

Clinical and laboratory characteristics of rickettsioses patient hospitalized in 108 Military Central Hospital

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Summary

Objective: To investigate clinical and laboratory characteristics of rickettsioses patients hospitalized in 108 Military Central Hospital. **Subject and method:** This was a descriptive, study on 38 cases of rickettsioses fulfilled case definition of CDC 2016, confirmed by PCR, hospitalized in 108 Military Central Hospital from June 2016 to June 2019. **Result and conclusion:** Mean of age was 49.5 ± 14.5 years with 63.2% male. Rickettsial disease occurs mainly in subjects related to environmental exposure where mice and fleas distribute (densely populated areas, poor hygiene), 84.2% patients were admitted in rainy season. Clinical manifestations: More than 96% of patients had fever, headache, myalgia, maculopapular rash (39.5%), skin congestion (31.6%). No eschar and lymphadenopathy was found. Laboratory: Normal WBC (78.9%); PCT increased $> 0.05\text{ng/ml}$ was recorded in 100% of patients with 97.4% slightly elevated; thrombocytopenia (76.3%); pleural effusion (9.09%); unilateral lung infiltrate (12.1%). The complications: Meningoencephalitis 7.9%, acute kidney injuries (AKI) 5.3%.

Keywords: Rickettsioses, exposure factors, clinical and laboratory manifestations.

1. Background

Rickettsiaceae has long been known to be zoonosis and among the oldest known vector-borne diseases. This is a family of obligatory intracellular bacteria, having diverse biological characteristics and is classified into two major genera. Genus *orientia* consists of *Orientia tsutsugamushi* causing scrub typhus, which has been known since the fourth century before christ, and *orientia chuto* have recently been discovered and proven to cause disease in humans [1]. Genus *Rickettsia* includes two large groups: Typhus group including *Rickettsia typhi*, which causes murine typhus and *Rickettsia*

prowazekii, causes epidemic typhus; spotted fever group includes many other species of *Rickettsia* [2]. Rickettsiaceae is the leading causative agent among patients with acute undifferentiated fever in Southeast Asia after malaria, Dengue hemorrhage and typhoid [1]. This study addressed clinical and laboratory characteristics of febrile patients caused by bacteria of the genus *Rickettsia*.

In Vietnam, the serum antibody prevalence of *Rickettsia typhi* causing murine typhus and other *Rickettsia* of spotted fever group in the community of northern Vietnam were 6.5% and 1.1% respectively [3]. In 2017, 108 Military Central Hospital successfully designed 2 PCR procedures to diagnose bacteria of the genus *Orientia* causing scrub typhus and to diagnose

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bacteria of genus *Rickettsia* by targeting the conservative gene segment of the genus *rickettsia* those procedures have been applied in routine clinical tests since then [5]. However, it is still of great challenging to diagnosis *Rickettsioses* because of the variable clinical manifestations with the typical eschar, rash or lymphadenopathy are not always presented; complications such as pneumonitis; and meningoencephalitis-vary from one disease to another. Therefore, it is easy to misdiagnose accompanied by complications and higher mortality. Moreover, bacteria of the family *Rickettsiaceae* cannot be cultured in normal environments, serological diagnostic tests have low sensitivity at an early stage of disease, molecular biology methods are sensitive and specific but not widely deployed.

An in-depth understanding of clinical, preclinical, and prognostic factors of the disease caused by *Rickettsiaceae* will help clinicians promptly diagnose with appropriate treatment, minimize complications and improve outcome of patients. Based on the aforementioned conditions, we implemented this project aimed to: *To describe clinical features; laboratory characteristics of febrile patients with rickettsioses.*

2. Subject and method

2.1. Subject

38 patients were diagnosed with *Rickettsioses* at 108 Military Central Hospital from June 2016 to June 2019.

Inclusion criteria: According to *Rickettsioses* case definition of the US Centers for Disease Control (CDC) 2016 [6]. PCR based method was used to confirm cases.

3. Result

3.1. Baseline characteristics of the study population

Exclusion criteria: Patients did not have enough research data and patients had evidence of infection with other organisms causing acute fever were excluded out of our study.

2.2. Method

Study design

This was a cross-sectional study. Eligible participants were performed clinical examination and investigations that consist of routine tests and recorded in a standard questionnaire form. Thereafter, the clinical presentation and laboratory results were determined based on these aforementioned data.

