International Journal of Contemporary Pediatrics
Govindarajulu S et al. Int J Contemp Pediatr. 2017 Jan;4(1):62-67
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20164413

Original Research Article

Clinical profile and etiological spectrum of fever of unknown origin in children aged 2 months to 12 years

Santhosh Govindarajulu*, Kumarasamy Kalyanasundaram, Karamath S. Pyarejan, Seenivasan Venkatasamy

Department of Pediatrics, Institute of Child Health and Hospital for Children, Egmore, Chennai, India

Received: 23 November 2016
Revised: 25 November 2016
Accepted: 29 November 2016

***Correspondence:**
Dr. Santhosh Govindarajulu,
E-mail: drsancmc@gmail.com

ABSTRACT

Background: Fever of unknown origin is one of the leading etiologies for morbidity and mortality among children worldwide and their spectrum keeps changing constantly from time to time. The objective of this study was to study the clinical profile and etiological spectrum of fever beyond 2 weeks duration in children aged 2 months to 12 years admitted in a tertiary care hospital.
Methods: A prospective observational study, done in tertiary care centre over six month period (May 2016 to October 2016). Children aged 2 months to 12 years presenting with fever beyond 2 weeks duration fulfilling the inclusion criteria were included in the study and evaluated further. Initial investigations include complete blood count including peripheral smear for MP/malignancy, urine routine, chest X-ray, mantoux, CRP, blood and urine cultures were done followed by specific serology tests and further relevant investigations. The etiological outcomes were mainly analysed.
Results: The etiological outcomes of the study were classified into 5 groups as infections, malignancies, connective tissue disorder, miscellaneous and undiagnosed. Among the study population, infection emerged as the major etiological outcome constituting 69.1% followed by malignancies (16.7%), connective tissue disorder (5%), miscellaneous (5.8%) and undiagnosed (3.4%).
Conclusions: Infections, especially enteric fever still remains the leading etiology of fever beyond 2 weeks duration or FUO in children aged 2months to 12 years. Irrational usage of antibiotics has been highlighted in general practice which needs to be amended by periodic discussions and epidemiological surveys to prevent the emergence of drug resistance.

Keywords: Children, Enteric fever, Fever, FUO, Infections

INTRODUCTION

Fever among children not only shoots up the temperature of child but also the anxiety of parents and pressure on the treating pediatrician to diagnose the condition as soon as possible. Fever beyond 2 weeks or for the practical purposes, FUO still remains the daunting challenge for any pediatrician.[1] The term fever of unknown origin came into light after the publication by Petersdorf and Beeson among the adult population and defined it as temperature >38.3°C on several occasions and lasting longer than 3 weeks with a diagnosis which remain uncertain after 1 week of investigations in the hospital.[2] Since then various studies had been conducted across the globe among different age groups to evaluate etiologies of FUO, which again revealed variations based on several

epidemiological factors. Also we have a battery of tests for fever work up as described in the literature; all of them could not be subjected due to financial and ethical reasons. Another challenge in Pediatrics, when compared to adults is the practical difficulty in obtaining repeated blood, urine or sputum samples.

It has to be accepted that the causes of FUO is not similar around the globe, neither a province too. It varies geographically, socioeconomically, ethnically, seasonally and so on. Level of health care facility, immunization practices, and advancement in diagnostic techniques, antibiotic policies and hygienic practices also play a major role in determining the causes of FUO.[3] With the development of some of the above factors in our country, the spectrum of FUO may vary from the previous years. Reviewing of earlier literature reveals paucity of published studies in India, especially in this particular region in the recent years. This study has been planned to give an insight on various etiological determinants of FUO among children in our region.

METHODS

The study was conducted from May 2016 to October 2016 at Institute of child health and hospital for children, Chennai which is an apex institute of this region in Pediatrics and receives referrals wide across the state and neighbouring states. It was a prospective observational study and evaluated the clinical profile and etiological spectrum of fever beyond 2 weeks duration in children aged 2 months to 12 years without an obvious diagnosis at presentation after a detailed history and clinical examination, which fulfils the definition of FUO as defined by Long and Edwards.[1] Children with a documented recurrent fever and periodic fever syndromes were excluded from the study.

