



CLINICO-ETIOLOGICAL PROFILE OF FEVER OF UNKNOWN ORIGIN IN A TERTIARY CARE HOSPITAL OF KOLKATA, WEST BENGAL

Medicine

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ABSTRACT

Fever may be classified as short duration fever (less than or equal to 14 days) and long duration or prolonged fever (more than 14 days). A small but important sub group of fever patients present with persistent fever (>2 weeks) and are often very difficult to diagnose in the tropical countries like India. A wide variety of serious diseases can cause prolonged and persistent fever as shown by various studies. The major causes of prolonged fever are infection, and collagen vascular diseases.

In this study attempt was made to find out the aetiology and clinical profile of the patients admitted with fever for more than two weeks duration in School of Tropical Medicine, Kolkata.

MATERIAL AND METHODS: The presenting symptoms and signs were recorded in a pre-designed proforma. The clinical course of the disease was recorded on a daily basis with reference to evolution of complaints and clinical findings along with investigation findings. All the relevant investigations were done at School of Tropical Medicine. Bone marrow aspiration and bone marrow biopsy samples were sent to the Department of Pathology, Medical College Hospital, Kolkata. ANA and ANA profile were sent to IPGME & R, Kolkata.

Result: The etiological outcomes of the study was Tuberculosis 14 (23.3%), Scrub typhus 4 (6.67%), Typhoid fever 3 (5%), UTI 4 (6.67%), RTI 3 (5%) and 1 (1.67%) bacterial endocarditis and we also observed amoebic liver abscess 3 (5%), cryptococcal meningitis 2 (3.3%), Visceral leishmaniasis 4 (6.67%), 2 (3.3%) was dengue with enteric fever and leptospirosis 2 (3.3%). Lymphoma 4 (6.67%), 4 (6.67%) was autoimmune disease like Systemic lupus erythematosus (SLE), HLH 2 (3.3%) and 2 (3.3%) was septicemia, 1 (1.67%) were Still's disease, MCTD 1 (1.67%), 1 (1.67%) was Kikuchi disease, 1 (1.67%) was brucellosis, 1 (1.7%) melioidosis and 1 (1.67%) patient was undiagnosed.

Conclusion: In our study major cause of FUO (fever of unknown origin) is infective (76%) and next common cause is inflammatory and malignancy disorder. our study could not detect any etiological cause in 1.67% cases.

Among the infective aetiology tuberculosis with associated HIV and viral hepatitis are more common cause of FUO. Other most common infective disorder is LRTI, VL and typhus fevers. Among the inflammatory disorder SLE most commonly present with FUO.

KEYWORDS

FUO, Infectious disease, auto immune disease, Malignancy, fever.

INTRODUCTION

Fever is defined as having a temperature above the normal range due to an increase in the body temperature set point. Fever is generally agreed to be present if the elevated oral temperature is more than 37.2°C Celsius or 98.9°F Fahrenheit in the morning (6 A.M) and 37.7°C Celsius or 99.9°F Fahrenheit in the evening (4 P.M). However, axillary temperature is 0.9°F lesser and rectal temperature is 0.9°F more than oral temperature.

Fever is the cardinal symptom of many diseases. It often represents the chief complaint of many diseases in the admitted patients. It is the major contributor of morbidity and mortality of many patients in the developed as well as developing country.

Fever for more than two weeks duration is still one of the challenging situations faced by the clinicians in a tertiary care hospital. Febrile illnesses of short duration are usually managed by primary care physician but when the illness is not resolved by standard treatment the patients are referred to tertiary care centre. Initial workup of a patient with fever for more than two weeks duration is crucial. Some clinical features may suggest an infective cause. Some other features may indicate it to be an inflammatory one.

In India, infectious disease is still the most common cause of fever persisting for more than two weeks. However, other non-infectious causes including malignancies are also becoming significant. The work-up for the cause is very crucial for treating the patient. The suspicion of the cause is very important to proceed for diagnosis to avoid wastage of money and valuable time. Due to the development of improved diagnostic techniques, the proportion of FUO caused by infectious diseases has decreased and the proportion of CTD, malignancies, and other diseases has increased.^{1,2}

This study is being undertaken to outline the clinical and etiological profile of patients presenting with fever for more than two weeks. The findings of the study will help to formulate a guideline for investigating these cases.

