Fever of Unknown Origin in Children: A 6 year- Experience in a Tertiary Pediatric Egyptian Hospital

Rasha H Hassan, [1] Ashraf E Fouda, [2] Shaimaa M Kandil [3]
Mansoura University Children's Hospital, Mansoura University, Mansoura, Egypt

Lecturer of Pediatric Infectious Disease and Malnutrition Unit, Mansoura University Children's Hospital, Mansoura Faculty of Medicine, Mansoura. Egypt. Email: rashahassan_74@yahoo.com [1]

Lecturer of Pediatrics, Mansoura University Children's Hospital, 35516, Faculty of Medicine, Mansoura University, Egypt.
Tel.: +20124295547 Fax: +20502262307 Email: ashraf_foda@mans.edu.eg [2]

Lecturer of Pediatrics, Pediatric Infectious Disease and Malnutrition Unit, Mansoura University Children's Hospital, 35516, Faculty of Medicine, Mansoura University, Egypt. Email: Shimaakandel@mans.edu.eg [3]

Abstract

Background: Fever of unknown origin (FUO) is among the most conditions which poses challenge in diagnosis. The presence of information on regional patterns of FUO will shorten the time for diagnosis and reduces health services costs. There are almost no previous studies describing the etiology of FUO in children of Egypt or nearby countries.

Aim of the Study: To determine different causes of FUO and the possible diagnostic procedures.

Methods: Data of patients with FUO, presented to the Infectious Diseases Unit of Mansoura University Children Hospital, were retrospectively collected in a 6 year-period from May 2006 to May 2011. The study included children with a fever of 38.3° C or more documented by a health care provider and for which the cause could not be identified after 3 weeks of evaluation as an outpatient or after a week of evaluation in hospital**.** Patients were then categorized into 5 groups.

Results: 127 patients met the diagnostic criteria. Infectious diseases were the commonest causes of FUO in 46 cases (36.22%) followed by the miscellaneous causes in 38 cases (29.9%). Meanwhile, collagen vascular diseases and malignancy were diagnosed in 13 cases (10.2%) and 10 cases (7.87%) respectively. While, 20 cases (15.75%) remained undiagnosed.

Conclusions: Infectious diseases are the commonest cause of FUO. The delay in diagnosis was due to atypical presentations or inappropriate use of antibiotic prior to the referral. Non infectious causes, malignancy and collagen or vascular disorders were diagnosed in rest of the patients. However, about 15% of our patients remained undiagnosed. The diagnosis was established by non-invasive means in more than two-third of the cases.

Correspondence:

Shaimaa M Kandil, MD
Lecturer of Pediatrics
Mansoura University Children's Hospital,
35516, Faculty of Medicine,
Mansoura University, Egypt.
Tel.: +20124295547
Fax: +20502262307
Email: Shimaakandel@mans.edu.eg

Introduction

After 60 years of the original description of Fever of unknown origin (FUO) by Petersdorf and Beeson in 1961, [1] FUO remains among the most challenging clinical situations in diagnosis for health care providers to approach and often involves referral to subspecialists. [2]

The term FUO is best reserved for children with a fever documented by a health care provider and for which the cause could not be identified after 3 week of evaluation as an outpatient or after 1 week of evaluation in hospital. Patients with fever not meeting these criteria, and specifically those who were not admitted to the hospital with an apparent site of infection nor a noninfectious diagnosis, may be considered to have fever without localizing signs. [4]

There is no diagnostic gold standard, the diagnostic approach in FUO should include a thorough history taking and repeated physical examinations. [5] There is no set of "routine" investigations that patients with FUO should be subjected to. Instead, diagnostic testing should be individualized and guided by abnormalities found on clinical examination and simple laboratory testing. [6] The presence of information on regional patterns of FUO would provide several benefits, such as shortening the time taken to establish a diagnosis and reducing hospital costs. [3]

Our study aimed to determine the different causes of FUO and the possible diagnostic procedures in a tertiary pediatric Egyptian hospital.

Subjects and methods

Mansoura University Children Hospital is a free of charge 400 bed tertiary hospital in the North Eastern Nile Delta region of Egypt. We receive and provide care for patients referred from 5 nearby governments with a population of about 15 million.

We reviewed the records of all children (age range from 1 month to 18 years) admitted or referred to the Infectious Disease Unit in Mansoura University Children Hospital during the period from May 2006 to May 2011 for evaluation of prolonged fever. Only those patients who fulfilled the following criteria were included in the study: children with a fever of 38.3° C or more documented by a health care provider and for which the cause could not be identified after 3 weeks of evaluation as an outpatient or after a week of evaluation in hospital). Patients with neutropenia (neutrophil count less than 500/mm^3), patients developing fever after hospital admission and human immunodeficiency virus (HIV) positive patients were excluded from the study.

