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Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990–2006

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Background:

The aim of this study was a systematic review of the literature related to adult fever of unknown origin (FUO) in Turkey.

Material/Methods:

To find the published series, three national and two international databases were searched.

Results:

Data for 857 patients with the diagnosis of fever of unknown origin were obtained from 13 articles. FUO was defined as fever over 38.3°C that continues at least for three weeks with no diagnosis reached after one week of inpatient investigation in all series (Petersdorf and Beason criteria). Infections, collagen vascular diseases, and neoplasms were found to be the reason of fever in 403 (47.0%), 137 (15.9%), and 126 (14.7%) of the in all 857 patients. The most common infectious disease was tuberculosis (147/403, 36.4%) followed by brucellosis (51/403, 12.6%) and infective endocarditis (39/403, 9.6%). The most common collagen vascular disease was adult-onset Still's Disease (49/137, 35.7%), followed by systemic lupus erythematosus (23/137, 16.7%). The most common neoplasms were Hodgkin's disease (32/126, 25.3%) and non-Hodgkin's lymphoma (32/126, 25.3%). The reason of fever could not be defined in 138/857 (16.1%) patients.

Conclusions:

Tuberculosis and brucellosis remain common causes of FUO in Turkey. In addition, lymphomas and adult-onset Still's disease should be considered in the differential diagnosis of a patient admitted with FUO.

key words:

pooled analysis • fever of unknown origin • pyrexia of unknown origin • FUO • PUO • Turkey • systematic review

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BACKGROUND

In 1961, fever of unknown origin (FUO) was defined by Petersdorf and Beason as fever over 38.3°C that continues at least for three weeks with no diagnosis reached after one week of inpatient investigation [1]. Worldwide data about FUO is usually confined to single-center experiences with inadequate patient numbers. While the main causes of fever of unknown origin (FUO) are infections, malignancies, and collagen-vascular diseases, in up to 15% of the cases the cause of fever cannot be identified. Infectious diseases, malignancies, and collagen-vascular diseases causing FUO vary widely [1–17]. In addition, the spectrum of diseases differs due to geographic differences [15–17]. Pooled analysis is advantageous in the understanding of the epidemiology of rare diseases or syndromes [18,19]. Pooled analysis of results of large series may also be useful for the development of national diagnostic guidelines. In this study it was aimed to review data on adult fever of unknown origin in Turkey by the pooled-analysis method.

MATERIAL AND METHODS

To find the published series, three national databases (Ulakbim Turkish Medical Literature Database, <http://www.turkishmedline.com>, <http://medline.pleksus.com.tr>) and two international databases (Pubmed and Science Citation Index-expanded (SCI-e)) were searched. The Ulakbim Turkish Medical Literature Database was founded by Tubitak (The Scientific and Technologic Council of Turkey) in 1996. Since data in congress abstracts were very heterogeneous, they were not included in the study. In order to increase the compass of the study beyond the articles in the mentioned databases, articles that were cited by the extracted articles were also included in the study.

Keywords for the national databases were “nedeni bilinmeyen ateş” or “nba” or “fever of unknown origin” or “pyrexia of unknown origin” or “fuo” or “puo”. Keywords for the Index Medicus and SCI were [(“fever of unknown origin” or “fuo” or “pyrexia of unknown origin” or “puo”) and Turkey]. In case of presentations from a single study with intersecting periods, the one with the longer period was chosen. Articles published before 1990, pediatric series, series below five patients, and series about human immunodeficiency virus or neutropenic fever patients were excluded.

RESULTS

Our search yielded 857 patients with the diagnosis of fever of unknown origin in 13 articles which were all published

Table 1. Causes of FUO in cases in whom it could be determined.

Causes of FUO	N (%)
Infectious diseases	403 (47.0)
Collagen vascular diseases	137 (15.9)
Oncological diseases	126 (14.7)
Other diseases	53 (6.1)
Reason of fever could not be determined	138 (16.1)
Total	857

Table 2. Infectious diseases-related causes of FUO.

