

Clinico-aetiological profile of fever of unknown origin (FUO) in children in a single centre

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Abstract

Objective: To identify the aetiology of children presenting with fever of unknown origin (FUO).

Method: A prospective study of children between 6 months to 18 years admitted for FUO at Employees State Insurance Corporation Medical College and Post Graduate Institute of Medical Science and Research, Bangalore, India, from March 2017 to February 2018 were included. All children were subjected to detailed history, clinical examination and baseline investigations. Further investigations were done based on the presumptive diagnosis

Results: Of the 3656 children admitted to the paediatric ward for various diseases during the study period, 24 fulfilled the inclusion criteria. Children between 12-18 years constituted the majority. Infections were the commonest cause of FUO (70.8%). Among them tuberculosis was the commonest (n=11). Mortality was 8.3%

Conclusions: In our study, infections were the cause of FUO in 70.8% and tuberculosis was the commonest infectious cause.

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Introduction

The term 'fever of unknown origin' (FUO) was first described by Petersdorf and Beeson in the adult population¹. It is best reserved for children

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with fever documented by a health care provider for which a cause could not be identified after three weeks of evaluation as an outpatient or after one week of evaluation in a hospital².

Objective

To identify the aetiology of children presenting with FUO

Method

A prospective observational study was conducted from March 2017 to February 2018, in the Paediatric Department of Employees State Insurance Corporation Medical College (ESICMC) and Post Graduate Institute of Medical Science and Research (PGIMSR), Bangalore, India. All children between 6 months to 18 years who had fever of 3 weeks at or after admission, with normal first line investigations were included in the study. A detailed clinical examination was performed. First line investigations like complete haemogram, routine urine test and urine culture, blood culture, Mantoux test, chest x-ray, malarial parasite (MP) smear, Widal test, leptospira antibody and Weil Felix tests were done in all patients. Additional tests like sonogram, serology, antinuclear antibody (ANA) profile, imaging studies, lumbar puncture, fine needle aspiration cytology (FNAC) of lymph node, bone marrow aspiration, culture and biopsy and bronchoscopy were done wherever indicated.

Results

During the study period, out of 3656 children admitted to the paediatric ward, twenty four children, who fulfilled the inclusion criteria of FUO, were enrolled for the study. Adolescents in the age group of 12-18 years constituted the majority (n=14, 58%). Four children were below 5 years (among them one was an infant) and six were aged between 5-12 years. No sex preponderance was noted with the male to female ratio 1.18:1. The duration of fever ranged from 15 days to 4 months at admission with a mean of 4.6 weeks. Eleven (45%) children had fever of 3 weeks duration whilst 8 (33.3%) children had fever of more than 1 month. In addition to fever, other symptoms noted were cough (n=5), joint pains (n=5), loss of weight (n=8), loss of appetite (n=4), headache, vomiting, weakness and convulsions (n=4) and abdominal pain (n=2). All the children had received a course of antibiotics and four children had received

antimalarial drugs before admission on an outpatient basis. History of contact with tuberculosis was elicitable in 3 (12.3%) and with pets at home in 2 (8.3%).

Four children weighed below the third percentile. Pallor was found in 10 (41%) children, significant cervical lymphadenopathy in 5 (20.8%), hepatomegaly in 10 (41%) and splenomegaly in 7 (29.2%) children. Detailed systemic examination was normal in the majority of t children.

Baseline investigations revealed anaemia in 50% of the children with a mean haemoglobin of 9.9g% varying from 6.9-13.5g%. Pancytopenia was noted in three (12.5%) children, erythrocyte sedimentation rate (ESR) was raised in 17 (70%) ranging from 35-120 mm in the first hour, and the C-reactive protein (CRP) was positive in 8 (33.3%) children.

Mantoux test was positive in eight children. Microbiological confirmation of tuberculosis using Zeel-Nielson staining or Cartridge Based Nucleic Acid Amplification Test (CBNAAT) for acid fast bacillus was positive in 3 children. Computerized tomography (CT) of thorax and abdomen was done in 12 children and showed hilar adenopathy in 7, lung nodule with splenomegaly in one, hepatomegaly with multiple haematomas in the IV segment of the liver in one and was normal in the other three. On 2D Echocardiography, one child showed vegetations, and the other had pericardial effusion.

Aspiration cytology of lymph node revealed reactive lymphadenitis in 4 children and one child had necrotizing granuloma. Bone marrow

examination done in 2 children showed evidence of histiocytic macrophages in a normal marrow.

The aetiology of FUO was categorized into infections (n=17, 70.8%), malignancy (n=2, 8.3%), connective tissue disorders (n=1, 4.1%), miscellaneous (n=2, 8.3%) and undiagnosed (n=2, 8.3%) as shown in Table 1.

