

Etiology and Outcome of Fever of Unknown Origin in a tertiary care center in South India-A prospective study

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Abstract

Background: Fever is a common symptom for which patient seeks medical attention. Globally, and especially in developing countries, Fever of unknown origin (FUO) is an important cause of morbidity and mortality. The pattern of fever has apparently changed over the years, though there are no data available in this regard. There is a perception of change in patterns among treating physicians. The present study aims at finding out the different etiology and factors causing delay in diagnosis should be identified and overcome to improve outcome of FUO. **Materials and Methods:** Consecutive patients admitted with a diagnosis of FUO admitted in the Department of General Medicine, Govt. Medical College Thrissur are enrolled into the study. The clinical and investigation findings and outcome were recorded in a proforma for analysis. **Results:** 53 patients were enrolled into the study and they were followed up till a definite outcome is met. 37 (71.2%) were males and 15 (28.8%) were females. Infection was the etiology in majority of the cases. 32 (91%), followed by malignancy and inflammatory disorders. Tuberculosis was found to be the most common infectious etiology followed by Urinary tract infections and enteric fever. Among the tuberculosis majority was extrapulmonary tuberculosis (87.5%). There were 2 cases of Vivax Malaria which is not endemic to this part of the country. HIV constituted (5.7%) among this population with various complications. Multiple metastasis, Multiple myeloma, Lymphoma, Leukemia and Hepato-cellular carcinoma were the malignant etiologies reported. A significant proportion (11.5%) of patients etiology of Fever could not be diagnosed. **Conclusion:** Infectious etiology, especially Tuberculosis was the most common cause for FUO in this part of the country. A thorough search for other infections, malignancy and inflammatory disorders should be undertaken in case of FUO. A significant (11.5%) patients' etiology could not be diagnosed despite thorough workup.

Keywords: PUO, Fever of Unknown origin

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Introduction

Fever is a common symptom for which patient seeks medical attention. Globally, and especially in developing countries, Fever of unknown origin (FUO) is an important cause of morbidity and mortality [1]. Fever of unknown is defined as a temperature > 38.3°C on several occasions lasting longer than 3 weeks with a diagnosis that remains uncertain after 1 week of investigations in a hospital or in an outpatient setting [2,3]. Revised criteria require an evaluation of at least three days in the hospital, three outpatient visits or one week of logical and intensive outpatient workup without finding a cause spectrum of FUO. Etiology of Fever of Unknown Origin may include more than 200 diseases [4]. It remains a challenge to elucidate the etiology in such cases. The four categories of potential etiology of Fever of Unknown Origin are classic, nosocomial, immune deficient and human immunodeficiency virus (HIV)-related [2]. Prevalence of FUO among adult hospitalized patients is reported to be 2.9% [5]. A comprehensive history, physical examination and exhaustive laboratory testing are no substitute for a focused FUO diagnostic

evaluation. Fever patterns add little to diagnostic work up [6]. Clinicians should also be aware of temporal relationships in appearance and disappearance of clinical and laboratory findings. Often early or late clinical or laboratory findings are overlooked, because physicians often recognize only the most common clinical findings has enhanced the detection of localized infections. The spectrum of fever has apparently changed over the years, though there are no data available in this regard. There is a perception of change in patterns of fever among treating physicians. Recently the emergence of new infective etiologies like Influenza, Dengue fever, Leptospirosis and even malaria raises new concerns. There is considerable surge of immigrant population in the recent past which also brings diseases which were not endemic to this part of the country. The data are lacking regarding the clinical profile of Fever of Unknown Origin nationally and internationally. The wide availability of advanced imaging and highly specific and sensitive immunologic testing has reduced the number of undetected cases of adult Still's disease, systemic lupus erythematosus and poly arteritis nodosa [7]. Common causes of FUO include Infections, Collagen vascular diseases, Neoplasms and less commonly Sarcoidosis, Thyroiditis, drug fever, inflammatory bowel diseases and Thrombophlebitis [8]. The present study aims at finding out the different etiology and common presentations of Fever of Unknown Origin to throw light into the changing trends.

