International Journal of Contemporary Pediatrics
Gandla N et al. Int J Contemp Pediatr. 2021 Nov;8(11):1842-1847
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20214157

Original Research Article

A study of etiology of fever of unknown origin in children aged 2 months to 18 years

Naveen Gandla*, Sheela A. Bharani, Tushar P. Shah

Department of Pediatrics, K.G. Patel children hospital, Vadodara, Gujarat, India

Received: 31 August 2021
Revised: 30 September 2021
Accepted: 04 October 2021

***Correspondence:**
Dr. Naveen Gandla,
E-mail: naveengandla12@gmail.com

ABSTRACT

Background: In an era of advance science of modern technologies, many diseases are diagnosed and excluded rapidly and now Fever of Unknown Origin (FUO) has been redefined for any fever of 380C lasting for more than 7 days without any clear cause. The aetiology varies according to different geographical regions, socioeconomical status, age, prevalence of resistance to antimicrobial drugs and genetic susceptibility.
Methods: It was a descriptive cross sectional, hospital-based study, carried out on 150 children from August 2018 to May 2020. All cases in the age group of 2 months to 18 years with fever of >38.0°C, lasting for more than 7 days without a clear source were included.
Results: The mean age of presentation was 5.8 years±Standard Deviation of 3.7 years with male to female ratio was 1.4:1. Nearly half of the cases, presented with the duration of fever between 8-14 days. Enteric fever in 52%, tuberculosis in 13.3% and acute lymphoblastic leukemia (ALL) in 8.5% were three common etiologies found in this study. Amongst all cases of FUO, infective causes were seen in 113 (75.3%) followed by malignancies in 15(10%) cases. In 10 (6.7%) cases, cause could not be established.
Conclusions: Enteric fever and tuberculosis were the leading etiologies from infective subgroup of FUO. ALL was the commonest cause from malignancies sub group. FUO presenting with low haemoglobin, platelet is a pointer towards malignancy. Occurrence of FUO with infectious diseases and malignancies was found in younger age group as compared to connective tissue diseases.

Keywords: FUO, Etiology

INTRODUCTION

In an office practice, around 20-30% of all pediatric consultations are done for fever.[1,2] Most fevers are viral fevers and are self-limiting but at times it is a diagnostic challenge to find a major serious condition, focus of infection, to take decision for laboratory investigations, hospitalization and treatment.

When fever remains for longer duration, it is stressful to a child, parents and even for a treating doctor. In an era of advance sciences of modern technologies of radio imaging and availability of rapid molecular diagnostic techniques for various infections, many causes are diagnosed and excluded rapidly and it is reasonable to consider Fever of Unknown Origin (FUO) for any fever of 380C (100.40 F) lasting for more than 7 days without any clear cause. Some basic primary investigations are usually done but are no more considered the prerequisites for the definition of FUO.[3-5]

The etiology of FUO is not same all over the world. It varies according to different geographical regions, socioeconomical status, age and genetic susceptibility.

Apart from these, availability of health facilities, coverage and country's policies for immunization, availability and affordability of advanced diagnostic techniques, safe drinking water and personal hygiene practices of families and prevalence of resistance to antimicrobial drugs also play a major role in determining a cause of FUO.

Present study has been taken to identify the etiology of FUO in children from the Western region of India, where the re/emerging infectious diseases keep on changing every few years. Certain endemic diseases have also developed resistant to various antimicrobial drugs which can present with prolonged pyrexia.

METHODS

This was a descriptive cross sectional, hospital-based study, carried out at Kashiben Gordhandas Patel (K.G.P) Children hospital from August 2018 to May 2020 after the approval from the Ethics and scientific committee of KGP Children Hospital, Vadodara, Gujarat. Minimum 144 patients were required to estimate various subgroups of etiologies by 40% with 20% relative precision and 95% confidence.150 patients fulfilling the inclusion criteria were included after the written consent from parents or relatives.

Inclusion criteria

All indoor and outdoor cases in the age group of 2 months to 18 years were taken who had presented with fever of > 38.0°C (100.4°F), lasting for more than a week without a clear source even after some basic preliminary investigations.[3,4,6]

Exclusion criteria

A diagnosed case of malignancy or collagen vascular disease who was readmitted and those children with primary immunodeficiency disorders, HIV infection, organ transplanted were excluded.

