A Prospective Study of Clinico-Aetiological Profile of Fever of Unknown Origin in Children Admitted to a Tertiary Care Center

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ABSTRACT

BACKGROUND

Fever among children not only shoots up the temperature of child but also the anxiety of parents and pressure on the treating paediatrician to diagnose the condition as soon as possible. Fever of unknown origin is one of the leading causes of morbidity and mortality among children worldwide and the spectrum keeps changing constantly from time to time. We wanted to study the aetiology of fever of unknown origin in different age groups, and clinical profiles. We also wanted to evaluate the importance of advanced investigations in the evaluation of fever of unknown origin.

METHODS

This is a prospective observational study conducted in the Department of Paediatrics for a period of 2 years. A total of 100 children were enrolled in the study who were admitted with fever > 101 F [38.3 °C] of at least 8 days duration, in whom no diagnosis was reached after initial outpatient or hospital evaluation.

RESULTS

A total of 100 cases was enrolled in the study: The male to female ratio was 1.3 : 1. Children in the age group of 3 - 6 years constituted the majority of the study population. Infections (38 %) were the commonest cause of the FUO, followed by malignancy (24 %) and NIID (22 %). Undiagnosed group was followed by ALL, JRA, TB, UTI, enteric fever and SLE in that order. Between 1 - 3 years, malignancy (especially acute lymphoblastic leukemia) was the commonest cause. Between 3 - 6 years, infections are the commonest cause of fever of unknown origin. After 9 years, non-infective inflammatory diseases were the most common cause of FUO. In infants UTI was the commonest infection in FUO. Between 1 – 12 years, tuberculosis was the commonest Infection. ALL was the commonest malignancy presenting as FUO in older children between 9 - 12 years of age.

CONCLUSIONS

Over a period of time, with the advent of newer diagnostic techniques and improved imaging facilities, more cases of undiagnosed FUO cases are diagnosed which will help in better management of patients with good outcome.

KEYWORDS

Fever of Unknown Origin, Infections, Tuberculosis

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DOI: 10.18410/jebmh/2020/468

How to Cite This Article:
Nalli RK, Velampalli S, Borigama N. A prospective study of clinico-aetiological profile of fever of unknown origin in children admitted to a tertiary care center. J Evid Based Med Healthc 2020; 7(40), 2255-2261. DOI: 10.18410/jebmh/2020/468

Submission 17-06-2020,
Peer Review 28-06-2020,
Acceptance 22-07-2020,
Published 05-10-2020.

BACKGROUND

Fever is the most common symptom in children. Fever among children not only shoots up the temperature of children but also the anxiety of parents and pressure on the treating paediatrician 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 paediatrician.[1] Fever of unknown origin (FUO) was first described in 1961 and was defined as fever with a body temperature 38 °C for at least 3 weeks duration with a failure to reach a diagnosis after 1 week of inpatient investigation or 3 outpatient visits. Most viral febrile episodes usually resolve within 1 week and parents typically take their children to the hospital when the fever lasts more than 7 days. Therefore, in recent studies, definitions of paediatric FUO have tended to include patients with unexplained fever that persists longer than 1 or 2 weeks. Since then various studies had been conducted across the globe among different age groups to evaluate aetiologies 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 Paediatrics, when compared to adults is the practical difficulty in obtaining repeated blood, urine or sputum sample.[2,3] 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.[4,5] 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. This study has been planned to give an insight on various aetiological determinants of FUO among children admitted to tertiary care center.

METHODS

It is Prospective Observational Study done in Institute of women and child health, Niloufer Hospital, Hyderabad for a period of 2 years from September 2016 - September 2018 A total of 100 children were enrolled in to the study who were admitted to Department of Paediatrics with fever>101 F [38.3 °C] of at least 8 days duration, in whom no diagnosis is apparent after initial outpatient or hospital evaluation that includes a careful history and physical examination and initial laboratory assessment.

Inclusion Criteria

Children presenting with fever age group of O months to 12 years. Fever > 101 °F [38.3 °C] of at least eight days duration, in whom no diagnosis is apparent after initial outpatient or hospital evaluation that includes a careful history and physical examination and initial laboratory assessment.

Exclusion Criteria

Children with known malignancy, those who are taking steroids, who had been diagnosed of HIV / Immunodeficiency. The parents / guardians of affected children who have refused to give consent.

