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STUDY OF ETIOLOGICAL OUTLINE OF FEVER OF UNKNOWN ORIGIN IN CHILDREN BETWEEN 3 YEARS TO 12 YEARS ADMITTED IN TERTIARY CARE CENTER AL AMEEN MEDICAL COLLEGE VIJAYAPURA

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ABSTRACT

Background: Fever of Unknown Origin (FUO) remains a significant clinical challenge, especially in paediatric patients. Prolonged fever with no apparent diagnosis demands a systematic approach for early identification and effective management. This study focuses on understanding the etiological spectrum of FUO in children aged 3–12 years and aims to improve diagnostic accuracy and treatment strategies. **Methods:** This prospective observational study included 100 children aged 3–12 years diagnosed with FUO. We collected data on patient demographics, clinical history, physical findings, and a structured diagnostic protocol including laboratory, serological, and imaging investigations. Statistical analysis was performed using IBM SPSS version 30 to identify associations between clinical features and final etiological diagnosis. **Results:** Of the 100 paediatric FUO cases, the most frequent diagnoses were acute lymphoblastic leukaemia (16%), juvenile rheumatoid arthritis (14%), and tuberculosis (12%). After a complete evaluation, 16% of the patients remained undiagnosed. WBC was elevated in most patients, with ESR and CRP significantly elevated in inflammatory conditions. The duration of fever varied according to the condition, with endocarditis cases lasting an average of 38 days. FUO was more common among girls (57%) and appeared in every age group, with conditions such as Kawasaki disease and myelodysplastic syndrome affecting older children. The important diagnostic factors are hepatosplenomegaly, lymphadenopathy, and joint swelling. **Conclusion:** Our study emphasises the diverse aetiologies of paediatric FUO, underlining the need for a careful diagnostic process. Although infections are prevalent, most occurrences are due to haematological malignancies and autoimmune conditions. The high percentage of undiagnosed cases underscores the necessity for advanced diagnostic tools and further research on paediatric FUO.

INTRODUCTION

Fever is a common symptom among paediatric patients, acting as an important indicator of underlying disease. Although most fevers resolve on their own, a subgroup persists despite extensive investigations and treatment. Fever of Unknown Origin (FUO) is an important clinical problem, requiring a careful diagnostic strategy. FUO refers to a protracted fever of unknown cause and may be due to a wide range of causes, such as infections, malignancies, autoimmune conditions, and uncommon conditions.[1] Paediatric FUO poses a peculiar diagnostic challenge due to its miscellaneous etiologies and superimposable clinical presentation.[2] Unlike adults, paediatric patients with FUO might have subtle signs, necessitating careful clinical evaluation and laboratory work-ups.

FUO was originally described by Petersdorf and Beeson in 1961 and has come to be refined into ambulatory evaluation, placing high importance on outpatient treatment. Classification of FUO includes a series of groups having different root causes and testing practices.[3-5] In paediatric patients, infections are the leading cause, but autoimmune conditions and cancers are being recognised more and more. Knowing the distribution of aetiological causes can help clinicians develop good diagnostic plans and decrease undiagnosed cases.[6,7] Geographic sites, access to healthcare, and advancements in diagnostic technology affect the occurrence of certain etiologies.[8]

The epidemiology of FUO in children is highly variable worldwide, depending on the prevalence of infectious diseases, access to healthcare, and diagnostic practices.[9,10] This variability is highlighted by studies carried out in different settings. For instance, one study reported a relatively common presentation of FUO in children admitted to hospital, whereas another highlighted the challenge of diagnosis, with the majority of cases remaining undiagnosed despite intensive investigations[11-14] This study fills the gap in paediatric FUO epidemiology by examining cases admitted to Al Ameen Medical College, Vijayapura. This study aimed to comprehend the etiological spectrum of FUO among children aged 3–12 years. Through the examination of clinical patterns, laboratory parameters, and final diagnoses, this study sought to present new insights into the epidemiology and management of paediatric FUO. Through the improvement of diagnostic procedures and the optimisation of patient management strategies, this study improves early diagnosis and minimises hospital stays for paediatric patients with FUO.

