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COMPLICATIONS SEEN IN RICKETTSIAL INFECTION

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ABSTRACT

Introduction: Rickettsial fever is a major health concern in different districts of Karnataka with serious complications, including morbidity and mortality, if diagnosed late. Hence with timely diagnosis optimum treatment and adequate care can be ensured. In this study we will be looking into detail regarding the complications associated with rickettsial infection if not diagnosed and treated at the right time. Some of the complications include acute renal failure, ARDS, thromboctyopenia with bleeding and pleural effusion with the latter being the most common. **Objectives:** To study the, complications seen in patients with rickettsial infections. **Methods:** This is a prospective observational study done from June 2019 to February 2020, Bengaluru, Karnataka, India. Weil Felix positive patients with four fold rise in titres were considered. **Results:** A total of 394 patients of Acute Febrile Illness were admitted during the study period. A total of 47cases(11.92%)were tested positive for rickettsia, out of which scrub typhus was the commonest 33 (72%). Most patients presented in the months of July -October. Weil Felix positive patients with four fold rise in titres were considered. 86%of the patients belonged to rural areas and most of them were farmers by occupation. Age group involved being 20 – 30 years. Males(56.2%) were affected more than females(43.17%) Fever(100%) was the complaint seen in all patients with rickettsial infection. They also had complaints like myalgia (86%), headache(79%),cough(31%),vomiting (34%), joint pain (30%),abdominal pain (19%) and diarrhoea (10%) Thrombocytopenia was in70% of the patients. When emphasis was given to scrub typhus(72%), the most common variant it was found 51%had splenomegaly,18%macular rash,16%hepatomegaly, 7%icterus, 7% lymphadenopathy and 1%eschar. Complications like pleural effusion was seen in 20%, non oliguric ARF(9%), ARDS(10%), liver cell failure (2%) and thrombocytopenia with bleeding (2%). **Conclusion:** Rickettsial infection is one of the most common causes of acute febrile illness. Due to its non specific signs and symptoms it should be considered in the differential of acute febrile illness. As the number of rickettsial cases have increased considerably well targeted history and clinical examination will aid in early diagnosis and prevent complications due to delayed diagnosis.

KEYWORDS: Complications, weil felix, thrombocytopenia.

