



Etiological Profile Of Fever Of Unknown Origin In Children Between 1 Month To 12 Years Admitted In An Urban Referral Centre

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Abstract

Background: The etiology of fever of unknown origin varies from region to region, and also with age. Although the relative frequencies are somewhat different, the three most commonly identified causes of fever of unknown origin in children are Infectious diseases, Rheumatological disorders, and Malignancies. The adage that a fever of unknown origin is more likely to be caused by an unusual manifestation of a common disorder than by a common manifestation of a rare disorder is true in pediatrics.

Aim Of The Study: 1 To study the etiological profile, of fever of unknown origin in children between 1 month to 12 years. 2. To utilize the outcome of the present study in the management of similar cases in the future to shorten the delay.

Materials And Methods: This Descriptive study. Department Of Pediatrics, Government Medical College, Thanjavur, Tamil Nadu, From August 2019 to March 2020. Totally 182 Children with a fever documented by a health care provider and for which the cause could not be identified after 3 wks of evaluation as an outpatient or after 1 wk of evaluation in the hospital Inclusion criteria: A documented fever of more than 38oC which is present at least twice weekly for longer than three weeks for outpatients. A child with a fever of more than 38oC with no apparent diagnosis even after one week of inpatient investigations.

Results: Infections were the most common cause of FUO constituting 37.4%. Among infections, tuberculosis was the commonest one causing 12% of FUO. Typhoid (6.6%) and UTI (6.6%) were the next common infections. The extrapulmonary tuberculosis was the commonest form of tuberculosis observed. Of these extrapulmonary forms, abdominal tuberculosis was most commonly observed. Brucellosis was observed as the cause of FUO in six cases. The triad of fever, arthralgia/arthritis, and hepatosplenomegaly was observed in all six cases. All three culture-negative infective endocarditis cases were diagnosed with the help of duke criteria. Malignancy was the second most common cause of FUO occurring in 24.2%. In this group, acute lymphoblastic leukemia (16%) was most commonly observed as a cause of FUO, followed by acute myeloid leukemia (3.8%) and Hodgkin's lymphoma (2.2%). Noninfectious inflammatory disorders were the next common cause of FUO, occurring in 22%.

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

Keywords: Child, Fever of unknown origin, Infection

Introduction

Fever has been defined as "a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host". Most fevers are both brief and self-limited and do not require extensive diagnostic investigation or specific therapy.¹ Some fevers are manifestations of more serious illnesses, most of which can be readily diagnosed and effectively treated. A small but important subgroup of fevers is both persistent and difficult to diagnose. Such a perplexing subgroup of fevers can be conveniently termed as a fever of unknown origin so it warrants a particular systematic approach to diagnostic evaluation and management.² Most fevers of unknown origin result from common diseases that may be atypical in the presentation. In some cases, the presentation of fever of unknown origin is typical of the diseases (Juvenile rheumatoid arthritis) but an explicit diagnosis can be established only after prolonged observation because there are no associated findings on physical examination and all laboratory results are negative or normal.³ Mechanism of fever from disease is complex, but by a brief sort of definition is produced by the action of certain substances (probably produced by the disease process from the tissues or WBC of the host) acting on thermoregulatory centers in the hypothalamus. The normal balance between the anterior center (concerned with heat dissipation by vasodilation and sweating related to parasympathetic activity) and the posterior center (concerned with conserving heat by vasoconstriction and shivering and related to sympathetic activity) is upset to produce a positive heat balance and raise the body temperature above normal.⁴ Fever may be provoked by many stimuli. Most often, they are bacteria and their endotoxins, viruses, yeasts, spirochetes, protozoa, immune reactions, several hormones, medications, and synthetic polynucleotides.⁵ These substances are commonly called exogenic pyrogens. Cells stimulated by exogenic pyrogens form and produce cytokines called endogenic pyrogens. Endogenic pyrogens centrally affect the thermosensitive neurons in the preoptic area of the hypothalamus increasing the production of heat and decreasing heat loss. The body temperature increases until it reaches the set

