

Original Research Article

Clinicoetiological profile of pyrexia of unknown origin in children 1-12 years of age in a tertiary care centre

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ABSTRACT

Background: A primary concern of the paediatricians in evaluating a child with PUO is the limited use of investigations that are case-specific especially in developing countries such as India where availability and affordability are the limiting factors. Hence, this study was conducted to evaluate the various etiological factors and the clinical profile of children presenting with PUO in this region.

Methods: A hospital based cross sectional study was conducted among 200 children presenting with fever i.e., temperature $>100.9^{\circ}\text{F}/38.3^{\circ}\text{C}$ of more than one week duration, with no clear diagnosis after initial investigations

Results: A total of 193 children were included in the study with a mean age of 6.2 ± 1.8 years. Most (62.5%) of the participants had infectious etiology, followed by collagen vascular disorders (10 %) and malignancies (9.5%). Among the participants, 10% remain undiagnosed. Among infectious causes, the most common was respiratory tract infections (17.5%), followed by scrub typhus (13.5%) and urinary tract infections (10%).

Conclusions: Our study was conducted to outline the clinic-etiological profile of pediatric patients with PUO in our region. After proper investigations, a diagnosis could be reached in most patients. The commonest aetiology was infectious, followed by collagen vascular disorders and malignancies. Further studies with a larger sample size are suggested.

Keywords: PUO, Fever, Infectious, Malignancy, Collagen vascular disorders, Investigations, Diagnosis

INTRODUCTION

Febrile illnesses are one of the leading causes of morbidity and mortality among children worldwide.¹ Fever, defined as a rectal temperature $>38.0^{\circ}\text{C}$ (100.4°F), is one of the most common reasons for seeking medical evaluation for children and infants, and the most common cause for which children are brought to emergency departments.² In the majority of cases the cause of fever is easily identifiable with no or few exams and appropriate treatment is straightforward.³ In spite of that fever in children requires special consideration and in a minority of cases the clinical picture may be complicated by its persistence in the absence of obvious causes i.e. fever of unknown origin (FUO), or by the recurrence of

fever episodes (recurrent fevers).⁴ There are five recognized patterns of fever: intermittent, remittent, continuous or sustained, hectic, and relapsing.⁵

Pyrexia of unknown origin (PUO) is a grouping of many unrelated medical conditions that share the feature of persistent unexplained fever that does not resolve spontaneously within the period for self-limited infections and whose cause cannot be ascertained despite adequate basic investigation and considerable diagnostic effort.⁶

The first definition of FUO dates back to the early 1960s, when it was defined by Petersdorf and Beeson as a body temperature of more than 38.3°C on several occasions,

lasting for more than 3 weeks and no diagnosis after 1 week of hospitalization.⁷ In 1991, Durak and Street re-defined FUO into four categories: classic FUO, nosocomial FUO, neutropenic FUO, and human immunodeficiency virus (HIV)-associated FUO, and proposed three outpatient visits and related investigations as an alternative to one week of hospitalization.⁸ In 1997, Arnow and Flaherty updated the FUO definition and considered the type of diagnostic panel to be more important than the duration of investigations.⁹

Although there is no standard definition of pediatric FUO, it is now generally accepted that unexplained fever that persists longer than 1 week in a child warrants preliminary investigations as fever from viral infections generally resolves within that time frame.¹⁰

When comparing data between developed and developing nations, infection is consistently the most common cause of FUO, but the type of infection varies; bacterial infections, including *Bartonella* infections are more commonly diagnosed in developed countries, whereas brucellosis, typhoid fever, tuberculosis, *Rickettsia* infections, and abscesses are more common in developing nations.⁴ Viral aetiologies for FUO were more commonly identified in developed countries, particularly Epstein-Barr virus infection.⁴ Among the chronic inflammatory and autoimmune disorders that can present as FUO, more common in children are IBD, and Crohn's disease in particular.⁴ Among neoplasia, the more common causing FUO are lymphoma and leukaemia. Rheumatic conditions, such as the systemic form of juvenile idiopathic arthritis are also a possibility.⁴ There are a lot of miscellaneous and rare causes of FUO, including drug fever, dysautonomia, diabetes insipidus, ectodermal dysplasia, pulmonary embolus, and haematoma.⁴