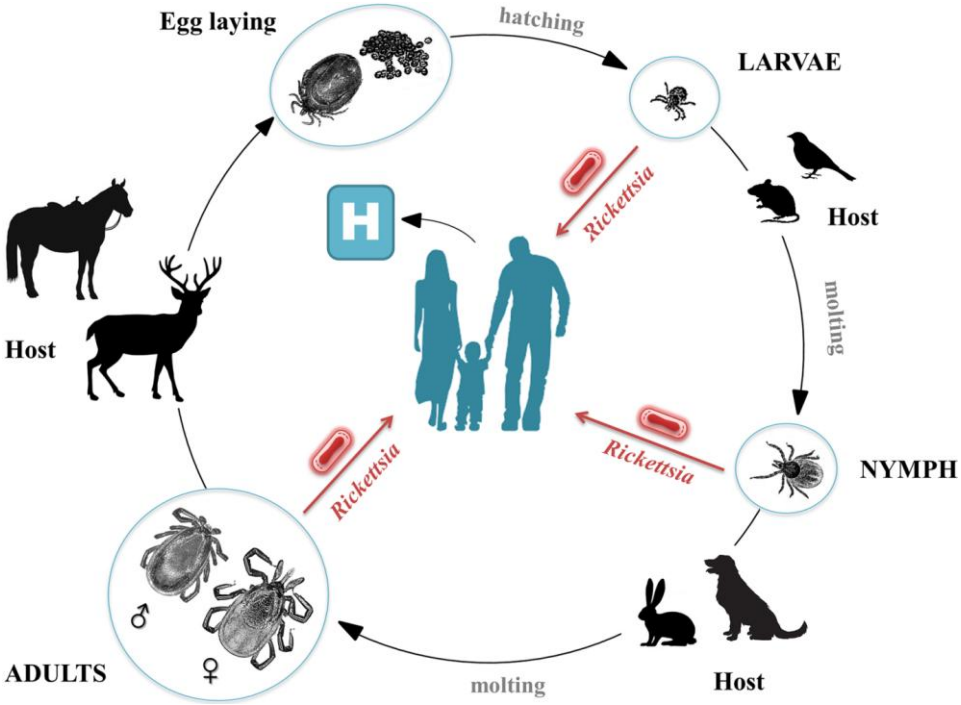
INTRODUCTION

Rickettsial diseases have reemerged as some of the most baneful insidious infections of the present time. The rickettsial diseases are generally incapacitating and notoriously difficult to diagnose. Untreated cases have a fatality of up to 30% but when promptly and properly diagnosed, it is often easily treated. The greatest challenge lies in overcoming the difficult diagnostic dilemma posed by these infections early in their courses, when antibiotic therapy is most effective. Rickettsial infections are reported from various parts of India. However, despite the surging number of cases, these diseases are often underdiagnosed. The factors that predispose to rickettsial infections are widely prevalent in this country, hence the physicians and pediatricians need to include rickettsial infections in their differential diagnosis of febrile thrombocytopenia or an acute febrile illness.[1]

The rickettsiae spread through lymph and blood, infect many foci of contiguous endothelial cells. Thrombotic occlusion causing ischemic necrosis is not the primary pathological mechanism responsible for tissue and organ injury but the increased vascular permeability, resulting in edema, hypovolemia, and ischemia, is responsible for the organ damage. Thrombocytopenia (secondary to platelet consumption) is common, but disseminated intravascular coagulation with hypofibrinogenemia is rare. Activation of platelets, generation of thrombin, and activation of the fibrinolytic system occurs as a homeostatic response to endothelial injury.

"Rickettsia rickettsii and R conorii have a propensity for the infection of endothelial cells of small vessels of skin, central nervous system, lung, myocardium, kidney, and liver". Endothelium has potent anticoagulant properties and any injury to endothelium alters the efficiency of anticoagulation property. Injury to endothelium, by

apoptosis exposes membrane phosphatidylserine which leading to activation of factor X by factor IX. "Apoptosis of endothelial cells leads to exposure of procoagulant subendothelial matrix, with or without cell detachment, and through cell retraction, apoptotic leukocytes and endothelial cells circulate as procoagulant bodies". Changes in endothelium following infection are associated with activation of the coagulation system.[4]



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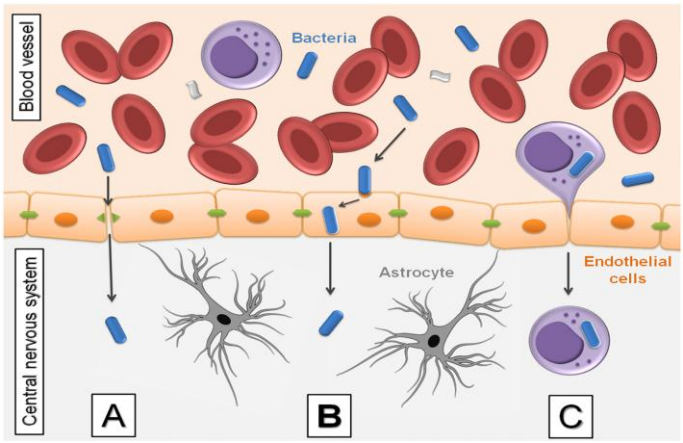
In most clinical scenarios the presentation of rickettsial infection does not fit into a particular pattern. The clinical presentation of rickettsial infection is wide and varied. Severity varies from subclinical illness to severe illness with multiple organ system involvement, which can be serious enough to be fatal, unless diagnosed early and treated. Untreated cases have case fatality rates as high as 30-45% with multiple organ dysfunction, if not promptly diagnosed and appropriately treated.[3]

Rickettsiae are intracellular bacteria living in the cytosol of infected cells. The endothelium is target of rickettsiae and infection results in vascular injury to small blood vessels resulting hematologic manifestations like thrombocytopenia, increased concentrations of fibrinogen and von Willebrand factor in plasma, and activation of coagulation, resulting in consumption coagulopathy. The occurrence of deep venous thrombosis seems to represent a specific clinical feature of Meditteranean spotted fever among rickettsioses. Vasculitis results in "skin rash, microvascular leakage, edema, and tissue hypoperfusion and end-organ ischemic injury". Formation of thrombi leads to tissue infarction and hemorrhagic necrosis. Rickettsial infective vasculitis may manifest as "interstitial pneumonitis, non-cardiogenic pulmonary edema, cerebral edema and meningoencephalitis".

