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A prospective study on the microbial profile of pyrexia of unknown origin from inpatients of tertiary care hospital in North Karnataka

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ABSTRACT

Introduction: Fever could have many causes including infective and non infective origin. PUO is a clinical syndrome that may result from much common etiology which was characterized by prolonged fever without the signs or symptoms indicative of a well defined disease process

Objective of the study: To find the infectious causes of fever of unknown origin for 2–7 days duration were tested for Leptospirosis, Malaria, Rickettsial disease, Dengue virus, Chikungunya virus, UTI and blood borne infections and to find out antimicrobial susceptibility pattern of the organisms isolated.

Materials and Methods: This prospective study conducted in the Department of Microbiology, Bidar Institute of Medical Sciences (BRIMS) Bidar of North Karnataka. Patients with fever of unknown origin for 2–7 days duration were tested for Leptospirosis, Malaria, Rickettsial disease, Dengue virus, Chikungunya virus and urine & blood culture tests. Statistical software package SPSS version 22 was used to analyse the data. Chi-square test was applied wherever necessary and P-value of < 0.05 was considered statistically significant.

Results : Among the 200 enrolled patients, 57 Dengue fever, 44 Enteric fever, 34 Chikungunya, 23 UTI, 21 Blood borne pathogens, 17 Leptospirosis, 14 Scrub-Typhus and 3 Malaria cases were confirmed. Mixed infection was seen in 26 cases. In our investigation, the current study revealed that the burden of Dengue, Enteric fever, Chikungunya, Leptospirosis, Scrub-Typhus & UTI disease is more in the current population.

Conclusion: Laboratory based syndromic information of PUO can make clinicians cautious with respect to the potential pathogens in neighborhood. However, some of the cases always elude diagnosis, although the patients may respond to empirical therapy.

1. Introduction

Pyrexia of unknown origin (PUO), also known as fever of unknown origin (FUO) is a syndrome that has long tested the skills of physicians to achieve a diagnosis in affected patients. It is a grouping of many unrelated medical conditions that share the feature of persistent unexplained fever despite basic investigation. Patients included in this syndrome will be more difficult to diagnose as they have already resisted classification during baseline investigations.[1] By definition, PUO means fever that does not resolve spontaneously in the period expected for self limited infection and whose cause cannot be ascertained despite considerable diagnostic effort.

In 1961, Petersdorf and Beeson described the criteria for PUO that subsequently became standard. This entailed having illness of more than 3 weeks duration, fever of 38.3°C (101 F) or more on several occasions lasting at least 3 weeks and for which no cause can be identified after 1 week days of investigations in hospital or after 3 or more outpatient visits.[2,3]

The undiagnosed cases of PUO are increasing over time. It is paradoxical that despite the introduction of computed tomography, magnetic resonance imaging, improved culture techniques, numerous new serologic assays, and polymerase chain-reaction studies. Therefore,

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only difficult-to-diagnose diseases are qualified as PUO, due to the increasing availability of diagnostic facilities, both in hospital and outpatient settings. In recent years more PUOs have actually eluded diagnosis and more than 51% of cases defied diagnosis.[1] In 2003, Vanderschueren and colleagues reported that in nearly a third of 290 immunocompetent patients in Belgium, no diagnosis was made, and in 2007, Bleeker-Rovers et al reported that among 73 immunocompetent patients from five hospitals in the Netherlands, no cause of PUO was identified in 51% of cases.[4]

In resource poor countries, PUO is more frequently due to infections comparing to high resource countries where inflammatory and malignant disorders account for most of the cases. This may partly represent differences in the geographic and temporal distribution of diseases, but is also explained by the comprehensiveness of the investigations performed prior to classifying a patient as having PUO and the diagnostic tests subsequently available to investigate it. For example, the availability of highly sensitive blood culture techniques and high quality echocardiography means that bacterial endocarditis is now a less common cause of PUO because the condition can be diagnosed relatively easily and is therefore unlikely to meet the PUO criteria.

According to studies conducted to date, the diseases taking part in PUO etiology and their rates are as follows: infections (21–54%), noninfectious inflammatory causes (13–24%), neoplasms (6–31%) and other causes (4–6.5%). The incidence of various causes differ with geographical, age and sex difference and development level of countries, vector distribution the availability of diagnostic tests and the experience of clinicians. Misleading factors in the diagnostic approaches made by the physician; regarding the anamnesis (24.6%), the clinical examination (22.6%), the wrong interpretation of a laboratory test (20.7%), and inadequacy in the evaluation of a symptom and/or a positive test (5.6%).

