Original article

Clinical spectrum and diagnostic tools of fever of unknown origin among hospitalized patients in Razi Hospital (2006-2008), Ahvaz

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Abstract

Introduction and objective: Fever of unknown origin (FUO) is still an important problem in clinical practice and is a challenging problem worldwide. The objective was to define the clinical spectrum, categories of the diseases and diagnostic tools.

Materials and methods: This retrospective study was undertaken from 2006 to 2008. All patients fulfilling the modified criteria for FUO, hospitalized in infectious disease ward of Razi Hospital in Ahvaz, were enrolled for analysis. Extracted data of patient's medical files including variables such as final diagnosis, diagnostic tools, and ESR values were analyzed in SPSS 11.5.

Results: The etiology of FUO was infectious diseases in 48.9% of the patients, collagen-vascular diseases in 17.8%, neoplasm in 8.3% and miscellaneous diseases in 8.3%. In 16.7% of the cases, the etiology could not be found. The two leading diseases were extra pulmonary tuberculosis (29.3%) and osteomyelitis (26.9%). Culturing, biopsy and CT-scan with the frequency of 31%, 16.7%, and 19.5% respectively were the frequent diagnostic tools. ESR with more than 50mm/h was associated with higher rate of serious disease.

Conclusion: In conclusion, tuberculosis was still the most important cause of FUO in our study. Culturing, biopsy and CT-scan were appropriate diagnostic tools. ESR with high value is a clue to the existence of a serious disease.

Keywords: Fever of unknown origin, Infectious diseases, Tuberculosis

Introduction

Fever of unknown origin (FUO) is an important cause of morbidity and mortality in the world, especially in tropical and developing countries [1]. FUO is defined as the body temperature higher than 38.3°C on several occasions and lasting longer than three weeks, with the etiology remaining uncertain after one week of investigation [2]. The etiology of FUO includes primarily infectious, collagen-vascular and neoplastic diseases. The distribution of the disorders causing FUO may differ according to the geographic area and the socioeconomic

status of the country. Moreover, the developments in radiographic and microbiologic methods have changed the spectrum of diseases causing FUO [3].

Although infectious diseases are the most common sources for the FUO, but the relative rate of infectious disease as etiologic category is varied in different countries and even through a definite country [3-8]. Tuberculosis (TB) was reported by Tabak et al. [3] as the most common (24%) cause of FUO, whereas in the report of Colpan et al. [4] TB was found to be 40% of the infectious causes of FUO. Since, there was no study of FUO in the past recent years in Khuzestan, and the changing recent trend of infectious sources of FUO is not clear in this region of Iran, this study was conducted.

Materials and methods

This retrospective study was undertaken in Razi hospital affiliated to Jundishapur University of Medical Sciences, Iran. Razi Hospital is a university-based referral centre, which is located in Ahvaz (capital city of Khuzestan) where about 4.4 million people live. From 2006 to 2008, only 84 patients fulfilled the criteria of Petersdorf and Beeson, revised by Durack and Street [9], for classical FUO. In this study, the patients, admitted because of fever, were often referred to our hospital from different hospitals of the region, where their FUO was not diagnosed. Patients with a known history of neutropenia, nosocomial infections and immunosuppressive diseases (e.g., HIV positive patient) were excluded.

In all patients, with a diagnosis of classical FUO, clinical history, physical examination, and required tests according to the guidelines to approach FUO [9,10] were performed. Final diagnoses reported in this study were made by the authors upon critical revision of the data and diagnoses mentioned in medical records. The causes of FUO were classified into five groups:

infections, neoplasms, collagen vascular diseases, other causes (miscellaneous), and undiagnosed. We also compared the prevalence of each cause of FUO found in the present study and previously published data. Data of patient's medical files including variables such as final diagnosis, diagnostic tools and ESR values were analyzed in SPSS 11.5.