In antithrombotic activity of endothelium, the protein C thrombomodulin pathway is of great importance. Endothelium expresses thrombomodulin, a surface glycoprotein, a receptor for thrombin. Thrombin bound to thrombomodulin activates the protein C - protein S pathway, Cytokines, which leads to inactivation of factors Va and VIlla. Antithrombotic property of endothelium is altered with introduction of inflammatory mediators, vascular injury, infection (viruses) and endotoxins. Interleukin 1 and infections by viruses can induce the expression of procoagulant tissue factor, acomplex of glycoprotein and phospholipids, which is not constitutively expressed on the surface of Endothelium. Tissue factor bound to factor VII activates factor X, initiating the extrinsic pathway of coagulation. In vitro infections by R. conorii and R. rickettsii have shown to induce injury to the endothelium and alter metabolic and secretory functions of endothelium, leading to increased secretion of fibrinolytic system factors (mainly plasminogen activator inhibitor 1) and an increase in platelet adhesion.

Release of VWF multimers from Weibel- Palade bodies has been reported for endothelial cultures infected by R. rickettsii. Rickettsial infections are vasculotropic diseases, often associated with haemostatic disturbances, which are more intense in patients with severe diseases.[4]



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Mechanisms of bacterial penetration through the blood–brain barrier.

(A) Intercellular or paracellular, described in extracellular pathogens. The physical barrier formed by endothelial tight junctions is disturbed by bacterial penetration. (B) Transcellular, passing through cells, e.g., direct invasion of endothelial cells. In this scenario, blood-borne bacteria directly invade CNS endothelial cells. (C) By leukocytes, within infected macrophages, named "Trojan horse" mechanism. Infected leukocytes adhere to endothelial cells, allowing the spread of bacteria or, alternatively, leukocytes can transmigrate and deliver bacteria to the CNS parenchyma. CNS, central nervous system.

MATERIALS AND METHODS

- All patients aged 18 years and above, admitted with acute febrile illness to a tertiary rural health care centre, Bangalore between June 2019 to February 2020 were evaluated.
- Demographic details of each patient were recorded.
- Basic haematological and biochemical tests were done in these cases (complete blood count, urine analysis, blood sugars, renal function and liver function tests).
- Investigations for malaria, dengue, enteric fever were done.
- Weil Felix test was done after exclusion of other infections and tests with a four fold rise in titre were considered in our study. Other investigations like ECG,Chest X-ray, Ultrasound abdomen and CSF analysis were done when indicated.
- The outcome of patients with complications was evaluated.

RESULTS

- A total of 394 patients of acute febrile illness were admitted during the study period. A total of 47 cases(11.92%)were tested positive for rickettsia, out of which scrub typhus was the commonest(72%).
- Most of the patients were young adults with mean age group of 30 years with male: female ratio of 2:1
- 86% of patients belong to rural area, most of them are farmers

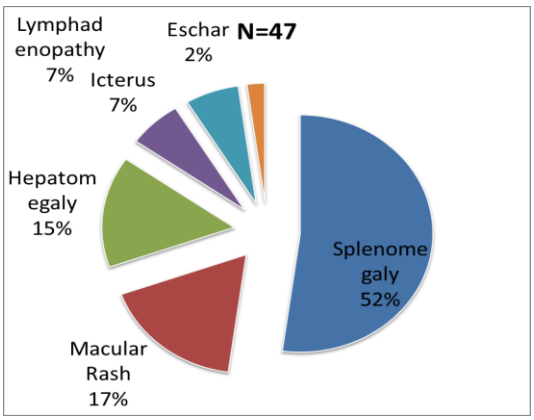
  Most patients with rickettsial infection presented in the months of July -October

