FEVER OF UNKNOWN ORIGIN AT A TERITIARY CARE TEACHING HOSPITAL IN PAKISTAN

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Abstract. The aim of this study was to determine the causes of fever of unknown origin (FUO) at a tertiary care teaching hospital in Pakistan. We conducted this cross sectional descriptive study at the Department of Medicine, Civil Hospital Karachi, from January 2006 to December 2011. We reviewed the medical records of all patients aged > 12 years with a primary diagnosis of FUO. We excluded those who did not meet inclusion criteria. Two hundred five patients were analyzed, 111 (54%) were male. The mean age of patients was 38±14 years. The mean duration of fever prior to hospitalization was 37±16 days and the mean time taken to reach a final diagnosis was 19±14 days. A diagnosis was established in 171 patients. Infections, especially tuberculosis, were the most common cause of FUO, followed by connective tissue diseases and malignancies. Causes of FUO and their frequencies in the population should be known because FUO is most often caused by an unusual presentation of a common disease, but may also be caused by a rare condition. Common diseases should be suspected first when investigating FUO. Factors causing delay in diagnosis should be identified and overcome to improve outcomes.

Keywords: fever of unknown origin, infections, connective tissue diseases, malignancy, Pakistan

INTRODUCTION

Globally, and especially in developing countries, fever of unknown origin (FUO) is an important cause of morbidity and mortality (Joshi *et al*, 2008). A broad spectrum of causes for FUO demands a correct understanding of the common causes. FUO is defined as a temperature > 38.3ºC on several occasions lasting longer than 3 weeks with a diagnosis that remains uncertain after 1week of investigations in a hospital or in an outpatient setting (Petersdorf and Beeson, 1961; Petersdorf, 1992). 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 (Durack, 1991).

FUO has been divided into four subtypes: classic, nosocomial, immune deficient (neutropenic), and HIV-associated (Mourad *et al*, 2003; Blecker-Rover *et al*, 2007). The etiology includes infectious

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diseases, autoimmune conditions, neoplastic disorders and some other rare conditions (Roth and Basello, 2003). The etiology can be affected by the sociodemography of the sufferers (Tabak *et al*, 2003). Enhancements in radiography/imaging and microbiologic methods have changed the frequencies of illnesses causing FUO (Tabak *et al*, 2003). The diagnostic workup for FUO is well described (Al-Mofleh *et al*, 1990; Knockaert *et al*, 1996; AbuRahma *et al*, 1997; Baicus *et al*, 2003a,b,c; Colpan *et al*, 2007) but there is no gold standard for the work-up. The evolution of FUO begins by taking a thorough history, carefully repeating the physical examination, and obtaining relevant laboratory tests, including a complete blood count with peripheral film, routine blood chemistry, urine analysis and microscopy, blood and urine cultures, sputum for acid-fast bacilli (AFB) smear and culture, radiographic studies, serological tests, biopsies and other invasive tests when required. Information obtained may direct the physician to perform other relevant lab tests which can help provide an accurate diagnosis (Knockaert *et al*, 1996; Baicus *et al*, 2003b).

In Pakistan, the majority of people live in rural areas and more than half of rural inhabitants have restricted health care (Wasif, 2010). This causes the evaluation and diagnosis of even common illnesses to be difficult or delayed. Sufferers may not be diagnosed until they arrive at a tertiary health care center. Varying presentations of typical illnesses, deficiencies in the work-up on the part of the doctors, noncompliance on the part of the patients, not following-up or changing from doctor to doctor are reasons for a delay in diagnosis. Published information about FUO in Pakistan is limited. The main objective of this study was to determine the etiology of FUO in our population to improve the understanding of the causes of FUO among patients presenting to a tertiary care center in Pakistan.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of all patients aged >12 years, admitted to the Medical Wards of the Civil Hospital, Dow Medical College Karachi with a primary diagnosis of FUO during January 2006 to December 2011. Inclusion criteria were patients aged >12 years with a history of a temperature >38.3ºC on more than one occasion lasting longer than 3 weeks without a diagnosis after 3 days evaluation in the hospital, three outpatient visits, or one week of logical and intensive outpatient workup without finding a cause (Durack, 1991).

