British Journal of Medicine & Medical Research
7(10): 839-846, 2015, Article no.BJMMR.2015.396
ISSN: 2231-0614

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Fever of Unknown Origin (FUO) in HIV Infection in the Era of Antiretroviral Treatment (ART) in India: Development of a Simple Diagnostic Algorithm

S. Anuradha[1], Sandeep Ghosh[1], Richa Dewan[1], Ravinder Kaur[2] and K. Rajeshwari[3*]

[1]Departments of Medicine, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India.
[2]Departments of Microbiology, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India.
[3]Departments of Pediatrics, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author SA designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SG, SA and KR managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/16868
Editor(s):
(1) Roberto Manfredi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
Reviewers:
(1) Mbirimtengerenji D. Noel, University of Malawi, Malawi.
(2) Anonymous, Rwanda.
(3) Alexander Sabre,Universidad Autonoma de Guadalajara, Mexico.
(4) Anonymous, Ghana.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=950&id=12&aid=8672

Original Research Article

Received 16th February 2015
Accepted 17th March 2015
Published 3rd April 2015

ABSTRACT

Objective: Fever of unknown origin (FUO) is a challenging problem among people living with HIV (PLHIV). With increasing access to Anti-retroviral treatment (ART), the spectrum of causes of FUO has evolved in the developed world. This study evaluated the etiology of FUO among PLHIV in the era of ART in India.
Methodology: This prospective study was conducted at a tertiary-care institution in New Delhi, India. Sixty four PLHIV with a diagnosis of FUO were assessed by detailed clinical evaluation and immunological assessment. Specific investigations to identify the etiology of fever: microbiological and radiological investigations, bone marrow and histopathological examination of biopsies were performed. A simple diagnostic algorithm for FUO was developed based on the findings.

**Corresponding author: Email: rajeshwari.dr@gmail.com;*

Results: Sixty five episodes of FUO were studied. Seventy percent of subjects were men, 76% were <40 years of age, and 39% were receiving ART. The mean CD4 count was 156.57±178.43 cells/mm^3 (5 to 1144 cells /mm^3) and 23% patients had CD4 counts <50 cells/mm^3. The mean duration of fever was 11.26±8.54 weeks. Infections were the most common cause for FUO, with Tuberculosis the most common (61.54%), particularly disseminated tuberculosis (41.54%). Cryptococcal meningitis (7.69%), bacterial pneumonia (4.62%), pyogenic abscesses (4.62%), *Pneumocystis jirovecii* pneumonia (PCP) (3.08%), visceral leishmaniasis (3.08%) were other infections observed. Non-infectious etiologies including lymphoma (4.62%) and progressive multifocal leucoencephalopathy (PMLE) (3.08%) were also seen. The etiology remained undiagnosed in 6.15% episodes. Importantly, two or more concurrent etiologies of fever were seen in 60% of patients.

Conclusion: Infections especially Tuberculosis remain the most common cause of FUO in PLHIV even in the era of ART in developing countries like India. Multiple concurrent infections and a rising trend to non-infectious causes are being observed. A simple diagnostic algorithm will help diagnose majority of FUO even at the peripheral centers.

Keywords: Fever of unknown origin; FUO; pyrexia of unknown origin; HIV.

1. INTRODUCTION

Prolonged fever is a common clinical presentation among PLHIV worldwide. The prevalence of FUO among PLHIV has been reported to be between 7.3 to 12% in developed countries [1,2]. India has the third highest number of PLHIV in the world and the adult prevalence of HIV infection in India is 0.27% [3]. According to the UNAIDS 2014 fact sheet, 51% of AIDS-related deaths in the Asia Pacific region are from India [4]. FUO in PLHIV has variable etiology depending upon the clinical profile, geography and pattern of endemicity of other diseases in the general population. Globally, studies have shown that among causes of FUO, infectious diseases greatly outweigh the non-infectious causes and *Mycobacterium tuberculosis* is the single most common cause of FUO in PLHIV [5-7]. In America and Europe, studies show that atypical *Mycobacterial* infection with *Mycobacterium avium* intracellulare (MAI) /disseminated *Mycobacterium* avium complex (DMAC) is commonest [5-7]. Though no data on the prevalence of FUO in HIV in India is available, fever is a common manifestation among PLHIV in India.