Methodology

It was a hospital based study and the patients who attended the outpatient department or came in emergency room were asked about the history of presenting symptoms. A detail history of fever in the form of onset, pattern, severity, duration, frequency, diurnal variation, evolution/progress and response to antipyretics drugs was evaluated. Associated symptoms with fever were also inquired and observed. A relevant past, family, birth, immunization, developmental and dietary history, exposure to any drugs or pets, raw milk ingestion, recent travel history and epidemic of any disease were also inquired.

A thorough general and systemic examination was done along with, appearance of child and vital signs. A head to toe physical examination had been done, to detect the presence of pallor, jaundice, red eye, joint swelling, skin rashes, bleeding spots, bony tenderness, lymphadenopathy and edema.

Complete blood count and peripheral smear were done in all cases. Complete blood count was done with an automated cell counter machine. Peripheral smear examination was done by using Giemsa stain. Other primary investigations such as rapid diagnostic test (RDT) for malaria parasite, liver function tests, renal function tests, blood culture, widal test, urine routine and culture, blood culture, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), dengue serological titer, chest X-ray, tuberculin test, ultrasound (USG) abdomen and other basic metabolic investigations were done as a first phase of investigations. CSF examination was done as and when required. Serology of viruses, brucella, rickettsia and other infections; ANA profile; serum LDH, serum uric acid, immunoglobulins, lymphocyte markers, serum ferritin, triglycerides and fibrinogen were done as second line investigations whenever indicated. Case based radiological investigations such as CT and/or MRI brain chest, abdomen was also carried out. Tertiary line investigations included molecular diagnosis of various microorganisms; bone marrow aspiration/biopsy; liver and lymph node biopsies; endoscopy and bronchoscopy examination.

A diagnosis was categorized as confirmed as per available diagnostic tests such as identifying microorganisms, histopathological confirmation, specific serology IgM for various infective etiologies and standard diagnostic criteria for non-infectious diseases. A probable case was considered based on supportive clinical, radiological and laboratory investigations but was not confirmed by gold standard ways.

Statistical methods

Descriptive statistics and one way ANOVA test was applied to compare subgroups. P value was considered significant at 5% level for all the tests. Statistical package for social sciences (SPSS) 20 version was used for statistical analysis.

RESULTS

Out of 7051 patients, aged 2months to 18 years who were admitted at K.G Patel children hospital from August 2018 to June 2020, 150 cases were included in this study. Out of total 150 cases, 88 (58.7%) cases were males as against 62 (41.3%) female cases. A mean age of presentation was 5.8 years±Standard Deviation (SD) of 3.7 years. There were 92 (61.3%) cases from the urban area in comparison to 58 (38.7%) cases from rural area.

Table 1 shows distribution of cases of FUO in relation to duration of fever. There were 68 (45.3%) cases presented with 8-14 days of fever and remaining 82 (55%) presented with fever for more than 2 weeks. There were 22 cases,

who presented with low grade fever, 59 cases with moderate grade and 69 cases with high grade fever.

Table 2 shows enteric fever, tuberculosis and acute lymphoblastic leukemia were three common causes of FUO found in this study. Different etiologies were categorized into various sub groups such as infections, malignancies, connective tissue diseases, miscellaneous and undiagnosed conditions.

Table 1: Distribution of cases of FUO in relation to duration of fever.

Age group (years)	8-14 days (%)	15-21 days (%)	>22 days (%)	Total (%)
2 month-4 years	32 (49.2)	12 (18.5)	21 (32.3)	65
5-9	20 (38.5)	19 (36.5)	13 (25)	52
10-13	14 (46.6)	8 (26.7)	8 (26.7)	30
14-18	2 (66.7)	1 (33.3)	0 (0)	3
Total	68 (45.3)	40 (26.7)	42 (28)	150 (100)

Table 2: Etiology of fever of unknown origin.

Aetiology	Frequency N=150	%
Enteric fever	78	52
Tuberculosis	20	13.
Acute lymphoblastic leukemia	13	8.5
Dengue fever with complications	6	4.0
Kawasaki disease	5	3.3
Empyema	4	2.7
Hepatitis A (isolated)	4	2.7
Sytemic lupus erythematosus	3	2.0
Haemophagocyticlymphohistiocytosis	2	1.3
Acute myeloblastic leukemia	1	0.7
Primitive neuroectodermal tumor	1	0.7
Kikuchi fuzimato	1	0.7
Juvenile Idiopathic Arthritis	1	0.7
Pyogenic Meningitis (in a case of sickle cell disease)	1	0.7
Undiagnosed	10	6.7
Total	150	100

Table 3A: Mean and SD of complete blood count and CRP in various subgroups of etiology.