All cases are evaluated initially by thorough history, physical examination and the following investigations: Complete blood count with differential WBC, acute phase reactant: CRP and ESR, routine blood chemistry (serum creatinine, liver enzymes, bilirubin and albumin), urine analysis and culture, blood culture, serology for typhoid (Widal test) and brucella (brucella agglutination test), Blood smear, imaging studies: abdominal ultrasound and chest X ray. Further investigations were done according to the clues obtained during the initial evaluation or otherwise dictated by the clinical course.

After evaluation of children with FUO, the causes were categorized into 5 groups: infection, collagen vascular diseases, malignancy, miscellaneous causes and undiagnosed group. FUO is classified as undiagnosed if no evidence of the cause of fever is obtained and if there is complete spontaneous recovery even though the fever has persisted for several weeks or months. [7] Here our study was descriptive and retrospective in design, with no comparison of data.

Results

The study included 127 patients. They were 71 males and 56 females. Their mean age of presentation was 5 years and 4 months [(65 months (range 5 months to 14 years)]. The median duration of fever before admission was 32 days (range 18 days to 5 years). The median time between admission and the definitive diagnosis as infection, collagen vascular diseases, malignancy and miscellaneous groups were 12, 29, 18 and 46 days respectively. About 95% of patients had received at least one course of antibiotics prescribed before referral or admission.

Infectious diseases were the commonest causes of FUO in 46 cases (36.22%) followed by the Miscellaneous causes in 38 cases (29.9%). Meanwhile, Collagen Vascular

diseases and Malignancy were diagnosed in 13 (10.2%) and 10 patients (7.87%) respectively. While, 20 cases (15.75%) remained undiagnosed. The different causes of FUO are listed in **Figure 1**.

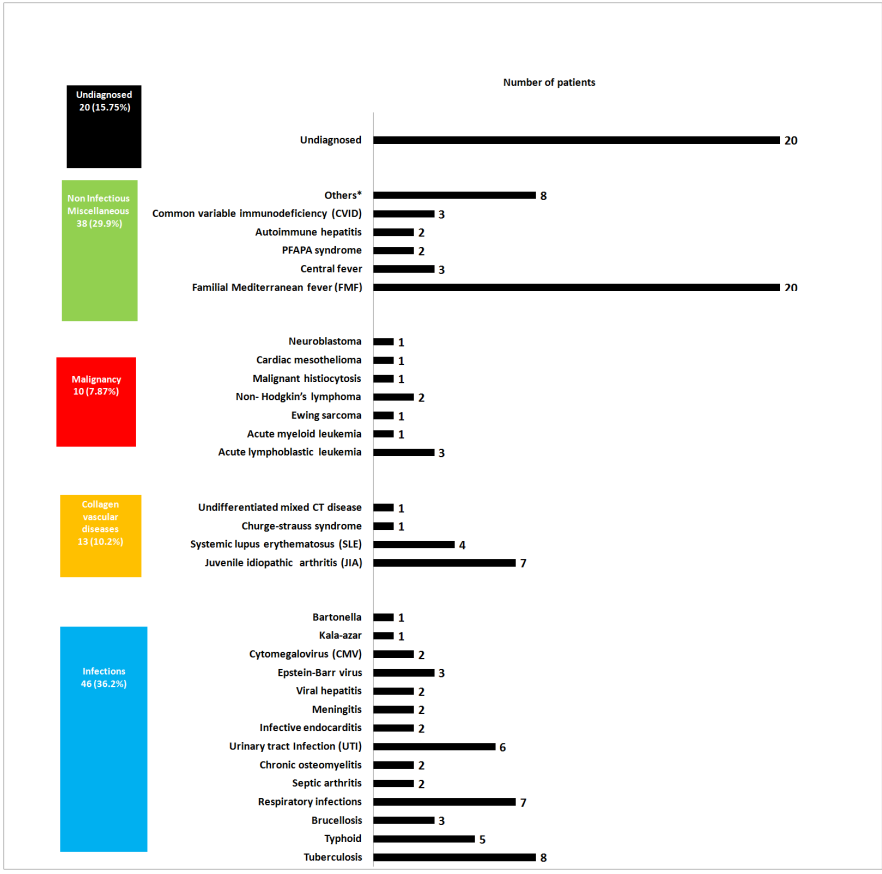

Figure 1: Final diagnosis in ١٢٧ children with FUO. *Others: Hyper IgD syndrome, Kawasaki disease, Crohn's disease, Diabetes insipidus, Sinus histiocytosis, Factitious fever, Oesinophilic gastritis, Chronic granulomatous disease (one patient for each diagnosis)

