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IP International Journal of Medical Microbiology and Tropical Diseases

Journal homepage: https://www.ijmmtd.org/

Original Research Article

# Study of rickettsia infection in patients suffering from fever of unknown origin

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ARTICLE INFO

*Article history:*
Received 01-01-2021
Accepted 27-01-2021
Available online 26-03-2021

*Keywords:*
Fever/Pyrexia of unknown Origin (FUO/PUO)
Spotted fever
Endemic fever
Epidemic fever
Scrub typhus fever
Weil felix.

ABSTRACT

**Introduction:** FUO/ PUO (Fever/Pyrexia of Unknown Origin) is referred to when temperature is observed above 38.3$^0$C (101$^0$F) on many occasions over a period of > 3 weeks and unable to diagnose despite 1week of thorough investigations. Different studies reported diagnosis of malaria in 5 to 50% cases; leptospirosis in 3 to 10% cases and influenza in 8 to 12% cases Dengue fever and malaria are arthropod born diseases and endemic in many parts of India during the monsoon season. Leptospirosis and scrub typhus are zoonotic infections and are widely prevalent in areas with heavy monsoon and agrarian way of life.
**Aim :** To evaluate the study of various Rickettsia infections in patients suffering from Fever Of Unknown Origin.
**Objectives:** To understand the occurrence of infections caused by rickettsial species in suspected cases of FUO. To increase awareness and clinical suspicion among doctors for these infections.
**Materials and Methods:** The assay was performed using P.vulgaris OX19, OX2, OXK strains according to manufacture's instructions by tube method. Serum will be diluted from 1/20 to 1/640 titer. A single Weil Felix titer of >1:160 or fourfold rise in titers on repeat testing starting from 1:40 will be accepted as a positive result.
**Result:** A total 100 cases were including in my study in which 28 cases were positive. Out of 28 positive rickettsial samples, females were 17 and males were 11. Spotted Fever(9), Endemic Fever(8), Epidemic Fever(7), Scrub Typhus Fever(4).
**Conclusion:** With the growing number of cases detected in India, scrub typhus is fast emerging as a public health threat and also due to limited diagnostics leading to underreporting, Weil Felix test could be used in adjunct with Enzyme-linked immunosorbent assay and blood parameters in the diagnosis of rickettsial diseases.



## 1. Introduction

FUO/ PUO (Fever/Pyrexia of Unknown Origin) is referred to when temperature is observed above 38.3$^0$C (101$^0$F) on many occasions over a period of > 3 weeks and unable to diagnose despite 1week of thorough investigations.[1] Different studies

reported diagnosis of malaria in 5 to 50% cases; leptospirosis in 3 to 10% cases and influenza in 8 to 12% cases Dengue fever and malaria are arthropod born diseases and endemic in many parts of India during the monsoon season. Leptospirosis and scrub typhus are zoonotic infections and are widely prevalent in areas with heavy monsoon and agrarian way of life.[2] Rickettsial infection was known in the past especially in times of war and natural calamities like famine, drought etc. Family Rickettsia is phylogenetically occupying position between bacteria and viruses. These are tiny, gram negative coccobacilli or sometimes variable in shape located intracellularly hence referred to as intracellular obligate parasitizes and they are majorly spread by arthropods.

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https://doi.org/10.18231/j.ijmmtd.2021.004

Arthropods those are responsible for their transmission are lice, fleas, ticks and mites in which they reside in the gastrointestinal system. In man, they mostly invade the endothelium of vessels and reticuloendothelial cells.

There are three genera: Rickettsia, Orientia and Ehrlichia which belong to its family. *Coxiella burnetii* causative agent of Q fever and *Rochalimaea quintana* causative agent of trench fever were previously included in the family however they have been removed from the group as they were not satisfying all the criterias of inclusion. Q fever is not primarily transmitted by arthropods while *Rochalimaea quintana* is not an obligate intracellular organism.

To These organisms cannot survive outside the cells and do not grow on basic cell free media therefore they are isolated in laboratory animals and can be cultivated in various tissue cultures and cell lines.[3]

Gram stain is not satisfactory for staining rickettsia and special stains like Giemsa or Giemenez stain give satisfactory results in the diagnostic modalities.

Hence it can be conveniently said that Rickettsial infection is caused by diverse group of organisms with variable characteristics however few general common features are mentioned below:

1. The natural hosts are mammals and arthropods
2. They are intracellular obligate parasites
3. They are transmitted to humans through bite of arthropods

Rickettsial disease in India is not as uncommon as believed. These diseases are commonly seen in the rainy season i.e. from the month of July to November as this time is favourable for the multiplication and development of arthropods.[4]

Rickettsial infections are diagnosed poorly in India as they present with non-specific symptoms, poor awareness and lack of suspicion among clinicians and also the diagnostic facilities are not up to the mark.[5]

### *1.1. Ethics approval*

Ethics approval was obtained from TMMC Moradabad institutional Ethics Committee (TMMC-IEC) Ref. No. TMMC & RC /IEC/18-19/087.

## 2. Materials and Methods

### *2.1. Setting*

The study were done on patients, admitted to Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh.