With the widespread and early initiation of Antiretroviral treatment (ART) and prophylaxis against opportunistic infections (OI), the prevalence of many infectious etiologies of prolonged fever in PLHIV like PCP, bacterial pneumonia, cytomegalovirus virus (CMV) infection, leishmaniasis, and MAC has decreased, especially in the developed countries [3,7]. Non-infectious diseases have emerged as leading causes of FUO in these settings where ART initiation is early and coverage is universal. Apart from malignancies, the phenomenon of immune reconstitution has emerged as an important cause of fever with a reported incidence of immune reconstitution inflammatory syndrome (IRIS) ranging from 7 to 30% [8-10]. Other multisystem diseases including rheumatic diseases, connective tissue disorders, non-infectious pulmonary disease may also contribute to FUO in the aging PLHIV. Also, in most studies, a variable proportion of patients have remained undiagnosed despite all possible efforts to reach the diagnosis.

The key to the diagnosis of FUO is an extensive array of laboratory and radiological investigations. In developed countries, the availability and access to these investigations, makes the work- up of FUO among PLHIV easier. In resource-limited settings, the access to investigations is restricted and the expenses involved are prohibitive. The diagnosis of FUO in PLHIV can be challenging under these circumstances. Hence a simple diagnostic algorithm consisting of easily available investigations will be really helpful in the initial work up of these patients reducing the need for referrals to tertiary centers.

The present study was done to evaluate the causes of FUO among PLHIV presenting to a tertiary care hospital in India. ART is now available freely under the National Programme to all PLHIV since 2004 and OI prophylaxis is routinely prescribed. Whether this universal availability of ART and/or OI prophylaxis has changed the pattern or etiology of FUO among PLHIV in India was studied. Finally, the

construction of a simple diagnostic algorithm for FUO that is applicable at a peripheral center was attempted.

2. METHODS

This prospective exploratory study was conducted in HIV infected subjects (age>18 years) presenting to a large, tertiary-care, public-health facility, in New Delhi, India from November 2010 to April 2012. The study was approved by the Institutional Ethics Committee and subjects were consecutively included in the study after obtaining informed consent.

HIV infected subjects who were diagnosed to have FUO as per the modified diagnostic criteria of Durack and Street [11] with:

1. Temperature of > 38.3°C (101 F) on at least 2 occasions;
2. Of more than 4 weeks durations as outpatient or;
3. More than 3 days duration as in-patient, including at least 2 days of incubation of microbial cultures and
4. Diagnosis remained uncertain after 3 days despite appropriate investigations were consecutively enrolled in the study.

All subjects underwent clinical evaluation including a detailed history, general physical and systemic examination. Anthropometric assessment including weight, height and body mass index (BMI) was done. Nutritional assessment was done by dietary assessment and biochemical assessment including haemoglobin and serum albumin levels. The WHO clinical staging was performed and CD4 counts were assessed in all the patients. ART related history: duration, regimen, was evaluated in all the study subjects on ART.

A step by step approach to determine the etiology of FUO in these patients was done as outlined below:

Step 1: Initial investigations: complete blood counts with peripheral blood smear examination, Thick and thin blood smears and rapid diagnostic tests for malaria, urine analysis and stool examination, Widal test, blood and urine cultures, liver and kidney function tests, a chest X-ray (even if done earlier), Ultrasonography (USG) of the abdomen and pelvis.

Step 2: Sputum examination for atypical organisms, Computerised tomography (CT) scan and /or magnetic resonance imaging (MRI) of head / chest / abdomen/pelvis (as clinically indicated), cerebrospinal fluid analysis, fine needle aspiration cytology.

Step 3: Bone marrow aspiration / biopsy, liver and other tissue biopsies, and specific serological testing (as appropriate).

Repeated physical examination, sequential radiological and laboratory investigations (complete blood count, peripheral smear for malarial parasite, blood and urine cultures, liver function tests including alkaline phosphatase, serological tests as relevant) were repeated as indicated to arrive at the etiological diagnosis. The descriptive data is presented as mean with standard deviation for continuous variables and as proportions for categorical variables.

3. RESULTS

Sixty four PLHIV with FUO were studied, of which 39% were receiving ART and 61% were ART naïve. Seventy percent were men, 76% were below 40 years of age and heterosexual transmission of HIV was seen in 85%. Sixty five episodes of FUO were assessed in these patients. Respiratory, gastrointestinal and nervous system involvement was seen in 18%, 26% and 46% patients respectively. All patients had at least one other associated symptom along with fever. Altered sensorium (41%), cough (37%), recurrent diarrhea (34%), weight loss (34%) and headache (32%) were the most common symptoms seen. Pallor was the most common physical finding present in 74% of patients. Neck rigidity (37%), crackles on chest auscultation (22%), hepatomegaly (20%) and splenomegaly (18%) were also seen. In 14% of subjects, the physical examination was entirely unremarkable, without any clues to the underlying cause. The demographic and physical characteristics of the study subjects are summarized in Table 1.

