

Fever of Unknown Origin in Children Aged Three Months to Fifteen Years

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Background: Fever of unknown origin (FUO) is defined as the presence of fever in a child for eight or more days that a careful history and physical examination and preliminary laboratory results failed to reveal the probable cause of the fever. The causes of FUO are different according to geographical regions and age.

Objectives: The current study aimed to evaluate the common causes of childhood FUO in Zahedan, Iran.

Patients and Methods: A six-year retrospective study was conducted on all admitted children aged from three months to fifteen years from January 2006 to January 2012 and those with the final diagnosis of FUO were selected for the study.

Results: Finally, 1100 patients were found eligible for the study. The FUO causes were infectious diseases (55.1%), collagen vascular (4.6%), neoplasm (6.7%), miscellaneous (23.3%) and undiagnosed (10.3%).

Conclusions: Most fever of unknown origin results from atypical presentation of common diseases like Tuberculosis, Salmonellosis, Brucellosis, and Pneumonia.

Keywords: Pediatrics; Infectious Diseases; Children

1. Background

Fever is defined as a centrally mediated elevation of body temperature in response to a stress or insult. Defining the limits of normal body temperature however is more difficult. Generally, the accepted range of rectal temperature is from 36°C to 37.8°C. Children tend to have higher body temperature than adults (1). Fever is one of the most common complaints in children and the second reason for referring to a physician. Based on history and physical examinations, a specific cause is not found for about 5% to 20% of febrile patients (1, 2). Fever with unknown resource is defined as a body temperature above 38.3°C which lasts for eight days or more and no clear cause is found for it despite providing physical and laboratory evaluation and general screening. One of the major causes of mortality and morbidity in children is Fever of unknown origin (FUO) in the developing countries. The most common causes of FUO in children are infectious diseases (40%-50%), collagen vascular disease with a lower incidence of 10% to 20%, and malignancies with the incidence of 5% to 10% (1, 3, 4). Malignancies are more unusual causes for FUO in children compared with adults and are counted for 10% of the cases. Approximately in 15% to 25% of the patients suffering from FUO the cause could not be diagnosed. The majority of hidden infections which cause FUO are unusual presentations of a common disease. The

various diseases in children, presented as FUO, differ according to the geographical regions and depend on the specific diseases in the area and their diagnostic conveniences (3). Many of the infectious causes of FUO in children are often bacterial and viral infections including cat scratch disease, Salmonellosis, Brucellosis, Tuberculosis, Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and hepatitis. Local bacterial infections usually include endocarditis, intra-abdominal abscess, liver abscess, and sinusitis or mastoiditis, and pyelonephritis or pre renal abscess. The incidence probability of infectious disease and collagen vascular for the majority of FUO is more dominant in children under six years. Inflammatory diseases that usually appear as FUO include rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), polyarthritis nodosa, rheumatic fever and Kawasaki. Among malignant diseases, Hodgkin lymphoma, Non-Hodgkin lymphoma, leukemia, Ewing sarcoma, sarcoma and neuroblastoma are more common than the others (1). The FUO treatment should not be started before determining its cause unless the patient is acutely ill. It must be considered because non-specific treatment is rarely effective and delays the diagnosis. There is an exception, to avoid serious complications in neutropenic patients, after taking blood cul-

tures treatment is performed with a broad spectrum antibiotic and according to the results of the blood culture a specific antibiotic is added. Human immunodeficiency virus patients with fever should be treated for possible Pneumocystis infection (2). Children with FUO have a better prognosis than adults. Although its outcome depends on the underlying diseases, in 25% of the cases no etiology is found even after detailed and acquired assessments. In many cases fever (usually harmless) finally heals. Although some patients possibly have recognizable symptoms of rheumatic diseases over time (1).

2. Objectives

The current study aimed to investigate causes of fever of unknown origin in the hospitalized children in Aliebn-E-Abitaleb Hospital in Zahedan, Iran from 2006 to 2012.

3. Patients and Methods

A retrospective study was conducted on children admitted in Aliebn-E-Abitaleb Hospital in Zahedan (South-eastern Iran) with the criteria of FUO from January 2006 to January 2012. All the admitted children's files were collected and assessed by census method from medical record section. After a deep review of the files 1100 cases were found qualified. Inclusion criteria were having FUO criterions and exclusion criteria were having known immune deficiency and taking immune suppressive medicines. Patients whose problems were not diagnosed at initial examination and investigations were selected for the study. After recording the acquired information, data were analyzed by statistical package for social science version 20 using descriptive statistics. Study limitations were incomplete files and early discharged patients due to parental consent.