### *2.2. Study Design*

Hospital based prospective observational study.

Study Period

Dec.2018 to Sep.2019

### *2.3. Sample collection*

All patients admitted in TMU Hospital with fever of unknown origin were tested for basic investigations and it were taken from those patients whom no diagnosis could be made after basic investigations and culture, the serum sample were subjected to Weil Felix(WF) Test.

The assay was performed using P.vulgaris OX19, OX2, OXK strains according to manufacture's instructions by tube method. Serum were diluted from 1/20 to 1/640 titer. A single Weil Felix titer of >1:160 or fourfold rise in titers on repeat testing starting from 1:40 were accepted as a positive result.

## 3. Results

The samples were obtained from patients admitted in Teerthanker Mahaveer Medical College & Research Centre, Moradabad. 100 clinical samples received as per inclusion and exclusion criteria were processed over the period of 10 months from September to December in which 28 samples were positive for Rickettsia. Out of 28 positive rickettsial samples, females were 17 and males were 11.

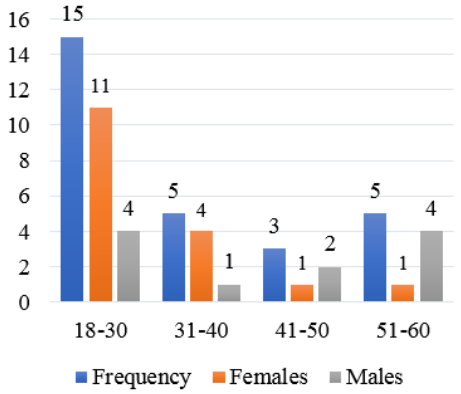


**Fig. 1:** Diagram showing age & gender wise distribution of fever of unknown origin cases:-

Most of the cases were seen between 18-30 years of age group corresponding to 53.57% of the total cases followed by 5(17.85%) seen in the age group of 31-40 years and 51-60 years and the lowest positivity rate was seen amongst 41-50 years age group 3(10.71%).

In our study, fever was the most common symptom seen in 100% cases as we selected patients with fever of unknown origin. Other symptoms commonly seen in our registered patients were vomiting 96.42% followed by abdominal pain 60.71% and Hepatosplenomegaly 57.14%.

Maximum number of rickettsial infection were found in the month of winter i.e. 16 (57.00%) followed by summer i.e. 10 (36.00%) and rainy season 2 (7.00%).

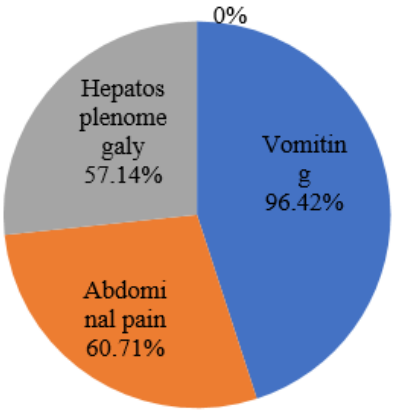


**Fig. 2:** Pie diagram showing the distribution of positive cases with clinical features:-

**Table 1:** Seasonal distribution of positive rickettsial cases

| Winter | Summer season | Rainy season |
|---|---|---|
| December-April | May-July | August-October |
| 16 | 10 | 2 |

**Table 2:** Showing the distribution of various rickettsial fever

| Rickettsial Fever | Percentage (%) |
|---|---|
| Spotted Fever | 9 (32.14%) |
| Endemic Fever | 8 (28.57%) |
| Epidemic Fever | 7 (28.00%) |
| ScrubTyphus Fever | 4 (14.28%) |
| Total | 28 (28.00%) |

In the present study the most common fever is spotted fever 9(32.14%) followed by endemic fever 8(28.57%), epidemic fever 7(28.00%) and scrub typhus fever 4(14.28%).

In the present study the most common fever is spotted fever 9(32.14%) in which female were 66.66% and male were 33.33% followed by endemic fever 8(28.57%) in which the male and female percentage were similar 50.00%, epidemic fever 7(28.00%) in which 71.42% were female & male were 28.57% and scrub typhus fever 4(14.28%) in which the female and male were 50.00%.

## 4. Discussion

Rickettsial disease is an acute infectious disease transmitted to humans by ticks mites or lice. They are underdiagnosed because of their varied presentation and lack of availability of reliable specific laboratory tests. Rickettsial fever can be present with conjunctivitis generalized oedema, meningoencephalitis and pupura fulminance.