Results

Of total eighty-four patients, 45(53.6%) were males and 39(46.4%) were females with a mean age of 49.2±16.7 years (range 17-72). Infection was the most common cause of FUO, in 41 cases (48.9% of total FUO); neoplasm accounted for 7 cases (8.3%); collagen vascular disease was the cause of fever in 15 patients (17.8%), and miscellaneous in 7 cases (8.3%). Undiagnosed FUO were 14 (16.7%).

Among infectious cases, the most important causes of FUO were represented by extra-pulmonary tuberculosis (12 cases), pulmonary tuberculosis (2 cases), osteomyelitis (11 cases) and infective endocarditis (2 cases). Among neoplasm cases, FUO was represented by lymphoma (4 cases), multiple myeloma (2 cases) and bladder cancer (1 case). In addition, FUO was also represented by collagen vascular diseases, rheumatoid arthritis (9 cases) Still's disease (2 cases) and systemic lupus erythematus (4 cases).

Signs, symptoms, and laboratory findings of the patients are shown in table 1. Diagnostic tools used in this study are shown in table 2. Infectious diseases causing FUO are shown in table 3. The two leading infectious diseases were extra pulmonary tuberculosis (29.3%) and osteomyelitis (26.9%). Culturing, biopsy and CT-scan with the frequency of 31%, 16.7% and 19.5% respectively were the frequent diagnostic tools. ESR with more than 50mm/h was associated with higher rate of serious disease.

Table1: Signs, symptoms and laboratory findings in studied patients with FUO

Clinical/laboratory findings	No.	%
General weakness	50	59.5
Abdominal pain	23	27.4
Back pain	20	22.8
Sweating	18	21.4
Head ache	16	19.0
Arthritis	15	17.9
Splenomegaly	15	17.9
Rigor	7	8.3
Cough	6	7.1
Lymphadenitis	4	4.8
Cardiac murmur	4	4.8
ESR >20mm/h	80	95.2
Anemia	80	95.2
Abnormal urinalysis	40	47.6
Positive CRP	31	36.9
Leukocytosis	15	17.9

Anemia: hemoglobine<12g/dl or MCV< 79 cubic micrometer, Leukocytosis: leukocyte count >10000 cell/ml

Table 2: Diagnostic tools used for diagnosis the cause of FUO in studied patients

Diagnostic tool	No	%	Diagnosed disease
Tuberculin test	42	50	Tuberculosis
Sputum smear	2	2.4	Pulmonary tuberculosis
Serology test	13	15.5	Brucellosis, toxocariasis, viral diseases (CMV, EBV)
Culture (sputum, blood, bone marrow aspiration, tissue samples)	26	31	Tuberculosis, osteomyelitis, endocarditis
Echocardiography	2	2.4	Endocarditis
Thoraccolumbar X-ray	4	4.8	Spinal tuberculosis
CT Scan	16	19.5	Extra pulmonary TB
MRI	4	4.8	Spinal TB
Gallium Scan	12	14.3	Osteomyelitis, liver toxocariasis
Bronchoscopy and lavage	2	2.4	Pulmonary TB
Laparoscopy and biopsy	4	4.8	Abdominal TB
Open biopsy	4	4.8	Abdominal and pelvic TB
Percutaneous biopsy	2	2.4	TB lymphadenitis
Mediastinoscopy and biopsy	2	2.4	Mediastinal TB lymphadenitis

Table 3: Infectious causes of fever of unknown origin in the studied population

Diseases	No	%
Extra pulmonary tuberculosis	12	29.3
Osteomyelitis	11	26.8
Brucellosis	4	9.8
Typhoid fever	3	7.3
Pulmonary tuberculosis	2	4.9
Infective endocarditis	2	4.9
Abdominal abscess	2	4.9
Renal abscess	2	4.9
Infectious mononucleosis	2	4.9
Toxocariasis	1	2.4
Total	41	100

Discussion

In the present study, the most frequent causes of FUO were infections (48.9%), followed by collagen vascular diseases (17.8%) and neoplasm (8.3%). These findings are in agreement with previous studies [1-10]. These findings suggested that FUO may have similar prevalence in populations with different ethnic and geographical backgrounds. In our study, causes of FUO were usually either unusual presentation of a well-known disease, namely, a common disease with a unique symptom, fever, or more rarely, an uncommon condition. Other symptoms and/or signs either did not appear or appeared later.

