A Study on common etiology of infections in Pyrexia of Unknown Origin at a tertiary care hospital

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Abstract— Pyrexia of unknown origin (PUO) is a clinical syndrome that may result from various etiologies which was characterized by prolonged fever without the signs or symptoms indicative of a well-defined disease process. The symptoms and differential diagnosis of these diseases are similar, making accurate clinical diagnosis difficult without laboratory confirmation. Etiology of PUO varies from vector borne (Malaria, dengue, Chikungunya), Bacterial infection (Enteric fever, Urinary tract infection, Blood stream infections). There are only few studies on Pyrexia of unknown origin (PUO) available from India. The objective of this study is to identify the common causes of infections in Pyrexia of Unknown origin. This cross-sectional study was carried out among Six thousand six hundred and thirty-seven patients from January to December 2022 at a tertiary hospital. Blood collected for serological tests including WIDAL, HbsAg , HCV , ELISA for Dengue, Malaria and Chikungunya. Blood cultures for suspected blood borne infections. Urine collected from suspected Urinary tract infection patients. Of the Six thousand six hundred and thirty seven samples, Five hundred and thirteen were positive for Dengue, three hundred and seven were positive for WIDAL, hundred and fifty six positive blood cultures , hundred and forty two were positive for urinary tract infection , eight positive for malaria, five positive for chikungunya and three positive for hepatitis. This study was done for a duration of one year, therefore we could compare the sample load with the change in climatic conditions. The knowledge about common etiologies and their prevalence will help in proper planning of clinical management and for implementing preventive measure like proper sanitation and vector control.

Keywords — Pyrexia of unknown origin, Infectious disease, WIDAL, Dengue, Blood cultures

I. INTRODUCTION

In a developing country, infectious disease remains the most important cause of fever.[1] PUO is a clinical syndrome that may result from various etiologies which was characterized by prolonged fever without the signs or symptoms indicative of a well defined disease process.[2] Patient with temperature $>38.0^{\circ}$ C on multiple occasions for more than 3 weeks in spite of investigations on 3 outpatient visits (or) 3 days of stay in the hospital or 1 week of intensive ambulatory investigation is defined as Pyrexia of unknown origin.[3]

The majority of patients present with non-specific symptoms such as low-grade fever, general malaise, headache, arthralgia, myalgia, and rash; and usually without a focal point of infection. The symptoms and differential diagnosis of these diseases are similar, making accurate clinical diagnosis difficult without laboratory confirmation.[4]

Vector-borne infections such as malaria and dengue are of major public health concern worldwide. The former is a parasitic disease transmitted by Anopheles mosquito, and the latter is a viral disease transmitted by Aedes mosquito. It is important; however, to differentiate between the two conditions, otherwise, it may result in a poor outcome due to complications like dengue haemorrhagic fever, dengue shock syndrome[5]. According to WHO, annually 50 million cases of DF occur world over with a mortality of 2.5%[6]. Chikungunya (CHIK) fever is a viral disease caused by an alpha virus that is spread by bite of Aedes aegypti mosquito.[7]

Typhoid fever is a systemic prolonged febrile illness caused by certain Salmonella serotypes including Salmonella typhi, S. paratyphi A, S.paratyphi B and S.paratyphi C. Human beings are the only reservoir host for typhoid fever, and the disease is transmitted by faecal contaminated water and food in endemic areas especially by carriers handling food. The World Health Organization (WHO) estimates about 21 million cases of typhoid fever with >600,000 deaths annually.[8]

UTI (Urinary Tract Infection) burden globally, 404.61 million cases, 236,790 deaths, and 520,200 DALYs were estimated in 2019.[9] The spectrum of key pathogens of Blood Stream Infections (BSI) in most low-resource settings includes Salmonella enterica. Rates of >300 cases of typhoid fever per 100 000 person-years have been reported from some African countries and India.[10]

