

Acute kidney injury and electrolyte abnormalities in patients with scrub typhus admitted to a tertiary care hospital in southern India

Raghav Grover, Vadivelan Mehalingam

Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

ABSTRACT

Introduction: Scrub typhus is an acute febrile illness that is seen in many parts of India. Acute kidney injury (AKI) can occur in patients with scrub typhus who are not diagnosed and treated in the early stage of the disease. Such patients can have associated electrolyte abnormalities also. **Objectives:** This study was done to find out the incidence of occurrence of AKI and electrolyte abnormalities among patients with scrub typhus and correlate the latter with the severity of AKI. **Methods:** This prospective, observational study included 38 patients with scrub typhus admitted to a tertiary care hospital in south India. Serum sodium and serum potassium levels of all the patients were measured at hospital admission. Also, serum creatinine levels of patients on all days of the hospital stay was measured along with other parameters like hemoglobin, leucocyte count, and platelet count. **Results:** The incidence of AKI among patients with scrub typhus was 13.16%. However, electrolyte abnormalities though seen in the patients did not correlate with AKI. **Conclusion:** AKI is not an uncommon phenomenon in patients with scrub typhus. Electrolyte abnormalities in these patients did not correlate with the severity of AKI.

Keywords: Acute kidney injury, electrolyte abnormalities, scrub typhus

Introduction

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi* and it is transmitted by the bite of an infected Trombiculid mite called chiggers. It is a zoonotic disease and is endemic in the part of the world known as the tsutsugamushi triangle. These insects crawl on blades of grass, shrubs, and small plants and attach themselves to small mammals and humans as they brush through the vegetation. It is transmitted accidentally during walking or lying down on the ground infested by the larva of the mites. Scrub typhus was endemic in India

during 1960–1970. Now, re-emergence of the disease has been noticed in the past decade in India. Various outbreaks have been reported from the sub-Himalayan region of India, Tamil Nadu, Pondicherry, Rajasthan, and West Bengal. Transmission seems to occur throughout the year in tropical areas and clustering of cases is usually observed during the rainy season. Outbreaks have also been reported during the cooler months in south India.^[1]

It is an important differential diagnosis in patients presenting with an acute unknown febrile illness. Patients most commonly present with fever and chills, headache, myalgia, maculopapular rash with eschar at the site of bite and lymphadenopathy. However, the diagnosis is often overlooked as the symptoms resemble other infectious diseases like malaria, dengue, typhoid, and leptospirosis. Eschar is a pathognomonic sign, but it is variably present. Eschar is difficult to detect in dark skinned people and

Address for correspondence: Dr. Vadivelan Mehalingam,
Department of Medicine, JIPMER, Dhanvantari Nagar,
Puducherry - 605 006, India.
E-mail: mevadivelan@hotmail.com

Received: 10-07-2020

Revised: 17-09-2020

Accepted: 14-10-2020

Published: 30-01-2021

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_1407_20

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How to cite this article: Grover R, Mehalingam V. Acute kidney injury and electrolyte abnormalities in patients with scrub typhus admitted to a tertiary care hospital in southern India. J Family Med Prim Care 2021;10:187-91.

also since it is usually present under the skin folds, it is not easily visible and is likely to be missed. Scrub typhus is a common illness in a tropical country like India. Primary care physicians can clinically diagnose the illness in the presence of eschar in patients. Laboratory diagnosis for scrub typhus is done with the help of Weil–Felix test in serum and scrub immunoglobulin M (IgM) antibody. These tests for diagnosing scrub typhus can help primary care physicians in the management of patients with an acute febrile illness.

Complications of scrub typhus include pneumonitis, sepsis, myocarditis, and renal dysfunction. Acute kidney injury (AKI) is thought to be a consequence of multiorgan dysfunction syndrome secondary to sepsis. Other proposed mechanisms for AKI include pre-renal failure, vasculitis, interstitial nephritis, and direct invasion of the organism in the renal parenchyma.^[2] Varying degree of kidney involvement is seen in patients with the spectrum of disease ranging from asymptomatic and transient change in laboratory parameters to reduction in urine output and imbalance of electrolytes.

