Evaluation of different patterns and etiologies of classic form of pyrexia of unknown origin in Assiut University fever unit

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Background
Pyrexia of unknown origin (PUO) is one of the most challenging diagnostic dilemmas in clinical practice. Despite the availability of different investigations, still diagnosis may not be reached. The aim of the study was to assess the relative frequency of the classical form of PUO among patients admitted to the Fever Unit of Assiut University Hospital (AUH) and to determine the causes and the different fever patterns of the classical form of PUO in the studied patients.

Patients and methods
This prospective study included patients with the classical form of PUO admitted to Fever Unit of Tropical Medicine and Gastroenterology of AUH during the period from January 2014 till July 2017. All patients who fulfilled the inclusion and exclusion criteria of classical form of PUO defined by Durack and Street were included.

Results
The relative frequency of patients who had classical form of PUO was 90 among 2431 (3.7%) patients admitted to the Fever Unit of Tropical Medicine and Gastroenterology of AUH. Bacterial infection was on the top of the diagnosis, where 45 (50%) patients had bacterial infections, comprising 14 (15.6%) salmonellosis, 11 (12.2%) tuberculosis, 10 (11.1%) brucellosis, seven (7.7%) pyelonephritis, and three (3.3%) pyogenic liver abscess. Different fever patterns were seen, where 58 (64.4%) patients presented with relapsing fever, 29 (32.3%) patients presented with continuous fever, and three (3.3%) patients presented with remittent fever.

Conclusion
PUO is detected in 3.7% among feverish patients, where salmonellosis and brucellosis still are the commonest causes. Relapsing fever is the commonest pattern of the classical form of PUO. Undiagnosed PUO cases are still a problematic condition that needs exhaustive investigations.

Keywords:
brucellosis, pyrexia of unknown origin, salmonellosis, tropical medicine and gastroenterology, tuberculosis

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Introduction

Fever is one of the common presenting symptoms in clinical practice [1]. If fever remains persistent and undiagnosed, it is termed as pyrexia of unknown origin (PUO) [2]. Most febrile conditions are readily diagnosed based on presenting symptoms and a problem-focused sign in physical examination. Occasionally, simple testing such as a complete blood count or urine culture is required to make a definitive diagnosis [3].

No cause was detected in 5–15% even after extensive evaluation of cases. The percentage of undiagnosed 'fever of unknown origin' had dropped from more than 75% in the 1930 to less than 10% in the 1950 [4,5].

Durack and Street [1] divided PUO into four groups: classical, nosocomial, HIV related, and neutropenic. Investigation and treatment of PUO requires extensive knowledge that is related to multiple medical specialties and awareness of the investigations required. In spite of extensive medical experience and the development of new technologies, this condition sometimes remains difficult to diagnose for physicians [6].

Despite the improvement in diagnostic techniques, especially imaging modalities, there is an increase in the number of percentage of undiagnosed cases of PUO [7].

Different patterns of fever

Intermittent pattern is defined by temperature reaching baseline for some hours and fluctuations are more than 1°C. It has high spike and rapid defervescence. It occurs in benign tertian malaria.

Remittent pattern is defined by temperature not reaching baseline and fluctuations are more than 1°C. It has fluctuating peaks and a baseline that does not return to normal. It occur in empyema and pus under tension.

Continuous pattern is defined by temperature not reaching baseline, and daily fluctuations do not exceed 1°C. It persists with little or no fluctuation and occur in typhoid fever.

Relapsing pattern is defined by fever for few days with interval of normal temperature for few days in between. It is afebrile for 1 or more days in between febrile episodes. It occurs in brucellosis and lymphoma [8].

Methods

Study design

This prospective study included patients who had classical form of PUO admitted to Fever Unit of Tropical Medicine and Gastroenterology of AUH during the period from January 2014 till July 2017.

Patients

All patients fulfill the inclusion and exclusion criteria of classical form of PUO defined by Durack and Street [1].

Methods

The collecting data were classified into the following:

The demographic data included age, sex and residence; clinical data included symptoms and signs through history such as drug history, contact history with animals, sexual history, occupational history, travel history, and family history; and there was exclusion of factitious fever.

Examination of the patients with classical form of pyrexia of unknown origin

Data from examination were obtained as pallor, jaundice, temperature (fever chart), confirmation of temperature measurement, localized tenderness, lymphadenopathy, lower limb edema, signs that accompany fever as tachycardia and chills, hepatomegaly, splenomegaly, and hepatosplenomegaly.

Laboratory investigations

Data from the laboratory investigations were obtained as complete blood picture, liver function tests, prothrombin time and concentration, serum creatinine level, blood urea level, urine analysis, and data from imaging studies such as pelvi-abdominal ultrasonography.