After informed consent, children were included in the FUO protocol. In the present study the choice of investigations was made from potentially diagnostic clues which are defined as all localising signs, symptoms or abnormalities potentially pointing towards possible diagnosis. The causes of FUO included four categories - infections, malignancies, connective tissue diseases, and undiagnosed cases. FUO was classified as undiagnosed if no evidence of the cause of fever was obtained and if there was complete spontaneous recovery even though the fever had persisted for several weeks or fever resolved during investigation.

Initial screening investigation for all the cases done by Complete blood count, differential count, Haemoglobin, erythrocyte sedimentation rate, CRP, peripheral smear, thick and thin smear for malaria parasite, Mantoux, retro viral screening and urine microscopic examination for the presence of pus cells. Venous blood was drawn from the patient and sent for culture of nonenteric organisms, enteric organisms and Mid - stream clean catch urine sent for culture and sensitivity on three consecutive days for children in infants, suprapubic aspiration was done.

Serological test for Blood Widal test using tube agglutination test for H & 0 agglutinins. In children with slide agglutination test positive for leptospirosis or dark field microscopy positive in urine or blood for leptospirosis, or with clinical suspicion of leptospirosis, blood was sent for microscopic agglutination test (MAT) and repeated after two weeks if the first titer was 100 or more for rise in titer. Brucella slide agglutination test, Liver function test and renal function test, Screening with ELISA for HIV 1 and 2 were done for all cases with consent obtained from the informant, USG abdomen and Chest x-ray done as per requirement. Other investigations in relevant cases as Xray sinus, or Xray of relevant bone, Hepatitis B surface antigen and IgM anti - Hbc if Hepatitis Ag positive, resting gastric juice contents in suspected tuberculosis patient, the material examined by Ziehl Neel son technique / CBNAAT for AFB. CSF analysis was done for children with convulsions, or altered sensorium or signs for meningeal irritation. CSF cell count biochemical analysis, culture and sensitivity were sent. ECHO for patients with suspicion of infective endocarditis in Children were evaluated for connective - tissue disorders in suspected cases in the Rheumatology clinic where ASO titer, CRP, rheumatoid factor and anti-nuclear antibodies were done for all suspected patients. In children with suspicion of SLE ds-DNA was done in a reliable institute nearby. Bone marrow aspiration in relevant cases. Barium meal study in appropriate cases. CT scan abdomen were suggested.

Statistical Analysis

SPSS 7.3 was used to analyse the data.

RESULTS

Total of 100 cases was enrolled in the study. The male to female ratio was 1.3 : 1. Children in the age group of 3 - 6 years constituted the majority of the study population.

Causes of FUO	N	%
Infections	38	38
Tuberculosis	12	12
UTI	7	7
Enteric Fever	7	7
Brucellosis	3	3
Malaria	4	1
Hepatitis B	4	1
Endocarditis	2	2
Leptospirosis	4	1
Bone & joint infections*	2	2
Other bacterial infections#	2	2
Malignancy	24	24
ALL	16	16
AML	4	4
Hodgkin Lymphoma	2	2
Non-Hodgkin Lymphoma	0	0
Histiocytosis	2	2
Non-Infectious Inflammatory Disease	22	22
Juvenile Rheumatoid Arthritis	14	14
SLE	6	6
Vasculitis	2	2
Undiagnosed	16	16

Table 1. Causes of Fever of Unknown Origin

*One case of osteomyelitis, one case of mastoiditis, #Splenic abscess, liver abscess

Diagnosis	0 – 1 (n =)		>1 - 3 (n = 24)		>3 - 6 (n = 26)		>6 - 9 (n = 23)		>9 - 12 (n = 23)	
	n	%	n	%	N	%	n	%	n	%
Infections										
Tuberculosis	1	8.33	2	16.67	3	25	4	33.33	2	16.67
UTI	2	28.57	1	14.29	1	14.29	2	28.57	1	14.29
Typhoid Fever	0	0	0	0	3	42.86	3	42.86	1	14.29
Brucellosis	0	0	1	33.33	1	33.33	1	33.33	0	0
Malaria	0	0	0	0	0	0	0	100	1	0
Hepatitis B	0	0	0	0	1	100	0	0	0	0
Endocarditis	0	0	1	50	0	0	1	50	0	0
Leptospirosis	0	0	0	0	1	100	0	0	0	0
Bone + joint infections	0	0	1	50	1	50	0	0	0	0
Other bacterial. infections	0	0	1	50	0	0	1	50	0	0
Total	3	7.89	7	18.42	11	28.95	12	31.58	5	13.16
Malignancy										
ALL	1	6.25	6	37.5	5	31.25	1	6.25	3	18.75
AML	0	0	2	50	1	25	1	25	0	0
Hodgkin Lymphoma	0 a	0	1	50	0	0	1	50	0	0
Histiocytosis	0	0	2	100	0	0	0	0	0	0
Total	1		11		6		3		3	
Non-infectious inflammatory diseases (NIID)										
JRA	0	0	2	14.29	2	14.28	2	14.28	8	57.14
SLE	0	0	1	16.67	0	0	1	16.66	4	66.66
Vasculitis	0	0	0	0	2	100	0	0	0	0
TOTAL	0		3		4		3		12	

