ORIGINAL ARTICLE

Increasing incidence of Rickettsial infection in patients of Pyrexia of Unknown Origin

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Abstract

Objective: To study the incidence of rickettsial infection in pyrexia of unknown origin (PUO) patients. To promote awareness and index of suspicion among clinicians for rickettsial infection.

Methods: Out of numerous patients who came to a tertiary care hospital in Delhi with fever, sera of 22 patients in whom no diagnosis could be made after basic investigations and cultures were subjected to Weil Felix (WF) test.

Results: Out of 22 patients, 14 patients tested reactive by WF test. 6 patients each were positive for OX-2 and OX-K antigens. In 3 patients, OX-2 antigen was positive with OX-19 antigen and in 3 with OX-K antigen. One patient showed a positive titer with all three Proteus antigens. All these patients responded well to standard treatment of rickettsial infections.

Conclusion: Rickettsial diseases are one of the many causes of PUO cases. Even if advanced diagnostic facilities are not available, simple and easy to perform WF test can aid in the diagnosis of rickettsial infections.

Introduction

Fever of unknown origin (FUO) is defined as a temperature above 38.3^{0}C (101^{0}F) on several occasions over a period of more than 3 weeks, for which no diagnosis has been reached despite 1 week of inpatient investigation. [(1)] A significant percentage, approximately 75%, of FUO cases used to remain undiagnosed in the 1930s, which dropped down to less than 10% in 1950s.[2,3] Since then, the proportion that remains unidentified has become greater, despite the introduction of many serological assays or better imaging technology.[4]

Amongst the many causes of FUO most common causes are *Enteric Fever, Malaria, Dengue* and *Tuberculosis*. *Rickettsial* infections are one of the important causes of fever of unknown origin (FUO); still it remains overlooked due to its non-specific clinical presentations, low index of suspicion amongst clinicians, limited awareness and limited diagnostic facilities in developing countries.[5] Once clinical suspicion is raised, conformation or any evidence supporting the diagnosis of *Rickettsial* infection is important as the treatment is different. Diagnosis of these infections is difficult because of non-availability of advanced laboratory diagnostic tests needed for confirmation.[6] Weil-Felix test is a simple to perform assay, which is based on detection of antibodies to Proteus species which has antigens with cross-reacting epitopes to antigens from *Rickettsia species* except *R. Akari*.

During the month of October 2015 when there was an epidemic of *Dengue* in Delhi, many patients presented with fever in which the cause could not be ascertained despite investigating them for *Dengue, Malaria, Typhoid, Tuberculosis* etc. Few patients amongst them had prolonged fever with variable symptoms like abdominal pain, headache, rash etc. As there was associated high morbidity present, the need for the exact cause of fever arose and serum samples of these patients were tested for antibodies against *Rickettsial* infection by Weil-Felix Test. The present study determines the magnitude of *Rickettsial* infection in such cases by Weil-Felix Test and in turn identification of suggestive clinical features and response to treatment in these cases.

Material and Methods

During the month of October, there is a sudden spurt in cases of fever, the majority of which are dengue cases. In few patients presenting to a tertiary care hospital, despite investigating them for Dengue, Malaria, Typhoid, Tuberculosis, Brucellosis cause of fever could not be found. High continued fever with different associated symptoms raised the clinical suspicion of *Rickettsial* infection and serum samples were tested for antibodies against *Rickettsia* by Weil Felix Test. The assay was performed using P. vulgaris OX19, OX2, OXK strains (PROGEN, Tulip Diagnostics (P) Ltd, Goa, India) according to manufacturer's instructions by tube method. Serum was 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 was accepted as a positive result.

Results

From the month of September to December, there were 22 patients with fever in whom no diagnosis could be made after all basic investigations and cultures. The age of these patients ranged from 8 to 80 years. These patients were investigated for Dengue, Typhoid, Malaria, Tuberculosis, etc. by Dengue NS1 Antigen, Dengue IgM/IgG antibodies, IgM antibodies to *Salmonella Typhi*, Widal tube agglutination test, blood and urine culture, X- ray chest and peripheral smear but no cause

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Table 1: Serological titers on Weil-Felix with duration of symptoms

Serial no.	Duration of fever and other symptoms in days	Serum weil- felix titers		
		OX 19	OX 2	OX K
1	4	NR	NR	1:160
2	5	NR	1:40	NR
3	6	1:40	1:160	1:40
4	7	1:40	1:160	1:320
5	7	NR	1:80	NR
6	7	1:40	1:80	NR
7	7	1:320	1:320	1:160
8	8	1:40	NR	NR
9	9	1:320	1:320	1:40
10	10	NR	1:40	NR
11	14	NR	1:40	1:320
12	15	NR	1:320	1:320
13	30	NR	NR	1:160
14	30	1:160	1:160	1:40

could be recognized. Out of these 22 patients in whom no other test was positive, 14 (63.6%) tested positive for Weil-Felix test and 11 (78.6 %) out of these 14 demonstrated titres of 1:80-1:320. Of these 14 patients, 10 were male and 4 were females.