At presentation with FUO, six (9.38%) patients were in WHO stage III while 58 (90.62%) patients were in WHO stage IV. Among the PLHIVs who were on-ART, 60% presented with FUO within one year of ART initiation. The mean CD4 count of the subjects was 156.57±178.43 cells/mm^3 (range 5 to 1144 cells/mm^3) and the median CD4 count was 117 (IQR 52-206). Among the subjects, 71.43% had CD4 counts<200 cells/mm^3 with 23.21% patients having very low CD4 counts <50 cells/mm^3.

Among the laboratory parameters, elevated Alkaline Phosphatase (ALP) levels were seen in 35/65 episodes and raised levels of liver enzymes (AST/ALT) were seen in 32/65 (53.8%) of subjects. Further, 23% of patients had bicytopenia / pancytopenia on haematological assessment.

The chest X-ray was normal in 44.66% patients. The common abnormalities on Chest X-ray were consolidation / patchy opacities /haze seen in 21.55% patients. In 5 instances, repeated X-rays were useful in diagnosing miliary tuberculosis (3/5) and *Pneumocystis carinii* pneumonia (2/5). On Ultrasonography of the abdomen and pelvis, hepatomegaly (47.92%), splenomegaly (39.58%) and intra-abdominal lymphadenopathy (39.58%) were common findings. Advanced radiological investigations like CT scan (head / chest / abdomen) and MRI brain were done in 34 and 9 patients respectively and revealed mediastinal lymphadenopathy in 67.5%, intra-abdominal lymphadenopathy in 60%, lung consolidation in 50%, brain infarcts in 42.86%, hydrocephalus in 38.09%, and meningeal enhancement in 33.33% patients.

CSF samples were analysed in 30 patients and in only 3/30 the assessment was non contributory. Bone marrow examination was performed in 11 patients. Plasmacytosis was a frequent finding (13.33%). The bone marrow examination was diagnostic of lymphoma, visceral leishmaniasis and tuberculosis.

The etiology of FUO in the subjects is summarised in Table 2. A single-agent diagnosis was seen in 40% (26/65) subjects only. Two concurrent etiologies were seen in 36.92% and three concurrent diagnoses in 16.92% of patients: common causes are summarised in Table 3.

Table 1. Characteristics of the PLHIV with FUO (N= 64)

Characteristic	Result
Mean Age in years (range)	35.92±10.54 (19 to 65)
Sex (N = Male: Female: Transgender)	45:16:3
Mean CD4 count cells / mm^3 (range)	156.57±178.43 (5 to 1144)
% subjects with CD4 < 100 cells / mm^3	41.3%
Subjects On ART (%)	37.5% (24 / 64)
Mean Duration of fever (weeks)	11.26±8.54
% subjects with fever duration > 3 months	30.77%
Mean BMI (kg / m^2)	18.74±2.95
Subjects with BMI < 18.5 kg /m^2 (%)	43.75%
Subjects with BMI < 16 kg / m^2 (%)	21.88%

Table 2. Diagnosis of FUO in the study subjects

Diagnosis	Percentage
Tuberculosis (TB)	61.54%
A)Disseminated	41.54%
B)Pulmonary	33.85%
C)Abdominal	36.92%
D)Intracranial (TBM+Tuberculoma)	36.92%
E)Lymph node TB	9.23%
F)Tubercular pleural effusion	4.62%
G)Miliary (lung/ liver/spleen)	10.77%
Cryptococcal meningitis	7.69%
IRIS	7.69%
Lymphoma (NHL)	4.62%
Bacterial Pneumonia	4.62%
Pyogenic Abscess	4.62%
Pneumocystis jirovecii pneumonia (PCP)	3.08%
Visceral leishmaniasis	3.08%
Progressive Multifocal Leucoencephalopathy (PMLE)	3.08%
Megaloblastic anemia	3.08%
Secondary Syphilis	1.54%
CNS Toxoplasmosis	1.54%

Diagnosis	Percentage
CMV Esophagitis	1.54%
Cerebral malaria	1.54%
Viral encephalitis	1.54%
Spontaneous bacterial peritonitis	1.54%
Myelopathy (HIV induced/ Herpes zoster associated/paraneoplastic)	1.54%