MATERIAL AND METHODS:

The study was conducted from July 2018 to June 2019 at School of Tropical Medicine, Kolkata. It was an observational study and the patients aged more than 12 years presenting with fever for more than 2 weeks were included in this study. Pregnant women and patients already on antitubercular drugs for tuberculosis were excluded. The clinical course of the disease was recorded on a daily basis with reference to evolution of complaints, clinical findings and investigation reports. All the relevant investigations were done at School of Tropical Medicine. Bone marrow aspiration and bone marrow biopsy samples were sent to the Department of Pathology, Medical College Hospital, Kolkata. ANA and ANA profile were done from IPGME & R, Kolkata. A pre-designed proforma was used to collect data by proper history taking, clinical examination and investigations of total 60 consecutive patients.

Documentation of fever was done by measuring oral temperature in all the patients. Detailed history was taken from the patients and their relatives regarding residence, mode of onset and progression of fever, associated symptoms like chills, rigors, anorexia, night sweating, weight loss, joint pain, cough, bowel/ bladder disturbance, abnormal bleeding manifestation, sore throat, headache, visual abnormality and convulsion. Patients were enquired about past history, contact history of tuberculosis, history of recent migration, occupational history and treatment history. Detailed personal (addictions, high risk sexual behaviour) and family history especially of diabetes, food habits, and

drinking water source were also noted. After admission we did a thorough clinical examination.

Ethical approval

The ethical Committee of the Calcutta School of Tropical Medicine, Kolkata, approved the study protocol. Informed consent of the patients or their legal guardians was obtained before recruitment of the patients in the study.

Results & Analysis

Major age group of our study was 12-24 years(30%),60% was male and 40% was female.

Table 1:Distribution of study population according to some relevant clinical features other than fever.(N=60)

Clinical features other than fever	Number	Percentage (%)
Pallor	26	43.33
Jaundice	5	8.33
Lymphadenopathy	14	23.33
Hepatomegaly	20	33.33
Splenomegaly	23	38.33

Chest X-ray showed findings among 33% of patients.

Table 2:Distribution of study population according to their chest X-ray findings.(N=60)

Chest X-ray findings	Frequency	Percentage
Cavity lesion	3	5.0
Consolidation	3	5.0
Mediastinal widening	5	8.3
Pleural effusion	8	13.3
Pulmonary plethora	1	1.7
No abnormality detected	40	66.7

Table 3:Distribution of study participants according to their findings in USG whole abdomen(n=60)

USG findings	Frequency	percent
Gread 1 fatty change	7	11.7
Liver abscess	4	6.7
Hepatosplenomegaly	14	23.3
Splenomegaly	6	10.0
Ascites	3	5.0
Multiple RPLN	3	5.0
Normal study	23	38.3

Major Ultra sonograph findings was hepatosplenomegaly 14(23.3%)

Table:4 Distribution of study participants according to their findings in some special serological tests: (N=60)

Name of Tests	Frequency	Percent
IgM Leptospira	2	3.3
IgM Scrub Typhus	4	6.7
IgM Brucellosis	1	1.7
ANA with profile (Hep2)	4	6.7
ELISA for HIV-I & II	6	10.0
HBsAg	6	10.0
AntiHCV	6	10.0

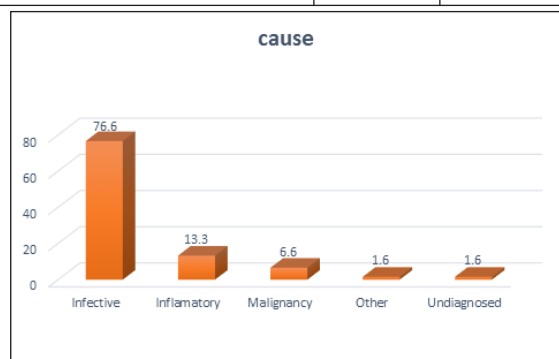


figure1: Distribution of study population according to their broad diagnosis (N=60)

Table 5: Distribution of study patients according to their etiological diagnosis (N=60)

DIAGNOSIS	NUMBER	PERCENTAGE (%)
Tuberculosis	14	23.3
lymphoma	4	6.67
Scrub typhus	4	6.67
Visceral leishmaniasis	4	6.67
Liver abscess	3	5
Systemic lupus erythematosus (SLE)	4	6.67
Typhoid fever	3	5
RTI	3	5
UTI	4	6.67
cryptococcal meningitis	2	3.3
Dengue + Enteric fever	2	3.3
HLH	2	3.3
Leptospirosis	2	3.3
endocarditis	1	1.67
Septicemia	2	3.3
Undiagnosed	1	1.67
Brucellosis	1	1.67
Kikuchi's disease	1	1.67
MCTD	1	1.67
Melioidosis	1	1.67
Still's disease	1	1.67

Discussion

This observational cross sectional study was done in the department of Tropical Medicine of Carmichael Hospital for tropical disease on patients with history of prolonged fever (more than 2 weeks of duration) from July /2018 to June 2019.