Table 2. Distribution of Diagnosis by Age Group

Infections 38% were the commonest cause of the FUO, followed by Malignancy (24 %) and NIID (22 %). Among individual causes after undiagnosed group, ALL, followed by JRA, TB, UTI, Enteric fever and SLE constitute the bulk of the cases.

In infancy, infections remain the commonest cause of FUO and no case in this age group remain undiagnosed. Between 1 – 3 years malignancy (especially acute lymphoblastic leukemia) was the commonest cause. Between 3 - 6 years infections are the commonest cause of fever of unknown origin. After 9 years non - infective inflammatory disease dominates causes of FUO. Infants UTI was the commonest infection in FUO between 1 - 12 years Tuberculosis was the commonest Infection presenting as FUO. In all the age groups ALL was the commonest malignancy presenting as FUO. In older children between 9 - 12 years, NIID was the commonest cause of FUO.

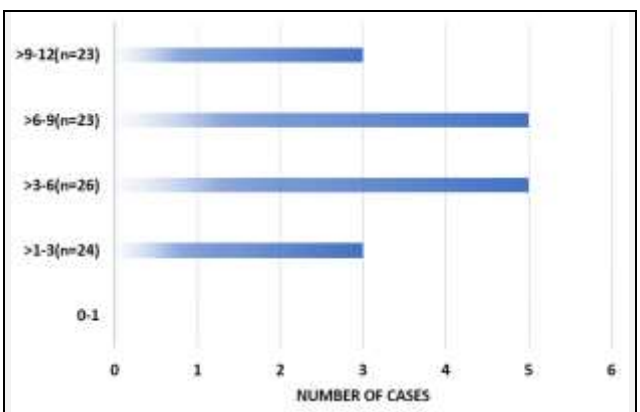

Figure 1. Distribution of Undiagnosed FUO by Age Group

Fever resolved spontaneously in 16 children before results of first line investigations were available and diagnosis could not be made with the first line investigations. Fever remained undiagnosed in the remaining children even after appropriate investigations were done and these children were discharged as FUO.

Diagnostic Method	All Patients with Diagnosis (n-84)	Early Diagnosis (<7 Days) (n-23)	Intermediate Diagnosis (7- 14 Days) (n-47)	Late Diagnosis (>14 Days) (n-14)
	n	n	n	n
History and evolution	14	4	10	7
Culture	8	3	5	
Infections serology	11	1	10	3
Standard radiology	1	1	-	-
Abdominal USG	1	1	-	-
ECHO	2	1	-	1
CT Scan	2	1	1	-
Bone marrow aspiration	20	5	7	-
Biopsy	9	1	7	-
Others / Combination	16	5	7	3

Table 3. Decisive Method of Diagnosis

The decisive method of diagnosis in which a diagnosis was obtained. Bone marrow aspiration was the most

rewarding technique, especially in the groups with early or intermediate diagnosis. Microbiological analysis (culture and serology) also had reasonable diagnostic yield (35 %). History and evolution of disease made a significant contribution in late group. Imaging techniques (Radiological, Echo, CT Scan, USG) although infrequently leading in isolation to definite diagnosis, were often contributory.