Table 3. Common multiple etiologies of FUO in PLHIV

Diagnoses	Number of subjects
Mycobacterium spp. and *Cryptococcus neoformans*	4
Mycobacterium spp and bacterial pneumonia	2
Mycobacterium spp and pyogenic abscess	1
Mycobacterium spp and *Cytomegalovirus*(esophagitis)	1
Mycobacterium spp and viral encephalitis	1
Mycobacterium spp and syphilis	1
Mycobacterium spp and cerebral malaria	1

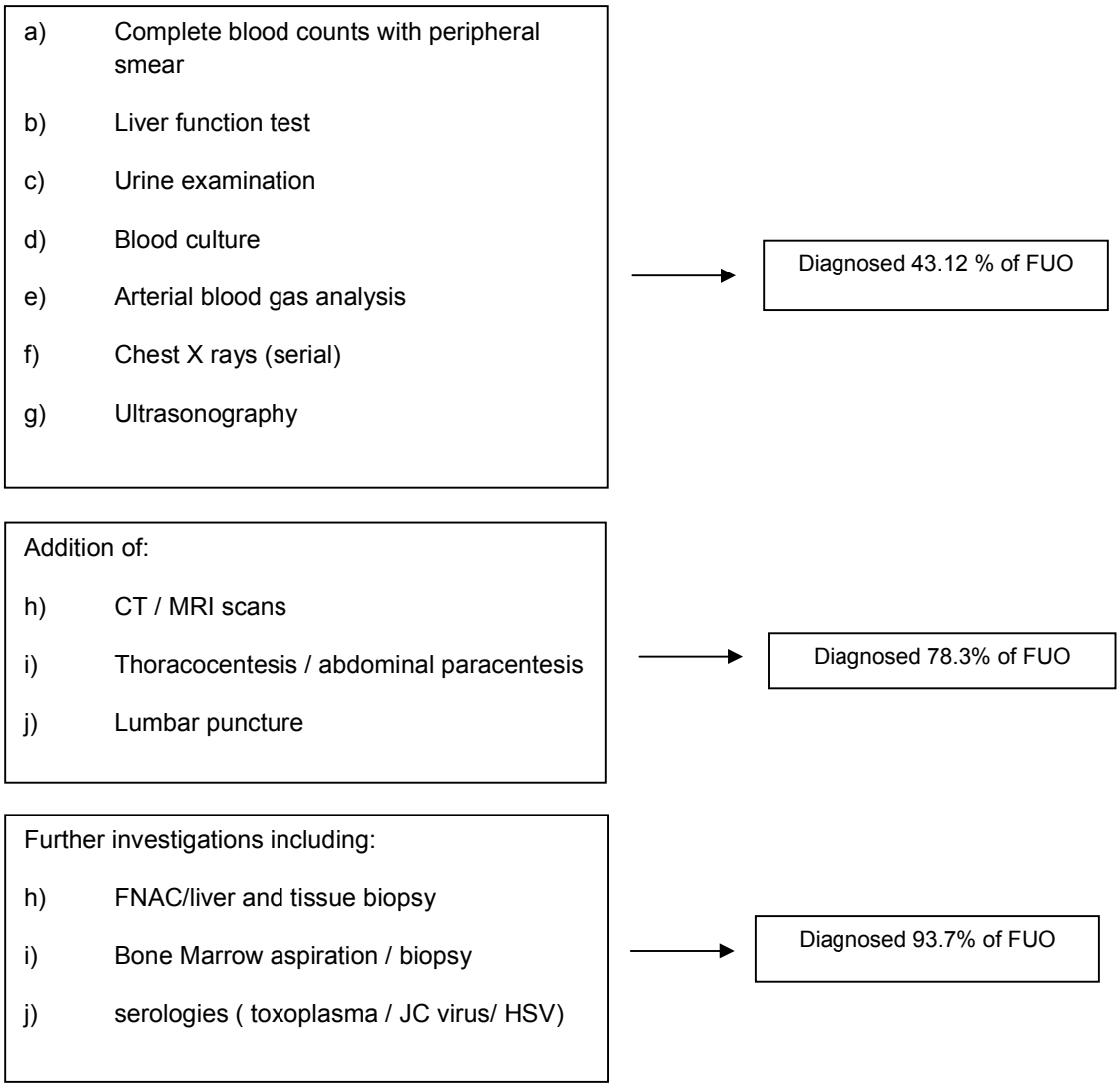
A correlation between CD4 count and common etiologies of FUO revealed that tuberculosis including disseminated/military tuberculosis was present in patients with mean CD4 150 cells/mm^3 (145.43±109.17). Cryptococcal meningitis was present in those who had a very low CD4 count of 50 cells/mm^3 (54.2±43.76). PCP and lymphoma were also seen at CD4 counts <100 cells/mm^3.