Special investigations were done according to each case such as immunological markers (antinuclear antibody, anti-double stranded DNA antibody, and rheumatoid factor), Malta test, Widal test, Comb's test, bone marrow studies, and lymph node biopsy.

Ethics and consent

An approval of the study from the local ethics committee of AUH was obtained which was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients were informed about the study, and a written consent was obtained.

Statistical analysis

Data were collected and analyzed using statistical package for the social sciences (SPSS, version 16; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD (range), whereas nominal data were expressed in the form of frequency (percentage).

Results

This study was conducted at the Fever Unit of Tropical Medicine and Gastroenterology Department in Assiut University Hospital from January 2014 to July 2017.

Demographic data, laboratory data, and other investigations in patients with classical pyrexia of unknown origin were as follows

Demographic data

This study included 90 patients with mean ± SD age of 45.02 ± 15.76 years, with an age range of 18–72 years. Most cases were in the age group 21–40 years (41.11). Most patients 53 (58.89%) were females, whereas 37 (41.11%) patients were males (Table 1).

Laboratory data

Concerning laboratory data, it was noticed that abnormal hemogram in the form of anemia was presented in 45 (50%) patients, 28 (31.12%) patients had leukocytosis, whereas leucopenia was presented in 12 (13.33%) patients.

Of the studied patients, 10 (11.1%) of them had abnormal liver function in the

Table 1 Demographic data, laboratory data, and other investigations in patients with classical pyrexia of unknown origin

Variables	*n*=90	Range
Age (mean±SD) (years)	45.02±15.76	18-72
<20	20 (22.22)	
21-40	37 (41.11)	
41-60	24 (26.67)	
>60	9 (10)	
Sex (male/female)	37 (41.1)/53 (58.8)	
Complete blood picture		
Hemoglobin (g/dl)	10.65±1.7	6.40-15
Hemoglobin 10-12 mg/dl	20 (22.2)	
Hemoglobin 8-10 mg/dl	12 (13.3)	
Hemoglobin >8 mg/dl	13 (14.5)	
Platelets (×10^3/l)	261.77±25.89	
Leucocytic count (×10^3/l)	12.44±4.23	55-345
Leucopenia	13.33 (12)	1.70-22.34
Normal count	55.55 (50)	
Leukocytosis	28 (31.12)	
Liver function tests		
Total bilirubin (mmol/l)	11.10±2.99	7.56-15.67
Direct bilirubin (mmol/l)	9.22±0.97	2.45-6.78
Aspartate transaminase (U/l)	48.80±16.56	12.34-76.43
Alanine transaminase (U/l)	37.68±8.98	21-53.45
Serum albumin (g/l)	25.56±6.34	18.56-41.23
Total protein (g/l)	87.03±23.68	67.09-101.35
International randomized ratio	1.23±0.15	1.01-1.40
Kidney function tests		
Creatinine (mmol/l)	78.98±22.12	111.29-45.31
Urea (mmol/l)	4.67±1.04	5.67-2.45
Urine analysis		
Normal	76 (84.4)	
Pus cells	5 (5.6)	
Albuminuria	9 (10)	
Abnormal ultrasonographic findings (60/90; 66.66%)		
Hepatosplenomegaly	22 (24.4)	
Splenomegaly	20 (22.2)	
Ascites	9 (10)	
Hepatomegaly	2 (2.2)	
Hepatic abscess	3 (3.3)	
Splenic focal lesions	4 (4.4)	

Data were expressed in the form of frequency (percentage) or mean±SD (range) as appropriate. Nominal data were expressed in the form of frequency (percentage), whereas continuous data in form of mean±SD.

form of hyperbilirubinemia and raised liver enzymes (1–2-folds above normal level). Moreover, five (5.6%) patients had abnormal kidney function in the form of raised blood urea and serum creatinine. In addition, 15 (16.7%) of them had impaired coagulopathy in the form of prolonged prothrombin time and concentration.

Of 90 patients in this study, 14 (15.6%) patients had abnormal urine analysis, where nine (10%) patients had albuminuria, whereas five (5.6%) patients had pus cells, so urine culture was done in those patients, which revealed positive growth for *E. coli*.

Other investigations were as follows

Abdominal ultrasonographic findings: Abdominal ultrasonographic findings were detected in 60 (66.66%) of 90 patients. Liver abscesses were presented in three (3.3%) patients. Culture and sensitivity was done in patient with hepatic abscesses, where two of them showed positive growth for *Staphylococcus aureus* (was sensitive to penicillin combination and third-generation cephalosporin), whereas the other patient showed positive growth for *Escherichia coli* (was sensitive to third-generation cephalosporin).