point. This information is transferred by the temperature of the blood that flows around the hypothalamus.⁶ The decrease in temperature is controlled by the activation of mechanisms regulating the increased outcome of heat to the surrounding area. The increased outcome continues in the favorable case until the new equilibrium is achieved. The most important endogenic pyrogens are IL-1, IL-6 and cachectin also called the tumor necrosis factor (TNF). In the hypothalamus, IL-1 and TNF trigger the synthesis of prostaglandins of group E from the arachidonic acid of cytoplasmic membranes of target cells. The precise mechanism by which prostaglandin PGE reset the central thermostat is not known.⁷ Etiology of fever of unknown origin varies from region to region, and also with age. Although the relative frequencies are somewhat different, the three most commonly identified causes of fever of unknown origin in children are Infectious diseases, Rheumatological disorders, and Malignancies.⁸ The adage that a fever of unknown origin is more likely to be caused by an unusual manifestation of a common disorder than by a common manifestation of a rare disorder is true in pediatrics. Early identification of the exact etiology will help in better management of similar cases in the future.^{9,10} Hence to know the exact etiology of fever unknown in children between 1 month - 12 years, in this region this study has been planned.

Materials And Methods

This Descriptive study. Department Of Pediatrics, Government Medical College, Thanjavur, Tamil Nadu, From August 2019 to March 2020. Totally 182 Children with a fever documented by a health care provider and for which the cause could not be identified after 3 wks of evaluation as an outpatient or after 1 wk of evaluation in the hospital Inclusion criteria: A documented fever of more than 38°C which is present at least twice weekly for longer than three weeks for outpatients. A child with a fever of more than 38°C with no apparent diagnosis even after one week of inpatient investigations. Inclusion criteria: A documented fever of more than 38°C which is present at least twice weekly for longer than three weeks for outpatients. All children who are satisfying the above criteria are included. Exclusion criteria: Immunocompromised children as defined by; Neutropenia: (WBC count <1000 per microlitre and or neutrophil count <500 per microlitre) Known HIV

patient, An intake of immunosuppressive drugs or prednisolone more than 2mg/kg/day at least for 2 weeks/>20mg if weight >10kg. Nosocomial FUI is a hospital-associated disorder in which patients first

manifest fever after having been hospitalized for at least 24 hours, not present, or incubating on admission.

Results

Table - 1 Distribution By Age And Gender

Age (In years)	Total	Male		Female	
	n	n	%	n	%
0-1	13	9	69.2	4	30.8
>1-3	35	24	68.6	11	31.4
>3-6	49	30	61.2	19	38.8
>6-9	41	25	61	16	39
>9-12	44	18	40.9	26	59.1
Total	182	106	58	76	42

Table :1 The male-to-female ratio was 1.3:1.Children in the age group of 3-6 years constitute the majority of the study population.

Table – 2: Causes Of Fever Of Unknown Origin According To Age Group

Age group	Infections	Malignancy	Non-infectious inflammatory diseases	Undiagnosed
0-1 (n=13)	9(69.2%)	4(30.7%)	0	0
>1-3(n=35)	6(17.14%)	18(51.4%)	5(14.28%)	6(17.1%)
>3-6(n=49)	22(44.9%)	11(22.4%)	8(16.3%)	8(16.3%)
>6-9(n=41)	21(51.2%)	5(12.1%)	6(14.6%)	9(21.9%)
>9-12(n=44)	0	6(13.6%)	21(47.7%)	7(15.9%)
Total	68 (37.4%)	44 (24.2%)	40 (22%)	30 (16.5%)

Table:2 In infancy infections remains the commonest cause of fever of unknown origin, and no case in this age group remains undiagnosed. Between 1-3years malignancy (especially acute lymphoblastic leukemia)

was the most commonest cause. Between 3-6 years infections are the commonest cause of fever of unknown origin. After 9 years non-infective inflammatory disease dominates the causes of FUO.