Infection still remains the most common cause of classical PUO all over the world even though the demographics vary from region to region. The rate of disease attributable to each category varies between different populations studied and the type of healthcare environment, but in general, in developed countries, infectious causes account for 17–35%, noninfectious inflammatory diseases account for 24–36%, neoplastic causes for 10–20%, miscellaneous causes 3–15%, and no diagnosis established in 16–39%.[5,6] In developing countries, infections are the major cause of PUO, whereas in developed countries NIID account for most cases. In several recent studies no cause could be found in a large proportion of patients.[7,8]

In India 2014,[9] a total of 91 cases (62 males and 29 females), with age ranging from 16 to 80 years were investigated. The mean duration of fever before hospitalization was 26±4 days. The etiology of PUO was delineated in (66%) of cases, whereas, (25%) remained undiagnosed. Most common group of PUO was that of infectious diseases (44%) followed by collagen vascular diseases and malignancies (12% each). Amongst the infection group, brucellosis and salmonellosis comprised the majority of cases (25% each). Thus, knowledge of local prevalence of PUO is mandatory in order to target clinical work up and treatment.[10] There are only a limited number of studies from Karnataka reporting on the etiology of PUO and reliable epidemiological data are not available.[11]

With this background, we aimed to conduct a hospital based prospective study to investigate and evaluate the causes and etiology of PUO, and their clinical spectrum among patients in teaching hospital of North Karnataka.

2. Materials and Methods

This cross sectional study was conducted in the Department of Microbiology of Bidar Institute of Medical Sciences (BRIMS) Bidar of North Karnataka. The study population consisted patients from urban and rural area of Bidar visiting to Outpatient Department's of Teaching hospital of Bidar Institute of Medical Sciences. Patients with undiagnosed fever for more than 3 weeks duration were included in this study. A total of 200 patients aged 13 and above were included in the study. Brief history about the illness and patient details like age, sex and address were recorded. This study protocol was approved by Institute's Ethics Committee, and samples were collected after obtaining informed consent from the patients.

The sample size (n=200) was estimated with an expected prevalence of pyrexia of unknown origin as 15% with 4% absolute precision and 95% confidence interval. An interim analysis was carried out and the estimate from the interim analysis was used to modify the sample size. Convenience sampling method was adapted to carry out this study.

2.1. Exclusion criteria

Patients with hematological malignancies, autoimmune disorders, and those on immuno suppressants were eliminated from the study.

2.2. Methods

Samples such as blood and urine were collected. Blood culture was done using Brain heart infusion broth and antimicrobial sensitivity test is done for the pathogens isolated. Further, the following Microbiological investigations were included in the Study to diagnose PUO.

1. A thick and thin smear was performed to recognize malarial parasites.

2. Rapid Dengue test to detect NS1Ag and anti-dengue IgM and IgG antibodies.
3. Enzyme-linked immunosorbent assay (ELISA) tests after the 7^{th} day of fever if tests for malarial parasites and blood cultures are negative. These include dengue IgM ELISA, Chikungunya IgM ELISA, Leptospira IgM ELISA, Weil Felix test for Scrub Typhus was done by tube agglutination method. Antibodies from patients serum was tested against antigens OX-19 for Endemic Typhus, OX-2 for spotted fever and OX-K for Scrub Typhus. Titer of 1:160 and above was considered significant. Widal tube agglutination test was done from patient's serum. Antibodies from patient's serum against *Salmonella typhi and Salmonella paratyphi* antigens were detected. *Salmonella typhi O, Salmonella typhi H, Salmonella paratyphi AH* and *Salmonella paratyphi* BH antigens were included. A titre of 100 or more for O antigen is considered significant and a titre in excess of 200 for H antigens is considered significant.
4. Blood culture is done for patients in BHI broth and then plated on Blood and MacConkey's agar. Antimicrobial drug susceptibility testing was done in cultures which showed the growth.
5. A clean catch mid-stream urine sample was collected in a sterile wide mouth container and processed for culture and antimicrobial drug susceptibility as per the routine microbiological techniques.

Recovering serological testing following a month was performed if the underlying serological finding is vague and if the patient is willing.

2.3. Statistical analysis

Statistical software package SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used to analyse the data. Chi-square test was applied wherever necessary and P-value of < 0.05 was considered statistically significant.

3. Results

A sum of 200 patients were assessed. Of these, 123 (61.5%) were males and 77(38.5%) were females. Out of 200 cases, 31 (15.5%) cases were undiagnosed for any of PUO like Dengue, Chikungunya, and Enteric fever, Scrub-typhus, Malaria and Leptospirosis. Among 84.5% Diagnosed cases, Dengue (57 cases – 33.7%) was the predominant disease reported in the affected population. In decreasing order fallowed by Enteric fever (44 cases – 26%), Chikungunya (34 cases – 20.1%), UTI (23 cases – 13.6%), Blood borne infections (21 cases – 12.4%), Leptospira (17 cases - 10.1%), Scrub-typhus (14 cases – 8.2%) and Malaria (3 cases – 1.8%). [Table. 1] Mixed infection was reported in 26 (15.4%) affected cases, out of which 14 cases reported mixed infection with Dengue and Chikungunya (8.2%). In decreasing order of mixed infection by Dengue and Scrub-typhus (9 cases – 5.3%) and Malaria and Scrub-typhus (3 cases – 1.8%).