Bone marrow studies: In this study, there were 15 (16.67%) patients who needed bone marrow studies, where bone marrow aspirate was done in three (3.3%) patients and bone marrow biopsies were performed in 12 (13.34%) patients. It was noticed that eight (8.9%) patients had normal findings. Acute myeloid leukemia was found in three (3.3%) and chronic myeloid leukemia was found in one (1.1%) patient. The other three (3.3%) patients had hypocellular bone marrow.

Lymph node biopsy

It was done in 15 (16.67%) patients, of whom two (2.2%) patients had Tuberculosis (TB) lymphadenitis and another two patients had reactive hyperplasia.

The other 11 (12.22%) patients had picture of lymphoma, where eight (8.9%) of them had Hodgkin lymphoma, whereas the other three (3.3%) had non-Hodgkin lymphoma.

Fever patterns and etiologies of classical pyrexia of unknown origin in the studied patients

Of 90 patients with criteria of classical PUO included in this study, 58 (64.4%) patients presented with relapsing fever, 29 (32.3%) patients presented with continuous fever, and three (3.3%) patients presented with remittent fever (Table 2).

Of 90 patients, 68 (75.6%) were diagnosed, whereas 22 (24.4%) were discharged without definite diagnosis.

Among 68 (75.6%) patients who were diagnosed, infection was the most common etiology in 46 (51.1%), where bacterial infection was seen in 45 (50%), malignancy was detected in 15 (16.7%), whereas connective tissue diseases were demonstrated in six (6.6%).

Among the infectious causes, salmonellosis was reported in 14 (15.6%) patients, and these patients had fever for 3 weeks. Their ages ranged between 20 and 30 years and neither of them presented with relative bradycardia. Blood culture was positive for the

Table 2 Fever patterns and etiologies of classical pyrexia of unknown origin in the studied patients

Pattern	Frequency (percentage)	Total
Relapsing fever		
Tuberculosis	11 (12.2)	58 (64.4)
Tuberculosis peritonitis	9 (10)	
Tuberculosis lymphadenitis	2 (2.2)	
Brucellosis	10 (11.1)	
Hodgkin lymphoma	8 (8.9)	
Non-Hodgkin lymphoma	3 (3.3)	
Connective tissue disease	6 (6.7)	
SLE	5 (5.6)	
Adult-onset stills disease	1 (1.1)	
Leukemia	4 (4.4)	
AML	3 (3.3)	
CML	1 (1.1)	
FMF	1 (1.1)	
Undiagnosed	15 (16.7)	
Continuous fever		
Salmonellosis	14 (15.6)	29 (32.3)
Pyelonephritis	7 (7.8)	
Undiagnosed	7 (7.8)	
Cytomegalovirus infection	1 (1.1)	
Remittent fever		
Pyogenic liver abscess	3 (3.3)	3 (3.3)

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; FMF, familial Mediterranean fever; SLE, systemic lupus erythematosis.

organism in 10 patients, urine culture was positive in five cases, and one patient had positive results for both blood and urine culture.

The undiagnosed cases 22/90 (24.4%) were discharged and followed up in the outpatient clinic, where 17 (77.3%) of them had no fever in the follow-up.

Discussion

PUO is caused by different etiologies and is considered one of the most challenging diagnostic dilemmas in clinical practice, and despite different investigations, diagnosis could not be reached in some cases. This study aims to explain the causes and different fever patterns of the classical form of PUO around the studied patients.

The relative frequency of classical PUO was 90/2431 (3.7%).

The total number of population studied by Mir *et al.* [9] was 91 patients, Petersdorf and Beeson [2] studied 100 patients, Kejariwal *et al.* [10] studied 100 patients, Bandyopadhya *et al.* [11] studied 164 patients, De Kleijn *et al.* [12] studied 167 patients, and Montasser *et al.* [13] studied 374 patients. These populations ranged from 91 patients to 374 patients [2,9–13].

In this study, diagnosis could be made in 68 (75.6%) patients, whereas 22 (24.4%) patients were discharged without definite diagnosis.

The reported range of the undiagnosed cases in previous researches ranged from 7 to 30% in the study by Petersdorf and Beeson [2], 7–12% in Bandyopadhya *et al.*[11], 14% in Kejariwal *et al.* [10], 29% in Montasser *et al.* [13], 30% in De Kleijn [12], and 27% in Mir and colleagues [2,9–13].