Table – 3: Causes Of Fever Of Unknown Origin

Causes of FUO	n	%
Infections	68	37.4
Tuberculosis	22	32.4
UTI	12	17.6
Enteric Fever	12	17.6
Brucellosis	6	8.8
Malaria	2	2.9
Hepatitis B	3	4.4
Endocarditis	3	4.4
Leptospirosis	2	2.9
Bone & joint infections*	3	4.4
Other bacterial infections#	3	4.4
Malignancy	44	24.2
ALL	29	65.9
AML	7	15.9
Hodgkins Lymphoma	4	9.1
Non-Hodgkins Lymphoma	1	2.3
Histiocytosis	2	4.5
Myelo Dysplastic Syndrome(refractory anemia with excess blast)	1	2.3
Non-infectious	40	22
Inflammatory disease		
Juvenile Rheumatoid Arthritis	25	62.5
SLE	10	25.0
Vasculitis	4	2.5
Kawasaki disease	1	10.0
Undiagnosed	30	16.5
Death	1	3.3

Table – 4:Distribution Of Non-Infectious Inflammatory Diseases By Age Group

Diagnosis	Age group (in years)									
	0-1 (n=13)		>1-3 (n=35)		>3-6 (n=49)		>6-9 (n=41)		>9-12 (N=44)	
	n	%	n	%	n	%	n	%	N	%
Juvenile Rheumatoid Arthritis	-	-	3	8.6	4	8.2	4	9.8	14	31.8
SLE	-	-	1	2.9	-	-	2	4.9	7	15.9
Non-specific vasculitis	-	-	-	-	4	8.2	-	-	-	-
Kawasaki Diseases	-	-	1	2.9	-	-	-	-	-	-

Table:4 In older children between 9 - 12 years, NIID was the most commonest cause of FUO. Among NIID JRA was the commonest cause of FUO in all age groups

Table – 5:Common Causes Of Fever Of Unknown Origin

CAUSES	n	%
1. Undiagnosed	30	16.5
2. Acute lymphoblastic leukemia	29	16
3. Juvenile rheumatoid arthritis	25	13.7
4. Tuberculosis	22	12.1
5. Urinary tract infections	12	6.6
6. Typhoid fever	12	6.6
7. Systemic lupus erythematosus	10	5.5
8. Acute myeloid leukemia	7	3.8
9. Brucellosis	6	3.3
10. Hodgkins lymphoma	4	2.2
11.Nonspecific vasculitis	4	2.2

12. Infective endocarditis	3	1.6
13. Bone and joint infections	3	1.6
14. Hepatitis B	3	1.6
15. Leptospirosis	2	1.1
16. Malaria	2	1.1
17. Kawasaki disease	1	0.5
18. Other bacterial infections	3	1.6
19. Other malignancy	4	2.2

Table:5 Infections (37.4%) were the commonest cause of FUO, followed by Malignancy (24.2%) and NIID (22%). Among individual causes, after the undiagnosed group, acute lymphoblastic leukemia, followed by Juvenile rheumatoid arthritis, tuberculosis urinary tract infections, enteric fever, and systemic lupus erythematosus constitute the bulk of the cases.

Table – 6: Causes Of Fever Of Unknown Origin By Timing Of Diagnosis.

Diagnosis	All patients with the diagnosis (n=152)	Early diagnosis (<7 days) (n=62)	Intermediate diagnosis (7-14 days) (n=64)	Late diagnosis (> 14 days) (n=26)
INFECTIONS	68(44.7%)	26(36.1%)	32(50%)	10(38.4%)
Tuberculosis	22	7	12	3
Urinary tract infections	12	5	6	1
Enteric fever	12	5	6	1
Brucellosis	6	1	2	3
Infective endocarditis	3	1	-	2
Hepatitis B	3	1	2	-
Leptospirosis	2	-	2	-
Malaria	2	2	-	-
Bone & joint infections	3	3	-	-
Other bacterial infections	3	1	2	-
MALIGNANCY	44(28.9%)	26(36.1%)	18(28.1%)	-
Acute lymphatic leukemia	29	19	10	-
Acute myeloid leukemia	7	5	2	-
Hodgkins lymphoma	4	2	2	-

Non-Hodgkins lymphoma	1	-	1	-
Histiocytosis	2	-	2	-
Myelodysplastic syndrome(rare)	1	-	1	-
NON-INFECTIOUS INFLAMMATORY DISEASES	40 (26.3%)	10 (13.9%)	14 (21.8%)	16 (61.1%)
Juvenile rheumatoid arthritis	25	7	6	12
Systemic lupus erythematosus	10	1	7	2
Non-specific vasculitis	4	2	1	1
Kawasaki disease	1	-	-	1

Table 6 lists the final diagnosis and the diagnostic categories in the 152 children with the diagnosis, subdivided according to the timing of diagnosis. In the group with late diagnosis, noninfectious inflammatory disease constituted the most prevalent diagnostic category. In the group with early diagnosis, infection & malignancy was the most common diagnosis.

