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Clinical and Etiological Profile of Classic Fever of Unknown Origin at Tertiary Care Hospital of a Hilly State

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Abstract: FUO is an important medical problem worldwide, especially in the undeveloped countries like India. To have a structured, sensible and effective approach the clinician must have an understanding of the spectrum of disease and test characteristics of various diagnostic modalities available in the evaluation of FUO. The aim of this study was to analyze the clinical and etiological profile of patients having classic FUO. It was a cross sectional study for one year duration from 1st June 2013 to 31st May 2014 and was performed in the Department of Medicine in I.G.M.C. Shimla. All the admitted Patients above 18 year of age and who fulfilled the Durack and Street criteria of FUO were included in the study. After initial history taking and physical examination, the patients were subjected to routine, serological & radiographic investigations. Data was entered using microsoft excel software and analyzed with the help of epi info v7. A total of 45 patients who admitted with FUO were included Mean age of the patients was 33 years and majority of the patients were in young age group of 18-40 years (76%).There was male preponderance (69%) and most of the patients were from rural background (71%).The mean duration of fever 46.6 days and mean duration of hospitalization was 14.4 days. Infections were responsible for 80% cases of FUO. These infections included tuberculosis (29%), enteric fever (17.5%), intra-abdominal abscesses (8.8%), chloroquine responsive fever (4.4%), brucellosis (7%), lieshmaniasis (4.4%), and UTI (2.2%). Non Infectious Inflammatory Disease (NIID) and neoplasms were were responsible for only 4.4% and 2.2% of cases, while 13.2% of the cases remained undiagnosed. Infections are the most important cause of fever of unknown origin in the developing countries like India and tuberculosis is the leading cause. Thus the initial investigations should always include tests for ruling out or confirming diagnosis of infectious disease.

Keywords: Fever of unknown origin (FUO), Infectious diseases, Tuberculosis.

INTRODUCTION

Fever of unknown origin (FUO) was defined by Petersdorf and Beeson [1] in 1961 as temperature of > 38.3°C (101°F) on several occasions, a duration of fever of > 3 weeks and, (3), failure to reach the diagnosis despite one week of inpatient investigation.

Durack and Street [2] proposed a revised system for classification of FUO that better accounts for non endemic and emerging diseases, improved diagnostic technologies, and adverse reaction to new therapeutic interventions. This updated classification include, (1) classic FUO, (2) nosocomial FUO, (3) neutropenic FUO, (4) and FUO associated with HIV infection.

Classic FUO corresponds closely to the earlier definition of FUO, differing only with regard to the prior requirement for 1 week's study in the hospital. The newer definition is broader, stipulating three outpatient visits or 3 days in hospital without elucidation of cause or 1 week of "intelligent and invasive" ambulatory investigation.

The following common conditions are sources of FUO: tuberculosis, abscesses, urinary tract infection, endocarditis, hepatobiliary infection, osteomyelitis, rickettsia, chlamydia, systemic bacterial illnesses, spirochetal diseases, herpes virus, fungal infections parasitic infections, lymphomas, leukemia's, solid tumors, malignant histiocytosis, collagen vascular and autoimmune diseases, sarcoidosis, granulomatous hepatitis, drug fever, endocrine disorders, giant cell

arteritis, polymyalgia rheumatic, polyarthritis nodosa, to name a few conditions. In children, infections are the most common cause of FUO, whereas neoplasms and connective tissue disorders are more common in elderly persons [3].

To have a structured, sensible and effective approach the clinician must have an understanding of the spectrum of disease and test characteristics of various diagnostic modalities available in the evaluation of FUO. Present study is an attempt to establish the various causes of classic FUO in our institute so as to formulate an appropriate protocol for diagnostic workup of fever of unknown origin.

Aims and Objectives of Study

The aim of this cross sectional study was to analyze the clinical and etiological profile of patients having classic FUO admitted in Indira Gandhi Medical College, Shimla.