CLINICAL CHARACTERISTICS

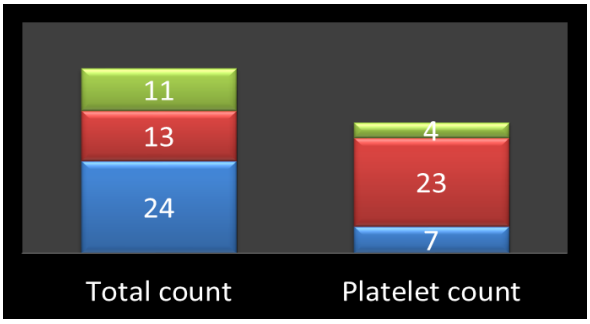
Symptoms	Rickettsial Infections(n=47)
Fever <7days	11(23%)
7-14 days	**31(67%)**
>14 days	5(10%)
Myalgia	**40(86%)**
Headache	**37(79%)**
Vomiting	**16(34%)**
Cough	14(31%)
Joint pain	14(30%)
Abdominal pain	9(19%)
Diarrhoea	5(10%)

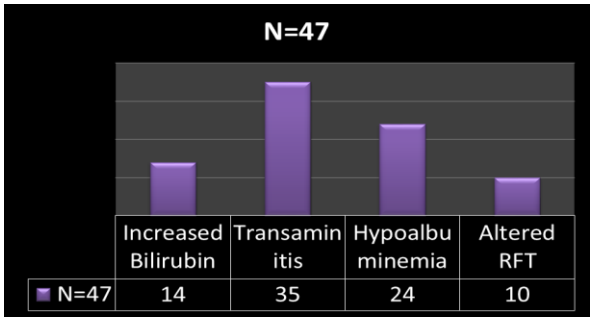
EXAMINATION FINDINGS

Signs	N=47
Splenomegaly	**24(52%)**
Macular rash	**8(17%)**
Hepatomegaly	7(15%)
Icterus	3(7%)
Lymphadenopathy	3(7%)
Eschar	1(2%)



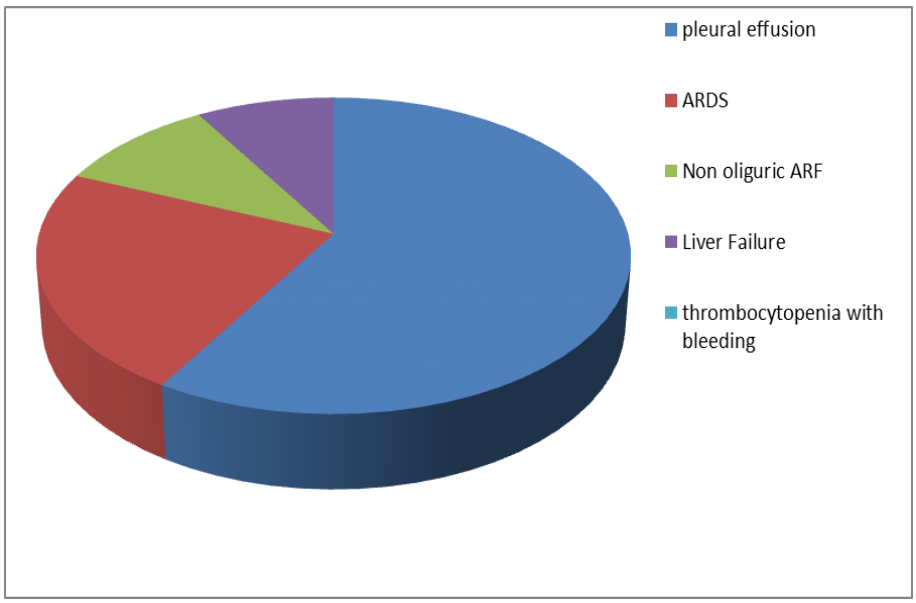
Laboratory data	n=47
Total Count	
<4000	**24(51%)**
4000-11000	13(28%)
>11000	11(23%)
Platelets	
>1.5 lakhs	7(15%)
1-1.5 lakhs	**23(49%)**
<1.0 lakhs	4(8%)
Increased total bilirubin	14(30%)
Increased SGOT/SGPT	**35(74%)**
Decreased Albumin	**24(51%)**
Increased Urea /Creatinine	10(21%)