Among the Infectious causes, Tuberculosis was diagnosed in 8 cases. Pulmonary TB was diagnosed in 5 cases and had 12 weeks as a mean duration of fever before diagnosis. The diagnosis was delayed despite a high index of suspicion because of absence of respiratory symptoms, normal chest roentgenograms and negative skin test. They were diagnosed by the presence of acid-fast bacilli in sputum sample stained with Zeil Nelsen stain, culture on mycobacterial growth indicator tube (MGIT) and PCR.

Typhoid fever was diagnosed in 5 cases with a mean of 5 weeks duration of fever. The diagnosis was missed early in these patients as they had received several courses of antibiotics and was non-responsive to ceftriaxone or ciprofloxacin and fever continued to exist. Repeated blood cultures and rising titer for Widal test were clue for diagnosis.

Respiratory tract infection was diagnosed in 7 cases. Two cases had retained foreign body in the respiratory tract which was removed by

the bronchoscope. Three cases had chronic otitis media and two cases had chronic sinusitis, in all of them the diagnosis was delayed with previous inappropriate antibiotic administration.

Urinary tract infection (UTI) was diagnosed in 6 cases with 7 weeks mean duration of fever. Two of them had previous episodes of UTI. All patients had received antibiotics for other presumed infections at the time of the first urine culture. Urine cultures yielded positive results eventually (*Klebsiella pneumoniae* in two, *Escherichia coli* in two, *Proteus mirabilis* in one, and Candida in another). One patient had evidence of pyelonephritis in ultrasound and two patients had evidence of vesicoureteric reflux evidenced by VCUG findings.

Partially treated meningitis was diagnosed in 2 cases. Repeated lumbar puncture after stoppage of antibiotics was positive for *Haemophilus influenza* type b in one case and *meningococci* in the other.

Infective endocarditis was diagnosed in two patients after 39 days of fever by Echocardiographic examinations and positive blood culture (one was *Staph. aureus* and the other was *E. coli*).

Familial Mediterranean fever (FMF) was the commonest cause of recurrent fever syndromes and was diagnosed in 20 patients with mean age of presentation of 5 years and 18 months duration of fever before diagnosis. The disease was considered after exclusion of all other causes of FUO and if the family history, clinical and laboratory findings were suggestive. Cases were confirmed by genetic study for MEFV mutation. Majority of cases had good response to colchicine therapy.

Central fever was diagnosed in 3 cases, 2 of them were known to have cerebral palsy. The third case was a 7 months old male who was macrosomic at birth with delayed mental and physical milestones. MRI brain showed mild ventriculomegaly. He was diagnosed as Soto's syndrome.

Meanwhile, 20 patients remained undiagnosed after investigations. Of these, 16 patients had fever that ultimately resolved with no sequelae. These patients had an illness, which best fits self-limited prolonged viral infection. While, the other four patients continued to have fever.

The procedures by which the diagnosis was established for 107 patients are shown in **Figure 2**. Non- invasive tests were able to establish diagnosis of the cause of FUO in 78 cases (72.8%) while invasive methods were required in 29 cases (27 %).