The rise of AIDS – associated tuberculosis has eliminated the expectation of it's virtual eradication from many countries. TB is likely to increase as a most frequent cause of F.U.O in years to come , even in patients not typically considered immune suppressed. We found 14 cases (23%) of TB , of which only 3 (5%) were associated with HIV . EPTB is most commonly associated with HIV. Two cryptococcal meningitis cases were associated with HIV. All 4 cases of VL were from Bihar which is still an endemic state of disease .

We found 4 (6.67%) cases of lymphoma. Lymphoma cases were present mostly with lymphadenopathy and hepatosplenomegaly and were diagnosed histopathologically.

Two cases (3.3%) of hemophagocytic lymphohistocytosis (HLH) were found in this study. Main presentation was pallor, hepatosplenomegaly & fever. Ferritin was elevated & fibrinogen reduced. Bone marrow was hypercellular with multiple haemophagocytes.

We found a single case of Kikuchi's disease presenting with fever, pallor and lymphadenopathy. Diagnosis was confirmed by FNAC of lymph node showing necrotic lesion with starry sky appearance. Besides this we found Enteric fever, RTI, UTI, liver abscess, scrub typhus, leptospiral disease, brucellosis, septicemia, endocarditis , even one melioidosis among the infective etiologies.

Among the auto immune disorders, we found 4 (6.67 %) SLE, 1 (1.67 %) still's disease. We could not evaluate the etiology in one case , probably it was in early phases of disease evaluation or it needs more elaborate evaluation.

Classic FUO in India is often also due to delayed diagnosis of acute febrile illnesses with lack of confirmation either through culture or molecular techniques and further compounded by lack of specificity of serology in an endemic setting. The previous studies elucidating the causes of classic FUO have used inconsistent and different definitions of disease processes thus questioning their validity and reliability.⁶ In addition there can be varying causes of FUO depending on the geographical location and prevalence of local diseases and hence causes of fever are often different in East, West, North and South India.^{3,4} We used very strict definitions of disease in our study validated in a previous published FUO study.¹¹ Infections as the major category of FUO has predominated over the decades and this has remained consistent^{3,5} in India.

There was a largest series of FUO from South India. Systematic sequence of investigations without start of empirical therapy led to a diagnosis in 99.4% which is the highest in described literature. In this study infections are most important cause of classical FUO with important cause of classical FUO with extrapulmonary tuberculosis being the most frequent, in India. Melioidosis is an emergent cause of FUO seen often in diabetics. Lymphoma is the commonest neoplasm FUO and SLE was the most common non-infectious inflammatory disease causing FUO. The number of cases in our series who remained undiagnosed was extremely small as compared to previous studies, probably due to a strict documentation of fever in hospital, an aggressive diagnostic approach to FUOs and avoidance of empirical therapy as much as possible.⁶

Bandyopadhyay D et al⁵ (2011) found that infectious disease still remains the most important cause of fever. Thus the initial investigations should always include tests for that purpose in a case of FUO. **Saini KC et al⁷ (2018)** found that infection was the commonest cause of thrombocytopenia and dengue was the commonest of the infections followed by malaria. Bleeding manifestations were seen in 42.7% of patients. 91.40% of patients with bleeding tendencies had petechiae/purpura as the commonest bleeding manifestation, followed by spontaneous bleeding in 57%. Spontaneous bleeding was noted when platelet counts were less than 20,000. Septicaemia accounted for 85.24% of deaths followed by malaria (6.55%) and dengue (5%). Fever with thrombocytopenia is an important clinical condition commonly caused by infections, particularly dengue and malaria. It was found that 24(40%) patients had Cough, 4(16.67%) patients had Productive, 20(83.33%) patients had Nonproductive, 34(56.67%) patients had Loss of appetite, 20(33.3%) patients had Nausea/ vomiting, 13(21.67%) patients had Headache / convulsion, 36(60%) patients had Loss of body weight/ weakness, 5(10%) patients had Diarrhoea, 2(4%) patients had Persistent, 3(6%) patients had Intermittent, 40(80%) patients had Abdominal swelling/ pain, 2(4%) patients had Dyspnoea / palpitation chest pain, 10(16.6%) patients had Morning's stiffness joint pain, 30(50%) patients had Night sweating, 6(10%) patients had Dysuria and 4(6.6%) patients had Pruritus. We found that 13(21.6%) patients had Continuous fever, 7(11.6%) patients had Remittent fever, 22(36.6%) patients had Intermittent fever, 6 patients had Single rise/ 24 hrs fever, 16 patients had Double / 24 hrs fever and 18(30%) patients had irregular fever.