MATERIALS AND METHODS

It was a cross sectional study for one year duration from 1st June 2013 to 31st May 2014 and was performed in the Department of Medicine in I.G.M.C. Shimla. All the admitted Patients above 18 year of age and who fulfilled the Durack and Street criteria of FUO were included in the study. After initial history taking and thorough physical examination, the patients were subjected to routine investigations like -Hb, TLC, DLC, ESR, Platlet count ,FBS/RBS, LFT, RFT, electrolytes as well various serological & radiographic investigations.

Informed written consent was taken from all the participants after persuading the patients about the possible benefits of the study. Strict confidentiality of the data was maintained. Data was entered using microsoft excel software. Data analysis was done with the help of epiinfo v7.

Inclusion criteria

Patients above 18 years of age and those patients who fulfill the Durack & Street criteria of classic FUO were included in the study i.e. (1) Temperature of > 38.3°C (101°F) on several occasions, (2) A duration of fever of > 3 weeks and, (3) Failure to reach the diagnoses despite 3 days of hospital.

Exclusion criteria

Patient with neutropenia (absolute neutrophil count<500/□l) patient developing fever 48 hours after hospital admission and human immunodeficiency virus (HIV) positive patients were excluded from study

RESULTS

In our study, a total of 45 patients who admitted with FUO were included. We stratified the patients into three age groups i.e. young age group: 18-40 years, middle aged 41-60 years and elderly 60 years and above. Mean age of the patients was 33 years (range 18 to 71 years) .The young age group consisted of maximum number of patients i.e. 34 (75.6%). Thirty one patients were male (69%) and fourteen patients (31%) were female. 71% of the patients were from rural background while 29% of patients were from urban background. (Table 1)

Table-1: Socio demographic characteristics of the study participants:

Age Group	Male	Female	Rural	Urban	Total
18-40	21(46.7%)	13(28.9%)	25	9	34(75.6%)
41-60	9(20%)	1(2.2%)	6	4	10(22.2%)
>60	1(2.2%)	0	1	0	1(2.2%)
Total	31(69%)	14(31%)	32(71%)	13(13%)	45(100%)

The interval between the onset of fever and hospitalization varied from 2 weeks to 3 months. Mean duration of fever prior to hospitalization was 46.6 days.(Figure 1) The commonest etiology with 10 days duration of hospitalization was enteric fever and pulmonary tuberculosis. With increasing duration of hospital stay malignancy, lieshmaniasis, neurobrucellosis and SLE were common etiologies. The mean duration of hospitalization was 14.4 days (range 10 days to 4 weeks).