Variables	Subgroups of etiology	N	Mean value	SD±
Haemoglobin (Hb) (gm/dl)	Infections	113	10.07	1.84
	Malignancies	15	5.62	2.05
	Connective tissue diseases	9	8.74	1.71
	Miscellaneous conditions	3	7.50	1.39
	Undiagnosed conditions	10	10.53	1.26
	Total	150	9.52	2.27
Total leukocyte count (TLC)/(Cells/cumm)	Infections	113	10196.1	7179.55
	Malignancies	15	95116.67	214779.18
	Connective tissue diseases	9	14400	10895.90
	Miscellaneous conditions	3	10700	8740.14
	Undiagnosed conditions	10	9162.0	4590.84
	Total	150	18881.53	70943.51
Platelet count (Cells/cumm)	Infections	113	321567.26	223547.2
	Malignancies	15	85333.33	111369.8
	Connective tissue diseases	9	440000.00	279661.8
	Miscellaneous conditions	3	169000.00	192953.36

Continued.

Variables	Subgroups of etiology	N	Mean value	SD±
	Undiagnosed conditions	10	284800.00	164465.3
	Total	150	299547.33	227153.4
CRP (mg/L)	Infections	113	53.18	48.64
	Malignancies	15	42.39	34.96
	Connective Tissue Diseases	9	56.34	69.74
	Miscellaneous conditions	3	34.50	40.44
	Undiagnosed conditions	10	56.84	24.00
	Total	150	52.16	47.22

Table 3B: ANOVA test applied to different variables mentioned.

		Sum of squares	Df	Mean square	F	P value
Haemoglobin (Hb) (gm/dl)	Between groups	289.966	4	72.49	21.92	<0.001
	Within groups	479.453	145	3.30		
	Total	769.408	149			
Total Leukocyte Count (TLC)/ (Cells/cumm)	Between groups	9.70E10	4	2.42E10	5.38	<0.001
	Within groups	6.52E11	145	4.50E10		
	Total	7.44E11	149			
Platelet count (Cells/cumm)	Between groups	9.74E11	4	2.43E11	5.25	<0.001
	Within groups	6.71E12	145	4.63E10		
	Total	7.68E12	149			
***CRP(mg/L)**	Between groups	2861.78	4	715.44	0.315	0.868
	Within groups	329392.11	145	2271.67		
	Total	332253.896	149			

Table 4: Etiology of FUO in various studies.

Author	Country	Year of study	Total cases	Infectious diseases	Malignancies	Connective tissue diseases	Miscellaneous conditions	Undiagnosed conditions
				N (%)	N (%)	N (%)	N (%)	N (%)
Govinda-Rajulu et al[8]	India	2016-2016	120	83 (69.1)	20 (16.7)	6 (5)	7 (5.8)	4 (3.4)
Joshi et al[12]	India	2006-2007	49	34 (69.4)	6 (12.2)	1 (2.1)	2 (4.1)	6 (12.2)
Tezer et al[13]	Turkey	2005-2007	77	39 (50.7)	11 (14.4)	6 (7.4)	21 (27.5)	0 (0)
Chien et al[14]	Taiwan	2006-2014	93	35 (37.7)	16 (17.2)	13 (14)	15 (16.1)	14 (15)
Antoon et al[3]	USA	2002-2012	102	42 (41.2)	18 (17.6)	28 (27.5)	0 (0)	14 (13.7)
Coagulu et al[10]	Turkey	1996-2001	80	47 (58.7)	2 (2.5)	5 (6.3)	16 (20)	10 (12.5)
Chow et al[15]	Multi centre study	1950-2009	1638	832 (51)	93 (6)	150 (9)	179 (11)	384 (23)
Sumathi sri et al[7]	India	2015-2016	75	68 (90.6)	3 (4)	1 (1.3)	0 (0)	3 (4)
Kim et al[16]	Korea	2000-2014	100	19 (19)	15 (15)	7 (7)	(16)	43 (43)
Present study	India	2018-2020	150	113 (75.3)	15 (10)	9 (6)	3 (2)	10 (6.7)

There were 113 (75.3%) cases due to infective causes followed by malignancies found in 15 (10%). In 10 cases, etiology could not be established even after various laboratory and radiological investigations. The duration of fever lasting for >14 days were higher in malignancies group.

Above table 3A shows the mean and SD of complete blood count and CRP which were done in all 150 cases. The mean and SD of different laboratory parameters were compared in between the subgroups. Mean Hb and platelet count were lowest but mean TLC was found to be very high in malignancies subgroup. No much difference was observed in the mean CRP in the various subgroups of etiologies.