After obtaining a written consent, children fulfilling the inclusion criteria were enrolled into the study. After taking anthropometry, weight for height calculated for children <5 years of age and BMI was calculated for children >5 years of age and plotted in WHO growth charts. Baseline investigations including hemoglobin, total count, differential count, hematocrit, platelet count, peripheral smear study, renal and hepatic parameters, urine albumin and deposits, chest X-ray, sonogram of abdomen and mantoux testing done initially. Subsequently investigations such as widal, QBC for MP, MAT for leptospirosis, gene expert (CBNAAT), serology for scrub typhus and brucella, retroviral screening, imaging studies, invasive procedures such as lumbar puncture, bone marrow biopsy, lymph nodal aspirate/ biopsy and procedures like broncho/ endoscopy were performed depending upon the clinical scenario.

RESULTS

In this study, clinical profile and etiological spectrum of fever beyond 2 weeks duration were evaluated in children aged 2 months to 12 years who were admitted in medical wards. Of the 124 children enrolled in the study initially after applying inclusion criteria, 4 children were dropped out during the study. Two of them absconded from the ward without notice and other two were discharged against medical advice before completion of treatment. A total of 120 children were included finally into the study during the study period.

About 84% of the study populations were below 9 years of age. The mean age of study population was 5.1 years and the median age was 4.4 years. Among the study population, 51.7% were males and 48.3% were females. As per modified Kuppusamy scale (updated 2014), majority of the study population (74.2%) belonged to class 4.[4] About 20 % the study population were in class 5 and only 5.8% were in class 3.

At the time of admission, it was observed that nearly 80% of the study population had fever of about 14-21 days duration. About 10.8% of the study population had fever of >28 days duration. About 8.4% of the study population had fever of about 22-28 days duration.

About 51.6% of the children in the study population were given oral antibiotics like amoxicillin, cefixime. Nearly 44% of the children had been given 1st line intravenous antibiotics like ampicillin, cephalosporins or aminoglycosides. About 4.2% of the study population had received even 2nd line intravenous antibiotics like meropenem, vancomycin or piperacillin.

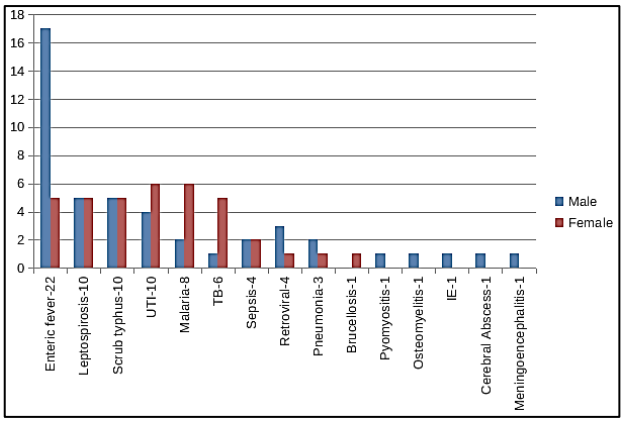

Figure 1: Details of infectious etiology in the study group.

It was observed that about 70% of children were moderately under nourished (moderate acute malnutrition/thinness) and 20.8% of the children were severely under nourished (severe acute malnutrition/ severe thinness). Only about 9.2% were in the normal range and none of them were in the over nutrition range. About 77.5% of the children in the study population had pallor at the time of admission. The mean hemoglobin was 8.75 g% in the study population ranging from 4.2 g%

to 12 g%. Majority of the study population (88.3%) had organomegaly.

The etiological factors were classified into 5 groups as infections, malignancies, connective tissue disorder, miscellaneous and undiagnosed (Table 1). Among the study population, infection emerged as the major etiological outcome constituting 69.1%, followed by malignancies (16.7%), connective tissue disorder (CTD) (5%), miscellaneous (5.8%) and undiagnosed (3.4%). The mean duration of fever was highest (41 days) among CTD followed by malignancy (38.9 days). Among the infection group, the mean total duration of fever was 22.5 days.

Table 1: Etiological outcome of the study.