Kumar N et al⁸ (2017) found that the prevalence of dengue fever is 14% (94), in which 72% (68) are male and remaining 28% (26) were female. Maximum number of dengue positive cases seen in the age group 21-30 years with least in above 60yrs of age groups. The co-infection of Dengue with typhoid fever in febrile patients was 34% (32) which includes 66% (21) were female and remaining 34% (11) are male. The occurrence of dengue fever is high in most active age group people with male gender while co-infection with typhoid fever observed mostly in female population. **Satpathy PK et al⁹ (2016)** found that the Lancet in 2010 reported the emergence of resistant New Delhi strain of metallo-beta-lactamase 1 Gram-negative *Enterobacteriaceae* from India, Pakistan, and the UK due to irrational use of antibiotics. Moreover, there are very scanty literature reports on "Short duration Fevers." This study is likely to advocate rational scientific approach to the management of short duration fever. This was an observational cross-sectional study comprising 200 fresh consecutive inpatients of fever of >2 weeks duration who has not been exposed to any antibiotic prior to hospitalization between July 2012 and September 2014. They were subjected to clinical, microbiological, and serological studies and other specific studies when indicated. Common aetiology for fever was found to be nonspecific viral fever (45%), which did not need antibiotics, then dengue fever (26.5%), enteric fever (7%), and malaria with *Plasmodium vivax* (4%) predominance.

An etiological study of fever of unknown origin was done among patients admitted to medicine ward of a teaching hospital of Eastern India. The main diagnosis in the end was tuberculosis, closely followed by hematological malignancy. A substantial number of cases remained undiagnosed despite all investigations. The provisional diagnosis matched with the final in around two thirds of the cases. While for younger patients leukemia was a significant diagnosis, for older ones, extra-pulmonary tuberculosis was a main concern. In India, infectious disease still remains the most important cause of fever. Thus the initial investigations should always include tests for that purpose in a case of FUO. Geographic variations and local infection profiles should always

be considered when investigating a case of FUO. However, some of the cases always elude diagnosis, although the patients may respond to empirical therapy.⁵ total of 91 cases (62 males and 29 females), with age ranging from 16 to 80 years were investigated. The mean duration of fever before hospitalization was 26±4 days. The etiology of FUO was delineated in (66%) of cases, whereas, (25%) remained undiagnosed. Most common group of FUO was that of infectious diseases (44%) followed by collagen vascular diseases and malignancies (12 % each). Amongst the infection group, brucellosis and salmonellosis comprised the majority of cases (25% each). Infections are the most common cause of FUO followed by collagen vascular diseases in our region.¹⁰

In our study we found among this 6, Tuberculosis 14(23.3%), Scrub typhus 4(6.67), Typhoid fever 3(5%), UTI 4(6.67%), RTI 3(5%) patients and 1(1.67) was bacterial Endocarditis. And also observed amoebic liver abscess 3(5%) , cryptococcal meningitis 2 (3.3%), Visceral leishmaniasis 4(6.67%), 2 (3.3%) was dengue with enteric fever and leptospirosis 2 (3.3). Lymphoma 4(6.67%), 4(6.67%) was autoimmune disease like Systemic lupus erythematosus (SLE), HLH 2 (3.3%) and 2 (3.3%) was septicemia , 1(1.67%) were Still's disease , MCTD 1 (1.67%), 1(1.67%) was Kikuchi disease, 1 (1.67%) was brucellosis, 1(1.7%) melioidosis and 1(1.67) patient was undiagnosed.

CONCLUSION

In our study major cause of FUO (fever of unknown origin) is infective (76%) and next common cause is inflammatory and malignancy disorder. In our study we could not detect any etiological cause only in 1.67% cases.

Among the infective aetiology tuberculosis with associated HIV and viral hepatitis are more common cause of FUO. Other most common infective disorder is LRTI, VL and typhus fever. Among the inflammatory disorder SLE most commonly present with FUO.

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