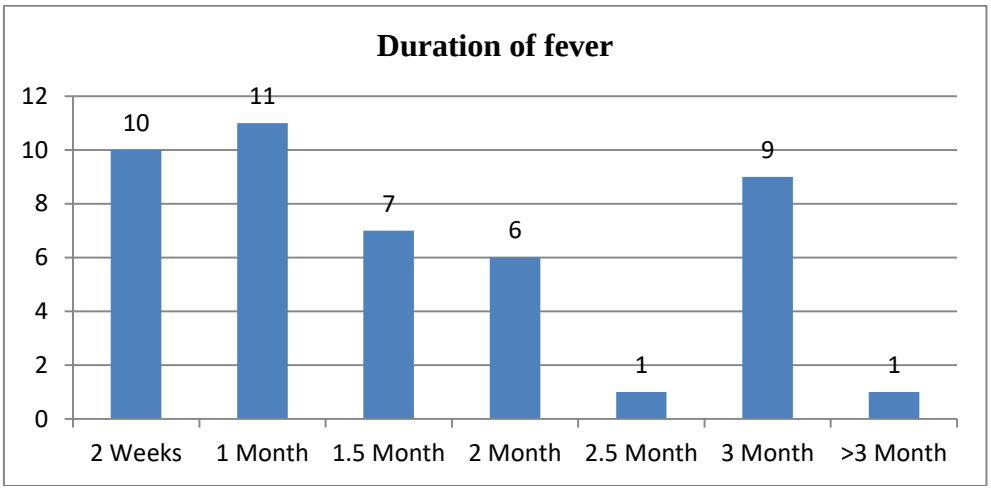

Fig-1: Duration of Fever among the study participants

Potentially diagnostic clues (PDCs)[4] defined as all localizing signs, symptoms, and abnormalities potentially pointing towards a possible diagnosis, were present in most of cases in our study. Headache was present in 20% of cases but it was a misleading PDC. Cough was present in 31% of cases and it was a true PDC in 9% of patients. Abdominal pain was present in 36% of cases, and it was a true PDC in 21% of patients. Other PDC's like constitutional symptoms, night sweats, burning micturition, vomiting, loose stools, chest pain and rash were mostly misleading. Splenomegaly was present in 31% of cases and it was true PDC in 20% of patients. Lymphadenopathy was present in 20% of the cases. This was a true PDC in 11% of the cases (Figure 2).

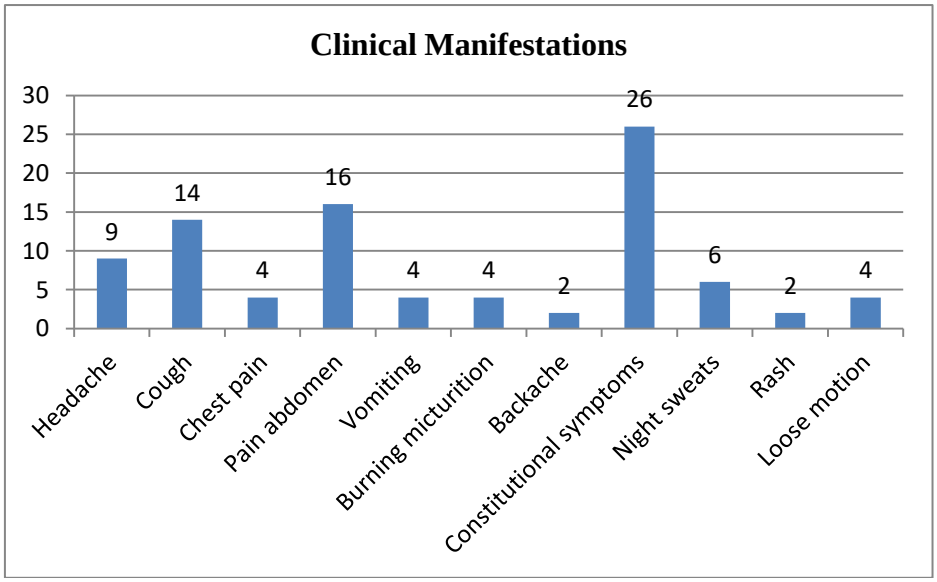

Fig-2: Clinical Manifestations among the study participants

Anaemia was present in 73% of cases while TLC was normal in 70% of cases. Neutrophilia was present in 38%, lymphocytosis in 4.4%, monocytosis in 2.2% and Pancytopenia in 4.4% of cases. ESR was high in 82% of cases. Serology was done in 60.4% of cases. It was helpful in making the diagnosis in 19.9% of cases. This included 3 cases of brucellosis, 3 cases of tuberculosis, one cases of amoebiasis, one case of SLE and one case of multiple myeloma. Montoux was done in 22.2% of cases and it helped in making the diagnosis in 6.6% of cases. Culture was sent in all the patients. Expect for one case all the cultures were negative. Out of four pus culture only one was positive for organism. Bone marrow aspiration was done in 31% of the cases. It was helpful in diagnosing only two cases of leishmaniosis and one case of multiple myeloma. Lymph node biopsy was done in 8.8% of the patients but the findings were non-contributory.

Table-2: Results of various biochemical and pathological investigation among the study participants