Escherichia coli was the predominant pathogen isolated from urine and showed high level of resistance to Ampicillin (82.53%), Cefuroxime (72.41%), Amoxicillin-clavulanic acid (71.90%), Ceftriaxone (66.58%), Ciprofloxacin (65.82%) and Cefepime (57.47%). The isolates were sensitive to Imipenem (96.71%), Nitrfurantion (92.41%), Amikacin (90.89%), Chloramphenicol (85.82%), Piperacillin-tazobactum (80.76%), Gentamicin (59.24%), Azetreonam (54.43%) and Norfloxacin (53.67%).

Blood culture yielded *Salmonella typhi* and *paratyphi A* and *Staphylococcus aureus*. All patients were responded to ceftriaxone. *Salmonella typhi* & *paratyphi A* were sensitive to ciprofloxacin and ceftriaxone.

4. Discussion

The current study revealed that the burden of Dengue, Enteric fever, Chikungunya, Leptospirosis, UTI and Scrub-Typhus disease is more in the current population and are the most common cause of PUO. In the study conducted by Kashiwagi et al.[12] infections was the most common cause of PUO. Infection is higher in this study (84.5%) than the study conducted by Kashiwagi et al[12] in which infections accounted for 55.0% cases of PUO. Previous studies conducted in different parts of India (northern and southern parts) reported similar results. A study conducted by Abrahmsen et al.[13] in southern India reported that majority of the PUO are bacterial infections, (38%) out of which 19% of are Tuberculosis.

Escherichia coli was the commonest organism isolated from UTI cases which shows Extended Spectrum Beta Lactamases (ESBL). This current study had discordant results with the results of Iikuni et al,[14] in which 1.3% of patients with PUO had UTI. This high incidence may be explained due to recurrent infection with predisposing factors like DM, CKD in this study group. Combined contamination with more than one etiological agent can bring about an ailment with covering indications, bringing about a circumstance where the detection and the handling of such a patient could be demanding for the treating physician.[15,16] Side effects of one illness may copy with other diseases which are additionally common around there. Along these lines, patients giving intense febrile sickness ought not to be ventured to experience the ill effects of single contamination alone. The clinician ought to explore completely to search for different reasons for fever.

The etiologies of PUO are region and country specific. PUO causes significant mortality and morbidity across the India. Mortality due to PUO are preventable.[17] In this study, undiagnosed cases of PUO were seen in 15.5% of patients. This was lower with study by FJ Barbado et al[18]

Table 1: PUO Cases along with Aetiologies

S. No.	Disease	Positive Cases	Percentage Affected
1.	Dengue	57	33.7
2.	Enteric fever	44	26
3.	Chikungunya	34	20.1
4	UTI	23	13.6
5	Blood borne infections	21	12.4
6	Leptospira	17	10.1
7	Scrub typhus	14	8.2
8	Malaria	3	1.8
9	Mixed infection- Dengue and Chikungunya	14	8.2
10	Mixed infection- Dengue and scrub-typhus	9	5.3
11	Mixed infection- Malaria and scrub-typhus	3	1.8

in which 21.0% and Deal et al[19] in which 20% of cases of PUO were undiagnosed. Out of 31 undiagnosed cases, fever subsided spontaneously in 12 patients may be due to antibiotic therapy or may be due to self limiting prolonged viral illness.

In the present study, PUO are most normal during stormy and harvest time seasons. The dormant water because of downpours aggravated by poor seepage framework in a large portion of the regions in growing nations turns into a rearing ground for the mosquitoes helping them to transmit the ailments. Occasional upsurge in fever is likewise an outstanding documentation in the preceding studies.[20]The precise finding of PUO is entangled by an absence of information about local pathogens, existence of comparative signs and manifestations and inaccessibility of the broad diagnostic panel prompting to mismanagement of PUO cases. The infectious operators causing PUO fluctuates by various regions proposing that the diagnosis and management should be founded on a deliberate assessment of territory explicit aetiologies dependent on the laboratory based syndromic observation.

Since this study was mainly focused on the common infectious causes and the corresponding investigations. Other rare causes like brucellosis, granulomatous diseases and certain neoplastic conditions would have contributed to the undiagnosed group.

5. Conclusion

In 84.5% of cases with fever more than 3 weeks were caused by infectious origin. Despite the availability of advanced diagnostic methods, 15.5% of undiagnosed cases indicating that PUO will continue to be a clinical challenge in Bidar. The etiological profile will be useful in the advancement of balanced rules for control and treatment of PUO.

6. Source of Funding

None.

7. Conflict of Interest

None.

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