Table – 7:Decisive Method Of Diagnosis

Diagnostic Method	All patients with diagnosis (n-152)	Early diagnosis (<7 days) (n-62)	Intermediate diagnosis(7-14days) (n-64)	Late diagnosis (>14 days) (n-26)
	n	n	n	n
History and evolution	25 (16.4%)	7 (28%)	6 (24%)	12 (48%)
Culture	14 (9%)	9 (64%)	5 (35%)	-
Infections serology	21 (14%)	3 (14%)	13 (61%)	5 (23.8%)
Standard radiology	2 (1.3%)	2 (100%)	-	-
Abdominal USG	1 (0.6%)	1 (100%)	-	-
ECHO	3 (1.9%)	1 (33%)	-	2 (67%)
CT scan	3 (1.9%)	1 (33%)	2 (67%)	-

Bone marrow aspiration	37 (24%)	24 (64%)	13 (36%)	-
Biopsy	17 (12%)	4 (23%)	13 (76.4%)	-
Others / Combination	20 (19%)	10 (34%)	12 (41%)	7 (24%)

Table 7 gives the decisive method of diagnosis in whom a diagnosis was obtained. Bone marrow aspiration was the most rewarding technique, especially in the groups with early or intermediate diagnoses. Microbiological analysis (culture and serology) also had a reasonable diagnostic yield (35%). The history and evolution of disease made a significant contribution to the late group. Imaging techniques (Radiological, Echo, CT Scan, Usg) although infrequently leading in isolation to definite diagnosis, were often contributory.

Table – 8 Outcome Final Diagnosis

Final Diagnosis	All patients with diagnosis (n=62)	Early diagnosis (< 7 days) (n=62)	Intermediate diagnosis (7 - 14 days) (n=64)	Late diagnosis (> 14 days) (n=26)
	n	n	n	n
Infections	68	26 (38%)	32 (47%)	10 (15%)
Malignancy	44	26 (59%)	18 (40.9%)	-
Noninfectious inflammatory diseases	40	10 (25%)	14 (35%)	16 (40%)

Outcome By Age Groups

Age Group	All patients (n = 182)		Diagnosed (n=152)		Undiagnosed (n=30)		Death (n=9)		Lost to Followup (n=8)	
	n	%	n	%	n	%	n	%	n	%
< 1 year	13	7.1	11	84.6	-	-	2	15.4		
>1 – 3 years	35	19.2	26	74.3	6	17.1	2	5.7	1	2.9
>3 – 6 years	49	26.9	36	73.5	8	16.4	-	-	5	10.2
>6 – 9 years	41	22.5	30	73.2	8	19.5	3	7.3	-	-
>9 – 12 years	44	24.2	33	75	7	15.9	2	4.5	2	4.5

Table 9 Nine children died during the index admission. In two cases death was unrelated to the febrile illness (died of aspiration). Four deaths occurred among malignancies (three cases of acute lymphatic leukemia, and one case of histiocytosis). A twelve-year female child diagnosed to have a splenic abscess died due to rupture, and two children diagnosed with systemic lupus erythematosus died of acute renal failure. While hematological malignancies constitute 24.1% of cases of fever of unknown origin, they were responsible for 4(57.1%) of the 7 fatalities related to the febrile illness.