Sample size and method of sample selection

A sample size of convenience was used. All eligible participants in the period from June 2016 to June 2019 at Institute of Clinical Infectious Disease - 108 Military Central Hospital were included in this study.

Research variables

Demographic features, background athologies, clinical and laboratory characteristics, life-threatening complications (ARDS according to Berlin 2002 criteria), septic shock according to Sepsis 3, meningoencephalitis according to European Consensus, acute kidney injury (AKI) according to KDIGO 2012.

Data collection methods

An identical medical record form was used for documenting obtained data consisting of both clinical and paraclinical manifestations.

Techniques used in the study: PCR reaction to diagnose pathogens of the genus *Rickettsia* family *Rickettsiaceae*, performed at Department of Molecular Biology - 108 Military Central Hospital on real-time PCR (Agilent - America).

Data processing: Use SPSS 22.0 software.

Table 1. Demographic profile

Variables		Cases	Percentages
Gender	Male	24	63.2
	Female	14	36.8
Residence	Urban	26	68.4
	Non-urban	12	31.6

Table 1. Demographic profile (Next)

Variables		Cases	Percentages
Occupation	Famer	3	7.9
	Worker	4	10.5
	Civil servant, student	14	36.8
	Military personel	3	7.9
	Freelance labor	14	36.8
Age	$\bar{X} \pm SD$ (year)	49.5 $\pm$ 14.5	

Comment: The average age of the study population was 49.5 $\pm$ 14.5 years. Men accounted for 63.2%. The number of cases were mainly distributed in urban areas (68.4%). There were no cases in mountainous areas in our study. High incidence of occupational diseases included: Freelance labor (36.8%), civil servant - student: (36.8%).

Table 2. Characteristics of exposure factors

Variables	Cases	Percentages
Rice field working 30 days before fever	7	18.4
Outdoor activities 30 days before fever	8	21.1
Having seen rats in house, work places	26	68.4
Sanitation of the living area	15	39.5
Distance from home to nearest market		
Very close < 300m	14	36.8
Close (300 - 499) m	7	18.4
Moderate (500 - 750) m	11	28.9
Far > 750m	6	15.8
Admission in rainy season	32	84.2

Comment: High rate of exposure activities included: Seeing mice in the house/around the house/workplace (68.4%), unsanitary environment and hygiene (39.5%), living very close to the market (36.8%). Other exposure activities accounted for a smaller percentage. The hospitalization rate in the rainy season was very high at 84.2%.

3.2. Clinical manifestations in patients with rickettsioses

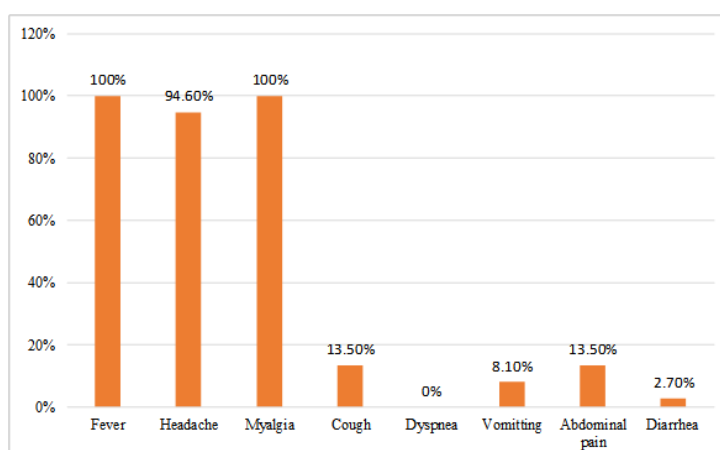


Chart 1. Acute symptoms at disease onset

Comment: Over 94% of patients in the study group had an onset of illness with fever, headache, myalgia. Respiratory manifestations (cough: 13.5%), gastrointestinal presentations (abdominal pain 13.5%, vomiting: 8.1%, diarrhea 2.7%).