Outcome of fever in the patients was good and 73.44% of them showed improvement and resolution of fever after appropriate treatment at the time of discharge and on follow up visits to the ART center. Eleven deaths occurred and death among those who were ART naive at presentation (63.98%) was more than those who were already on ART (36.02%).

4. DISCUSSION

FUO among PLHIV in India is still primarily due to infectious causes, accounting for 92.3% of all diagnoses in the present study. Globally also infections, especially opportunistic infections, are the most important cause of fever in HIV infected subjects responsible for 82.2%-90% of FUO diagnosis in Europe and America [12-15]. Other studies from Thailand and India have also identified infectious agents to be the leading cause of FUO in PLHIV [16,17]. The predominant infectious agent(s) vary with geography and the prevalent endemic infections in different series. In the US, disseminated Mycobacterium avium *complex* (MAC) is the commonest infectious agent causing FUO in PLHIV accounting for 31% of cases in a study by Armstrong et al. [3]. Worldwide, *Mycobacterium tuberculosis* is the leading cause of FUO in HIV infected subjects [18]. In our study also, *M. tuberculosis* was the most important pathogen, accounting for >60% of cases of FUO, manifesting in varied forms- from pulmonary to disseminated and military TB. The universal access to and early initiation of ART, especially in the developed countries, has substantially reduced the incidence of opportunistic infections and FUO among HIV infected patients [3,19]. However, the etiological profile of FUO among the PLHIV who were ART naive and on- ART was similar. The timely introduction of prophylaxis against OI is also contributory. However, the spectrum of OI in these patients continues to remain more or less unchanged in the era of HAART.

Free ART through the National Programme and OI prophylaxis has been made universally available in India since April 2004. In the studies from the pre-ART era published from India on prolonged fever in HIV infected subjects, Tuberculosis, PCP and Cryptococcal infections were the leading causes [17,20]. In the present study in the ART era, TB and crytococcosis are still the most important causes of FUO. However, the incidence of PCP is lower compared to the pre ART studies and early cotrimoxazole prophylaxis may have been contributory. Multiple, concurrent pathogens were identified in more than 60% of the cases of FUO. *M. tuberculosis* was usually one of the agents among the multiple diagnoses. Similar findings have been reported by other studies from Thailand [16,21]. This is in contrast to FUO in non HIV situations where single diagnosis is the norm. This implies that PLHIV, due to severe immunosuppression, may be suffering from more than one opportunistic infection concurrently. This may result in inadequate clinical response or no response to treatment or a worsening of



clinical condition despite treating for one OI. This re-emphasises the need for detailed work up in all patients of FUO in HIV and to suspect and evaluate for multiple infectious etiologies when appropriate clinical response to treatment is not achieved. Non infectious causes and malignancies are also emerging as important causes of FUO. In the present study, 7.7% of FUO was related to non infectious etiology. In the future times of increased access to ART, the non infectious diseases especially malignancies will be important entities.

ART is available in India through more than 450 public health facilities throughout the country. Many of these ART centers are in district hospitals and secondary level centers where the diagnostic abilities are limited. Hence one of the important objectives of this study was to develop a simplified protocol for the work up of FUO even in these peripheral centers so that majority of the patients can be diagnosed at these centers itself. This will reduce the need for referrals to tertiary hospitals and expenses involved in travel and investigations. The diagnostic ability of the various tests is summarised above.

This demonstrates that with simple investigations combined with a thorough clinical evaluation keeping in mind the local disease patterns, almost 45% of FUO can be diagnosed at peripheral centers itself. Addition of advanced radiology improves the diagnostic ability. This simplified protocol may be adopted by centers to approach the diagnosis of FUO.

5. CONCLUSION

In conclusion, FUO remains an important diagnostic challenge among PLHIV. Infections are the leading cause of FUO, especially TB. Multiple etiologies may be seen in a single patient and concurrent OIs may be present in PLHIV. This possibility should be entertained when the clinical spectrum is not explained by the diagnosis and / or an inadequate response to treatment is seen. A step-wise approach is suggested for the diagnosis of FUO, moving from simpler investigations to the more invasive and expensive tests.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=950&id=12&aid=8672