PUO is thus a challenging medical problem. Formulation of regional guidelines for evaluation of children with FUO would be useful in this regard.¹¹ Thus, this study was planned to evaluate the various etiological factors and the clinical profile of children presenting with FUO in this region, which could also be helpful in formulating suitable regional guidelines and management strategies for these cases.

METHODS

Study design

It was an institutional based cross-sectional study.

Study setting

The study was carried out in the paediatric department, RIMS, Imphal.

Study duration

Study conducted from January 2021 to December 2022.

Study population

Children between 1-12 years of age were selected.

Inclusion criteria

Febrile children with temperature $>100.9^{\circ}\text{F}$ / 38.3°C admitted in the paediatric ward with persistent fever for >1 week duration with no clear diagnosis after initial investigations.

Exclusion criteria

Patient on steroids/ other immunosuppressant drugs were excluded from the study.

Sample size

The calculated sample size was 193 children of 1 year to 12 years of age group.

Independent variables

Age, sex, height (cm), weight (kg), residence (urban/rural) were used as independent variables.

Dependent variables

Variables used were clinical features, laboratory profile, duration of hospital stay, outcome and causes of PUO.

Sample collection

Under all aseptic conditions, venous blood sample was collected in sterile vials (EDTA vial, plain vial) appropriate for blood investigations in the study.

Procedure

After obtaining permission from the research ethics board, RIMS, Imphal, an informed consent was obtained from the parents/legal guardian for conducting the study. For all patients fulfilling the eligibility criteria, a detailed history was taken, clinical examination was done and anthropometric measurements such as weight for height for children <5 years of age and BMI for children >5 years of age was calculated and plotted in WHO growth charts.

Sample collection

Under all aseptic conditions, venous blood sample was collected in sterile vials (EDTA vial, plain vial) appropriate for blood investigations included in the study. Samples for blood culture was collected aseptically before initiation of antimicrobial therapy and sent to microbiology department. For urinalysis and urine culture, early morning voided urine was collected in sterile containers. Faecal specimens for stool examination

was submitted in a clean, dry wax free container. For CBNAAT test, two sputum samples (one spot sample, one early morning sample) were collected to rule out Mycobacterium tuberculosis. Alternately gastric lavage specimen could be collected in children < 3 years of age. When indicated, CSF was collected in sterile vials for analysis through lumbar puncture. Similarly, other body fluids such as pleural and peritoneal fluid will be collected in sterile containers and was send for analysis.

Investigations

Preliminary investigations including complete blood count (hemoglobin, total count, differential count, hematocrit, platelet count) with ESR, C-reactive protein (CRP), complete urine examination, stool examination, blood sugar, serum electrolytes, renal function tests, liver function tests, blood culture, urine culture, PBS for MP, Widal test, typhi dot, scrub typhus serology, dengue serology, Japanese encephalitis(JE) serology, chest X-ray, ultrasound abdomen and Mantoux test will be done initially. Further investigations would include CBNAAT for Mycobacterium tuberculosis, HIV screening, lipid profile, serum ferritin, lactate dehydrogenase, ASO titer, RA factor, ANA and X-ray of paranasal sinuses or affected bone. Imaging studies like CT and MRI studies will be done if indicated. Invasive procedures such as lumbar puncture for CSF analysis, bone marrow aspiration and biopsy, lymph nodal aspirate/ biopsy and procedures like broncho/endoscopy done if indicated.

Data management and Statistical Analysis

Data was checked for consistency and completeness and was entered and analyzed using SPSS version 21.0 (IBM, INC, ARMONK, NY, USA). Descriptive statistics like mean and SD was used to summarize age, height, weight, duration of hospital stay and laboratory findings.