Investigations	Results	Number (%)	Diagnosis
Hb	Normal	12(27%)	Enteric, No diagnosis, Chloroquine responsive fever, Tuberculosis
	Low	33(73%)	Tuberculosis, Enteric
TLC	Normal	31(70%)	Tuberculosis, Enteric, Brucellosis
	High	7(15%)	Tuberculosis, SLE, PAN
	Low	7(15%)	Enteric, Lieshmaniasis
DLC	Normal	23(51%)	Tuberculosis, Enteric, No diagnosis, Trial
	Neutrophilia	17(38%)	Tuberculosis, Enteric, SLE, Multiple myloma
	Lymphocytosis	2(4.4%)	Tuberculosis
	Monocytosis	1(2.2%)	Brucellosis
	Pancytopenia	2(4.4%)	Lieshmaniasis
ESR	0-20	8(18%)	Enteric, Chloroquine responsive fever, Brucellosis
	21-100	29(64%)	Enteric, Tuberculosis
	>100	8(18%)	Tuberculosis
Mountoux & Serological Tests	Montoux	10(22.2%)	Tuberculosis
	Igm Scrub	9(20%)	None
	Ana	8(17.7%)	SLE
	Brucella Serology	8(17.7%)	Brucella
	Widal	6(13.3%)	Enteric
	Rh Factor	4(8.8%)	None
	Amoebic Serology	3(6.6%)	Amoebiasis
	Hep-B/C	4(8.8%)	None
	Hb- Elect	2(4.4%)	Multiple myeloma
	Ada	6(13%)	Tuberculosis
Culture, Biopsy & Bone Marrow	Culture	45(100%)	UTI
	Biopsy	4(8.8%)	None
	Bone marrow	14(31%)	Lieshmaniasis, Multiple myeloma

CXR was done in all the patients. Opacity was present in 9% of cases, pleural effusion in 7%, hilar prominence and cardiomegaly in 4% each, fibrosis and infiltration in 2% each. Most of these patients were diagnosed with tuberculosis, except the cases having opacity in chest x-ray. They were subjected for CT-chest for further diagnosis. USG findings were present in 46.3% of the cases which included splenomegaly in 15.5% of cases, hepatomegaly in 8.8%, hepatic-splenomegaly in 6.6%, and lymphadenopathy in 6.6% and abscesses in 4.4%. While abdominal ultrasound was almost diagnostic in abscesses, the findings like matted lymph nodes and gut wall thickening were very helpful in diagnosing abdominal tuberculosis. CT-scan findings were present in 61% which also included findings like lymphadenopathy in 19.2% cases which included necrotic lymph nodes (8.8%), alveolar infiltrates and consolidation in 11%, gut wall thickening in 8.8%, splenic abscess in two cases and caries spine in one patient. The diagnosis of caries spine and splenic abscess was also based on CT-scan findings. MRI was done in two cases which were diagnosed as neurobrucellosis (Table 3).

Table-3: Results of Various Radiological investigations among the study participants

Investigations	Results	Number (%)	Diagnosis
Radiological Investigations	CXR	45(100%)	Tuberculosis
	USG	33(73%)	Enteric, Tuberculosis, Abscess, Lishmaniasis
	CT-scan	22(49%)	Tuberculosis
	MRI	2(4.4%)	Neurobrucellosis
	2-D Echo	2(4.4%)	Pericardial effusion
CXR Findings	Pleural effusion	3(7%)	Tuberculosis, SLE
	Cardiomegaly	2(4%)	Tuberculosis
	Infilteration	1(2%)	Tuberculosis
	Hilar prominence	2(4%)	Tuberculosis
	Fibrosis	1(2%)	Tuberculosis
	Opacity	4(9%)	No diagnosis
Ultrasonographic Findings	Splenomegaly	7(15.5%)	Enteric, Tuberculosis, Abscess
	Hepatomegaly	4(8.8%)	Tuberculosis, Brucellosis
	Hepatosplenomegaly	3(6.6%)	Tuberculosis, Lishmaniasis
	Lymphadenopathy	3 (6.6%)	Tuberculosis
	(a)Matted lymph nodes	1(2%)	Tuberculosis
	Abscess	2 (4.4%)	Liver abscess, perinephric abscess
	Gut wall thickening	2 (4.4%)	Tuberculosis
CT-Abdomen, CT-Chest & CT-Spine	Lymphadenopathy	9 (19.2%)	Tuberculosis
	(a) Necrotic lymph nodes	4 (8.8%)	Tuberculosis
	(b) Matted lymph nodes	1 (2.2%)	Tuberculosis
	Alveolar infiltrates/ consolidation	5 (11%)	Pulmonary tuberculosis, SLE
	Gut wall thickening	4 (8.8%)	Tuberculosis
	Splenomegaly	3 (6.6%)	Tuberculosis
	Hepatomegaly	2 (4.4%)	Tuberculosis
	Hepatosplenomegaly	2 (4.4%)	Splenic abscess
	Abscess	2 (4.4%)	Splenic abscess
	Caries spine	1 (2.2%)	Tuberculosis