Proteus antigen OX2 showed a titer of 1:80 in 2 (14.2%) patients. In both of them doxycycline was not started. One of them succumbed due to illness and second one recovered before giving specific treatment for rickettsial disease. On WF test, 3 (21%) sera showed a titer of 1:160 titer and 3 sera showed 1:320 titer, to proteus OX2 antigen. Similarly, to Proteus OXK antigen 3 sera showed 1:160 and 3 sera showed 1:320 titers. All patients responded well to the treatment started for Rickettsia. One patient with 1:160 titers for Proteus antigen OXK (Scrub typhus) stopped responding to doxycycline after one week of treatment and fever relapsed. Patient was started on tetracycline 500mg QID and patient became afebrile.

In our study more than 1 antigen came positive in 5 (35.7%) patients considering ≥1: 160 as significant titer. In no patient OX19 antigen showed raised titer alone. In 3 patients OX 19 antigen was positive with OX2 antigen and in 1 patient all three antigens were positive. In 3 patients OX2 and OXK antigens were positive. All these 5 patients showed titer of ≥1: 160 and all responded well to standard regimen of doxycycline. Details of titers on WF test and relationship with duration of fever and symptoms are shown in Table 1.

Retrospectively analyzing the clinical presentation of these serologically positive cases revealed that 100 % patients had fever ranging from 5-30 days.14.2% had fever of around 1month. Towards the end of the study period as an index of suspicion was high amongst clinicians, few cases were detected early with less than 10 days of fever. Predominant clinical symptoms along with fever were vomiting (100%); hepato-splenomegaly (71.4%); abdominal pain and thrombocytopenia (64.3%); headache (57.1%); rash and congestion of eyes (35.7%). Exposure to pets could be elicited in 64.3%.

Discussion

Rickettsial infections are one of the important causes of fever of unknown origin (FUO) and this need to be distinguished from other febrile illnesses like enteric fever, malaria, dengue, leptospirosis, infectious mononucleosis, *etc*.[4] This differentiation will help in initiation of early and accurate treatment which in turn will lessen the associated morbidity and mortality with the disease. In practice the main difficulty with recognition of Rickettsial diseases is the lack of facilities for its definitive diagnosis. Weil Felix test is easy to perform, low cost, low expertise test which detects agglutinating antibodies. These antibodies which are predominantly of immunoglobulin M (IgM) type are detected 5-10 days following the onset of symptoms [(6)]. It involves demonstration of heterophile antibodies to the strains of Proteus mirabilis (OX-19, OK-2, OX-K). However, the test lacks sensitivity and specificity; it may be used in developing countries as an aid in the diagnosis of Rickettsial diseases where advanced diagnostic tests are not readily available.

In the present study, Weil Felix test was positive in 63.6% of cases in whom no alternative diagnosis could be made which is higher than previous studies where the test was positive in 33.3% of cases.[7] Small sample size and study being done in the cooler months of the year may be reasons for the difference. The present study demonstrates a disease predilection towards months following the monsoon, leading to winter, which has been seen in many studies.[4,8,9] Scrub typhus outbreak during relatively cooler months of the year (September to March) has been noted down from rural population of Puducherry and Tamil Nadu.[8] More number of cases are needed to make our results statistically significant. The most common symptoms found in these cases was vomiting 100% and abdominal pain 64.3%. Hepato-splenomegaly and thrombocytopenia were seen in more than 60% of cases in the study. Rash was seen in only 35% of cases. Similar picture of varying associated clinical features has been found in many studies.

In our study there was no suggestive symptom or laboratory marker present, which could alert clinician for suspecting Rickettsial infection. In many previous studies, weil felix test showed one proteus antigen coming positive and suggesting type of rickettsial infections but in our study, in many patients more than one proteus antigen showed high titers. That is why no single type of rickettsial infection could be attributed as causative agent in patients. Three patients who tested reactive showed titer of 1:40.These patients were started empirically on doxycycline because they were not responding to any other treatment and they responded well with doxycycline. Repeat samples could not be arranged in these patients after discharge. Outcomes in our study were very favorable to all the patients responding to the standard regimen for the disease.

Conclusion

Rickettsial disease is an important differential diagnosis in fever of unknown origin, especially in the cooler months of the year and with some suggestive symptoms. Extremely favorable response to readily available drug signifies the importance of suspecting the disease in prolonged and undifferentiated fever cases. Weil Felix test can serve as an initial method to recognize the disease and then more sensitive and specific tests can be added to the facility to aid in the diagnosis. Study with a larger sample size is needed to add more value to the data related to clinical presentation, epidemiology and diagnosis. So with high index of suspicion and use of the Weil Felix test, especially where definitive investigations are not available, a large number of patients can be benefitted.

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