Infectious disease	N
Tuberculosis	147
Brucellosis	51
Endocarditis	39
Intra-abdominal abscess	28
Typhoid fever	21
Malaria	10
Pneumonia	8
Pyelonephritis	8
Pelvic inflammatory disease	8
Infectious mononucleosis	8
Dental abscess	7
Bacteremia	6
Atypical pneumonia	5
Sinusitis	5
<i>E. histolytica</i> abscess	4
Meningitis	4
Mucormycosis	4
Pericarditis	3
Toxoplasmosis	3
Visceral leishmaniasis	3
Cytomegalovirus infection	2
Chronic active hepatitis	4
Soft tissue abscess	2
Soft tissue infection	2
Lung abscess	2
Prostatitis	2
AIDS and Cryptococcosis	1
Cat-scratch disease	1
Psoas abscess	1
Paravertebral abscess	1
Acute fulminant hepatitis	1
Ascariasis	1
Disseminated candidiasis	1
Encephalitis	1
Echinococcosis	1
Leptospirosis	2
Parvovirus infection	1
Prosthetic joint infection	1
Psittacosis	1
Pulmonary aspergillosis	1
Cholecystitis	1
Rickettsiosis	1
Total	403

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Table 3. Collagen-vascular disease-related causes of FUO.

Collagen-vascular disease	N
Adult-onset Still's disease	49
Systemic lupus erythematosus	23
Systemic vasculitis	14
Rheumatoid arthritis	8
Temporal arteritis	6
Polymyalgia rheumatica	6
Periarthritis nodosa	5
Rheumatic fever	4
Ankylosing spondylitis	4
Behcet's disease	4
Other connective tissue diseases	3
Wegener's granulomatosis	3
Juvenile rheumatoid arthritis	2
Mixed connective tissue disease	2
Takayasu arteritis	2
Henoch-Schonlein vasculitis	1
Dermatomyositis	1
Total	137

in peer-reviewed articles (including Turkish ones) [2–14]. FUO was defined as fever over 38.3°C that continues at least for three weeks with no diagnosis reached after one week of inpatient investigation in all series [1–14]. The causes of FUO were classified into five groups: a) infectious diseases, b) collagen-vascular diseases, c) neoplasms, d) miscellaneous, and e) no diagnosis (Tables 1–5).

Infections, collagen vascular diseases, and neoplasms were found to be the reason of fever in 403 (47.0%), 137 (15.9%), and 126 (14.7%) of 857 patients, respectively (Table 1). The most common infectious disease was tuberculosis (147/403, 36.4%), followed by brucellosis (51/403, 12.6%) and infective endocarditis (39/403, 9.6%) (Table 2). The most common collagen vascular disease was adult-onset Still's disease (49/137, 35.7%), followed by systemic lupus erythematosus (23/137, 16.7%) (Table 3). The most common neoplasms were Hodgkin's disease (32/126, 25.3%) and non-Hodgkin's lymphoma (32/126, 25.3%) (Table 4). The reason of fever could not be clarified in 138 of 857 patients (16.1%).

Overall, invasive procedures helped diagnosis in 234 of 857 patients (27.3%), but details of invasive procedures were clearly described in only five studies [3,4,8–10]. The most common invasive diagnosis that helped diagnosis was lymph node biopsy (Table 6).

DISCUSSION

Our findings suggest that the spectrum of diseases causing FUO appears to be determined by geographic and econom-

Table 4. Oncological diseases-related causes of FUO.

Oncological disease	N
Hodgkin's disease	32
Non-Hodgkin's Lymphoma	32
Leukemia	9
Other hematological Malignancies	7
Malignancy of unknown origin (metastatic adenocarcinoma)	5
Solid organ tumor (origin not mentioned)	5
Lung cancer	4
Other gastrointestinal system malignancies	3
Renal cell carcinoma	3
Other neoplasia	3
Primary liver cancer	3
Gastric adenocarcinoma	3
Myelodysplastic syndrome	3
Colon carcinoma	3
Breast cancer	2
Peritonitis carcinomatosis (origin unknown)	2
Multiple myeloma	2
Hairy cell leukemia	1
Ewing's sarcoma	1
Skin cancer	1
Mesothelioma	1
Cerebellopontin-angle tumor	1
Total	126

ic factors. Kazanjian [15] reported a review of 86 cases from the United States and the most common infectious, neoplastic, and collagen vascular diseases were pyogenic abdominal abscesses, non-Hodgkin's lymphoma and Still's disease, respectively. Abdulsalam et al. [16] from Saudi Arabia reported a series of 20 FUO cases; although infections were the most common causes of fever, there was no brucellosis or typhoid fever. In another study from Taiwan in which Chin et al. [17] reported a series of 94 FUO cases which were followed up prospectively, infectious diseases were the most common causes of FUO with 57.4%, followed by relatively low rates of neoplasms (8.5%) and rheumatological diseases (7.4%); in this prospective study there was no case of brucellosis reported to be the cause of FUO. When we compared the number of tuberculosis, brucellosis, adult-onset Still's disease, SLE, and lymphoma cases in the Kazanjian and Chin series with our data we found that tuberculosis and brucellosis were significantly more common in Turkish FUO patients [15,17] (Chi Square, $p < 0.05$).