In the present study, infections represent the most important cause of FUO accounting for the 80% of the cases. Tuberculosis was the cause of FUO in 29% of the cases in our study. Pulmonary tuberculosis constituted 4.4%, extra pulmonary tuberculosis 15.4% while 8.8 % had started empirical ATT. Enteric fever was the cause of FUO in 17.6%, Chloroquine responsive fever in 4.4% and intra-abdominal abscess in 8.8% of cases. Although our state is non endemic for visceral leishmaniosis we reported 4.4% cases of this disease. We reported 6.6% cases of brucellosis. UTI was the cause of FUO in only one case. NIID and neoplasms were responsible for only 4.4% and 2.2% of cases FUO.

Table-4: Cause of FUO in all 45 Patients

Diagnostic Category	Number of cases (%)	Etiological diagnosis
Infections	36 (80%)	Pulmonary Tuberculosis 2 (4.4%), Extra-pulmonary Tuberculosis 7 (15.4%) Empirical ATT 4 (8.8%) Enteric 8 (17.6%) Abscess 4 (8.8%) Chloroquine responsive fever 2 (4.4%) Lieshmaniasis 2 (4.4%) Brucellosis 3 (6.6%) UTI 1 (2.2%) Therapeutic Trial 3 (6.6%) (Inj. Meropenem, Inj. Metrogyl, Tab Azithromycin)
NIID	2 (4.4%)	
Malignancy	1 (2.2%)	
Undiagnosed	6 (13.2%)	

DISCUSSION

Fever is one of the most perplexing clinical signs. It may occur in such diverse conditions as infections, malignancy and drug effect and due to environmental toxicity. Even after intensive search, the etiology of a sizable proportion of fevers remains unclear.

It was a cross sectional study of one year duration from 1st June 2013 to 31st May 2014 and was performed in the Department of Medicine in I.G.M.C. Shimla .Mean age of the patients was 33 years. The young age group consisted of maximum number of patients i.e. 34 (76%). Lower mean age of patients may be explained by fact that India like other developing countries, mainly consist of young population and our findings are similar to the studies of Kejriwal *et al.* [5] and Handa *et al*. [6].

In the present study Male to female ratio was 2:1. Male predominance was also reported by Jung *et al*. [7] with 64.4% male patients. In the country like India, there is male dominant society having more ready access to health care facilities and this fact explains the male predominance.

Seventy one percent patients were from rural background. Himachal Pradesh is an agricultural state and according to the census-2011, 89.97% of population of Himachal Pradesh lives in villages, so we had proportional number of patients from rural background.

The interval between the onset of fever and hospitalization varied from 3 weeks to 3 months. With duration of fever of 3 weeks, enteric fever was the most common diagnosis and with increasing duration of fever tuberculosis, leishmaniosis and neurobrucellosis were the common diagnosis. Our observation was similar to most of the studies reported in literature e.g. Knockaert *et al*. [8] and Tabak *et al.* [9] reported mean duration of fever to be 42 day and 45 days respectively.

Length of hospital stay ranged from 10 days to 4 weeks. The commonest etiology with 10 days duration of hospitalization was enteric fever and pulmonary tuberculosis. With increasing duration of hospital stay malignancy, brucellosis and SLE were common etiologies. Knockaert *et al.* [8] and Vanderschueren *et al*.[10] reported the mean duration of hospitalization of 25± 15 days and 16 days respectively. Bandyopadhayay *et al*.[11] from India reported mean duration of hospitalization of 14.47 days. The lower mean duration of hospitalization in our study was explained by the observation that infections was the most common cause of FUO in our study while malignancy and NIID constitutes a significant proportion of cases of FUO in western studies[8-10]. Over a period of years the cost of hospitalization has decreased at government level and now we have more sophisticated technology e.g. CT-scan, MRI, PET-scan etc. at our disposal to investigate the patients. So more number of patients is being diagnosed earlier.