In this study, bacterial infection was on the top of diagnosis, as 45 (50%) patients had bacterial infections: salmonellosis in 14 (15.6%) patients, brucellosis in 10 (11.1%) patients, tuberculosis peritonitis in nine (10%) patients, pyelonephritis in seven (7.7%) patients, pyogenic liver abscesses in three (3.3%) patients, and tuberculosis lymphadenitis in two (2.2%) patients.

In this study, hematological malignancies in the form of Hodgkin lymphoma was diagnosed in eight (8.9%) patients, non-Hodgkin lymphoma in three (3.3%) patients, acute myeloid leukemia in three (3.3%) patients, and chronic myeloid leukemia was diagnosed in one (1.1%) patient.

However, connective tissue diseases such as systemic lupus erythematosis were diagnosed in five (5.5%) patients and adult still disease diagnosed in one (1.1%) patient.

A study done by Mir *et al.* [9] that enrolled 91 patients with classical PUO showed that the diagnosis of PUO was achieved in 77% (n = 66) cases. In 66 cases, diagnosis was possible; infections were the most common cause of PUO (44%), followed by malignancies (12%), and connective tissue disorder (12%) [9].

Another study done in Abbasia Fever Hospital by Montasser *et al.* [13] showed that infections still represented the main cause of PUO in Egypt. A total of 374 patients were enrolled; 248 (66.3%) patients were diagnosed with an infection etiology, 27 cases diagnosed as collagen diseases, 27 patients diagnosed as malignancy, and 43 patients diagnosed as miscellaneous (inflammatory bower disease (IBD), drug fever, Behcet disease, and familial Mediterranean fever) [13].

Moreover, in a study done by Salla *et al.* [14] that enrolled 34 patients, 23 patients were diagnosed; 22/34 patients (64.7% of PUO) had infectious cause and only one patient (2.9% of PUO) had noninfectious causes for PUO. They demonstrated that among the infectious causes, four patients (11.6% of PUO) had tuberculosis. For non-TB causes, 5/34 (14.7%)

patients had salmonellosis, 2/34 (5.9%) patients had brucellosis, and one patient had urinary tract infection (UTI) (2.9%) [14].

A study done by Gompf [15] on 290 patients with PUO showed noninfectious inflammatory diseases in 35.2% of cases, infections in 29.7%, miscellaneous causes in 19.8%, and malignancies in 15.1%.

Another study done by Barbado *et al*. [16] showed that infectious diseases (41/133, 31%) were the most frequent cause of PUO. The second commonest cause was neoplastic diseases. There were 11/133 (8.27%) cases of Hodgkin's disease and 5/133 (3.75%) cases of non-Hodgkin's lymphoma (16).

In contrast to the study done by Naito *et al*. [17] which showed that noninfectious inflammatory disease (37/121, 30.6%) is the most common cause, infections remain the predominant cause of PUO in Egypt [17].

Concerning fever pattern in this study, it was noticed that relapsing fever presented in 58/90 (64.4%) patients, continuous fever in 29/90 (32.3%) patients, and remittent fever in 3/90 (3.3%) patients.

Among patients who presented with relapsing fever, 10 (11.1%) patients of them were diagnosed as brucellosis, 11 (12%) patients of them were diagnosed as lymphoma, six (6.6%) patients of them were diagnosed as connective tissue disease, four (4.4%) patients of them diagnosed as leukemia, one (1.1%) patient was diagnosed as familial Mediterranean fever, and in 15 (16.6%) patients of them, diagnosis could not be reached.

This study was similar to a previous study reported by Ogoina [18], where it found that relapsing fever was seen in lymphoma.

Another study done by Montasser *et al*. [13] found continuous fever in 211 (58.3%) patients, 58 (16%) patients presented with a remittent pattern, and 6 (1.6%) patients had relapsing fever.

In this study, patients who presented with continuous fever, 14 (15.6%) patients of them were diagnosed as salmonellosis, seven (7.8%) patients of them were diagnosed as pyelonephritis, seven (7.8%) patients of them were undiagnosed, and one (1.1%) patient of them was diagnosed as cytomegalovirus.

This study was similar to a study done by Ogoina [18] which found that salmonellosis and urinary tract infections presented with continuous fever. However, Brusch *et al*. [19] reported that continuous fever was found in 12% of cases.

Our unicenter results were done over a small number of patients. Further multicenter studies will be needed over a large scale, as PUO may vary from region and time period to another.

Conclusion

Diagnosis of PUO is one of the problems most frequently encountered in medical practice. The most common pattern of classical form of PUO is relapsing fever, followed by continuous and at last remittent fever. An undiagnosed case of PUO perplexes both the physician and the patient in spite of advances in diagnostic modalities.

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Conflicts of interest

There are no conflicts of interest.

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