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Fever of unknown origin in children: An etiological profile

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Abstract
Background/purpose: Fever of unknown origin (FUO) can be caused by many clinical conditions and remains a diagnostic challenge in clinical practice. The etiology of FUO varies markedly among different age groups, geographic areas, and seasons. Although huge advances have been made in the field of medicine, fever of unknown origin (FUO) continues to be a significant health problem and an important cause of morbidity and mortality, especially in children. The aim of this study was to study current spectrum of FUO, newly emerging challenges and outcome of FUO. A prospective observational study was conducted over a 16 month period (May 2018-September 2019).
Study Design: 50 children aged 4 months to 15 years met the definition of FUO and were included. Children with known immunodeficiency disorders or other chronic disorders were excluded. A diagnosis was reached in 45 (90%) patients.
Results: Infections were the commonest cause accounting for FUO in 35(70%) patients. Haematological disorders were found in 8 (16%) and autoimmune diseases in 2 (4%) patients. Among infections, the most common causes of FUO were tuberculosis (TB) (30%), enteric fever (24%), Epstein-Barr virus (EBV) (8%) and brucellosis (8%). TB was extra-pulmonary in 12 cases and pulmonary in 3 cases.
Conclusion: A well-designed systemic review of the epidemiological information, medical history, physical examination, laboratory analysis, and adequate invasive procedures provide adequate data to identify the most common causes of FUO in children.

Keywords: FUO, children

Introduction
Fever is a common symptom of many clinical conditions, and infection is the most common cause, especially in children [1]. "Fever of unknown origin (FUO)" in adults was first described in 1961 and was defined as well-documented fever of at least 3 weeks' duration without an apparent source after 1 week of investigation [2]. Although there is no standard definition of pediatric FUO, fever lasting anywhere from 10 days to 3 weeks is generally accepted as the working definition of FUO in children [3, 4, 5, 6].
There is no diagnostic gold standard, the diagnostic approach in FUO should include a thorough history taking and repeated physical examinations [7]. 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. 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 [8].
The aim of this study was to study current spectrum of FUO, newly emerging challenges and outcome of FUO. A prospective observational study was conducted over a 16 month period (May 2018-September 2019).

Materials & Method
The study was conducted in dept. of pediatric, govt. medical college, Srinagar. 50 children aged 4 months to 15 years met the definition of FUO and were included. Children with known immunodeficiency disorders or other chronic disorders were excluded. It was a prospective observational study which evaluated children presenting with a febrile illness of more than 3 weeks duration or 1week of hospital stay for evaluation of febrile illness for which no diagnosis could be reached.

After taking a detailed history and conducting a physical examination and screening laboratory tests, thus qualifying as FUO. The definition of FUO was based on criteria proposed by Long & Edwards. Screening laboratory tests included complete blood count, erythrocyte sedimentation rate (ESR), peripheral smear for malarial parasites, urine analysis and culture, blood culture, tuberculin test and chest roentgenogram. This definition assumed exclusion of protracted symptoms from acute self-limiting respiratory tract infections, well documented periodic fever and repeated episodes of fever with identifiable causes. Infants under 4 months of age were excluded.

The next steps in laboratory evaluation were guided by serial clinical examinations and regular follow-up. Investigations included serological tests, e.g. anti streptolysin O (ASO) titres, Widal titres, liver function tests, hepatitis A and B antibodies, anti-malarial antibodies, anti-nuclear antibodies, HIV antibodies, repeat blood and urine cultures, repeat chest roentgenogram, CSF analysis, bone marrow aspiration/ biopsy, fine-needle aspiration cytology, echocardiography, abdominal ultrasound, abdominal CT, chest CT and liver biopsy.

Results

50 children aged 4 months to 15 years met the definition of FUO and were included. Children with known immunodeficiency disorders or other chronic disorders were excluded. A diagnosis was reached in 45 (90 %) patients Fifty children with FUO were evaluated over the 1-year period. There were 35 (70%) males with a male: female ratio of 2.5:1. The mean (SD) duration of fever before evaluation was 8.1 (7.4) weeks. A diagnosis was established in 45 (90%) children after thorough investigation. No diagnosis was made in the remaining five (10%). Of the 50 patients, 45 (90%) were diagnosed successfully, treated and discharged. Infections were the commonest cause accounting for FUO in 35 (70%) patients. Haematological disorders were found in 8 (16%) and autoimmune diseases in 2 (4%) patients. Among infections, the most common causes of FUO were tuberculosis (TB) (30%), enteric fever (24%), Epstein-Barr virus (EBV) (8%) and brucellosis (8%). TB was extra-pulmonary in 12 cases and pulmonary in 3 cases. Amongst the hematological disorders, 3 patients had haemophagocytic lymphohistiocytosis (HLH), 3 had leukemia, 1 had non-Hodgkin lymphoma and 1 had autoimmune lymphoproliferative syndrome. Juvenile idiopathic arthritis with systemic onset and polyarteritis nodosa accounted for the two cases of autoimmune disease. Elevated C-reactive protein (CRP) levels were associated with an infectious etiology. Bone tenderness, thrombocytopenia and neutropenia predicted haematological malignancy. 1 patient of HLH died of complications during initial hospitalization . TB, especially extrapulmonary, and enteric fever are still significant public health problems and were the commonest causes of FUO in our population. Due to advances in diagnostic facilities, some diseases like urinary tract infection (UTI) and hepatitis have become less common; however, other diseases like EBV have become more common causes of FUO. HLH is emerging as a significant cause of morbidity and mortality in FUO patients.

Serology and bone marrow examination together diagnosed 72% of cases, the majority of whom were identified as infectious cases. In all patients with suspected enteric fever, serial Widal test, blood culture confirmed the diagnosis. The next most useful investigation was bone marrow examination which identified the diagnosis in 14 of 15 patients in whom it was conducted, thus diagnosing 33% of all cases. It played an important role in detecting malignancies and infections. Fine-needle aspiration cytology was the third most useful investigation, establishing the diagnosis in five of 43 (12%) cases. Lymph node biopsy, and urine culture were required in one case each.

Diagnosis	No. (%)
Infection, n= 35	
Tuberculosis	15(30)
Enteric fever	12(24)
Epstein-bar virus(EBV)	4(8)
brucellosis	4(8)
Hematological Disorder, n=8	
Hemophagocytic lymphohistiocytosis (HLH)	3(6)
non-Hodgkin lymphoma	1(2)
autoimmune lymphoproliferative syndrome	1(2)
leukemia	3(6)
Autoimmune Disease, n=2	
Juvenile idiopathic arthritis with systemic onset and polyarteritis nodosa	2(4)

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 [9]. The general pattern of FUO in our study is similar to previous published studies of children in developing countries. The percentage of patients with FUO in whom it was possible to establish a final diagnosis in the present study was 90% [8, 10, 11].

Infectious disease was the most common cause of FUO (35 cases). This was also documented in many previous studies. Specific infections especially tuberculosis, typhoid and brucellosis are endemic in India. 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 India [7]. 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.

There are many differences between developed and developing countries as regard causes and investigation approaches, which were well discussed in a previous study [12]. 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 [12]. 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.

Conclusion

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. Education about the indiscriminate use of antibiotics for any febrile presentation and familiarising primary care physicians about the common causes of FUO is important in improving the diagnosis and management FUO in developing countries. 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.

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