4. Results

In the present study 1100 files were found qualified and assessed from the children admitted to the pediatric ward of Aliebn-E-Abitaleb Hospital in Zahedan, the capital city of Sistan and Baluchistan Province in South-east Iran.

All the patients had FUO criteria. These children had fever for an average of 13 days. Out of these patients, 384 (34.9%) were boys and the mean age of the children was 4.1 ± 2.99 years ranging from three months to fifteen years.

The table shows the results of the analysis according to descriptive statistics. Of the 1100 patients, 606 (55.1%) had infectious disease. In this group Tuberculosis, Salmonellosis, Brucellosis, and respiratory infections were more common. Respiratory infections were diagnosed based on the availability of symptoms in radiography and laboratory tests. Salmonellosis was approved by investigation on blood and bone marrow culture. Brucellosis was diagnosed by serology and blood cultures. Tuberculosis was confirmed by chest x-ray, Computerized Tomography (CT) scan of the chest, and sputum or gastric lavage smear and culture. In this evaluation, 51 patients had a final diagnosis of diseases of collagen vascular in which the most common ones were Juvenile Rheumatoid Arthritis (JRA) and the least common ones were Systemic lupus erythematosus (SLE) and Kawasaki. In the current study, malignancy was diagnosed in 74 patients. Leukemia, lymphoma, and neuroblastoma were the most common forms of neoplasm, respectively. Unfortunately, secondary analysis of 265 patients was negative and 113 cases were discharged before a definitive diagnosis.

5. Discussion

In the present study, the most common causes of FUO in children were infectious diseases, malignancy, and collagen vascular which was similar to the findings of many other studies. In a study conducted by Zhonghua Nei on 449 children with FUO criteria, the most common cause were infectious diseases with high incidence of Tuberculosis. The second common cause was collagen vascular disease with the highest incidence for still disease and SLE. In the third grade neoplasms were diagnosed and finally about 13.8% of the cases could not be determined (5). In the current study, the most common causes of FUO were infectious diseases and were comparatively similar in respect of other causes. In the recent years Chow did the same study on 1638 Canadian patients with FUO criterion

Table 1. The Distribution of Fever of Unknown Origin Causes

Causes	Days With Fever ^a	Age ^b	Frequency ^c	Gender	
				Male	Female
Infectious	11.6 ± 3.79	4	606 (55.1)	212	384
Neoplasm	13.1 ± 3.10	5.1	74 (6.7)	48	26
Collagen vascular	14.6 ± 3.27	3.4	51 (4.6)	19	32
Idiopathic	15.3 ± 3.59	4.5	256 (23.3)	42	214
Own discharge	15.1 ± 3.34	3.4	113 (10.3)	19	94

^a Data are presented as Mean ± SD.

^b Data are presented as Mean.

^c Data are presented as No. (%).

in 2011 and concluded the following frequency for the causes. Infectious, collagen vascular, and malignancy of 51%, 7% and 5%, respectively, which was more similar to the findings of the current study (6). Parallel to Chow's study, a survey by Mohammad Abdelbaky on Egyptian patients with FUO concluded that infectious disease with the highest rate (50%) and collagen vascular (24%) and neoplastic (7%) diseases were the common causes, similar to the results of the current study. In 2011 another study was conducted on 816 patients with FUO and the results showed the likeness in comparison to the current study findings. Infectious diseases with the highest importance for TB were the most common followed by collagen vascular with the high prevalence in still disease, and malignancy respectively (7). Zhiyong et al. conducted a study on 208 Chinese patients with FUO and concluded that infectious diseases were the most common cause with respect to Tuberculosis, typhoid fever, and septicemia (8). Other causes were collagen vascular diseases and neoplasm. In general, according to the results of the current study and also the other studies, the prevalence of infectious diseases varied from 30% to 86%. The reason for this variation would be the place of the study and variation in age of the patients (8). The prevalence of FUO related diseases is different according to the geographical region and age (4, 9-15). In the developing countries such as Iran, the most common cause of FUO is infectious disease and in conclusion, infectious respiratory along with TB are the most common infectious diseases for the children with FUO. Bearing in mind the high prevalence of infectious diseases for FUO in Sistan and Baluchistan Province, all physicians should pay more attention to infectious causes of FUO in children and adolescents.

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Authors' Contributions

All authors had an equal contribution in this study.

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