COMPLICATIONS

Complications	N=47
Pleural effusion	**9(20%)**
ARDS	**5(10%)**
Non Oliguric ARF	4(9%)
Liver failure	1(2%)
Thrombocytopenia with bleeding	4(9%)



COMPLICATIONS CONTINUED

- All 47 patients were screened for systemic complications and requirement for support either in the form of need for transfusion of blood and blood products, oxygen therapy, need for dialysis and ventilation. Out of 47 patients, none of the patients required HDU admission.
- Total counts were normal in 28% of the population, but had relative 23%lymphocytosis.
- Leucopenia at admission was observed in 51% and leucocytosis in 23% of the study group respectively.
- Thrombocytopenia was a prominent finding being manifested in 57% of the patients.
- 10patients with thrombocytopenia received platelet transfusions).
- **Renal dysfunction:** Urinalysis at the time of admission revealed some abnormality in the form of proteinuria, haematuria or pyuria in 21% of the patients while it came as normal in 70%. Out of 47patients with abnormal urine test, proteinuria and haematuria were the major urinary abnormalities and were present in 18% and3% of the patients.
- **Renal dysfunction was defined as a serum creatinine greater than 1.1 mg/dl** and was present in ten patients. Mean creatinine in the study group was 1.0. Of the patients with renal failure none of the patients required dialysis. Four patients had non

oliguric renal failure.. Renal failure resolved in all patients with none of them requiring permanent renal replacement therapy, instead they improved with optimum hydration.

- **Hepatic dysfunction-** Hypoalbuminemia was noted in 51% of the patients. Jaundice was present in 30% of the patients and was relatively mild.
- **Coagulopathy** was present in a minority (11.1%), but without significant bleeding manifestations.
- **Pleural effusion** was the most common complication seen in 20% of the patients.