Diagnosis	Frequency	Percentage
Infections	**83**	**69.1**
Enteric fever	22	18.3
Leptospirosis	10	8.3
Scrub typhus	10	8.3
Urinary tract infection	10	8.3
Malaria	8	6.7
Tuberculosis	6	5
Retroviral disease	4	3.4
Sepsis	4	3.4
Pneumonia	3	2.5
Brucellosis	1	0.8
Osteomyelitis	1	0.8
Pyomyositis	1	0.8
Infective endocarditis	1	0.8
Cerebral abscess	1	0.8
Meningoencephalitis	1	0.8
Malignancies	**20**	**16.7**
Acute lymphoid leukemia	14	11.7
Acute myeloid leukemia	2	1.7
Hodgkins lymphoma	1	0.8
Nonhodgkins lymphoma	2	1.7
Burkitt lymphoma	1	0.8
Connective tissue disorder	**6**	**5**
Kawasaki disease	3	2.5
SOJIA	3	2.5
Miscellaneous	**7**	**5.8**
HLH	6	5
Langerhan cell histiocytosis	1	0.8
Undiagnosed	**4**	**3.4**
Total	**120**	**100**

Among the infections, enteric fever was the major etiology accounting for 26.5% of all infections and 18.3% of overall cases of fever beyond 2 weeks.

Next to it, there was nearly equal occurrence of leptospirosis, scrub typhus and UTI (12% each). Malaria was the next most important cause constituting 9.7% and tuberculosis contributed to 7.2 % among infection group. Retroviral disease was also present in 4.8% of the children with infectious causes (Figure 1).

Among malignancies, acute lymphoid leukemia (14 out of 20 cases) was the major etiological outcome, followed by acute myeloid leukemia (2 out of 20 cases). There were 2 cases of non-Hodgkin lymphoma and 1 case of Hodgkin and burkitt lymphoma each.

Among connective tissue disorders (6 out of 120 cases), Kawasaki disease and Systemic onset juvenile idiopathic arthritis were the etiologies and were distributed in equal proportion (3 each).

Among miscellaneous causes (7 out of 120 cases), 6 cases had HLH and 1 case had Langerhans cell histiocytosis.

Among 4 in the total of 120 cases, diagnosis could not be arrived in spite of extensive clinical and laboratory investigations.

Three cases of the total study population expired in spite of effective treatment during the study period. Their etiologies were langerhans cell histiocytosis, invasive aspergillosis and retroviral disease with interstitial pneumonia.

DISCUSSION

The etiologies of FUO were classified into 5 groups namely infection, malignancy, connective tissue disorder, miscellaneous and undiagnosed. Results analysis revealed infection was the major etiology among all other groups, contributing to 69.1% of the total study population. The above categorization of outcomes was based on the popular study conducted by Petersdorf and Beeson in among adult population where the results came as infection (36%), malignancy (19%), rheumatological problems (15%), miscellaneous (23%) and undiagnosed (7%).[2] Most of the studies done subsequent to Petersdorf and Beeson over various time periods and at various geographical areas revealed infections as the major cause of FUO in both children and adult population. They are compared below (Table 2 and 3).

It seems obvious that infections remain the major cause for FUO, even though it varies in proportion from 30% to 78% over various time periods at varied geographical locations both in developed and in developing countries. In our study also, infections (69.1%) contributes for majority of the cases of FUO.

It was inferred from our study that enteric fever is the major etiology among all infections causing FUO. Similarly enteric fever was found to be the major or one of the major etiologies among all other infections in the studies conducted in our country (Table 4). Since tropical diseases are known to vary from region to region due to multiple factors like hygienic living conditions,

vaccination practices, prevalence of resistant organism and so on, we tried to compare only with available evidence from Indian sub-continent.

Now with the evidence of enteric fever as a major threat for FUO, further analysis from our study infers that all these patients received one or more antibiotics either orally or parenterally and yet continued to have fever at time of admission. The reason for above fact could be either incorrect choice or inadequate dosage or inadequate duration of antibiotics or a resistant organism.

In our study it was noticed that 68.2% were sensitive to injection ceftriaxone and remaining 31.8% were resistant to it as assessed by clinical response to subsequent drugs like ciprofloxacin or azithromycin. Although vaccination against typhoid is available, most of the children were found to be unvaccinated in our study. This can be attributed to the fact that it has not been included in the National immunisation schedule in our country. This study also stresses the need for induction of typhoid vaccine into the national immunization schedule and also the judicious and appropriate usage of antibiotics.

Table 2: Observations of various similar studies.