Potentially diagnostic clues (PDCs), were present in most of cases in our study. As described in the study of De Klejn *et al*,[5] PDCs led to the diagnosis in 62% of cases. Wanvarie *et al*.[12] showed that chances of reaching the diagnosis were low when PDC's were absent.

In our study though infection was the cause of FUO in 80% of the cases but the laboratory investigations e.g. anaemia, leukocytosis and neutrophilia were not associated with any particular infection as seen in many studies except for pancytopenia which was associated with lieshmaniasis. Baicus *et al*.[13] reported that anaemia, abnormal white cell count, high ALT and bilirubin are associated with severe outcome. Barrot O [14] showed in their study that monocytosis in peripheral blood was associated with tuberculosis, brucellosis, IBD and solid tumor e.g. Hodgkin's disease.

Serology was helpful in making the diagnosis in 19.9% of cases similar to the study by Kejriwal *et al*.[5] in which serological studies diagnose 17.4% of the cases. Montoux helped in making the diagnosis in 6.6% of cases. We observed that cultures were not useful in reaching the diagnosis. Expect for one case all the cultures were negative. Larson and Featherstone [15] also observed that cultures were diagnostic in only 5% of the cases. We also observed that bone marrow examination had low diagnostic yield. Riley *et al*.[16] and Rothman *et al*.[17] observed that diagnostic yield of bone marrow examination was between 0 to 2%. Lymph node biopsy was done in 8.8% of the patients but the findings were non-contributory. Bleeker Rover *et al.*[18] utilized lymph node biopsy as a diagnostic method in 14.6% of cases and it was positive in 44% of cases.

Imaging techniques were found to be very useful in our study. CXR was done in all the patients. Most of these patients were diagnosed with tuberculosis, except the cases having opacity in chest x-ray. They were subjected for CT-chest for further diagnosis. USG findings were present in 46.3% of the cases while CT-scan findings were present in 61% .Thus we can say that CT-scan is single most important diagnostic tool in the workup of FUO. MRI was done in two cases which were diagnosed as neurobrucellosis. Bleeker Rover *et al*.[18] studied the sensitivity of imaging techniques in diagnostic workup of FUO. They found that chest X-ray had 60% sensitivity, abdominal USG had 86% sensitivity, abdominal CT had 92% sensitivity and chest CT had 82% sensitivity.

In the literature, the causes of classic FUO have been divided into infections, neoplasms, NIID and

miscellaneous causes. Upon analysis we found that infections represent the most important cause of FUO in our study accounting for the 80% of the cases. This is in accordance with most of the earlier series on FUO expect for some studies done in western countries where either neoplasms or NIID represent the most important cause of FUO.

In western studies, Petersdorf *et al*.[1] reported infections in 39.6% of cases, neoplasms in 20.9%, NIID in 18.7% , miscellaneous causes in 20.9% while 9% of cases remained undiagnosed. So in western studies, neoplasms and NIID are important cause of FUO besides infections and over a period of time proportion of undiagnosed cases have increased. Among Asian studies, Liu *et al*. [19] reported infections in 42.3%, neoplasm in 6.4%, NIID in 20.5% and miscellaneous cause in 7.7% while 23.1% of cases remained undiagnosed. So in Asian studies infections were the cause of FUO in up to 50% of cases. Among Indian studies, Kejriwal *et al*.[5] reported infection in 53%, neoplasms in 17% , NIID in 11% , miscellaneous cause in 5% of cases while 14% of cases remained undiagnosed. When we analyze Indian studies it becomes clear that infections are the most important etiology of FUO and initial investigations should always include tests for ruling out or confirming the diagnosis of infectious diseases.