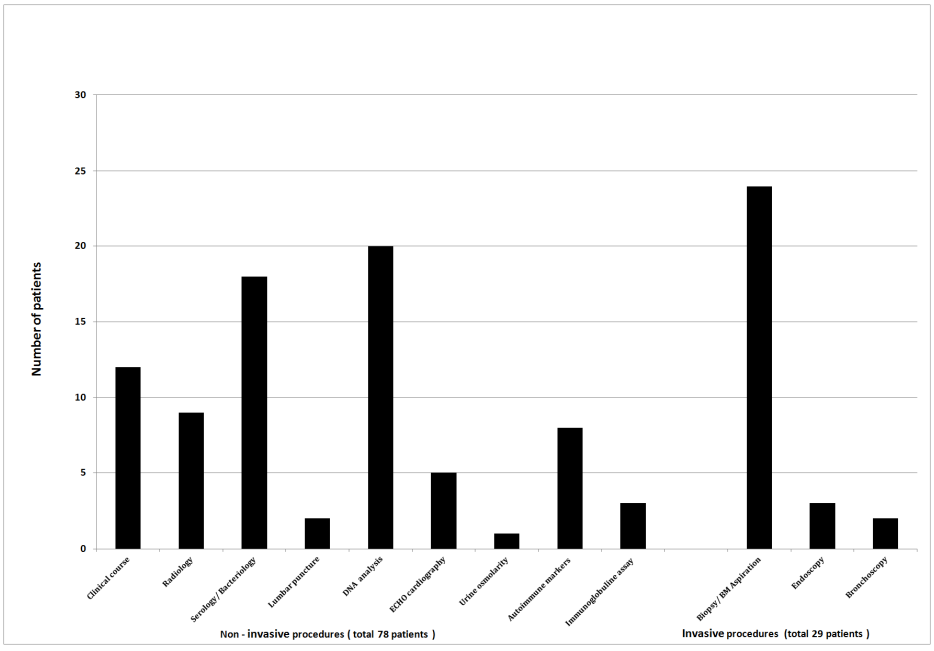

Figure 2: The procedures by which the diagnosis was established for 107 patients

Discussion

FUO continues to be one of the most challenging clinical situations for pediatricians. Comparison between series of patients with FUO is difficult because of the large number of possible causes and the influence of numerous factors on the relative proportion of the various diagnostic categories such as: Geographic factors, referral patterns, time of the study and age of the patients. [4]

This study is the first of a large number of children with FUO in Egypt. The general pattern of FUO in our study is similar to previous published studies of children in developing countries **(Figure 3).** The percentage of patients with FUO in whom it was possible to establish a final diagnosis in the present study was 84.25%. [8, 9, 10, 11, 3, 12]

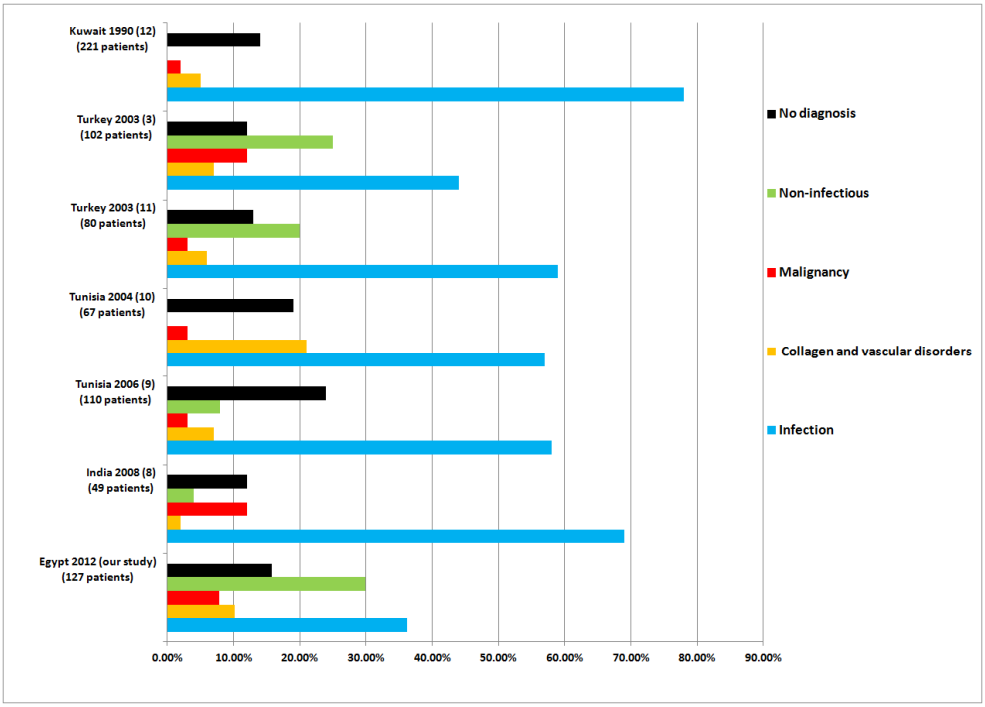

Figure 3: Comparison of the patterns of FUO in different developing countries.