Table 1: Aetiology of FUO in our study (n=24)

Diagnosis	No. (%)
Tuberculosis	11 (45.8)
Enteric fever	02 (08.3)
Rickettsial fever	01 (04.2)
Plasmodium vivax malaria	01 (04.2)
Infective endocarditis	01 (04.2)
Hepatic haematoma	01 (04.2)
HLH	02 (08.3)
Systemic lupus erythematosus	01 (04.2)
Reactive arthritis	01 (04.2)
Subcutaneous panniculitis	01 (04.2)
Undiagnosed	02 (08.3)

HLH: Haemophagocytic lymphohistiocytosis

The commonest infective cause for FUO was tuberculosis (n=11, 45%) with pulmonary tuberculosis in 4 and extra-pulmonary TB in 7 (TBM in 3, Lymph node tuberculosis in 3, disseminated tuberculosis in 1). Out of the two undiagnosed children, one child improved after 25 days of fever with symptomatic treatment and another child died at the end of three weeks with sudden onset of multi-organ dysfunction.

The diverse aetiologies of FUO in various studies are shown in Table 2.

Table 2: Aetiologies of FOU in various studies

Study	No. of cases of FOU	Infection (%)	Connective tissue diseases (%)	Malignancy (%)	Miscellaneous (%)	Undiagnosed (%)
Present	24	70.8	04.1	08.3	08.3	08.3
Landge A A et al	49	79.0	14.0	0.0	06.1	12.0
Govindarajulu S et al	120	69.1	05.0	16.7	05.8	03.4
Joshi et al	49	69.4	02.1	12.2	04.1	12.2
Chantada et al	113	36.3	13.2	10.0	22.0	19.5
Cogulu et al ¹³	80	57.7	06.3	02.5	20.0	12.5
Bakasvilli et al	52	61.5	04.0	04.0	17.3	13.5
Hashan et al	127	36.2	10.2	29.9	7.87	15.8
Ching-Yi Cho et al	126	27.0	12.7	16.6	19.8	23.8
Ya-Li Chien et al ¹⁴	93	37.6	14.1	17.2	16.1	15.1

Definitive diagnosis of TB based on the gold standard was arrived at in 8 (33.3%) children. Three had microbiologically confirmed tuberculosis, 1 had urine culture positive for Klebsiella, 2 had HLH based on bone marrow

examination, one had SLE based on ANA titres and one had infective endocarditis based on vegetations in the 2D Echo. Invasive investigations like bone marrow, lumbar puncture, FNAC, pleural

aspiration and broncho-alveolar lavage (BAL) was done in a total of eight (33.3%) children

Twenty (83.3%) children recovered from the illness and one child diagnosed as subcutaneous panniculitis was lost to follow up. Two (8.3%) children died in the study group out of which one was diagnosed as hepatocellular T cell lymphoma with haemophagocytic lymphohistiocytosis (HLH) and the other was undiagnosed. One child diagnosed as T cell lymphoma is currently on chemotherapy.

Discussion

FUO in children remains a diagnostic challenge for pediatricians. The aetiology of FUO varies depending on the geographical location, economy of the region studied, presence of vectors of infection, referral patterns, age of children, time of the study and the availability of diagnostic tests³. The incidence of FUO is around 0.5-3% in various studies². Our study showed an incidence of 0.6% similar to a study by Chouchane S et al which showed an incidence of 1.02%⁴. Majority of children in the study group were adolescents (58%) similar to a study by Bakashvili *et al* where they constituted 87%⁵. The mean duration of fever in our study was 34 days with the majority (45%) having fever of 21 days. Sixteen percent had fever for more than 2 months. This was similar to Chouchane S *et al* and Ching Yicho *et al* who had a mean fever duration of 30 days and fever of more than 60 days in 6.3%.^{6,7}

Aetiology of FUO is broadly classified as infectious, connective tissue disorders, malignancies and miscellaneous. Infections are the main cause for FUO constituting 60-70%⁸. In our study they accounted for 70.8% similar to studies by Landge A A *et al* (79%), Santosh G *et al* (69.1%) and Joshi N (69%)^{9,10,11}. Table 2 shows the percentages of various causes in different studies. Tuberculosis constituted the majority of infections (45%) in our study, similar to a study by Chantada *et al* and A A Landge *et al* (35%)^{6,9}. However Joshi N *et al* and Santosh G *et al* have documented enteric fever as the commonest cause of FUO in their studies, while Ching Yicho *et al* have documented Epstein Barr virus and cytomegalovirus as the commonest aetiological factor. In our set up, enteric fever is a common infection diagnosed by cultures early in the course of illness. Hence not many cases of enteric fever pose a diagnostic challenge as FUO and also, our study group excluded children with fever of less than three weeks.

Definitive diagnosis of FUO was made in 33.3% as against a study by Landge A A *et al* which showed definitive diagnosis in 55%. Diagnosis was

established in two thirds of the cases by noninvasive methods similar to the study by Rasha AH *et al* showing that a good history and relevant investigations help in reaching the diagnosis¹². All children diagnosed as infections recovered. The mortality in our study was 8.3%.

FUO in children poses a challenge to paediatricians. The aetiology varies depending on the geographical factors and economy of the nation. Infections still remain predominant cause of FUO in developing nations. Diagnosis can be established in the majority of the cases by noninvasive methods. Tuberculosis continues to be the leading cause of FUO among children. CT of thorax and abdomen has emerged as an important diagnostic tool in children with FUO.

Conclusions

In our study, infections were the cause of FUO in 70.8% and tuberculosis was the commonest infectious cause.

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