Table 3. Physical symptoms during hospitalization

Variables	Cases	Percentages
Fever > 7 days before admission	9	23.7
Skin congestion	12	31.6
Rash	15	39.5
Eschar	0	0
Lymphadenopathy	0	0
Hepatosplenomegaly	3	7.9
Crackles rale	6	15.8
Altered mental status	0	0
Meningeal sign	4	10.5
Max temperature ($\bar{X} \pm SD$)	39.45 $\pm$ 0.39	
Total duration of fever ($\bar{X} \pm SD$)	10.63 $\pm$ 2.68	

Comment: Skin - mucosal manifestations were less common with the rate of maculopapular rash was 39.5%, followed by skin congestion 31.6; hepatosplenomegaly 7.9%. Eschar and lymphadenopathy were not detected. Respiratory symptoms were uncommon (crackles rale 15.8%), meningeal sign 10.5%. There were no altered mental status in the study group.

3.3. Subclinical manifestations of fever caused by *Rickettsia*

Table 4. Test results

Variables		Cases	Percentages
Thrombocyte (G/L)	Thrombocyte $\leq$ 150	29	76.3
	Thrombocyte < 50	2	5.3
	50 $\leq$ Thrombocyte < 100	14	36.8

	100 ≤ Thrombocyte < 150	13	34.2
Leukocyte (G/L)	Leukocyte < 4	3	7.9
	4 ≤ Leukocyte ≤ 10	30	78.9
	Leukocyte > 10	5	13.2
PCT (ng/mL)	PCT > 0.05	38	100.0
	0.05 ≤ PCT < 2	37	97.4
	2 ≤ PCT ≤ 10	1	2.6
	PCT > 10	0	0.0
Liver enzyme (U/L)	AST > 40	37	97.4
	AST > 200	8	21.1
	ALT > 40	36	94.7
	ALT > 200	5	13.2

Comment: Thrombocytopenia, increased liver enzyme (ALT) were common manifestations in the study group with the rates of 76.3% and 94.7%, respectively. The majority of patients had normal white blood cell counts (78.9%). There was 100% increase in PCT > 0.05ng/ml, mainly a slight increase (97.4%).

Table 5. Imaging diagnosis manifestations

Variables	Cases	Percentages
Chest X-ray		
Unilateral infiltrate	4	12.1
Bilateral infiltrate	0	0
Ultrasound		
Pleural effusion	3	9.09

Comment: Lung damage on chest X-ray was rarely seen and manifested only on one side of the lung (12.1%). The rate of pleural effusion on ultrasound: 9.09%.

3.4. Some complications

Table 6. The rate of some life-threatening complications

Variables	Cases	Percentages
Respiratory failure	0	0
Septic shock	0	0
Meningoencephalitis	3	7.9
Acute kidney injury	2	5.3
Mortality	0	0.0

Comment: There were no patients with respiratory failure or septic shock in the study group. Encephalitis - meningitis accounted for 7.9%, acute kidney damage accounted for 5.3%. No patients died.

4. Discussion

General characteristics of the study population

Following the studies at Bach Mai Hospital and the National Hospital for Tropical Medicine, our study once again confirmed the presence of *Rickettsia* in Vietnam. Rickettsial disease in our research group was mainly distributed in urban areas (68.4%). This is consistent with the epidemiological results studying three groups of the family Rickettsiaceae, in which *Rickettsia typhi* was more commonly distributed in urban areas. In contrast, scrub typhus and other spotted fever rickettsioses were more common in rural areas [1]. The disease has been reported among city dwellers in developed countries like Singapore.

Research on Rickettsial exposure activities has shown that *Rickettsia typhi* is transmitted through rat fleas (*X. cheopis*), which are widely distributed in markets, grain stores, and factories, beer and landfills [1]. This is also where rats - the main host of *R. typhi* present in large numbers. Moreover, cramped living conditions and poor sanitation are ideal conditions for the spread of disease caused by *R. typhi*. These things explain the high rate of exposure activities including: Having seen mice in the house/around the house/workplace (68.4%), poor sanitation (39.5%), living very close to the market (36.8%). This result is similar to a study of Laos 2010 addressed some risk factors related to rickettsioses [7]. Freelance labor was found to be the most popular occupation in our study group, accounted for 36.8%, these are the people at risk of being exposed to the above mentioned vector's habitat. There was a very high rate of hospitalization in the rainy season at 84.2%, which is also proportional to the period of time for development of the vector (mouse flea) and the main host of the disease (rodents, mainly rats).