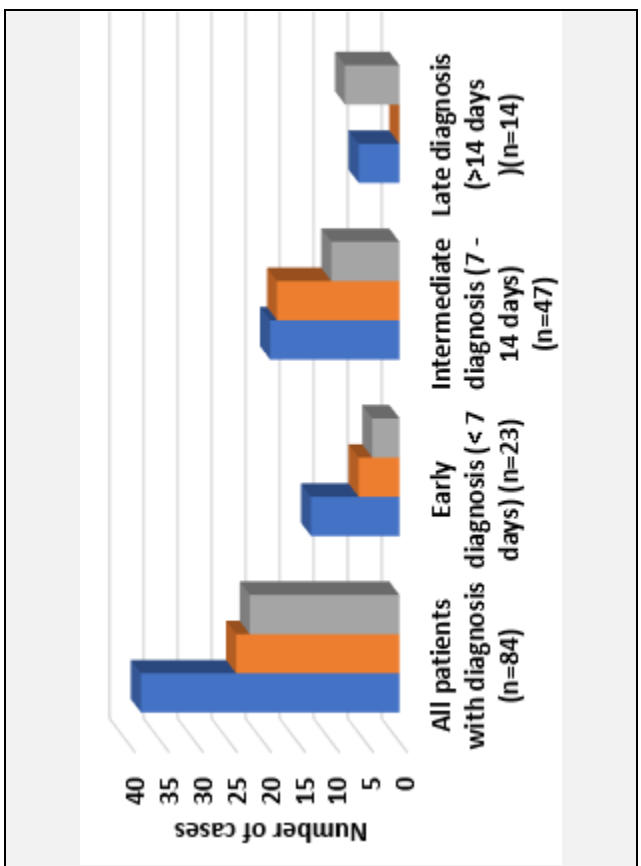

Figure 2. Final Diagnosis in the Present Study

In among infectious diseases 12 children, 6 (50 %) were male and 6 (50 %) were female. Commonest age group was between 6 - 9 years. Contact history was positive only in 3 (25 %). Mantoux positivity was as high as 10 (83 %) BCG scar was seen in 10 children. There was predominance of non-specific symptoms like anorexia, weight loss and low-grade intermittent fever.

DISCUSSION

Despite advances in diagnostic tools, FUO remains a challenging clinical problem. The diagnostic spectrum of FUO has changed since its original definition over 30 years ago. In contrast, many diseases that previously caused FUO no longer attain this status because of dramatic improvements in diagnostic imaging in the last several decades. Due to the development of improved diagnostic techniques, the proportion of FUO caused by infectious diseases has tended to decrease and the proportion of CTD, malignancies, and other diseases has tended to increase since then various studies had been conducted across the globe among different age groups to evaluate aetiologies 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 paediatric group, when compared to adults is the practical difficulty in obtaining repeated blood, urine or sputum samples.[6]

In general, infection accounts for about 20 – 25 % of cases of FUO in Western countries; next in frequency are neoplasms and non - infectious inflammatory diseases. In geographic areas outside the West, infections are much more common cause of FUO (43 % vs. 22 %). Up to 50 % of cases caused by infections in patients with FUO outside Western nations are due to tuberculosis. In India, infectious disease notably tuberculosis is the most important cause of FUO as showed by previous studies. The aetiologies of FUO were classified into 4 groups namely infection, malignancy, connective tissue disorder and undiagnosed.

In our study, analysis of results revealed infection was the major aetiology among all other groups, contributing to 38 % of the total study population, remaining are malignancy (24 %), NIID (22 %) and undiagnosed (16 %). In infancy, infections remain the commonest cause of FUO, and no case in this age group remained undiagnosed. Between 1 – 3 years, malignancy (especially acute lymphoblastic leukemia) was the commonest cause. Between 3 - 6 years infections remain the commonest cause. After 9 years, NIID dominates causes of FUO. Pizzo et al, [7] also concluded that in children less than 6 years were more likely to have an infectious aetiology while 80% of collagen inflammatory disease occurred in the group older than 6 years.

Study	Infections	Malignancy	Connective Tissue disorders (NIID)	Un-Diagnosed
Present study	38 %	24 %	22%	16 %
Kejariwal et al[8]	53 %	17 %	11 %	14 %
Hassan et al[9]	36.2 %	7.8 %	10.2 %	15.75 %
Mahmoudi et al[10]	26.3 %	7.4 %	14.7 %	18 %
Ching- yi-chu et al[11]	27 %	16.6 %	12.7 %	23.8 %
Santhosh et al[12]	69.1 %	16.7 %	5 %	3.4 %
Yi-Seul Kim et al[13]	19 %	7 %	28.3 %	20 %

Table 4. Comparison of Aetiological Causes in Various Studies

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 disorders are emerging as an important cause of FUO. In present study infections constitute 38% of FUO cases, confirming earlier trends that infections were the commonest cause of pyrexia 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 for infections.