Study	No. of cases	Fever duration (in weeks)	Infection (%)	Malignancy (%)	CTD (%)	Misc (%)	Un-diagnosed (%)
Indian studies							
Kejariwal, et al[5]	100	>3	53	17	11	5	14
Joshi, et al[3]	49	>2	69.4	12.2	2.1	4.1	12.2
Mir T, et al[6]	91	>3 OP visits/ >3 days IP	44	12	12	7	25

Table 3: Observations of various similar studies.

Studies outside India							
Study	**No. of cases**	**Fever duration (in weeks)**	**Infection (%)**	**Malignancy (%)**	**CTD (%)**	**Misc (%)**	**Un-diagnosed (%)**
Petersdorf and beeson[2]	100	>3	36	19	19	19	7
Mc Clung[7]	99	>3	29.3	11.1	8	30.4	21.2
Pizzo et al[8]	100	>2	52	6	20	10	12
Chantada et al[9]	113	>3	36.3	10	13.2	22	19.5
Cogulu et al[10]	80	>2	57.7	2.5	6.3	20	12.5
Bakasvilli[11]	52	>2	61.5	4	4	17.3	13.5
Hashan et al[12]	127	>3	36.2	29.9	10.2	7.87	15.75
Our study	120	>2	69.1	16.7	5	5.8	3.4

Leptospirosis accounted for about 12% of all infections in our study, which seems comparable with the study conducted by Cruz ML et al (about 12.2%).[13] All the cases of leptospirosis were responded to crystalline penicillin and improved well without any mortality in our study.

Scrub typhus accounted to 12% of all infections causing FUO as implied in our study, which seems as a higher proportion when compared with other studies. This could be attributed to the region of our study where scrub typhus has been more commonly reported in recent past. Also it is a largely undiagnosed disease because it closely mimics other tropical infections like leptospirosis or dengue fever and due to limited availability of its specific serology testing at many centres. In our study eschar was present in 8 out of 10 cases (80%). Presence of Eschar rules in a diagnosis of scrub typhus although its absence does not rule out the disease because previous studies quote a varied occurrence of eschar ranging from 9.5% as observed in the study conducted by Sharma et al to 89% as observed in Premaratna et al.[14,15] Also Eschar is not an obvious finding until it is specifically looked for in the hidden areas like axilla and groin. Since scrub typhus was an anticipated cause of FUO and serological tests are readily available at our center, higher proportion of cases have been diagnosed.

Tuberculosis still remains as one of the most important causes of FUO as cited in most studies from our country despite its awareness and National programme for its control. In our study, tuberculosis accounted for about 5% of the total infections. The reason for its endemicity is the difficulty in diagnosing the disease in early stages unless it is severe. Also it has chronic course and atypical presentations.

Urinary tract infections contributed to 12% of all infections causing FUO in our study, almost 90% were below 5 years of age. Chow et al in their study found that

it was highest among children below 5 years of age.[16] Hence, it must be insisted that UTI is one of the major cause of FUO in children less than 5 years of age and needs to be evaluated with priority in this age group.

Table 4: Comparison of leading etiologies in various Indian studies.

Study	Leading infectious etiology		
Kejariwal, et al[5]	Tuberculosis (24%)	Abscesses (7%)	Enteric fever (5%)
Joshi, et al[3]	Enteric fever (41%)	Leishmaniasis (29%)	Tuberculosis (15%)
Mir T, et al[6]	Enteric fever (32.3%)	Brucellosis (32.3%)	Tuberculosis (22.6%)
Our study	Enteric fever (26.5%)	Leptospirosis (12%)	Scrub typhus (12%) UTI (12%)

Next to infections, malignancy (16.7%) was the leading cause of FUO in our study. Again it holds well when compared with most of the studies (Kejariwal et al, Joshi et al and Mir et al) except in some studies (Pizzo et al, Chantada et al and Cogulu et al) where connective tissue disorders dominated the malignancy category.[3,6,5,8,10] However connective tissue disorders and malignancy are known to have genetic and racial influences, it may be an explanation for the above variation. Also center of study might have influenced the outcome because diagnosis of malignancy and connective tissue disorder requires expertise intervention of that specialty which may not be available in all centers.