Two hundred five patients fulfilled the criteria for FUO. The data collected included age, gender, duration of fever before hospitalization, duration of hospitalization, time to reach diagnosis after hospitalization, investigations used to obtain diagnosis and outcome (lost to follow-up, recovery, death). Statistical analysis was performed with SPSS version 15 (SPSS, Chicago, IL). Continuous variables, such as age, duration of fever before hospitalization, duration of hospitalization, time to reach diagnosis after hospitalization, were expressed as mean ±SD. Discrete variables, such as gender, diagnostic tests and diagnosis were expressed as percentages.

RESULTS

Two hundred five patients were included in the study; 111 (54.1%) were males. The mean age of the study group was 38±14 years. The mean duration of fever before hospitalization was 37±16 days,

Table 1
Characteristics of patients (*n*=205).

Variables	No. of patients /mean±SD
Gender	
Male	111 (54%)
Female	94 (46%)
Age	38±16 years
Duration of fever prior to hospitalization	37±16 (range 32 days)
Duration of hospitalization	26±11 (range 27 days)
Time to reach diagnosis	19±14 (range 26 days)
Mortality	16 (7.8%)

Table 2
Lab tests use to establish the final diagnosis (*n*=171).

Diagnostic tests	No. of patients (%)
Culture and sensitivity	30 (17.5)
Blood	12 (7.1)
Bone marrow	7 (4.3)
Urine	3 (1.7)
Other body fluids	8 (4.7)
Biopsy	54 (32.9)
Bone marrow	14 (8.5)
Lymph node	15 (9.1)
Liver	3 (1.8)
Other organs and tissues	22 (13.4)
Radiology based diagnosis	27 (16.5)
Serology based test	31 (18.1)
Clinical course relevant test based diagnosis	29 (17.7)

the mean time taken to reach a diagnosis (after hospitalization) was 19±14 days and the mean duration of hospitalization was 26 ±11 days (Table 1).

Culture results established the diagnosis in 30 patients (17.5%), biopsy revealed the diagnosis in 54 patients (31.6%), serology revealed the diagnosis in 31 patients (18.1%) , imaging revealed the diagnosis in 27 patients (15.7%) and multiple investigations and clinical course revealed the diagnosis in 29 patients (16.9%) (Table 2).

A specific course of the fever was found in 171 patients (83.4%). Infections were found to be the cause of fever in 100 patients (48.8%), while connective tissue diseases and malignancies were the cause of fever in 26 patients (12.7%) each (Table 3).

Tuberculosis (TB) (35 patients), disseminated TB (7 patients) and extra-pul-

Table 3
Causes of fever of unknown origin (n=205).

Disease	No. of patients (%)
Infectious disease	100 (48.8)
Tuberculosis	35 (17)
Disseminated TB	7 (3.4)
Extrapulmonary TB	28 (13.7)
Abdominal TB	
Intestinal TB	5 (2.0)
Tuberculous ascites	3 (1.5)
Abdominal lymph node TB	3 (1.5)
TB meningitis	5 (2.0)
Urogenital TB	5 (2.0)
Cervical and mediastinal lymphnode TB	3 (1.5)
Musculoskeletal TB	
Pott's disease	2 (1.0)
TB arthritis	2 (1.0)
Abdominal abscess	11 (5.4)
Liver abscess	5 (2.0)
Subphrenic abscess	2 (1.0)
Splenic abscess	2 (1.0)
Pelvic abscess	2 (1.0)
Bacterial infections	28 (13.7)
Subacute bacterial endocarditis	2 (1.0)
Acute bacterial endocarditis	1 (0.5)
Urinary tract infection	1 (0.5)
Prostatitis	2 (1.0)
Cholangitis	3 (1.5)
Typhoid fever	6 (2.9)
Paratyphoid A or B	6 (2.9)
Brucellosis	2 (1.0)
Secondary syphilis	3 (1.5)
Neuro syphilis	2 (1.0)
Malaria	7 (3.4)
Faciparum malaria	5 (2.0)
Vivax malaria	2 (1.0)
Viral infections	16 (7.8)
HIV infections	7 (3.4)
Infectious mononucleosis	3 (1.5)
Cytomegalovirus infections	4 (2.0)
Herpes Simplex Virus infections	2 (1.0)
Fungal infections	3 (1.5)
Candidiasis	2 (1.0)
Histoplasmosis	1 (0.5)
Connective tissue disease	26 (12.7)
Still disease	11 (5.4)

Table 3 (Continued).