As shown in the table 3B, on applying ANOVA test, to compare the means in between the subgroups and within groups of various etiologies of FUO, p values of < 0.001 was found in the variables of hemoglobin, total count and platelets count but not in CRP.

There were 124 discharges, and 2 deaths were occurred in infectious diseases category only; 24 cases took discharge against medical advice. Discharge against medical advice was highest in malignancies subgroup.

DISCUSSION

There were 7051 patients admitted to this hospital during this study period of which 3,868 were males and 3,183 were females with male to female ratio of 1.2:1. From 150 cases who presented with FUO, male to female ratio was 1.41:1 with mean age of presentation was 5.8±SD of 3.7 years. The studies done by Sumathisri R et al, Govindarajulu et al and Solimani G et al found mean age of 7.2 years, 5.1 years and 4.1 years respectively.[7-9] Other studies done by Cogulu et al and Antoon et al found mean age of 3.8 years and 6.5 years respectively.[10,3] As most studies showed the mean age which was comparable to the present study and was ranging from 3.8 years to 7.2 years. It shows that FUO is presenting more in earlier age groups than older children. Only 2% cases of FUO were in the age group of 14-18 years and 20% cases were in 10-13 years of age group. A study done by Bakasvilli et al found more cases of FUO amongst older age group as compared to the present study and a study done by Cogulu et al.[10,11]

Enteric fever 78 (52%) was the most common etiology of FUO found in the present study followed by tuberculosis which was seen in 20 (13.3%), acute lymphoblastic leukemia was seen in 13 (8.5%) cases. Blood cultures were positive in 33 (42.3 %) cases of enteric fever. Serological diagnosis was suggestive of enteric fever in 45 (57.7%) cases. Infectious diseases were still the leading causes of FUO found in 113 (75.3%) cases. From total 20 cases of tuberculosis who had presented as FUO, 10 cases were of tubercular meningoencephalitis, 5 cases of pulmonary tuberculosis, 3 cases of disseminated tuberculosis, 1 each case was of abdominal tuberculosis and tubercular empyema.

Usually, dengue fever does not present with prolong fever but present study showed 6 cases of dengue fever (DF) with other co morbid conditions and had presented as FUO. There were 3 cases of DF with septicemia of methicillin resistant staphylococcus aureus; 2 cases were associated with Hepatitis A and 1 case had urinary tract infection along with dengue fever. In cases of DF, if fever lasts longer, then one should search for associated other etiologies or nosocomial infections. Following table shows the comparison of subgroups of various studies with the present study.

As seen from the above table 4, all studies from India showed the infectious diseases were leading causes of FUO which varied from 69.1% to 90.6%. In comparison to a study from USA, we found less number of cases of connective tissue disorders (27.5% versus 6 %). Various studies showed cases of malignancies in the range of 2.5% to 17.6%. Present study showed 113 (75.3%) cases with infective etiologies and 15 (10%) cases with malignancies who had presented as FUO. Duration of fever lasting for more than 14 days was found more in malignancies group than infectious and connective tissue subgroups. Most adult studies also showed infective conditions were the common causes of FUO which was ranging from 54.8%-60%.[17,18]

The mean age for FUO was found 5.8±3.4 years in infectious diseases, in malignancies group (5.6±4.4 years), and in connective tissue diseases (7.3±5.1 years) and in miscellaneous diseases (2.1±3.3 years). In a study done by Chien et al, mean age of patients with FUO caused by infectious diseases, malignancies, collagen vascular diseases, miscellaneous diseases were 7±5.4 years, 8.9±5.2 years, 6.5±4.3 years, 8.5±6.4 years, respectively.[14] Another study done by Tezer et al found mean age of patients with FUO amongst infectious diseases, malignancies, collagen vascular diseases, miscellaneous diseases were 4.9±4 years, 2.3±1.8 years, 5.6±2.5 years, 3.6±5.3 years respectively.[13] The mean haemoglobin and platelets were low in malignancies as most cases were of acute leukemia. The mean total counts were high in malignancies group. CRP was ranging from 34.50 mg/dl to 56.34 mg/dl in various different subgroups of etiology. On applying ANOVA test on various parameters as shown in table 3B, $p<0.05$ with a significant difference in parameters of haemoglobin, total count, platelet counts but not in CRP (p-value of 0.86)

The mean duration of fever before hospitalization was 12.88 days and duration of stay in the hospital was 9.69 days. Total duration of fever was high in malignancies group.

