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Changing pattern of infectious etiology of fever of unknown origin (FUO) in adult patients in Ahvaz, Iran

Abstract

Background: Although infectious diseases are the most common sources for the fever of unknown origin (FUO), but the spectrum of infectious diseases is changing overtime. The purpose of the study was to define the clinical spectrum and changing the pattern of FUO.

Methods: This existing data based study was undertaken from 2007 to 2011. One hundred-six patients fulfilling the modified criteria for FUO referred in a teaching hospital in Ahvaz were enrolled for analysis. The data extracted from the patient's medical files and etiologic agents caused FUO to be assessed.

Results: Infections were the most common cause of FUO in 48.4% of the patients. Among the infections, the most important causes of FUO were represented by extra-pulmonary tuberculosis 15 (31.9%), osteomyelitis 10 (21.3%) and abdominal abscesses 6 (12.8%).

Conclusion: The pattern of FUO in the region is thought to be changed to extra pulmonary TB and osteomyelitis. Tuberculosis is still the leading cause of FUO in our region.

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

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Fever of unknown origin (FUO) is said when the body temperature increases to 38.3°C (101°F) or more several times a day lasting longer than 3 weeks and failure to reach a diagnosis despite 1 week of inpatient evaluation (1, 2). FUO is an important medical problem worldwide, especially in the undeveloped countries. Infections are the most prevalent and important causes of FUO. The distribution of the infectious causes of FUO differs from one country to another according to health status and socioeconomic conditions (1-3). Recent advanced imaging techniques (e.g., computed tomography scanning, ultrasonography, magnetic resonance imaging) have enabled early detection of abscesses that were previously difficult to diagnose, therefore, the pattern and spectrum of infectious diseases as a main cause of FUO have changed due to the developments in diagnostic methods such as imaging, antigen or anti-body detection tests (3-5). The relative rate of infectious disease as etiologic category for the FUO varied in different countries and even on a specific country (1, 2, 6-15). In the past, infectious agents such as *M.tuberculosis*, *Salmonellatyphi* and *Brucella spp* were the most common bacterial agents of FUO whereas, in the recent years, perhaps due to the effectiveness of current diagnostic approach, viral infections like HIV and HCV have been the predominant infectious etiology (3, 5, 15, 16). Since, we found no study on spectrum of infectious sources of FUO and changing pattern of infections in adults in Khuzestan except our previous published study on FUO, and for having a better knowledge on this field, this study was conducted (17).

Methods

In this existing data-based study which was conducted in Ahvaz from 2007 to 2011, the medical charts of the FUO patients in Razi Hospital were studied. Razi Hospital affiliated to Jundishapur University of Medical Sciences is a University-based referral center, located in Ahvaz (capital city of Khuzestan) with 4.5 million population.

During the period of study, among the 148 patients registered as FOU, 121 patients fulfilled the criteria for classic FOU, among them only 106 patients had completed our required data. In this study, the patients were often referred to our hospital from the different hospitals of the region, in which their FOU was not diagnosed.

The patients with a known history of neutropenia, nosocomial infections and immunosuppressive diseases (e.g., HIV positive patient) were excluded. The patients were defined as FOU if the body temperature was 38.3°C (101°F) or more several times a day lasting longer than 3 weeks and remained undiagnosed despite 1 week of inpatient evaluation. In all patients, with a diagnosis of classic FOU, medical history, physical examination, and the required tests according to the guideline for approach in FOU (3, 5, 15) were performed. Final diagnoses reported in this study were made by the authors upon the critical revision of the data and the diagnosis mentioned in medical records. The causes of FOU with infectious etiology were studied. We compared the prevalence of each infectious cause of FOU found in the present study and the previously published data. The data of

the patient's medical files were analyzed in SPSS Version 16 using chi square and Fisher exact tests when appropriate. A p-value of less than 0.05 was considered significant.

Results

Out of the one hundred and six patients, 57 (53.8%) were males and 49 (46.2%) were females, the mean age was 49.9±16.1 years (range 18–76). Infection was diagnosed as the main cause of FOU in 47 cases (44.3% of total FOU); collagen vascular diseases were the cause of fever in 19 (17.9%), neoplasm accounted for 13 (12.3%), and miscellaneous in 11 (10.4%) cases. The undiagnosed FOU was 16 (15.1%). Among the infections, the most common causes of FOU were extra pulmonary tuberculosis 15 (31.9%), osteomyelitis 10 (21.3%) and abdominal abscesses 6 (12.8%). Infectious diseases causing FOU are shown in tables 1 and 2. Localized infection in bones or abdomen was the most common cause of FOU with the rate of 66% (31.47). Table 3 compares the data of our study with previous studies in Iran and other countries.