Ethical approval

The written informed consent was taken before the recruitment for study. The approval of protocol of the thesis was sought from the research ethics board for ethical approval, RIMS, Imphal.

RESULTS

In the present study among 193 children, 52% were male and 48% were females with a M:F ratio of 1.08. The mean age of the study population was 6.2±1.8 years. Majority (72%) of the participants were from rural area. Most (54%) of them belonged to Hindu religion .62% of the study population were coming from lower middle-class family. While (70%) of the patients had normal weight, 30% of the participants had underweight. Most of them (62.0%) got admitted during the period of April to October. A significant travel history was not seen in most (88%) of them. Most (52%) of them were having a temperature of 100.9-102 F during hospital admission.

Majority (32.5%) of patients presented with fever of 1-2 weeks at admission and significant (78%) proportion of patients had intermittent fever. The most common (40%) symptom at admission was cough followed by abdominal pain. In complete blood count, most (53%) of the patients had neutrophilic leukocytosis, 21% had lymphocytosis and 8% had thrombocytopenia. Among the participants, 12% had normal CBC finding. Among the participants, 60% had high CRP, blood culture was positive in 14.5%, deranged LFT was seen in 20%, scrub typhus IgM was positive in 13.5% of the patients. The most common radiological finding was abnormal chest x-ray (48%) followed by abnormal abdominal ultrasound. Among other investigations, 21.5% of the patients had abnormal urine R/E, 8% of the participants had positive Mantoux test. Considering the etiology, majority (62.5%) of the participants were having infectious causes followed by malignancy (9.5%) and Collagen vascular disorders (10%). Among participants 10% of participants remained undiagnosed even after extensive investigations. Among infections, most common (17.5%) diagnosis was respiratory tract infection, followed by scrub typhus (13.5%) and urinary tract infections (10%). Collagen vascular disorders was found mainly in 7-12 years of age group. Mean days of hospital stay was 12±7 days and ranged from 7-40 days. Majority (88.5%) of participants recovered without sequelae whereas 9.5% developed sequelae/underwent into remission after chemotherapy.

Table 1: Age distribution of study population, (n=200).

Age (Years)	1 to 3	4 to 6	7 to12
Frequency	60	80	60
Percentage (%)	30	40	30

Table 2: Month of admission in hospital, (n=200).

Month of admission	N	Percent (%)
November to March	76	38
April to October	124	62
Total	200	100

Table 3: Temperature on admission of study participants, (n=200).

Temperature on admission (F)	N	Percent (%)
100.9-102	104	52
102-103	80	40
>103	16	8

Table 4: Duration of fever at admission, (n=200).

Duration of fever at admission (Weeks)	N	Percent (%)
1-2	56	32.5
3-4	65	28.0
4-5	56	28.0
> 5	23	11.5

Table 5: Type of fever at admission, (n=200).

Type of fever	N	Percent (%)
Intermittent	156	78.0
Remittent	24	12.0
Continuous	20	10.0

Table 6: Complete blood count profile in PUO, (n=200).

CBC findings	N	Percent (%)
Normal	24	12
Neutrophilic leucocytosis	106	53
Lymphocytosis	21	10.5
Thrombocytopenia	8	4
Eosinophilia	4	2
Others	37	18.5

Table 7: Radiological profile of study participants, (n=200).

Radiological profile	N (%)
Abnormal chest x ray	96 (48)
Abnormal ultrasonography	45 (22.5)
Abnormal echocardiogram	4 (2)
X ray paranasal sinuses s/o sinusitis	8 (4)

Table 8: Other investigations (n=200).

Other investigations	N (%)
Stool RE + C/S-abnormal	4 (2)
Mantoux test-induration > 10 mm (positive)	16 (8)
Urine RE + C/S-abnormal	43 (21.5)
CBNAAT (MTB)-positive	4 (2)

Table 9: Category of disease as per cause, (n=200).