Chow and Robinson[3] concluded that there was difference in the types of infections responsible for paediatric FUO between developing and developed countries. Bartonella infection was more common in developed countries, while brucellosis, typhoid fever, and tuberculosis were more common in developing countries.

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 12 % of the total infections. The reason is 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. From, Haq SA[14] et al., from Dhaka in 1996, Kejariwal D et al [8] 2002 from eastern India, showed that among infections, Tuberculosis was the commonest cause of FUO. Study done by Sarala Rajaji et al [15] Chennai, showed that infections were the common cause of FUO. Among infections enteric fever and tuberculosis lead the category.

In the present study also, tuberculosis was the predominant cause under infections, 12% of 84 diagnosed cases. Haq SA et al[14] in their study of 212 children with prolonged fever noted tuberculosis in 52 children (24.55 %) as the cause. Pleura were the commonest site, followed by lymph node and abdomen in their study. In the present study Tuberculosis lymphadenitis was the commonest cause followed by abdominal tuberculosis.

It was inferred from our study that enteric fever is the second major aetiology (7 %) among all infections causing FUO. 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. Sarala Rajaji [15] et al in their study of 75 children with FUO found that typhoid fever was the most common cause in 20 (26.6 %) patients with FUO. Mouaket AE[16] et al studied 221 children with FUO in Kuwait between 1985 - 1987, and found out that infections were found in 78 % of causes of FUO. Among infections brucellosis constituted 38 %, followed by typhoid fever.

Urinary tract infections contributed to 7 % of all infections causing FUO in our study, almost 90 % were below 1 year of age. UTI is one of the major causes of FUO in children less than 1 year of age and needs to be evaluated with priority in this age group. This can be compared with Kejariwal study. [8] In our study in infancy there was predominance of UTI in male children as compared to female children ratio being 3 : 1. There was predominance of non - specific signs like vomiting, loose stools & lethargy. Vesicoureteral reflex was observed in two children. Phimosis was seen in one case. Out of 7 culture positive UTI cases, 4 were observed to have normal routine urine analysis. Microcytic hypochromic anaemia was seen in three children, and normochromic normocytic anaemia in four children. Handa R et al[17] prospectively studied 121 cases of Fever of unknown origin and 50 occupationally exposed individuals. Four patients with FUO had acute brucellosis (3.3 %) while 8 (6.6 %) had serological evidence of previous Brucella infection. Seven of the 50 (14 %) asymptomatic, at risk individuals screened were seropositive for Brucella. He suggested that persistence of the animal reservoir of infection, low physician awareness, poor availability of diagnostic facilities, and the non-existence of regional data bases contribute towards the perpetuation of this zoonosis in India, while it has been eradicated from most developed countries. In the present study Brucellosis was observed in 3 (3 %) cases of FUO. The triad of fever, arthralgia and hepatosplenomegaly was observed in all three cases. There was no well - defined literature regarding brucellosis among children and it remains elusive as a cause of FUO in children. The commonest mode of spread in children was through drinking of unpasteurized milk. In rural India majority of people live in a close association with cattle. Therefore, they remain in close contact with domestic animals. They carry a risk for zoonotic diseases though diagnosed less often. It may be due to failure of seeking medical advice or unavailability of proper investigation. So, it is very important to consider other diseases like brucellosis, leptospirosis during evaluation of FUO patients.

Most cases of typical staphylococcal or streptococcal endocarditis are easily diagnosed as a cause 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 Modified Duke criteria were confirmed to be more sensitive for diagnosis of infective endocarditis. The specificity of the modified Duke criteria [18] was calculated to be 0.99 (95 % confidence interval, 0.97 - 1) and we should have high degree of suspicion to diagnose infective endocarditis.

In the present study two cases of infective endocarditis masquerading as Fever of unknown origin were noted. In two cases of previously well children without a focus, vegetation involving tricuspid valve were found. This suggests that high degree of suspicion should be there to diagnose infective endocarditis. In all the two cases cultures were negative even when three blood samples were taken appropriately; this phenomenon might be due to prior administration of antibiotics. All the two cases were diagnosed with the help of modified Duke Criteria. In one case there was an underlying undiagnosed ventricular septal defect which had predisposed it.