Thus, scrub typhus should be included as a differential diagnosis in patients presenting with fever and AKI as the prompt institution of highly effective antibiotics like doxycycline and azithromycin can alter the course of the disease and prevent further deterioration of the patient's condition.^[3] Various laboratory parameters such as serum sodium and potassium may correlate with the occurrence of AKI among patients with scrub typhus.

Aims and Objectives

1. To find the incidence of occurrence of AKI as a complication in patients with scrub typhus.
2. To assess electrolyte abnormalities in patients with scrub typhus and to correlate them with the severity of AKI.

Material and Methods

This was a prospective observational study that was conducted in the Medicine wards and emergency ward in a tertiary care teaching hospital in south India over a period of 2 months (August & September 2019) after obtaining clearance from the Institutional Ethics Committee. (JIP/IEC/2019/0273 dated 22/07/2019)

Adult patients with confirmed scrub typhus infection (detected to be IgM antibody positive by Enzyme linked immunosorbent assay (ELISA) method) were included in this study. Patients with AKI due to other causes were excluded from the study. Patients were explained about the study procedure in simple terms in a language that they could understand, and only those who agreed to participate voluntarily in this study were included after taking their informed, written consent.

Sample size for the study was calculated using nMaster 2.0. Considering the incidence of AKI in scrub typhus among adults

to be 53%, with a relative precision of 30% and 95% confidence level, sample size was estimated to be 38.^[3] Convenient sampling technique was used for this study.

The socio-demographic details of the study subjects were noted and a brief clinical examination (measurement of temperature, pulse rate, and blood pressure along with evaluation for lymphadenopathy and presence of eschar on the body) was performed.

The laboratory parameters which were included in this study are baseline leucocyte and platelet count. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criterion.^[4] According to this criterion, AKI is defined as either an increase in serum creatinine by ≥ 0.3 mg/dl within 48 h; or as an increase in serum creatinine to ≥ 1.5 times baseline within 7 days; or if urine output is < 0.5 ml/kg/h for 6 h. Also, the severity of AKI is classified in three stages with stage 1 being defined as serum creatinine 1.5–1.9 times baseline or ≥ 0.3 mg/dl increase and urine output < 0.5 ml/kg/h for 6–12 h. Stage 2 AKI is defined as serum creatinine 2.0–2.9 times baseline and urine output < 0.5 ml/kg/h for ≥ 12 h. Stage 3 AKI is defined as serum creatinine 3.0 times baseline or increase in serum creatinine to ≥ 4.0 mg/dl or initiation of renal replacement therapy or decrease in eGFR to < 35 ml/min/1.73 m² in patients > 18 years. Serum creatinine was done in all study subjects on a daily basis (from hospital admission to discharge) to look for AKI.

Apart from these, the serum levels of sodium and potassium were noted in all the study subjects at admission to the hospital. Sodium level of below 135 mEq/L was considered as hyponatremia and potassium level of below 3.5 mEq/L was considered as hypokalemia.

Categorical variables like age, gender, presence, or absence of AKI and staging were summarized as proportions and continuous variables like sodium, potassium, and creatinine levels were summarized as mean and standard deviation.

Incidence of occurrence of AKI in patients with scrub typhus was expressed in percentage with 95% confidence interval. The correlation between electrolyte abnormalities and severity of AKI was tested using Chi-square test for statistical significance. A *P* value of less than 0.05 was considered to be statistically significant.

Results

This study included 38 subjects, out of which 23 were males and 15 were females. The baseline laboratory parameters of the study subjects are given in Table 1.

The mean presenting creatinine of the study population was found to be 1.53 ± 1.70 mg/dL. On applying the KDIGO criterion, five subjects (13.16%) had AKI in the study population

and all of them had stage 3 AKI as shown in Table 2. Remaining 33 participants constituted the group of subjects not having AKI.

It was observed that out of the five subjects with AKI, three had hyponatremia. However, 25 out of 33 study subjects without AKI also had hyponatremia as shown in Table 3.

On correlation of serum sodium values with the presence or absence of AKI, *P* value was found out to be 0.456 as shown in Figure 1.