This study adds value to what already exists by offering a detailed review of FUO cases in a tertiary hospital setup. These results improve clinical knowledge, opening doors to future research and development in the management of fever in children. By merging clinical knowledge with systematic explorations, this study enhances early diagnosis and treatment outcomes, eventually impacting paediatric patients with FUO.

Objectives

This study aimed to identify the etiological factors behind FUO and examine the clinical presentations and laboratory parameters involved in FUO among children in the age group of 3–12 years.

MATERIALS AND METHODS

This 18-month prospective observational study was carried out on 100 children in the age group of 3–12 years who had FUO and were admitted to the Tertiary Care Centre in Al-Ameen Medical College Hospital, Vijayapura, Karnataka.

Inclusion Criteria

- Children aged 3–12 years with documented evidence of fever >38.6°C were included.
- This included outpatients with recurring fever at least twice a week for > three weeks and inpatients with fever lasting longer than one week after diagnostic investigation.

Exclusion Criteria

Children were excluded if they were immunocompromised, defined as neutropenia (WBC <1000/μL or neutrophil count <500/μL), confirmed HIV infection, or receipt of immunosuppressive therapy, such as defined doses of prednisolone. Patients with nosocomial FUO (fever after 24 h of admission without pre-existing evidence of infection), inadequate baseline investigations at admission, and pre-existing diagnoses based on referring physicians were also excluded.

Sample Size Calculation

The sample size (n) was determined using the formula $n = (z^2 \times p \times (1-p))/e^2$, where z=1.96 for a 95% confidence level, p=50% (0.50), and e=10% (0.10). Therefore, $n = ((1.96^2) \times 0.50 \times (1-0.50)/(0.10)^2) = 96.04 \approx 100$.[15]

Methods

A systematic sampling strategy was used to obtain representative samples of eligible paediatric patients. Data collection consisted of a structured diagnostic protocol, which included a thorough clinical evaluation by history-taking that elicited the pattern and duration of fever, related symptoms, previous treatments, and pertinent medical background. Thorough physical examinations were conducted to identify clinical clues that suggested a possible diagnosis.

Extensive laboratory investigations were performed, including complete blood count (CBC), differential count, haemoglobin estimation, erythrocyte sedimentation rate (ESR), and peripheral smear.

Investigations included microbiological tests (e.g., thick and thin smears for malaria, Widal test), immunological tests (Mantoux, Weil-Felix, ELISA), biochemical tests (liver and renal function), and imaging (chest X-ray and abdominal ultrasound). Blood cultures and bone marrow biopsies were performed when clinically indicated. This systematic approach was designed to allow adequate assessment and proper identification of the causes of FUO in children.

Statistical Analysis

Data were analysed using IBM SPSS Statistics version 30. Descriptive statistics summarised continuous variables as mean, and standard deviation, and categorical variables as percentages and frequencies. Visual representation was used to present the findings, and a p-value <0.05 was deemed statistically significant.

Ethical Considerations

This study was conducted under the ethical standards following approval from the Institutional Ethics Committee of Al-Ameen Medical College. Informed consent was obtained from the parents or guardians of the participating patients, ensuring transparency and voluntary participation.

RESULTS

The study included 100 children (57 females and 43 males). The age distribution had peaks at 4 and 6 years, each with 20 patients, and other ages were more uniformly distributed, with 10 patients per age group. Continuous fever was the most common type, occurring in 40 patients, followed by remittent, intermittent, and relapsing fevers, each occurring in 20 patients. The most frequent diagnoses were undiagnosed conditions (16%), acute lymphoblastic leukaemia (16%), juvenile rheumatoid arthritis (14%), and tuberculosis (12%).