Most of the cases of FUO with various subgroups of etiologies had low mortality. Present study had 2 deaths from infectious subcategory due to meningitis, one due to

pyogenic and second from tuberculous meningoencephalitis.

Limitations of study

Few cases remained undiagnosed because of lack of adequate resources and due to prolonged hospital stay, some of them took discharge against medical advice.

CONCLUSION

Among all cases of FUO, enteric fever and tuberculosis were the two most common infectious diseases presented as FUO in this study. Acute lymphoblastic leukaemia was the commonest malignancy presenting as FUO in children. FUO presenting with low haemoglobin and platelet is a pointer towards malignancy. In younger age group, etiologies of FUO were more frequently due to infections and malignancies rather than connective tissue diseases.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Sahib A, El-Radh, James C. Clinical Manual of Fever in Children. Berlin: springer. 1-24.
2. Mahajan P, Batra P, Thakur N, Patel R, Rai N, Trivedi N, guidelines on evaluation and management of the febrile child presenting to the emergency department in India. Indian Pediatr. 2017;54:652-60.
3. Antoon JW, Potisek NM, Lohr JA. Pediatric fever of unknown origin. Pediatr Rev. 2015;36(9):380-90.
4. Chusid MJ. Pyogenic hepatic abscess in infancy and childhood. Pediatr.1978;10(1)554-9.
5. Kumar DP, Kumar DA, Rajeshwari K, Neeharika D, Sindhu G, Sreevidya B. Fever of unknown origin (FUO): evolution of case definition, changing aetiological spectrum. J Clin Sci Res. 2016;5:33-9.
6. Attard L, Tadoline M, De rose DU, Cattalini M. Overview of fever of unknown origin in adult and pediatric patients. Clin Exp Rheumatol. 2018;36:10-24.
7. Sumathisri R, Pandi K, Srinivasan S. Fever in the tropics: aetiology and clinical profile of fever of unknown origin in children-a prospective observational study in a tertiary care hospital in South India. Int J ContempPediatr. 2019;6:1834-8.
8. Govindarajulu S, Kalyanasundaram K, Pyarejan KS, Venkatasamy S. Clinical profile and etiological spectrum of fever of unknown origin in children aged 2 months to 12 years. Int J Contemp Pediatr. 2017;1:4:62-7.
9. Solimani G, ShafigjiShahri E, Salari Z, Shahrakipoor M, Teimouri A. Fever of Unknown Origin in Children Aged Three Months to Fifteen Years, Int J Infect. 2015;2(1):e22906.
10. Cogulu O, Koturoglu G, Kurugol Z. Evaluation of 80 children with prolonged fever. Pediatr Int. 2003;45:564.
11. Bakashvili LZ, Makhviladze MA, Pagava EK, Pagava KI. Fever of unknown origin in children and adolescents in Georgia: a review of 52 patients. Georgian Med News. 2006;55:66-9.
12. Joshi N, Rajeshwari K, Dubey AP, Singh T, Kaur R. Clinical spectrum of fever of unknown origin among Indian children. Ann Trop Paediatr. 2008;28:261-6.
13. Tezer H, Ceyhan M, Kara A, Cengiz AB, Devrim İ, Seçmeer G. Fever of unknown origin in children: the experience of one center in Turkey. Turk J Pediatr. 2012;54:583-9.
14. Chien YL, Huang FL, Huang CM, Chen PY. Clinical approach to fever of unknown origin in children. J MicrobiolImmunol Infect. 2017;50(6):893-8.
15. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr. 2011;7:5-10.
16. Kim YS, Kim KR, Kang JM, Kim JM, Kim YJ. Etiology and clinical characteristics of fever of unknown origin in children: a 15-year experience in a single center. Korean J Pediatr. 2017;60(3):77-85.
17. Efstathiou SP, Pefanis AV, Tsiakou AG, Skeva II, Tsioulos DI, Achimastos AD, et al. Fever of unknown origin: discrimination between infectious and non-infectious causes. Eur J Intern Med. 2010;21:137-43.
18. Naito T, Mizooka M, Mitsumoto F, Kanazawa K, Torikai K, Ohno S, et al. Diagnostic workup for fever of unknown origin: a multicenter collaborative retrospective study. Br Med J. 2013;3.

Cite this article as: Gandla N, Bharani SA, Shah TP. A study of etiology of fever of unknown origin in children aged 2 months to 18 years. Int J Contemp Pediatr 2021;8:1842-7.