II. MATERIALS AND METHODS

The study included patients presenting with fever with oral temperature over 38.0° C, duration of fever more than 3 weeks in spite of investigations on 3 outpatient visits (or) 3 days of stay in the hospital. Diagnosis was confirmed by suitable laboratory tests after exhaustive clinical examination. A proper and complete history was collected and documented from each patient regarding duration of illness and clinical symptoms. Blood collected from each patient for serological tests including WIDAL test using Tydal kit, HbsAg using Hepaview Rapid kit, HCV using Standard Q rapid kit, ELISA test for Dengue and Chikungunya using MAC – ELISA kit supplied by NIV Pune and SD Biosensor capture ELISA for NS1 antigen detection. Complete Blood Picture & thick and thin smears for malarial parasite stained with Jaswant Singh- Bhattacharji (JSB) stain were done using EDTA blood samples. Blood cultures for suspected blood borne infections cases. Urine collected from suspected UTI patients for urine culture and sensitivity testing. Blood samples collected for monitoring platelet count ,WBC count .

Inclusion criteria :

• Patients of all age of both sex

• Patient with temperature $>38.0^{\circ}$ C on multiple occasions for more than 3 weeks in spite of investigations on 3 outpatient visits (or) 3 days of stay in the hospital or 1 week of intensive ambulatory investigation.

• Patients willing to give consent

Exclusion criteria :

• Patients not willing to give consent

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

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III. RESULTS AND DISCUSSION

A total of 6637 patient samples with fever were evaluated. Among them 5005 samples were subjected to serological tests like WIDAL, Dengue, chikungunya, malaria and Hepatitis markers and 1632 samples were collected for bacterial culture (fig 1). Of these, 58.7 % (3896) were males and 41.29% (2741) were females.



Figure 1 Total patient samples collected with month wise distribution

A total of 1632 samples were collected for culture, among which blood culture contributed to 915, urine culture contributed to 717. Escherichia coli is the most common organism isolated from urine culture especially from female patients. Salmonella species is most commonly isolated from blood culture of patients suspected from blood borne infections.





Among the serological tested samples, 836 were positive in which 513 (45.2%) were positive for Dengue (month wise positive cases seen in fig 4), 307 (27.07%) were positive for WIDAL, 8 (0.7%) positive for malaria, 5 (0.44%) positive for chikungunya and 3 (0.26%) positive for hepatitis. Among the samples tested for culture, 298 were positive in which 142 (12.52%) were positive for urinary tract infection, 156 (13.75%) positive blood cultures (shown in fig 2,3). Among the total samples processed for Dengue serology, IgM (296) positivity was more than (217) NS1 since samples from patients presenting with acute fever were excluded from the study (fig 4).



Figure 4 Dengue cases with IgM and NS1 positive comparison



Figure 5 Clinical outcome in Dengue positives

The fig 5 shows clinical outcomes of Dengue cases where more patients presented with thrombocytopenia than leukopenia. As the study period was for a duration of 1 year, we observed gradual increase in sample load from late summer to monsoon season with the peak of cases in the month of August followed by september (Fig 1). The study revealed the heavy burden of tropical infections such as Dengue, Enteric fever.

In developing countries WIDAL test remains one of the best, economic , and simple method for the diagnosis of typhoid fever.

STUDY	Dengue fever	Enteric fever	Chikungunya	UTI	Blood borne pathogens	Malaria	Hepatitis
Present study	45.2%	27.07%	0.44%	12.52%	13.75%	0.7%	0.26%
Kulkarni S, Chillarge C [2] 2020	33.7%	26%	20.1%	13.6%	12.4%	1.8%	-
Garima Mittal et al [11] 2015	37.54%	16.64%	-	-	10.3%	6.8%	-

IV. CONCLUSION

This study revealed highest incidence of Dengue followed by Typhoid cases . Males were more commonly suffering from fever due to infections, which might be because of their increased exposure to outdoor works and activities. Dengue cases were most common, as monsoon period is convenient time for mosquitoes to breed. Water contamination during outpours of rain in early monsoon is most important cause for increased Typhoid cases. In India , infectious disease still remains most important cause of fever. Active fever surveillance is necessary as clinical diagnosis is not always sufficient to detect all febrile cases. Laboratory confirmation is essential to refine disease burden estimates of common causes of PUO. If accurate epidemiologic database is established on different etiologies of fever in every region , it would help in anticipating epidemic preparedness in terms of resources and health care delivery. The knowledge about common etiologies and their prevalence will help in proper planning of clinical management and for implementing preventive measure like proper sanitation maintenance and vector control programmes.