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Materials and Methods

This study was conducted in the Department of General Medicine, Govt. Medical College Thrissur- which is situated in the mid region of Kerala state- between April 2014 to May 2015. Consecutive patients admitted with a diagnosis of Fever of Unknown Origin above the age of 12 were enrolled to the study. Operational definition of Fever of Unknown origin is defined as a temperature $> 38.3^{\circ}\text{C}$ on several occasions lasting longer than 3 weeks with a diagnosis, that remains uncertain after one week of investigations in a hospital or in an outpatient setting. Revised criteria require an evaluation of at least three days in the hospital, three outpatient visits or one week of logical and intensive outpatient workup without finding a cause. The detailed symptomatology, clinical findings, baseline investigations and specific investigations are recorded in the proforma for analysis. Patients were followed up till a definite outcome is reached. Outcomes were defined as Cured, Expired, Undiagnosed. Data obtained from the pro forma were coded systematically and results were analysed for rates and proportions. Results are expressed as text, tables and diagrams.

Results

The present study was conducted among 52 patients who were admitted for evaluation of Fever of unknown Origin. There were 37 males (71.2%) and 15 females (28.8%). The mean age \pm SD was 41.13 ± 16.29 (range 14-64 years). Majority were from a low socio economic strata. Manual laborer constituted 25 patients (48.1%) followed by house wives 15 (28.8%) and students 10 (19.2%). 4 (3.8%) were drivers. In 34 (65.4%) subjects fever was present from 3 weeks to one month duration. 12 patients (23%) had fever for one month to 3 months. 6 patients (11.5%) had fever persisting more than 3 months. The mean duration of hospital stay was 14 days \pm 6. (Figure 1) On Symptom analysis Headache was the most common associated symptom. 32 patients (61.5%) had head ache. Followed by loss of appetite in 31 (59.6%) and loss of weight 24 (46.2%). Vomiting 16 (30.8%) 0 cough and expectoration 15 (28%) abdominal pain 14 (26%) loose stools 9 (17.3%) muscle pain 8 (15.4%) and chest pain 8 (15.4%). Altered sensorium was the presenting symptom in 6 patients (11.5%). 3 patients (5.8%) had joint pains and one patient had skin rashes. Diabetes was the most common comorbidity in 6 (11.5%) patients. Followed by Chronic liver disease in 4 (7.7%) and chronic kidney disease in 2 (3.8%). 7 patients (13.5%) were smokers, and 5 patients (9.6%) were alcohol abusers. (Figure 2) Physical examination revealed pallor for 29 patients (55.8%), meningism for 11 patients (21.2%). However only 7 patients had a final diagnosis of meningitis. Peripheral Lymph node enlargement was present in 9 patients (17%). Jaundice were noted in 7 patients (13.5%) clubbing was present in 4 patients (7.7%). Hepatomegaly and splenomegaly were present in 12 patients each (23.1%) 36 patients (69.2%) had Anemia and Leucopenia was found in 20 patients (38.5%). Leukocytosis was found in 14 (26.9%). 6 patients with leukocytosis had tuberculosis as etiology. Necrophilia was found in 10 cases (19.2%). Monocytosis was found in 7 patients (13.5%). 5 patients with Monocytosis had a consistent diagnosis of Tuberculosis.