Category of disease	N	Percent (%)
Infectious cause	125	62.5
Malignancy	19	9.5
Collagen vascular disorders	20	10
Miscellaneous	16	8
Undiagnosed	20	10
Total	200	100

Table 10: Association between age of the patients and the category of diagnosis, (n=200).

Age of participants (Years)	Category of diagnosis, n (%)				
	Infectious cause	Malignancy	Collagen vascular disorders	Miscellaneous	Undiagnosed
1 to 3	47 (78.3)	2 (3.3)	0	7 (11.6)	4 (6.6)
4 to 6	40 (54.7)	9 (12.3)	0	8 (10.9)	16 (21.9)
7 to 12	38 (56.7)	8 (11.9)	20 (29.8)	1 (1.4)	0
Total	125	19	20	16	20
P value	0.01				

DISCUSSION

During the study period, 193 children from 1-12 years of age group admitted in Pediatric ward with PUO were enrolled to determine the clinico-etiological profile of PUO. Considering the demographic characteristics of the study population, 52% were male with a M:F ratio of 1.08. The mean age of study population was 6.2±1.8 years. Majority (72%) came from rural area and most (54%) of them belonged to Hindu religion. The participants were mostly (62%) from lower middle family. Among the participants 30% had underweight. Majority (62.0%) of the patients with FUO got admitted from April to October. A significant travel history could not be obtained in most (88%) patients.

Axillary temperature of patients were recorded during admission and it was found that majority (52%) were having a temperature in the range of 100.9-102 F. Majority (32.5%) of the patients with PUO presented

with fever of 1-2 weeks duration. Most (78%) of the patients had intermittent fever at admission. Regarding symptoms, the most common symptom observed was cough (40%) followed by abdominal pain. On physical examination the most common finding was lymphadenopathy (25.5%) followed by hepatosplenomegaly (21%). A similar finding was noticed by Tezer et al in his study in which the most common findings were hepatosplenomegaly (15.5%) and lymphadenopathy (15.5%) in pediatric PUO patients.¹²

Following a detailed history and physical examination, the study participants were evaluated with staged investigations. Initial investigations in the study participants included complete blood count, erythrocyte sedimentation rate (ESR), urine analysis and culture, blood culture, tuberculin test, chest X-ray, Serology for scrub typhus and Widal test. A complete blood count in most (53%) of the participants revealed neutrophilic leukocytosis denoting bacterial infection. However, 21%

of the patients had lymphocytosis and 8% of participants had thrombocytopenia as the predominant CBC picture.

Further, 60% of the admitted patients had high CRP, a marker of acute inflammation. Blood culture was positive in 14.5%. Deranged Liver function test was seen in 20% of the participants. Scrub typhus IgM was positive in 13.5% of patients, which points towards the importance of including it in the initial panel of investigations in our area. Among the participants, 21.5% of patients had urine routine examination suggestive of urinary tract infection. Among participants 8% had positive Mantoux test and they further investigated with CBNAAT. Radiological investigations in admitted patients showed abnormal chest x-ray in majority (48%) followed by abnormal abdominal USG findings such as hepatosplenomegaly.

After proper history, physical examination and investigations a diagnosis could be reached in 90% of the patients, but 10% of the participants still remained undiagnosed even after extensive investigations. Kejariwal et al also in his prospective study in a tertiary care hospital in Kolkata could not reach a specific diagnosis in 14% of cases of PUO.¹³ Among 20 undiagnosed patients, spontaneous resolution observed during study period in 12 patients whereas 8 participants continued to be febrile without an established cause.