Clinical manifestations

According to the literature of Harrison: "The clinical manifestations of all the acute *Rickettsial* presentations are similar during the

first 5 days and consist of nonspecific symptoms: Fever, headache, and myalgia with or without nausea, vomiting, and cough". Based on the data on Chart 1: More than 96% of patients in the study group had an onset of illness with fever, headache, myalgia, following by respiratory manifestations such as cough: 13.5%, rale explosion 15.8%, and gastrointestinal symptoms (abdominal pain 13.5%, vomiting 8.1%, diarrhea 2.7%). These are all nonspecific symptoms that can occur in any other patient with acute viral infection; In contrast, the total duration of fever ($\bar{X} \pm SD$) was about 11 days, which is typically longer than common viral infection. This finding is in line with Civen R [8] and is one of the interesting finding implicated that rickettsioses should be consider as possible diagnosis in sub-acute undifferentiated fever.

Skin - mucosal manifestations are generally considered as an indication of disease caused by *Rickettsia* and distinguish some pathogens in the disease group caused by Rickettsia. In our study, the rate of maculopapular rash was 39.5%, followed by skin congestion 31.6%; hepatosplenomegaly 7.9%. It is worth noting that, in this study, no patient with fever caused by Rickettsia had eschar and lymphadenopathy was not detected. This result is similar to Hamaguchi (Eschar were not detected in murine typhus patients) [4]. In comparison to a study about Murine typhus, at the end of the first week of illness, rash often occurs in some patients and the frequency has ranged from 20 to 54 percent [8]. In our study, 76.3% patients were admitted to the hospital at the first week of illness hence the frequency of rash was quite high.

Subclinical characteristics and life-threatening complications

Thrombocytopenia, an increase in liver enzymes were very common in the study group, with 76.3% and > 94.7%, respectively. This data is similar to the results of Vu Minh Dien [9] and

Hamaguchi demonstrated the prevalence of symptoms. Therefore, in the guidelines for diagnosis and treatment of vector-mediated disease, CDC has considered thrombocytopenia and increased hepatic enzyme as the criteria for suspected rickettsioses. However, these are also nonspecific test results, which can be found in many other diseases such as Dengue hemorrhage, which is more common in Vietnam. Therefore, with a patient having reduced platelets and elevated liver enzymes, it is necessary to eliminate Dengue hemorrhage and not to forget Rickettsia in the list of differential diagnosis to have appropriate testing and empiric treatment.

Results of Table 3 indicated that the majority of patients have normal white blood cell counts (78.9%), which is also a nonspecific value. There was a 100% patients increase in PCT > 0.05ng/ml, mainly a slight increase (97.4%) with the $\bar{X} \pm SD$ level of 0.926 ± 0.451 ng/ml. This result is similar to the Vu Minh Dien study with 91.7% patients had the same finding [9]. Our results are also one of the few studies that mention the value of PCT in Rickettsial disease and a significant difference between Rickettsial disease and other acute viral infection. For instance, with Dengue hemorrhage, PCT value is usually < 0.5ng/ml.

Lung damage on chest X-ray was uncommon and only manifested in 1 side of the lung (12.1%), pleural effusion on ultrasound was detected in 9.09% patients. It should be kept in mind that, the diagnostic imaging features are nonspecific, the research samples size is small,

there should be further studies with a larger number of samples to be able to make more accurate judgments about the disease caused by Rickettsia.

Mortality rates between 1 and 4% and higher in the absence of specific antibiotics or misdiagnose have been reported [8]. In our study, it is possible that due to the small sample size, there were no deaths in the study group, no respiratory failure or septic shock; encephalitis - meningitis accounted for 7.9%, acute kidney damage accounted for 5.3%.

5. Conclusion

Rickettsial disease occurs mainly in subjects related to environmental exposure where mice and fleas distribute (densely populated areas, poor hygiene), 84.2% patients were admitted in rainy season.

Clinical manifestations: More than 96% of patients had fever, headache, myalgia, maculopapular rash (39.5%), skin congestion (31.6%). No eschar and lymphadenopathy was found.

Laboratory: Normal WBC (78.9%); PCT increased > 0.05ng/ml was recorded in 100% of patients with 97.4% slightly elevated; thrombocytopenia (76.3%); pleural effusion (9.09%); unilateral lung infiltrate (12.1%).

The life-threatening complications: Meningoencephalitis 7.9%, acute kidney injuries 5.3%.

References