Other 2 patients had Hepatitis C and Alcohol liver disease. 40 patients had elevated ESR (77%) 9 patients (17.3%) had an ESR between 30-50 mm /1st hour, 18 patients (34.61%) had an ESR of 50 – 100 mm /1st hour and 13 patients (25%) had an ESR of > 100 mm /1st hour. All patients with an etiological diagnosis of Tuberculosis had an elevated ESR. Majority of them had an ESR of > 100 mm /1st hour. Thrombocytopenia was noted in 15 patients (28.8%). Among those with thrombocytopenia, in 5 patients could not make a diagnosis. Malaria (1), HIV (2), Enteric fever (2), Scrub typhus (1), Dengue (2) fever, Tuberculosis (3) were other diagnoses. Peripheral smear examination reported as Normochromic Normocytic anemia in 15 patients (28.8%). Hypochromic microcytic anemia and dimorphic anemia were reported in 2 patients each (3.8%). One patient has atypical cells in the peripheral smear which later reported as acute lymphatic Leukemia. (figure 3) Bone marrow study was conducted for 5 patients. There were 2 cases of Multiple Myeloma, One case of Acute Lymphatic leukemia, One case of disseminated tuberculosis. Features of cystitis in 5 patients, Intra abdominal lymph nodes in 5 patients, fatty liver in 3 patients, hepatocellular carcinoma in one patient, hepatosplenomegaly in one patient and thickened ileum in one patient on Ultrasound examination of the abdomen. CSF study was done in 7 patients. 4 patients had features of tuberculous meningitis, viral, bacterial and cryptococcal meningitis were seen in one patient each. Among the 52 patients enrolled, 6 (10.53%) patient's etiology could not be diagnosed. Majority of the patients had infectious etiology. Tuberculosis was the most frequent diagnosis. 16 cases of Tuberculosis (30.76%) were diagnosed as the etiology of fever. Extrapulmonary tuberculosis 14 (26.9%) was the most frequent diagnosis among tuberculous etiology. Tuberculous lymphadenitis, tuberculous meningitis, Tuberculous Pleural effusion, Genitourinary TB were the extrapulmonary sites mostly encountered. 2 patients (5.76%) had pulmonary tuberculosis as the final diagnosis. Urinary infection was the other frequent diagnosis among infections 6 (10.53%). Enteric fever 2 (3.8%), malaria 2 (3.8%) Retroviral infection 3 (6.76%) and one case of Scrub typhus. The second common etiology was neoplasm. 2 cases each of multiple myeloma (3.8%) followed by hepatocellular carcinoma, metastatic malignancy, acute lymphatic leukemia and lymphoma contributed one case each. Noninfectious inflammatory disorders were the third etiology encountered. One case of Systemic onset juvenile inflammatory arthritis and one case of Drug fever. Out of 6 diabetics, Tuberculosis was the most common etiology in 3 cases (50%) followed by 2 cases (33%) of Urinary Tract Infections. We couldn't arrive at a diagnosis in one patient with diabetes. However he had resolution of fever after 6 weeks. (chart 1). Coming to the outcomes, 37 patients had a definite diagnosis and treatment. 5 patients died during the evaluation, however a definite diagnosis could be made. 6 patients clinical condition could not be diagnosed. Among patients with fever duration between three weeks to one month, Tuberculous meningitis, Urinary infections, Malaria, Enteric fever were the common diagnoses. Those patients who had fever between one month to 3 months duration, Genito-urinary tuberculosis and Leukemia were the diagnoses. Considering the duration of fever of more than 3 months, the most common diagnosis were Tuberculosis and multiple myeloma, malignancy and retroviral infection.