Infectious disease was the most common cause of FUO (46 cases). This was also documented in many previous studies **(Figure 3)**. Specific infections especially tuberculosis, typhoid and brucellosis are endemic in Egypt. [13] The diagnosis of these cases was delayed despite a high index of suspicion. This was probably due to either atypical presentation or inappropriate antibiotic use. Antibiotic use is common and unrestricted in many developing countries including Egypt. [14] About 90% of our patients had at least one antibiotic course before referral. This rendered the diagnosis more difficult in those who had infectious diseases. Antibiotics should be used on firm basis with confirmed causative organisms using cultures, serology or PCR to avoid emergence of resistant strains. Available data suggest that antibiotics resistance has reached unacceptable and rising levels in the pathogens which are most commonly reported from developing countries. The antimicrobial agents most affected by resistance are inexpensive, older antimicrobials, simply because they are available or affordable. [15] Strategy for resistance control should be adapted by developing countries, such as unregulated drug availability, inadequate antimicrobial drug quality assurance, inadequate surveillance and cultures of antimicrobial. [16]

Miscellaneous causes group was the second most frequent cause of FUO. The percentage of this group seems to increase in recent studies, probably because physicians become more oriented with the different etiologies included in this group together with the advancement of diagnostic modalities. FMF is the most common among the miscellaneous causes and it is a relatively common diagnosis in our locality. The diagnosis is based on family history and clinical presentation and confirmed by genetic study.

The incidence of FUO of indeterminate cause ranged from 12% to 24% in previous series, and in the present study, it was about 15.75%. The prognosis of our patients with idiopathic fever was relatively good, in agreement with previous findings. [17]

There are many differences between developed and developing countries as regard causes and investigation approaches, which were well discussed in a previous study. [17] A higher incidence of infections such as tuberculosis or parasitic disease in developing countries may relate, among other differences to the availability of diagnostic tests. [17] So the approach for diagnosis of FUO in developing countries should be different from developed countries including different pattern and prevalence of endemic diseases and available, cost effective step by step approach.

Conclusions

Infectious diseases were the commonest cause of FUO. The delay in diagnosis was due to atypical presentations or inappropriate use of antibiotic prior to the referral. Non infectious causes, malignancy and collagen or vascular disorders were diagnosed in rest of the patients. FMF was the most common among the miscellaneous group and it was a relatively common diagnosis in our locality. However, about 15% of our patients remained undiagnosed. The diagnosis was established by non-invasive means in more than two-third of the case. While rest of patients required invasive procedures like biopsy, bone marrow aspiration, endoscopy and/or bronchoscopy.

References:

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore), 1961, 40:1-30.
2. Tolan RW Jr. Fever of unknown origin: a diagnostic approach to this vexing problem. Clin Pediatr (Phila). 2010, 49(3):207-13.
3. Ciftçi E, Ince E, Doğru U. Pyrexia of unknown origin in children: a review of 102 patients from Turkey. Ann Trop Paediatr , 2003, 23(4): 259-63.
4. Nield LS, Kamat D. Fever. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RF. eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Saunders Elsevier; 2011:e169-1-169-3.
5. Dienye PO, Gbeneol PK. Fever of unknown origin in an infant with an unexpected blood film report: a case report. Rural Remote Health, 2010, 10(1):1242.
6. Wong SY, Lam MS. Pyrexia of unknown origin--approach to management. Singapore Med J, 1995, 36(2):204-8.
7. Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. J Postgrad Med. 2001; 47(2):104-7.
8. Joshi N, Rajeshwari K, Dubey AP, Singh T, Kaur R.Clinical spectrum of fever of unknown origin among Indian children. Ann Trop Paediatr. 2008; 28(4):261-6.
9. Chemli J.; Bouafsoun C.; Boussetta S.; Dalhoumi A.; Harbi, A. Prolonged fever in children: about 110 cases. Journal de Pediatrie et de Puericulture, 2006, 19(8): 297-303.
10. Chouchane S, Chouchane CH, Ben Meriem CH, Seket B, Hammami S, Nouri S, et al. Prolonged fever in children. Retrospective study of 67 cases. Arch Pediatr. 2004, 11(11):1319-25.
11. Cogulu O, Koturoglu G, Kurugol Z, Ozkinay F, Vardar F, Ozkinay C Evaluation of 80 children with prolonged fever. Pediatr Int. 2003 Oct; 45(5):564-9.
12. Mouaket AE, el-Ghanim MM, Abd-el-Al YK, al-Quod N. Prolonged unexplained pyrexia: a review of 221 paediatric cases from Kuwait. Infection. 1990; 18(4):226-9.
13. Crump JA, Youssef FG, Luby SP, Wasfy MO, Rangel JM, Taalat M, et al. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries.Emerg Infect Dis. 2003; 9(5):539-44.

14. Aboul Fotouh AM, el-Damaty SE, Abdel Megeid FY. J Egypt Public Health Assoc. 1998; 73(1-2):57-69.
15. Okeke IN, Klugman KP, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part II: strategies for containment. Lancet Infect Dis. 2005; 5(9):568-80.
16. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis. 2005; 5(8):481-93.
17. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr. 2011; 7(1):5-10.