Sarala Rajajee [15] et al in their study of 75 children found malaria as the cause of Fever of unknown origin in eleven children. In the present study all the children were screened with peripheral smear for malarial parasite before they are included in the study. In the present study though the initial screening test are negative, subsequent peripheral smear examination yielded a positive result. This suggests that repeated peripheral smear examination was needed. Plasmodium falciparum was the organism responsible for the one case. This case had received chloroquine as outpatient. This implies that it might be chloroquine resistant.

Next to infections, malignancy (24 %) was the leading cause of FUO in our study. again, it holds well when compared with most of the studies (Kejariwal et al[8] and Joshil[5] except in some studies, Pizzo et al[7] and Cogulu et al[19]) where connective tissue disorders dominated the malignancy category. 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. Among malignancy especially acute lymphoblastic leukemia was observed to be the commonest cause of FUO between 1 - 3 years. Sharma BK[20] et al also observed that lymphoreticular malignancies

constitutes 21.32 % of FUO cases. Among malignancies, acute lymphoid leukemia (16 out of 24 cases) was the major aetiological outcome, followed by acute myeloid leukemia (4 out of 24 cases). There were 2 cases of Hodgkin lymphoma and 2 cases of Histiocytosis.

Fever, anaemia and bone tenderness were present in most of the cases of acute leukemia. Total WBC count is normal in 4 (25 %) children with leukemia. Among seven children who presented with total count in leucopenic range four children did not show blast cells in peripheral smear. Bone marrow aspiration cytology was the decisive investigation in acute leukemia. Early diagnosis is important to reduce mortality. Therefore, appropriate imaging studies or early invasive procedures such as bone marrow examination should be performed in certain patients with suspicious presentation for malignancies.

In the present study out of 14 cases of juvenile rheumatoid arthritis males outnumbered the female in the ratio of 1.8 : 1. A similar observation has been made by Porkodi R[21] et al, (1.27 : 1) In older children noninfectious inflammatory diseases were observed to be the commonest cause of FUO. History and evolution form the main decisive methods of diagnosis, as all other investigation were negative in JRA, except for raised inflammatory markers. Commonest joint involved was knee 12 (84 %), followed by ankle 11 (76 %) and wrist 8 (48 %). Symmetrical joint involvement in 9 (64 %) and asymmetrical joint involvement in 5 (36 %) children. Maculopapular rash which characteristically occurs in systemic onset was observed in 4 cases (28 %) only. Other causes of arthritis were ruled out before making a diagnosis of JRA, history and evolution of the disease was the decisive method of diagnosis. No cases of pauciarticular onset of JRA presented as FUO. Based on 2015 ACR / SLICC REVISED CRITERIA for diagnosis of systemic lupus erythematosus, American College of Rheumatology six (6) cases of SLE were diagnosed.

Out of 6 children, 4 (66 %) were between 9 - 12 years, youngest age observed was 3 years. Female children constitute 5 (80 %), male children 1 (20 %). Though skin manifestation was the predominant clinical feature, typical skin manifestation like malar rash was present only in 2 (33 %) children. Small joints of the hands were the commonest joints to be involved in children presenting with polyarthritis, followed by knee joint, and ankle joint. In two children predominant presenting clinical feature was seizures. ESR was elevated in all children with mean value more than 50. Commonest haematological manifestation observed was normochromic, normocytic anaemia in 5 (80 %), followed by thrombocytopenia in 3 (50 %). Total count was normal in 4 (60 %). In one child predominant presenting feature was anaemia with haemolysis (autoimmune haemolytic anaemia). Ds - DNA was positive in only in 2 (33 %) cases. 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, in spite of a detailed evaluation about 16 % of the cases could not be diagnosed, although all these children recovered well without any complications.

CONCLUSIONS

The common causes of FUO were infections followed by malignancy, NIID and few of them undiagnosed. Infections were the most common cause of FUO constituting 38%. Among infections tuberculosis was the commonest one causing 12 % of FUO. Typhoid (7 %) and UTI (7 %) were the next common infections. Over a period of time, with the advent of newer diagnostic techniques, and improved imaging facilities, more cases of undiagnosed FUO cases may be diagnosed which will help in the better management of patients with good outcome.

Financial or Other Competing Interests: None.

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