Among infections associated with FUO, tuberculosis and osteomyelitis were the most common; this was the case in other studies too [1-4,8]. Extra-pulmonary TB caused special diagnostic problems. The difficulties were disseminated diseases, without the characteristic miliary pattern on chest X-ray, or without clear localized lesions, with negative sputum smears and tuberculin skin test. Imaging facilities such as CT scan, MRI as well as rapid diagnostic tests in body fluid, such as polymerase chain reaction, was helpful in making the diagnosis. Bacteriological cultures and histopathological investigations were also important in confirming the diagnosis [9,10].

Collagen vascular diseases, which include connective tissue diseases and vasculitis, were the second most important cause of FUO in our study. Fever preceded more typical manifestations and serological evidence by weeks or months. In particular, rheumatoid arthritis and Still's disease were the first line causes of this subgroup of FUO. This finding is similar to previous study in Iran, but in contrast to the data shown by other authors [11-14]. Because of substantial increase in the elderly population, as well as advances in the diagnosis and treatment of diseases common in this population, malignancy has become a common etiologic consideration in elderly patients.

In our study, we found that neoplasm were the third most important cause of FUO. As expected, some hematological malignancies (lymphoma) and tumors of the urinary tract (bladder cancer) remain difficult to diagnose and therefore remain a cause of FUO, because of lack of localizing symptoms or difficulty in obtaining appropriate biopsies. Nevertheless, the use of CT and MRI imaging has allowed tumors to be found more easily in the last decade [9,10]. Comparing with the previous studies (medical student proposals), we encountered two new findings in this study: the first; changing of the most prevalent infectious disease from brucellosis (from 28.7% to 9.8%) and typhoid fever (from 25.9% to 7.3%) to extra pulmonary TB (from 6.3% to 29.3%) and osteomyelitis (from 2.9% to 26.8%), the second; replacement neoplasm by collagen vascular diseases as the second most common disease category. We believe the reasons for these changes may be as follows: availability of new diagnostic tools such as gamma scanning, CT scan and MRI techniques, new laboratory tests, and

changing of the pattern of epidemiology of the infections in the region.

In our study, the number of undiagnosed cases was 14(16.7%) which was higher than or similar with others [12-16]. Regarding undiagnosed FUO, its prevalence has always been around 10-20% during the years since the study of Petersdorf and Beeson [16] to the most recent one of Vanderschueren *et al.* [17], despite the progress in laboratory and radiological technologies, as well as the attention and experience of researchers. Our undiagnosed cases with FUO were not followed up, but, according to existing data the outcome of undiagnosed FUO is generally good (more than 80%), so observation of the patients and waiting is probably better than ordering more screening investigations, in the hope that something abnormal will come up [1, 9,10].

There were some cases of FUO, such as salmonellosis or brucellosis which could be diagnosed earlier than three weeks and be excluded. We think these FUO have been the result of several concomitant misleading factors in the diagnostic approaches made by the physician, the clinical examination, the wrong interpretation of a laboratory test, and inadequacy in the evaluation of a symptom and/or a positive test. This means that a few cases of FUO were the result of misleading factors in the diagnostic approaches as made by the physician, who might skim over the anamnesis, not be careful in the clinical examination, and not correctly apply the diagnostic methodology, and the laboratory tests. We also cannot exclude the existence of individual genetic factors, influencing the atypical and silent course of undiagnosable illnesses.

There were some limitations in our study. The principal limits of our study were that it was a single centre, retrospective and small sample size. Further multi-centre, prospective studies, of good design, with larger population are required.

Because of the diversity of patients with FUO, prospective studies are needed that either are large enough and/or focus on certain subgroups.

Conclusion
Tuberculosis was still the most important cause of FUO in our study. Culturing, biopsy and CT-scan were appropriate diagnostic tools. ESR with high value is a clue to the existence of a serious disease.

Acknowledgment

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