DISCUSSION

- All over the country the proportion of rickettsial fever in cohorts analysing febrile illness is found to have increased significantly over the past two decades. It is believed that increasing use of antibiotics for treatment of febrile illnesses in the community during recent times may be contributing to unmasking of rickettsial fever as rickettsiae are inherently resistant to them.[4]
- Renal involvement is fairly common in rickettsial fever especially scrub typhus. AKI is seen in over 50% cases, and is an important predictor of mortality. Earlier renal involvement was thought to be a consequence of multi-organ dysfunction syndrome secondary to sepsis. Impaired renal perfusion due to volume depletion or increased vascular permeability is now considered the main reason for AKI in rickettsial fever. Other potential mechanisms include direct tubular toxicity leading to acute tubular necrosis, interstitial nephritis, pigment nephropathy due to rhabdomyolysis and thrombotic microangiopathy secondary to disseminated intravascular coagulation. Renal biopsies have shown mild mesangial hyperplasia, acute tubular necrosis or tubulointerstitial nephritis. Rickettsial fever shows excellent response to antibiotics – tetracycline and chloramphenicol in majority of cases especially if initiated early on. **Doxycline was the antibiotic of choice in our study**. Excellent response was observed with majority of patients becoming a febrile in a short while after admission. Mean duration of fever post admission was 2.04 days. Higher antibiotics were initiated in cases where patients presented late, had worsening MODS and were admitted in high dependency units. The optimal duration of treatment has not been established, but current recommendation suggests at least 3-7 days for life threatening cases to a maximum of 15 days for severe or complicated disease. **Rapid resolution of fever following doxycycline is so characteristic that it can be used as a therapeutic test.**
- As delay in treatment may lead to complications and higher mortality, empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected and facilities for diagnosis are not available. Rickettsial fever is known to produce serious complications and has a mortality rate of 7-30%. In this study there were no mortalities. Deaths are attributable to late presentation, delayed diagnosis and drug resistance. This can be vastly prevented by increased awareness among physicians, early institution of appropriate antibiotics & increased availability of serological tests for diagnosis.[3]
- In a study, conducted by Kamath V et al,out of 81 patients who were diagnosed with scrub typhus, only five patients had neurological manifestations. Therefore, in newer emerging areas, ST should be considered as one of the causes of aseptic meningitis during the seasonal outbreaks of ST. In this study, all patients presented with altered sensorium. GCS was decreased in all patients. It was <10 in 60% cases. Neck rigidity and signs of meningeal irritation were present in 80%of cases.there were no signs of pappiledema,focal neurological deficits or cranial nerve involvement.Two patients had seizures which was GTCS in semiology[5]
- In a case report, conducted by Cascio A et al on a 5 year old Italian boy Haemophagocytic lymphohistiocytosis was observed as a complication of Mediterranean spotted fever. Haemophagocytic lymphohistiocytosis (HLH) (haemophagocytic syndrome) is a potentially fatal hyperinflammatory syndrome that is characterized by histiocyte proliferation and haemophagocytosis. HLH may be inherited (primary, familial) and occurs generally in infants or may be secondary to any severe infection, malignancy or rheumatological condition and occurring at any age. HLH is diagnosed using clinical criteria developed by the HLH Study Group of the Histiocyte Society (Gupta & Weitzman, 2010; Henter et al., 2007).
- The diagnosis is established by fulfilling one of the following criteria. (i) A molecular diagnosis consistent with haemophagocytic syndrome (e.g. PRF mutations, SAP mutations, MUNC13-4 mutations). (ii) Having five out of eight of the following: fever; splenomegaly; cytopenia (affecting more than two cell lineages), <or =9 g haemoglobin dl21 , ,100 000 platelets ml 21 , ,1000 neutrophils ml 21); hypertriglyceridaemia (>or =265 mg /dltriglycerides) and/or hypofibrinogenaemia (<or=150 mg/dl fibrinogen); haemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy; low or absent natural killer (NK) cell cytotoxicity; hyperferritinaemia (>or =500 ng/ml ferritin); elevated soluble CD25(>or =2400 IU interleukin-2Ra chain ml21)[6]
- In another case report conducted by Herath H.M.L.Y., Jayasundara.J.M.H.D et al, on A 53 years old manual worker in Sri Lanka who presented with fever for 5 days and a skin rash. He was in circulatory failure on admission and developed severe hypoxaemia with gross changes in chest radiograph by next day requiring assisted ventilation. He had myocarditis causing left ventricular failure and acute respiratory distress

syndrome. He was confirmed to have spotted fever rickettsial infection with rising titre of indirect immunofluorescence antibodies to Ricketssia conorii and made a complete recovery with appropriate antibiotic therapy and supportive care. Hence by this study we come across two other complications which can be seen in rickettsial infection which is myocarditis and ARDS.[7]

- In a study conducted by Premaratna R,et al, Departments of 1 Medicine, 2 Parasitology, and 3 Pharmacology, Faculty of Medicine, University of Kelaniya, Sri Lanka, and 4 Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia. They describe how 6 patients with scrub typhus who presented with acute hearing loss, a forgotten complication of this reemerging disease. They were admitted with fever of 10–14 days duration and had clinical evidence of deafness and pneumonitis. Five patients had eschars, which prompted the diagnosis of typhus fever which further led to early institution of treatment. Deafness had been described as a clue to the diagnosis of scrub typhus; awareness of this symptom facilitated early diagnosis in 4 of 5 patients who recovered. Hence acute hearing loss or hearing impairment in a febrile patient should arouse strong suspicion of scrub typhus which is a long forgotten complication.[8]

CONCLUSION

Rickettsial fever poses a significant challenge to any physician, especially in the early course because of its varied clinical presentations. Thus it becomes important to have high degree of clinical suspicion based on clinical cues to diagnose early, if not rickettsial fever can cause considerable morbidity, mortality and financial liability to the patient. One should suspect Rickettsial infection even in “spotless fever.” Early suspicion in endemic areas prevents morbidity and mortality. Rickettsial CNS infections range from meningitis to lethalencephalitis. Another forgotten complication, acute hearing loss which is now reemerging should be kept in mind while assessing a patient with acute febrile illness. Though the above mentioned complications seem trivial at first, if the cause is not diagnosed promptly it can lead to a not so promising clinical course and later death.

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