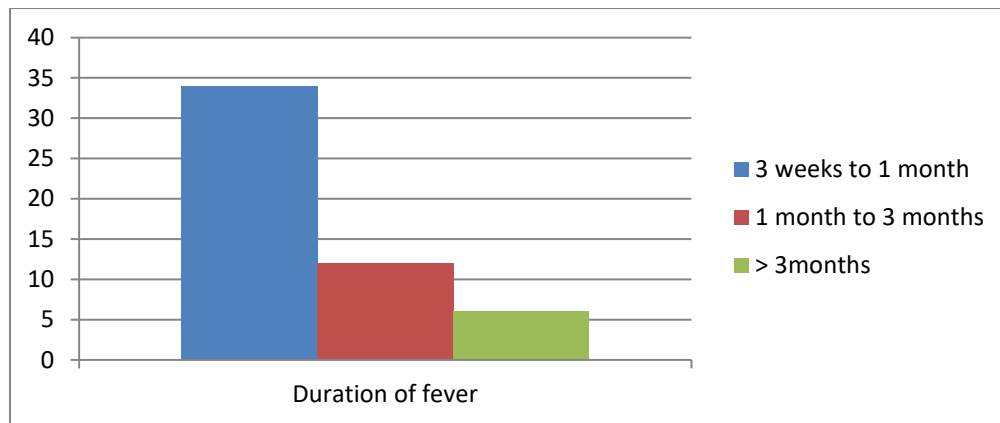


Fig 1: Duration of fever

Table 1: Final Diagnosis of 52 patients with fever of Unknown Origin

Infections	
Tuberculosis	16
Urinary Tract Infections	6
HIV	3
Enteric Fever	2
Scrub typhus	1
Menigitis	7
Malaria	2
Hepatitis C	1
Neoplasms	
Lymphoma	1
Hepatocellular Carcinoma	1
Multiple myeloma	2
Metastatic Malignancy(Primary Unknown)	1
Acute lymphatic Leukemia	1
Non infectious inflammatory disorders	
Systemic idiopathic Juvenile arthritis	1
Others	
Drug Fever	1
Undiagnosed	6