Table 5. Other diseases causing FUO.

Disease	N
Subacute thyroiditis	16
Familial Mediterranean fever	7
Sarcoidosis	4
Drug fever	4
Cirrhosis	3
Inflammatory bowel disease	3
Hyperthyroidism	2
Basedow-Graves Disease	2
Sweet's Syndrome	2
Diverticulitis	1
Acute hepatitis	1
Guillain-Barre Syndrome	1
Thrombotic thrombocytopenic purpura	1
Weber-Christian disease	1
Histiocytosis X disease	1
Granulomatous hepatitis	1
Toxic hepatitis	1
Reactive arthritis	1
Hemolytic anemia	1
Total	53

Brucellosis is prevalent in Turkey [20–22]. *Brucella* seroprevalance (Standard Wright Test positivity, titer $\geq 1/160$) was reported as 7% (18/257) in the Ovakent-Tire-Izmir area [19]. Tuberculosis is also an emerging global health problem [23–26]. Ucan et al. [23] from Turkey reported a tuberculosis skin test (TST) positivity rate (>10 mm induration) of 67.3% in 2835 people aged 25.3 ± 13.9 years. In another study in which 948 people were screened for tuberculosis with TST and chest radiogram, tuberculosis infection prevalence and the proportion of annual infection risk were reported to be 46% and 3.4%, respectively [24].

Despite the fact that adult-onset Still's disease is known to be a common cause of FUO, the result that it is the most common cause of FUO among rheumatological diseases in Turkey is of interest. Although there are data about the prevalence of the disease in Turkish children [27], to our knowledge there is no field study dealing with this issue in adults.

Overall, the aid of invasive procedures in diagnosis was reported to be 25% by Abdulsalam [16] et al. and 47.8% by Kazanjian [15]. Details of invasive procedures that helped diagnosis of the cases were sufficiently provided in five studies and the aid of invasive procedures in diagnosis was 60.3%. In contrast to the study of Kazanjian et al. [15], our data show that bedside invasive procedures were more useful than procedures performed in the operation room. There

Table 6. Yield of invasive procedures in 126 patients with FUO.

Invasive procedure	Diagnostic yield
Lymph node biopsy	20/25
Liver biopsy	16/31
Bone marrow biopsy/aspiration	13/37
Laparotomy	8/10
Renal biopsy	7/7
Muscle biopsy	6/7
Parasynthesis	3/3
Prostate biopsy	2/2
Temporal artery biopsy	1/3
Lumbar puncture	0/1
Total	76/126

were four meningitis and one encephalitis case reported as the cause of FUO in our study. For this reason the fact that lumbar puncture did not yield any diagnosis in any of the cases in Table 6 is probably due to the lack of details of the invasive procedures yielding the diagnosis in the majority of the studies.

Pooled analysis is advantageous in understanding of the epidemiology of rare diseases or syndromes such as mucormycosis or nocardiosis [18,19]. While pooling the data, the inclusion criteria is important. Retrospective studies carry the disadvantage of dependence on patient records. In this study all the extracted data were obtained by retrospective analysis of patient records and fever of unknown origin (FUO) was defined as fever over 38.3°C that continues at least for three weeks with no diagnosis reached after one week of inpatient investigation in all series [1]. In the presented study, data from articles published before 1990 were not included since it was not possible to search those articles in the mentioned databases, and series below five patients were excluded since patients in these small series would intersect with the presented 13 articles. Other disadvantages of our study are the facts that in only two studies how the etiology of FUO was diagnosed (clinical criteria used, histology, serology, etc.) was clearly mentioned [5,7] and the specific causes of bacteremia, pneumoniae, etc. were not detailed. In addition, the FUO data presented here are all from tertiary-care centers; to our knowledge there are no published data from other centers and we do not have any idea how often FUO is seen and what the spectrum of diseases causing FUO is in other centers. Although all articles were from tertiary-care educational hospitals, we cannot exclude a possible double reporting of a single patient from two different centers. In spite of these disadvantages, this is the first pooled-analysis about this topic and we believe that it gives major clues about the causes of FUO in Turkey.

CONCLUSIONS

Infectious disease, especially tuberculosis and brucellosis, remains as a common cause of FUO in Turkey. Although

several diseases may lead to FUO, lymphomas, adult-onset Still's disease, and particularly tuberculosis should be considered in the differential diagnosis of a patient admitted with FUO in Turkey. These data on the etiology of FUO in the Turkish population may provide a guide to future studies and national guidelines.

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