Tuberculosis was the cause of FUO in 29% of the cases in our study. Pulmonary tuberculosis constituted 4% while extra pulmonary tuberculosis 15.4% of cases. When we analyze western studies, we observed that tuberculosis as a cause of FUO has decreased in frequency in west like Vanderschueren *et al*.[10] reported 4.1% while De Kleijn *et al*.[4] reported only 1.7%. Tuberculosis remains an important cause of FUO in India. Handa *et al*.[6] reported 43.8% cases of tuberculosis, among these 21% cases were extra pulmonary, Bandyopadhyay *et al.* [11] Kejriwal *et al*. [5]and Jung *et al*.[7] reported 28%, 24% and 11.1% cases of tuberculosis respectively. For the diagnosis of tuberculosis, we depended on sputum examination, montoux test, chest X-ray and ADA levels. Also in some cases, a therapeutic trial with anti- tubercular drugs was used.

Enteric fever was the cause of FUO in 17.6% of the cases. Our finding of combination of proportionately high number of enteric fever cases and young age group was comparable to the findings of study by Jung *et al*.[7] which reported 29.6% of enteric fever cases.

Chloroquine responsive fever qualified as the cause of FUO in 4.4% of cases. This can be explained by the fact that peripheral smears were consistently negative for malaria parasite in our study. So we had to depend on clinical findings and response to therapy to reach the diagnosis. Bandhyopadhyay *et al*.[11] reported 6% of patients of malaria after initial clinical examination out of which 50% cases were confirmed after laboratory investigations.

We reported intra-abdominal abscess as a cause of FUO in 8.8% of cases. De Kleijn, *et al*.[4] and Knockaert *et al*.[8] reported 3.5%, and 4% cases of abscesses respectively. So abscess still continue to be an important cause of FUO and there is important role of CT-scan abdomen in FUO.

Visceral lieshmaniasis is an important cause of FUO in Indian subcontinent. Although our state is non endemic for visceral lieshmaniasis we reported 4.4% cases of this disease. Visceral lieshmaniasis constituted 5% of cases of FUO in Kejriwal *et al*.[5] study. Visceral liesmaniasis was particularly associated with pancytopenia and massive splenomegaly.

We reported 6.6% cases of brucellosis. Handa *et al*.[6] reported 3.3% cases of brucellosis. In our cases, history of contact with animals was present, and it was an important clue in reaching the diagnosis.

UTI was the cause of FUO in only one case in our study. Bandyopadhayay *et al*.[11] reported 3.6% and Kejriwal *et al*.[5] reported 4% cases of UTI. Thus our observation was similar to the above mentioned studies.

NIID and neoplasms were responsible for only 4.5% and 2.2% of cases FUO in our study. In the western studies, Petersdof *et al*.[1] reported 18.7% cases of NIID and 20.9% of neoplasm, respectively. Among Asian studies, Likuni *et al*.[20] reported 34.8% cases of NIID and 16.3% of neoplasms. Among Indian studies, Kejriwal *et al.* [5] reported 11% and 8%, Handa *et al*. [6] reported 15.7% and 8.3% cases of NIID and neoplasms respectively.

Low percentage of neoplasms and NIID can be explained by fact that our study had relatively younger age group of patients and high number of patients from rural background where infections are the most important cause of fever

After a mean duration of stay in hospital for 14.4 days, we were able to reach the diagnosis in 86.8% of the cases Kejriwal *et al*.[5] was able to reach the diagnosis in 86% of cases, Bandhyopadhyay *et al*.[11] in 87.9% cases and Handa *et al*. [6] in 77% of cases. However this was in contrast to the western studies where up to 50% of the cases remained undiagnosed. Knockaert *et al*.[8] & Barbado *et al*.[21] reported 25.6% & 21.8% of undiagnosed cases. The reason for high proportion of undiagnosed cases in their studies was more stringent criteria of FUO and referral by specialists.

CONCLUSION

Infections are the most important cause of fever of unknown origin in the developing countries like India and tuberculosis is the leading cause. This holds true for our state also. Thus the initial investigations should always include tests for ruling out or confirming diagnosis of infectious disease particularly tuberculosis. Signs and symptoms can guide us to the final diagnosis in majority of the cases.
Keywords: Fever of unknown origin (FUO), Infectious diseases, Tuberculosis,

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