Discussion

Comparison of the present study with the FUO case series from various hospitals, which includes at least four studies from India revealed that apart from a rise in malignancy cases, an increase in the noninfectious inflammatory disease category was also noted. Among 182 cases, infections constitute 68(37.4%), malignancy 44(24.2%), noninfectious inflammatory diseases 40(22%), and undiagnosed in 30(16.5%).¹¹ In infancy infections remain the commonest cause of fever of unknown origin, and no case in this age group remained undiagnosed. Between 1-3years malignancy (especially acute lymphoblastic leukemia) was the most commonest cause. Between 3-9 years infections remain the commonest cause of fever of unknown origin.¹² After 9 years, non-infectious inflammatory disease dominates causes of FUO.¹³ Gamboa Marrufo JD *et al.*, also concluded that children less than 6 years were more likely to have an infectious etiology while 80% of collagen inflammatory disease occurred in the group older than 6 years. Noninvasive methods helped in arriving at a decisive diagnosis in 102 (67.1%) cases, invasive methods helped in diagnosis in 50 cases (32.8%). The prognosis of children in the present study with undiagnosed fever was relatively good, in agreement with the other case series. Infections remain the most common cause of FUO, constituting about a third of cases in various case series over the last five decades. Although in earlier studies in western literature infections were predominant, now connective tissue^{9,10,11,38} disorders are emerging as an important cause of FUO.¹⁵ In the present study infections constituted 37.4% of FUO cases, confirming earlier trends that infections were the commonest cause of fever of unknown origin. The increased incidence of infection found in our study may be attributed to the fact that most of the children were of low socio-economic status, living in crowded areas, and half of them were from slums and hence more prone to infections.¹⁶ Tuberculosis is endemic in this part of

our country. The diagnosis was delayed despite a high index of suspicion because of a normal chest x-ray, negative skin test, inconclusive imaging, and histopathological examination. In the present study also tuberculosis was the predominant cause of infections.¹⁷ In the present study of extrapulmonary tuberculosis, tuberculosis of the abdomen was the commonest. The barium meal series helped in the diagnosis of all children with intestinal tuberculosis.¹⁸ Among infections brucellosis constituted 38%, followed by typhoid fever. In the present study typhoid fever constitutes 12(6.6%) cases of FUO. In the present study blood, culture was positive only in 2(16%), the low positivity may be due to antibiotics taken by the patient before admission and most patients were admitted after one week.¹⁹ In diagnosing urinary infection, the sensitivity, and specificity of proteinuria were 79 and 80% respectively, that of bacteriuria 78 and 96%, and that of pyuria > 10 WBC/HPF 80 and 82% respectively. 61% among the culture-positive groups had all these three parameter present, as against only 0.5% in the culture-negative group ($P < 0.001$). All these 3 parameters were absent in 70% of the culture-negative group, as against 8% in the culture-positive group ($P < 0.001$). Bacteriuria in association with either proteinuria or Pyuria > 10 Wbc/hpf had 98% specificity in diagnosis. In the diagnosis of UTI, Pyuria > 10 Wbc/HPF was significantly more specific than the conventional > 5 WBC/HPF. Isolated proteinuria, isolated pyuria, isolated bacteriuria, and microscopic haematuria were not features of urinary tract infection in children.²⁰ In the present study UTI observed in 12(6.6%) cases of FUO. In the present study, UTI was the commonest cause of FUO in infancy. Among 12 culture-positive children, proteinuria was present in 6(50%) and pyuria was absent in 4(33%) cases. Four patients with FUO had acute brucellosis (3.3%) while 8 (6.6%) had serological evidence of previous brucella infection. Most cases of typical staphylococcal or streptococcal endocarditis are easily diagnosed as a cause of acute

fever. FUO is more likely to be encountered in patients who have culture-negative endocarditis due to prior antibiotic use or difficult-to-culture organisms. The recently proposed Duke criteria were confirmed to be more sensitive for the diagnosis of infective endocarditis. In the present study, three cases of infective endocarditis masquerading as fever of unknown origin were noted. In two cases of previously well children without a focus, vegetation involving the tricuspid valve was found.²¹ This suggests that a high degree of suspicion should be there to diagnose infective endocarditis. In all three cases, cultures were negative even when three blood samples were taken appropriately, this phenomenon might be due to prior administration of antibiotics. In the present study malignancy (24.2%) follows infection (37.4%) as a cause of fever of unknown origin. Among seven children who presented with a total count in the leucopenic range, five children did not show blast cells in the peripheral smear. Bone marrow aspiration cytology was the decisive investigation in acute leukemia.^{23,24,25}

Conclusion: Infectious diseases were the commonest cause of FUO. The delay in diagnosis was due to atypical presentations or inappropriate use of antibiotics before the referral. Noninfectious causes, malignancy, and collagen or vascular disorders were diagnosed in the 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-thirds of the case. While the rest of the patients required invasive procedures like biopsy, bone marrow aspiration, endoscopy, and/or bronchoscopy.

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