rate 37% caused by brucellosis.

In the present study, neoplastic diseases were about 2% of examined cases, and lymphomas were the most common neoplastic disease diagnosed in 42.8%. This data agreed with El-Sayed *et al.* (2013) reported that according to the Middle East Cancer Consortium in Egypt, the NHLs age-standardized rates were (16.3/100.000person). They added that the very high incidence made NHLs the 3rd most common cancer in men and the 2nd most common cancer in women accounted for 10.9% of all cancers diagnosed annually.

Apart from the infections and diseases etiological agents, insects bite while taking blood meals the secreted saliva cause mild as to high fever (Morsy, 2012). Mosquito bite may cause allergy with fever or Skeeter syndrome (Abdel-Motagaly *et al,* 2017), bug cause skin reactions with fever in children (El-Bahnasawy *et al,* 2018), as well as spider (Al-Agroudi *et al,* 2016)

Conclusion

Infections are still the major cause of FUO in Egyptian adults. The most prevalent infections were brucellosis and pneumonia. Further prospective studies with close observation of FUO patients in the future years, along with focus on a new spectrum of diseases such as auto-inflammatory spectrum and the use of new diagnostic procedures, may help in decreasing undetermined FUO.

Recommendations

The improved technology and availability of more sophisticated laboratory tests and imaging studies with advances in interventional radiology is a must for best diagnosis of FUO etiologies in ambulatory settings.

Therefore, the more complicated, mysterious cases currently admitted to the fever hospitals, make it difficult for physicians to determine etiologic causes of fevers (FUO).

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Explanation of figure

Fig.1: Co-morbidities and past history among FUO patients.