Disease	No. of patients (%)
Polymyalgia rheumatica	9 (4.4)
Systemic lupus erythematosus	3 (1.5)
Polyarteritis nodosa	2 (1.0)
Mixed connective tissue disease	1 (0.5)
Neoplasms	26 (12.7)
Hodgkin's lymphoma	5 (2.0)
Non-Hodgkin's lymphoma	4 (1.9)
Colon cancer	5 (2.0)
Stomach cancer	3 (1.5)
Acute myeloid leukemia	1 (0.5)
Acute lymphocytic leukemia	2 (1.0)
Multiple myeloma	2 (1.0)
Waldenstorm's macroglobinemia	1 (0.5)
Thyroid cancer	1 (0.5)
Osteosarcoma	1 (0.5)
Rahabdomyosarcoma	1 (0.5)
Granulomatous disease	12 (5.9)
Sarcoidosis	5 (2.0)
Wageners granulomatosis	3 (1.5)
Granulomatous hepatitis	2 (1.0)
Crohn's disease	2 (1.0)
Miscellaneous	7 (3.4)
Subacute thyroiditis	3 (1.5)
Kikuchi disease	2 (1.0)
Temporal arteritis	2 (1.0)
Lost to follow-up	10 (4.9)
Remained undiagnosed	24 (11.7)
Total	205

monary TB (28 patients) were the most frequent infections. Of the extrapulmonary TB cases, abdominal TB (11 patients) was the most common followed by tuberculous meningitis (5 patients) and urogenital tuberculosis (5 patients). Intra-abdominal abscesses (11 patients) and typhoid and paratyphoid fevers (11 patients) were other common infectious diseases.

Of the connective tissue diseases, Still's disease was the most common (11 patients) followed by polymyalgia rheumatica (9 patients). Of neoplasms, Hodgkin's and non-Hodgkin's lymphomas (9 patients) and carcinoma of the colon (5 patients) were the most common. Twenty-four patients remained undiagnosed despite an extensive work-up; 10 patients were either lost to follow-up or left against medical advice.

DISCUSSION

Comparisons of FUO patients between series is challenging because of the

large number of causes of FUO and the impact of various factors on the relative proportions of causes. Geographic factors, referral patterns, length of studies and ages of patients have been shown to have an impact on the distribution of the various diagnostic categories (Knockaert *et al*, 2003).

In this study, infections (48.8%) were the most common cause of FUO, similar to other studies worldwide (Petersdorf and Beeson, 1961; Knockaert *et al*, 1993b; De Kleijn *et al*, 1997; Kejariwal *et al*, 2001; Mert *et al*, 2003; Tabak *et al*, 2003; Colpan *et al*, 2007; Hu *et al*, 2008; Moawad *et al*, 2010). A large meta- analysis of 857 patients with FUO showed infections (47.0%) were the most common cause of FUO (Sipahi *et al*, 2007). In a study of 98 Saudi patients (Moawad *et al*, 2010) and 164 Romanian patients (Baicus *et al*, 2003a), infectious diseases were found to be the cause of FUO in 32.7% and 45.1%, respectively. Similar findings were reported by Handa *et al* (1996) and Kejariwal *et al* (2010) where infections comprised 53% and 43.8% of causes of FUO, respectively. Moawad *et al* (2010) and Hu *et al* (2008) reported infections comprised lower percentages of FUO cases than other earlier studies (Handa *et al*, 1996; AbuRahma *et al*, 1997; Kejariwal *et al*, 2001; Baicus *et al*, 2003a; Colpan *et al*, 2007) but were still the most common cause of FUO.