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REFERENCES:

- Bandyopadhyay D, Bandyopadhyay R, Paul R, Roy D. Etiological study of Fever of unknown origin in patients admitted to medicine ward of a teaching hospital of eastern India. J Glob Infect Dis. 2011 Oct;3(4):329-33. doi: 10.4103/0974-777X.91052. PMID: 22223993; PMCID: PMC3249985.
- 2. Kulkarni S, Chillarge C. A prospective study on the microbial profile of pyrexia of unknown origin from inpatients of tertiary care hospital in North Karnataka. IP Int J Med Microbiol Trop Dis 2020;6(3):179-183.
- 3. PETERSDORF RG, BEESON PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961 Feb;40:1-30. doi: 10.1097/00005792-196102000-00001. PMID: 13734791.
- 4. Wangdi K, Kasturiaratchi K, Nery SV, Lau CL, Gray DJ, Clements ACA. Diversity of infectious aetiologies of acute undifferentiated febrile illnesses in south and Southeast Asia: a systematic review. BMC Infect Dis. 2019 Jul 4;19(1):577. doi: 10.1186/s12879-019-4185-y. PMID: 31272417; PMCID: PMC6610835.
- 5. Shah PD, Mehta TK. Evaluation of concurrent malaria and dengue infections among febrile patients. Indian J Med Microbiol. 2017 Jul-Sep;35(3):402-405. doi: 10.4103/ijmm.IJMM_15_455. PMID: 29063886.
- 6. Shanmugan P, Soundararajan N, Ravi V, Venkatesan P. A study on the prevalence of Dengue fever in Kelambakkam in comparison to an earlier study. Indian J Microbiol Res 2016;3(2):102-106
- 7. Chhabra M, Mittal V, Bhattacharya D, Rana U, Lal S. Chikungunya fever: a re-emerging viral infection. Indian J Med Microbiol. 2008 Jan-Mar;26(1):5-12. doi: 10.4103/0255-0857.38850. PMID: 18227590.
- 8. Andualem G, Abebe T, Kebede N, Gebre-Selassie S, Mihret A, Alemayehu H. A comparative study of Widal test with blood culture in the diagnosis of typhoid fever in febrile patients. BMC Res Notes. 2014 Sep 17;7:653. doi: 10.1186/1756-0500-7-653. PMID: 25231649; PMCID: PMC4177418.
- 9. Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi F. Disease burden and long-term trends of urinary tract infections: A worldwide report. Front Public Health. 2022 Jul 27;10:888205. doi: 10.3389/fpubh.2022.888205. PMID: 35968451; PMCID: PMC9363895.
- 10. Kern WV, Rieg S. Burden of bacterial bloodstream infection-a brief update on epidemiology and significance of multidrugresistant pathogens. Clin Microbiol Infect. 2020 Feb;26(2):151-157. doi: 10.1016/j.cmi.2019.10.031. Epub 2019 Nov 9. PMID: 31712069.
- 11. Mittal G, Ahmad S, Agarwal RK, Dhar M, Mittal M, Sharma S. Aetiologies of Acute Undifferentiated Febrile illness in Adult Patients - an Experience from a Tertiary Care Hospital in Northern India. J Clin Diagn Res. 2015 Dec;9(12):DC22-4. doi: 10.7860/JCDR/2015/11168.6990. Epub 2015 Dec 1. PMID: 26816892; PMCID: PMC4717819.