Of the 20 cases of malignancy group, acute lymphoid leukemia accounted for 14 cases (70%) and it has been shown in accordance with studies of Mc Clung et al (50%) and Joshi et al (50%), both of them have studied FUO among children.[3,7]

Connective tissue disorders were the minor contributors for FUO both in our study as well as in the previous studies (Joshi et al, Cogulu et al and in Bakashvilli et al).[3,10,11] It accounted for <7% of all etiological outcomes in these studies. Of the 6 cases of CTD in our study, Kawasaki disease and systemic onset juvenile idiopathic arthriris (SOJIA) constituted 3 each. Though it may be a smaller proportion it must be considered in all cases where there is no obvious focus of infection and laboratory investigations for infectious diseases remain non-contributory.

The category of miscellaneous illnesses in the above studies including our study had a variety of conditions like hemophagocytic lymphohistiocytic syndrome (HLH), inflammatory bowel disease, langerhan cell histiocytosis, diabetes insipidus, Sotos syndrome, immunodeficiency, Rosai Dorfmann syndrome, factitious fever, inflammatory bowel disease, familial mediteranean fever and periodic fever syndromes and so on. Due to varied inclusions in this category the results are not comparable. However, in most of the studies it remained in 4th category in the hierarchy of etiologies causing FUO. Our study had 5.8 % of cases in this category. Of the 7 cases of miscellaneous causes encountered in our study were HLH (6 out of 7 cases) and Langerhan cell histiocytosis (1 out of 7 cases). HLH was diagnosed by clinical, lab criteria and demonstration of hemophagocytic cell in the bone marrow. Langerhan cell histiocytosis was diagnosed with skin biopsy of the cutaneous lesion in our study.

Finally, the category of undiagnosed cases cannot be compared as it is obvious that diagnostic facilities and techniques vary from place to place and time to time. In our center with reasonably good facilities, about 3.4% of the cases could not be diagnosed in spite of a detailed evaluation although all these children recovered well without any complication in our study.

CONCLUSION

Infections still dominate the spectrum of FUO in children and enteric fever continues to be the major etiology for FUO in children. It is high time to include typhoid vaccine in our national immunization schedule. Irrational usage of antibiotics has been highlighted in general practice which needs to be amended by periodic discussions and epidemiological surveys to prevent the emergence of drug resistance.

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

REFERENCES

1. Long SS, Edwards KE. Prolonged, recurrent and periodic fever syndromes. In: Principals and Practice of Pediatric Infectious disease, 4th ed, Elsevier, Churchill Livingstone; 2012:117-118.
2. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine Baltimore. 1961;40:1-30.
3. 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.

4. Oberoi SS. Updating income ranges for Kuppusamy's socio-economic status scale for the year 2014. Indian J Public Health. 2015;59:156-7.
5. Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. J Postgrad Med. 2001;47:104.
6. Mir T, Dhobi GN, Koul AN, Saleh T. Clinical profile of classical FUO. Caspian J Intern Med. 2014;5(1):35-9.
7. McClung HJ. Prolonged fever of unknown origin in children. Am J Dis Child. 1972;124(4):544-50.
8. Pizzo PA, Lovejoy FH, Smith DH. Prolonged fever in children: review of 100 cases. Pediatr. 1975;55(4):468-73.
9. Chantada G, Casak S, Plata JD, Pociecha J, Bologna R. Children with fever of unknown origin in Argentina: an analysis of 113 cases. Pediatr Infect Dis J. 1994;13(4):260-3.
10. Cogulu O, Koturoglu G, Kurugol Z, Ozkinay F, Vardar F, Ozkinay C. Evaluation of 80 children with prolonged fever. Pediatr Int. 2003;45(5):564-9.
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;(135):66-9.
12. Hassan RH, Fouda AE, Kandil SM. Fever of unknown origin in children: a 6 year- experience in a tertiary pediatric Egyptian hospital. Int J Health Sci Qassim. 2014;8(1):13-9.
13. Cruz ML, Andarali J, Perira MN. Leptospirosis in children. Rev SOC Bras Med Tropical. 1994;27(1):5-9.
14. Sharma A, Mahajan S, Gupta ML, Kanga A, Sharma V. Investigation of an outbreak of scrub typhus in the himalayan region of India. Jpn J Infect Dis. 2005;58(4):208-10.
15. Premaratna R, Loftis AD, Chandrasena TG, Dasch GA, de Silva HJ. Rickettsial infections and their clinical presentations in the Int J Infect Dis. 2008;12(2):198-202.
16. Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. World J Pediatr. 2011;7(1):5-10.

Cite this article as: 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;4:62-7.