Most (62.5%) of the participants were having infectious aetiology followed by malignancy (9.5%) and collagen vascular disorders (10%). Infectious diseases were responsible for majority of the PUO in all age groups. Most of previous studies also concluded infectious diseases as most common cause of FUO. For example, in a retrospective study conducted by Sumathisri et al infectious disease was responsible for 90.6%, similarly Nalli et al¹ got an incidence of 38% as infectious cause of PUO, Govindarajulu et al found incidence of 69.1%.^{1,11,14}

Among infectious causes, the major proportion (17.5%) was respiratory tract infection, followed by scrub typhus (13.5%), urinary tract infections (10%). Typhoid and TB contributed 8% each to PUO in the study population. Chantada et al also got similar findings in their study with the most common infectious cause being respiratory tract infection among infants.¹⁵ The higher incidence of scrub typhus as a cause of PUO may be due to its endemicity in our area. However Sumathisri et al who conducted a observational study in a tertiary care hospital in Puducherry, South India had a higher incidence of scrub typhus as the cause of FUO compared to our study and was the most common (52%) infectious aetiology of PUO in their study population.¹¹ But other studies had variable aetiologies of most common infectious causes such as, TB as found by Nalli et al enteric fever in study done by Joshi et al, brucellosis as concluded by Ergin et al EBV infection in the study done by Pasic et al etc.^{1,16-18}

After infectious causes malignancy and collagen vascular disorders were the most common causes of PUO.

Sumathisri et al depicted a higher incidence of malignancy (4%) compared to collagen vascular disorders (1.3%).¹¹ However, Kim et al in his study depicted collagen vascular disorders as the second most common (15%) cause of PUO in children, especially in those participants with a prolonged fever duration of more than 28 days.¹⁸ Other studies as done by Nalli et al, Govindarajulu et al also had findings similar to our study and in both studies, malignancy was the second most common cause of PUO with a higher proportion than collagen vascular disorders.^{1,14}

Among participants with malignancy, the most common diagnosis was acute lymphoblastic leukemia (7%) followed by acute myeloid leukemia (2.5%). Nalli et al also in his prospective, observational study discovered the commonest malignancy causing PUO in pediatric patients being acute lymphoblastic leukemia.¹

In participants with collagen vascular disorders included in our study, the most common diagnosis SLE (6%) followed by JIA (4%) and Kawasaki disease (2%). These findings were not corresponding to the study conducted by Chantada et al in which the most common collagen vascular disorder causing PUO was Juvenile rheumatoid arthritis.¹⁵ In our study collagen vascular disorders were found predominantly in 7-12 years of age group.

Considering the morbidity in patients with PUO, the mean days of hospital stay was 12±7 days and ranged from 7 days to 40 days. Majority (88.5%) of the participants recovered without sequelae whereas 9.5% developed sequelae or underwent into remission after chemotherapy. However, 2% of the participants expired during hospital stay.

Our study on the clinico-etiological profile in pediatric patient with PUO could be considered as the first with a representative sample size to be done in this area. Another strength of our study is that the use of dedicated software for the analysis kept a minimum error. As with all the other cross-sectional studies, the problem that cause effect relationship could not be ruled out in our study, which could well be regarded as one of the limitations of our study. The other limitation could be the time constraint without which a considerably larger proportion of the children could have been included in the study. Therefore, further studies with a larger sample size on a multicentric level could add robustness to our study results thereby helping in better understanding and management of PUO in children of 1-12 years.

CONCLUSION

PUO is a diagnostic challenge in pediatric patients. Our study was conducted to outline the clinic-etiological profile of pediatric patients with PUO in our area, 200 children from 1-12 years of age group admitted in Pediatric ward with PUO were enrolled in our cross-sectional study. A detailed history, physical examination

and staged investigations were done in the study population. Lymphadenopathy and hepatosplenomegaly were the commonest examination findings. After proper investigations, a diagnosis could be reached in most patients. The commonest aetiology was infectious followed by malignancy and collagen vascular disorders. Among infectious causes, respiratory tract infections were found to be the commonest cause followed by scrub typhus. After analyzing the result, we recommend that a proper epidemiological review, history, physical examination and staged investigations could identify most of the causes of PUO in pediatric patients. However, the study is limited by its sample size and time constraint, hence we recommend further studies with a much larger sample size to elucidate the clinic etiological profile of PUO in pediatric patients.

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