Analysis of age wise distribution of positivity for rickettsial infections revealed that it was predominantly seen in young age group. In our study majority isolation was seen

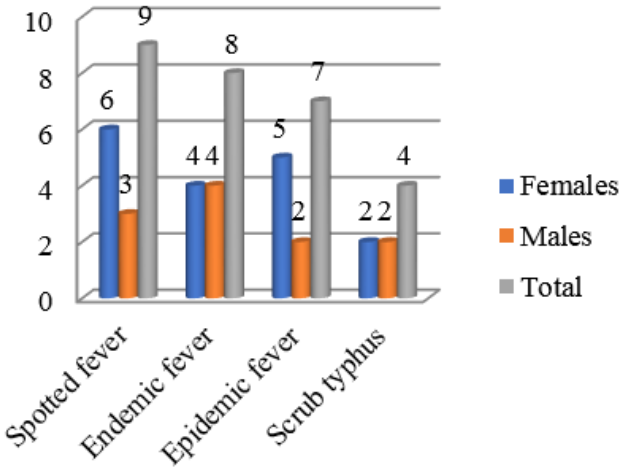


**Fig. 3:** Column diagram showing the Sex wise distribution of various Rickettsial infections

in adults belonging to the age group of 18-30 years then between 31-40 years and 51-60 years accounting for 17.85% of cases and the least cases seen in the age group of 41-50 years. This is in accordance Vinod Kumar C.S et al shown the commonest age group was of the age < 40 years.[6]

In contrast Raghu Kumar KG et al showed the rickettsial infection was in old age group[62] and Mita D. Wadekar observed in their study that out of 73 seropositive samples for rickettsial disease all positive cases were observed in children (1-18 years age).[7]The possible reason for rickettsial infection in young age group could be due to increased exposure of adults for outdoor activities.

The present study demonstrates the common symptoms found in these cases were vomiting 96.42% abdominal pain 60.71% and Hepatosplenomegaly 57.14 %. This is in agreement with some earlier studies like Pawan K.G. et al. showed in their study the most common symptoms found was vomiting100%, abdominal pain 64.3% and Hepatosplenomegaly 60.0%.[1] In contrast, few investigators showed various results. Vinod Kumar C.S. et al showed in their study pyrexia was the major clinical presentation then myalgia and headache were also common presenting features.[6]

Hence we can safely say that the clinical picture observed in the current study is quite similar to any other febrile illness like malaria, dengue, chikungunya etc. and hence it can be considered as a tool for diagnosis.

Seropositivity during this study clustered after rainy season, this is because mites are active during or at the end of rainy season. Earlier studies from India reported a similar period of disease occurrence.[8]

In Rickettsial infections the common detected fever was spotted fever 32.14% followed by endemic fever 28.57 epidemic fever 25% and scrub typhus 14.28%. The other

studies reported by other investigators Mittal et al tested 87 sera samples from suspected cases of rickettsial infection in whom 29(33.3%) were positive for rickettsial antibodies. Out of these 29 positive 14(48.2%) were positive for scrub typhus 8(27.5%) for spotted fever group and 2(6.8%) for typhus group while remaining 5(17.24%) were positive for two rickettsial illnesses.[9]

Weil Felix test is a common modality used for the diagnosis of rickettsial infections. There are many advantages associated with this test and to name the few are easy availability, cheap kits, no expertise needed to perform the test and many more.[8] It is based on the principle of Heterophile agglutination where the patients infected with rickettsial diseases cross react with the commercially avaible antigens prepared from Proteus spp. OX-19, OK-2, OX-K.

However sensitivity and specificity of this test is very low and it can be of help in areas where advanced diagnostic modalities are not available especially in developing countries like India. There was no specific symptom detected in these cases and therefore clinical suspicion is weak. So it is suggested that all patients presenting with PUO/FUO should be screened for rickettsial infections and it should be kept in the differential diagnosis of PUO/FUO.[10]

## 5. Conclusion

Our result is providing current information regarding the occurrence of rickettsial infection in our area. Our hospital caters large rural as well as urban population and hence further study can be done to assess the demographic distribution of various species in both the areas. This will also provide an opportunity to prevent infection by effective control measures like destruction of arthropods in areas where there is high prevalence. Treatment can be initiated at an early stage leading to reduction in complications and associated mortality. This study further gives an opportunity to fight this disease unitedly by clinicians and microbiologists, to validate clinical presentation of rickettsial infection and to understand the relation between clinically suspected and laboratory confirmed cases. This study also extends to evaluate utility of serodiagnosis in our catering population and found useful in early diagnosis and treatment of these pathogens.

Spotted fever is an underdiagnosed disease in India. It should always be kept in the differential diagnosis of patients presenting with fever specially with pneumonitis, thrombocytopenia, elevation of liver enzyme, serum urea and serum creatinine.

Rapid and specific diagnostic method like ELISA can also be used for early diagnosis of spotted fever in patients with FUO. Now molecular methods are coming in a big way for the diagnosis of these diseases thereby making the confirmation simpler in future. An early empiric therapy can be given to reduce serious complication and mortality.

General health education and public awareness about the disease, including the methods of transmission, is necessary for their prevention and control. As this study had small sample size large scale studies are needed to understand the magnitude of rickettsial infection, in this region and other parts of India

## 6. Conflicts of Interest

All contributing authors declare no conflicts of interest.

## 7. Source of Funding

None

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**Cite this article:** Parveen C, Sharma SR, Farooq U, Singh S, Sharma V, Ahamad I, Mohan S, Nudrat S. Study of rickettsia infection in patients suffering from fever of unknown origin. *IP Int J Med Microbiol Trop Dis* 2021;7(1):12-16.