Table 1. Infectious causes of fever of unknown origin in the studied population

Diseases	Number
Extra pulmonary tuberculosis	15 (31.9)
Osteomyelitis	10 (21.3)
Brucellosis	4 (8.5)
Typhoid fever	2 (4.3)
Pulmonary tuberculosis	3 (6.4)
Infective endocarditis	3 (6.4)
Abdominal abscess	6 (12.8)
Sinusitis	1 (2.1)
Infectious mononucleosis	2 (4.3)
Toxocariasis	1 (2.1)

Table 2. Distribution of frequent localized infection according to site of infection

Infectious disease	Site of infection	Number
Extra pulmonary tuberculosis: (n=15)	Spinal	6 (12.8)
	Abdominal	3 (6.4)
	Meningitis	2 (4.3)
	Mediastinum	2 (4.3)
	Pelvic	2 (4.3)
Osteomyelitis: (n=10)	Spinal	3 (6.4)
	Femur	3 (6.4)
	Ribs	2 (4.3)
	Sternum	2 (4.3)
Abdominal abscess: (n=6)	Hepatic	3 (6.4)
	Kidney	2 (4.3)
	Spleen	1 (2.1)

Table 3. Comparison of the infectious causes of FUO in our study with other studies

Inf.diseases	Eilami et al, Iran, 2008	Mansueto,et al, Italy, 2006	Ertan et al, Turkey,2005	Salives et al, Mexico, 2005	Chin et al, Taiwan, 2003	Sipahi,et al, turkey, 2006
No. FUO	52	91	57	45	94	857
No. Inf	19 (36.5)	29 (31.8)	24 (42%)	19 (42.2)	54 (57.4)	403 (47)
EPTB	4 (21.1)	4 (13.7)	12 (50)	2 (10.5)	19 (35.2)	147 (36.5)
OSM	2 (10.5)	0	0	0	2 (3.7)	0
AbAb	4 (21.1)	7 (24.1)	1 (4.2)	1 (5.3)	0	28 (6.9)
Bruc	3 (15.8)	1 (3.4)	5 (20.8)	2 (10.5)	1 (1.8)	51 (12.6)
Typ F	2 (10.5)	0	2 (8.3)	1 (5.3)	1 (1.8)	21 (5.2)
IE	2 (10.5)	1 (3.4)	2 (8.3)	2 (10.5)	0	39 (9.7)
IM	0	0	0	0	2 (3.7)	10 (2.5)

Inf: Infectious diseases FUO: fever of unknown origin EPTB: Extra pulmonary tuberculosis OSM: Osteomyelitis Bruc: Brucellosis AbAb: Abdominal abscess Typ F: Typhoid fever IE: infective endocarditis IM: infectious mononucleosis. Figure in parenthesis are percent.

Discussion

In the present study, infectious diseases with the frequency of 44.3%, was the most common cause of FUO, followed by collagen vascular diseases (17.9%) and neoplasm (12.3%). These findings are in agreement with previous studies (5, 13, 14, 18-20). Among the infections associated with FUO, tuberculosis and osteomyelitis were the most common; this was the case in our previous study and in other studies, too (2, 7, 8, 10, 16, 17). Extra pulmonary tuberculosis was more frequent than pulmonary TB (31.9% vs.6.4%). This finding was in consistent with other studies (2, 7, 8, 10-12). Extrapulmonary tuberculosis 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 (PCR), were helpful in making the diagnosis. Bacteriological cultures and histopathological investigations were also important in confirming the diagnosis (3, 5).

Spines both in tuberculosis and osteomyelitis were the most common sites of infection. This finding is in consistence with newly published reports (2, 3, 5, 8). It may be concluded that modern diagnostic facilities such as MRI and gamma scanning give the chance for earlier detection of lesion and enable the physician to prevent spinal complications such as wedge fracture and cord injuries. The other infectious causes of FUO such as abdominal abscesses,

brucellosis, typhoid fever, were not as frequent as these two abovementioned diseases. This finding is opposite to the studies performed in countries with similar epidemiological pattern such as Turkey, Mexico and Iran (2, 8, 10, 11). The reason of these differences is not clear, but we believe that because in our center at the first visit of patients with FUO, we evaluate them for endemic and most probable diseases such as brucellosis, typhoid fever and abdominal abscess, Majority of these infections were diagnosed in early phase and excluded FUO categories.

The frequency of abdominal abscess, brucellosis and typhoid fever in our study was lower than previous studies in Iran and other areas (2, 8, 10, 12). Like our previous study, we found a changing pattern on the most prevalent infectious disease from brucellosis and typhoid fever to extra pulmonary TB and osteomyelitis. We believe the reason for these changes may be due to the availability of health facilities, improvement of public health, access to new diagnostic tools such as gamma scanning, CT scan and MRI techniques, new laboratory tests such as PCR, and new methods for culturing resulted in the change of pattern of epidemiology of infections in the region.

We also found similar results with our previous study in the region; some cases of salmonellosis or brucellosis and even pulmonary tuberculosis could be diagnosed earlier than 3 weeks and be excluded of FUO. We think these FUO cases have been the result of several concomitant misleading factors in the physician's approaches, the wrong

interpretation of a laboratory test, and inadequacy in the evaluation of a symptom and/or positive test.

Limitation of the study: Although, in this study we extended the duration of study from 2 years to 5 years and increase the sample size from 84 cases to 106 cases, yet the limitations were likewise a single center and retrospective design. Further multi-center, prospective studies of good design with larger population are required. In conclusion, the frequency of abdominal abscess, brucellosis and typhoid fever in our study was lower than previous studies in Iran and other areas.

The pattern of FUO in the region is thought to be changed to extrapulmonary (TB) and osteomyelitis. Tuberculosis is still the leading cause of FUO in our region and it is important to identify this treatable disease from all the causes of FUO. Osteomyelitis and abdominal abscesses were also the common causes of FUO in the region.

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