Infectious etiologies of FUO vary by location. Handa *et al* (1996) and Jung *et al* (1999) found infective endocarditis and enteric fever were the most common infectious causes of FUO, while our study found various forms of tuberculosis as the most common infections among patients with FUO. Other studies have also found tuberculosis as the most common infection among FUO patients (Kazanjian *et al*, 1992; Handa *et al*, 1996; Kejariwal *et al*, 2001; Colpan *et al*, 2007; Moawad *et al*, 2010). Abdominal TB was the most common extra-pulmonary form of TB found in our study followed by tuberculous meningitis, urogenital TB, TB lymphadenitis, TB arthritis and Pott's disease. Ferhadi *et al*, (1999) found peritoneal TB was the most common type of extra- pulmonary TB among FUO patients. Extra-pulmonary TB causes diagnostic problems. CT scans, MRI scans and rapid diagnostic tests on body fluids may be required to make the diagnosis.

Abdominal abscesses, typhoid fever and falciparum malaria were frequent infectious causes of FUO in our study, but other studies (Hu *et al*, 2008; Moawad *et al*, 2010) did not find these causes very frequently. The frequency of these diseases in our study may be explained by an unhealthy environment, contaminated drinking water, unhealthy food handlers and a paucity of health facilities.

Connective tissue diseases and neoplasms were other causes of FUO in this study at 12.7% each. Our findings are similar to those of Moawad *et al* (2010) who found connective tissue disease comprised 14% of FUO cases. Tabak *et al* (2003) and Kucukardali *et al* (2008) found connective tissue disease comprised 23% and 30.5% of FUO cases, respectively. In our study, adult Still's disease was the most common connective tissue disease found in younger patients and polymyalgia rheumatica was the most common in older patients, similar to other studies (Knockaert, 1993a; Hu *et al*, 2008; Moawad *et al*, 2010). Adult Still's disease has been recognized as an important cause of FUO (Mert *et al*, 2003; Kucukardali *et al*, 2008). A retrospective study (Abid and Khalid, 2009) from Pakistan found only 13 patients with Still's disease in a 10 year period. In another multicenter prospective study

at a tertiary care hospital, Still's disease was the most common non-infectious inflammatory disease causing FUO (13.6%) (Mert *et al*, 2003).

Hodgkin's lymphoma and non-Hodgkin's lymphoma were the most common neoplasms causing FUO in our study, similar to other studies (Kejariwal *et al*, 2001; Hu *et al*, 2008; Moawad *et al*, 2010). CT and MRI imaging have markedly improved the detection of tumors (Arnow and Flaherty, 1997). However, the diagnosis of hematological malignancies can still be difficult because of the absence of localizing features and the diverse nature of these diseases.

The mean duration of fever in this study prior to hospitalization was 37±16 days and the mean time taken to reach a diagnosis (after hospitalization) was 19±14 days. Some studies from the West (De Kleijn *et al*, 1997; Vanderschueren *et al*, 2003) found the duration of hospitalization to range between 17 and 27 days.

Approximately 11.7% of cases in our study remained undiagnosed, similar to other studies (Knockaert *et al*, 1993b, Kejariwal *et al*, 2001; Hu *et al*, 2008; Moawad *et al*, 2010). The mortality rate and number of undiagnosed cases of FUO in our study were higher than in the above mentioned studies.

The outcomes of FUO depend on the cause, complications and time to reach the diagnosis. Sixty percent of the rural population of Pakistan has inadequate access to quality health care (Wasif, 2010), which is a main factor in the delay in diagnosis and outcomes.

The importance of imaging in the work-up of FUO cannot be overemphasized. Rural health care systems should be equipped with conventional radiology and ultrasonography facilities and tertiary care hospitals should be equipped with a spiral CT and an MRI (Strickland, 2000). In Pakistan many public and private tertiary care hospitals do not have an MRI, leukocyte scans or important rheumatologic investigations, such as p-ANCA, c-ANCA and glycosylated ferritin. The diagnostic delay in FUO patients has multifactorial etiologies at all levels: the disease level, patient level, referring physician level and health care facility level.

The causes of FUO and their relative frequencies in a population should be known because FUO is usually caused by either an unusual presentation of a common disease or an uncommon condition. Frequent diseases, rather than rare ones, should be considered first when investigating FUO cases. Factors responsible for delay should be identified and overcome to improve the prognosis.

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