Endocarditis had the longest fever duration (38 days), whereas RAEB and non-Hodgkin's lymphoma had the shortest (15 days). The highest WBC count was observed in patients with endocarditis (18,000 cells/mm^3), while the lowest was observed in patients with hepatitis B (8,900 cells/mm^3)

Laboratory reports showed an evident immune and inflammatory response in the patients. The mean WBC count was 10,630 cells/mm^3, with the majority in the range of 9,200-12,000 cells/mm^3. The median ESR was 46.5 mm/hr, while the mean CRP was 32.4 mg/L, going up to as high as 50 mg/L in some. Platelet counts reveal a mean of 2.75 Lakh/μL, with ranges between 1.5 and 3.1 Lakh/μL, demonstrating normal clotting function in the majority of patients

The "Undiagnosed" category is the most frequent, with 14 females and 2 males. Acute lymphoblastic leukaemia and juvenile rheumatoid arthritis were the most commonly diagnosed conditions. Tuberculosis affects both sexes equally, whereas hepatitis B, Hodgkin's lymphoma, and non-Hodgkin's lymphoma are seen only in females, and leptospirosis, vasculitis, and RAEB are seen only in males. Some diseases showed a uniform sex distribution, whereas others were sex-specific or rare ALL, juvenile rheumatoid arthritis, and tuberculosis are among the most common conditions affecting multiple age groups. The "Undiagnosed" category appeared in every age group, highlighting the diagnostic challenges. Some diseases, such as hepatitis B (age 7), leptospirosis (age 7), RAEB (age 6), and Kawasaki disease (ages 10 and 12), were more isolated to specific age ranges. The data suggest that certain illnesses are more prevalent at particular ages, indicating possible age-related risk factors or diagnostic patterns.

DISCUSSION

FUO in children still represents a diagnostic challenge that necessitates a systematic and methodical approach to diagnosing its varied aetiologies. This report emphasises the importance of incorporating careful clinical evaluation with focused laboratory tests to enhance the precision of diagnosis. By exploring clinical presentations, laboratory findings, and ultimate diagnoses, the investigation not only reconfirms known patterns but also fills some of the current gaps in paediatric FUO epidemiology to make additional diagnostic and management interventions more effective within tertiary care practices. Our findings align with previous research emphasising the predominance of infectious causes in FUO cases. Studies conducted by Bandyopadhyay et al. have highlighted infections such as tuberculosis, enteric fever, and viral infections as common causes.[15]

Even with the use of a systematic diagnostic methodology, several challenges were experienced in this study. The use of traditional microbiological tests has the limitation of detecting some pathogens that need specialized diagnostic procedures, including polymerase chain reaction (PCR) assays or next-generation sequencing technologies. Additionally, the variability in disease presentation renders clinical suspicion an essential yet challenging factor in diagnosis. The relatively small sample size was another limitation, which may not fully capture the diverse etiological spectrum of FUO in paediatric populations. Larger multicentre studies are necessary to validate these findings and develop more robust diagnostic protocols.

Longitudinal studies assessing treatment outcomes can provide valuable insights into the long-term prognosis of paediatric FUO. In the studies by Chien et al. and Cho et al., advice was passed on to future research, emphasising us to prioritise the integration of advanced diagnostic tools, including whole-exome sequencing, cytokine profiling, and cutting-edge imaging techniques.[22,23]

CONCLUSION

Our study emphasises that infections, especially tuberculosis, enteric fever, and viral illnesses, are the most common causes of paediatric FUO. Autoimmune diseases, such as SLE and juvenile rheumatoid arthritis, are also major contributors. The persistence of undiagnosed cases highlights current diagnostic limitations and supports the need for integrating advanced tools such as molecular diagnostics and genetic testing. Early recognition, supported by a systemic approach to evaluation and contextual clinical judgment, is key to optimising outcomes and diminishing diagnostic delays in children with FUO. Future research should focus on incorporating novel biomarkers and genetic studies to enhance the diagnostic precision in FUO cases.

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