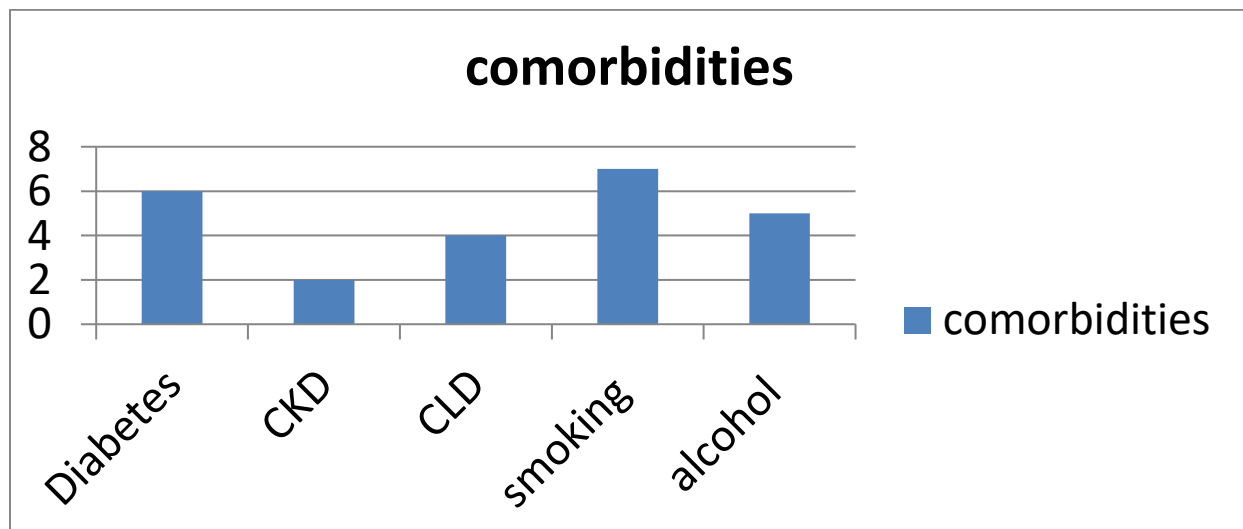


Fig 2: Number of patients with comorbidities

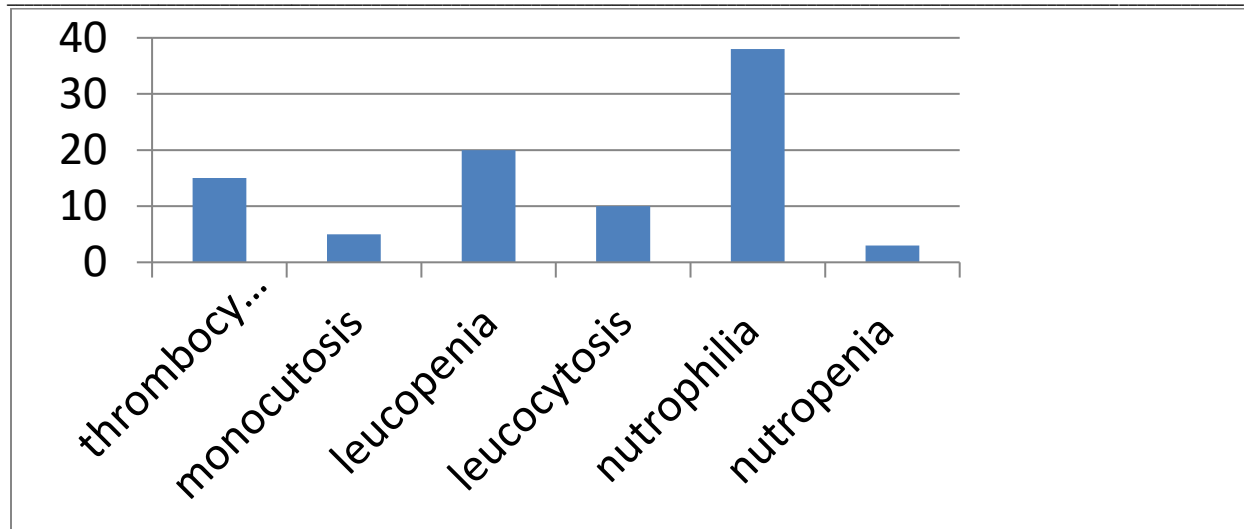


Fig 3: Hematological changes

Discussion

Petersdorf et al studied 100 cases during 1952-1957 reported infections as etiology in 36% of cases. Neoplasms contributed 19%, non infectious inflammatory diseases. 7% were undiagnosed [1]. Handa et al reported infectious etiology in 43.8%, non infectious etiology in 15.7% and neoplastic etiology in 8.3% cases [9]. Whereas D Kejariwal et al reported 53% infectious etiology, 11 % non infectious etiology and 17% Malignancy [10]. Joshi N et al reported 69% occurrence of infectious etiology followed by malignancy in 12 % . However this study was done among pediatric population where enteric fever , visceral leishmaniasis, tuberculosis were the common infections [11]. Similarly Dipanjan Bandyopadhyay reported 58.5% , 11% non infectious causes and 22 % malignancies [12,13]. During 1970-1980, Larson et al studied 105 patients with FUO and reported 30% infections, 31% neoplasms, 16% non infectious inflammatory diseases and 12% they could not diagnose the etiology [14]. Knockaert et al studied 199 patients with FUO and found out 22.5% as infectious etiology, 7% neoplasms, 23% noninfectious inflammatory diseases etiology and in 25%, they couldn't diagnose the etiology [15]. De Kleijn et al in 1992 – 1994 studied 167 patients with 26 infectious etiology, 12.5% malignancy, 24 noninfectious inflammatory diseases and in 24% they couldn't diagnose the etiology [16]. Bleeker-Rovers et al studied 73 patients with FUO during 2003-2005. They could find 16% infectious, 7% malignant etiology, 22 % non infectious inflammatory diseases and they couldn't diagnose as many as 51% of patients [17]. As these studies were undertaken in hospital setting, there could be referral bias which can have profound impact on the results. The present study reports results of 52 patients with FUO. Up to 60% had an infective etiology followed by 14% malignancy. Non infectious inflammatory diseases constituted 6 % of the patients. 20% patient's etiology could not be diagnosed. The present study has results in accordance with the previous studies as well. The difference reported by various studies could be due to the selection of patients by the respective hospitals. The outcome of patients with Fever of Unknown origin largely depends on the underlying etiology. Compared to the old studies, the proportion of undiagnosed cases is less owing to the development of advanced diagnostic facilities. However detailed clinical examination and repeated examinations is the major tool for diagnosis of FUO. In the present study, 80% of patients were diagnosed with a definitive etiology. This study also reports death of 5 patients though they had a definite diagnosis. However 6 (11.5%) had no definite diagnosis even after the possible investigations. In the

present study, FDG PET was not done in any patients owing to the non availability of the investigation. Currently FDG PET would help in localizing the pathological area in cases of FUO, especially when the inflammatory markers are elevated.

Conclusion

Infectious etiology, especially Tuberculosis was the most common cause for FUO in this part of the country. A thorough search for malignancy and inflammatory disorders should be done in case of Fever of Unknown Origin. A significant (11.5%) of patients etiology could not be diagnosed despite thorough workup. In southern India , infectious diseases are still continues to be the most common etiology for FUO. A thorough clinical history and physical examination followed by focused investigations can clinch the diagnosis in majority of cases.

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