On correlation of serum potassium values with the presence or absence of AKI as shown in Table 4 and Figure 2, *P* value was found out to be 0.578.

Figure 3 depicts serum sodium levels of the study subjects. 28 out of 38 study subjects had hyponatremia of whom 13 patients had mild hyponatremia (130–134 mEq/L), 13 patients had moderate hyponatremia (120–129 mEq/L), and 2 patients had severe hyponatremia (<120 mEq/L). Remaining 10 subjects had serum sodium levels in the normal range (135–144 mEq/L).

Table 1: Baseline laboratory parameters of study subjects

Parameter	Mean±S.D	Minimum value	Maximum value
Serum sodium (mEq/L)	130.67±6.85	113	144
Serum potassium (mEq/L)	4.21±0.69	3.12	6.4
Hemoglobin (g/dL)	11.56±1.75	7.9	15.4
Leucocyte count (cells/mm ³)	9956.31±4998.68	3070	23500
Platelet count (lakh cells/mm ³)	1.28±0.79	0.11	3.3

Table 2: Severity of AKI according to KDIGO criterion

Severity of AKI	n=5
Stage 1	0
Stage 2	0
Stage 3	5

Table 3: Correlation of hyponatremia with presence or absence of AKI

Sodium levels	Subjects with AKI (n=5)	Subjects without AKI (n=33)
Normal	2	8
Mild hyponatremia (130-134 mEq/L)	0	13
Moderate hyponatremia (120-129 mEq/L)	3	10
Severe hyponatremia (<120 mEq/L)	0	2

Table 4: Correlation of serum potassium in subjects with AKI

Potassium levels	Subjects with AKI (n=5)	Subjects without AKI (n=33)
Normal	4	26
Hypokalemia (<3.5 mEq/dL)	1	3
Hyperkalemia (>5.5 mEq/dL)	0	4

Figure 4 depicts serum potassium levels of the study subjects. 30 study subjects had their serum potassium levels in the normal range (3.5–5.5 mEq/L), 4 subjects had hypokalemia (<3.5 mEq/L), and 4 subjects had hyperkalemia (>5.5 mEq/L).

Summary

- 13.16% of the study subjects with scrub typhus were found to have AKI.
- Hyponatremia was present in 28 study subjects; however, only three patients with AKI had hyponatremia.
- Potassium values were found to be abnormal in 8 study

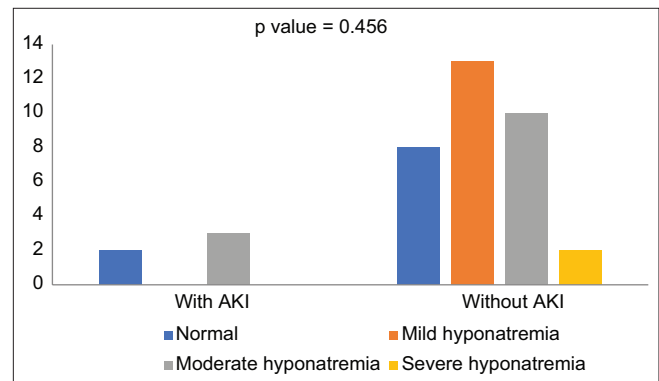


Figure 1: Correlation of hyponatremia with presence or absence of AKI

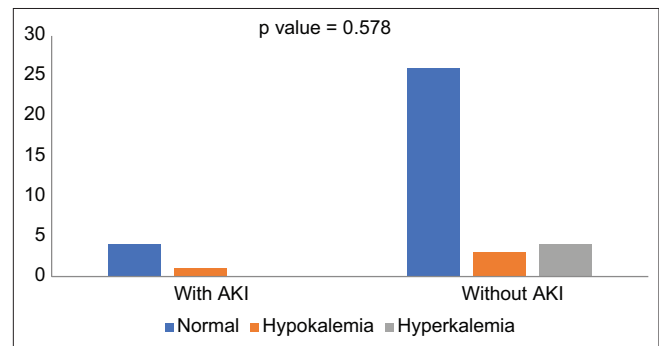


Figure 2: Correlation of serum potassium with presence or absence of AKI

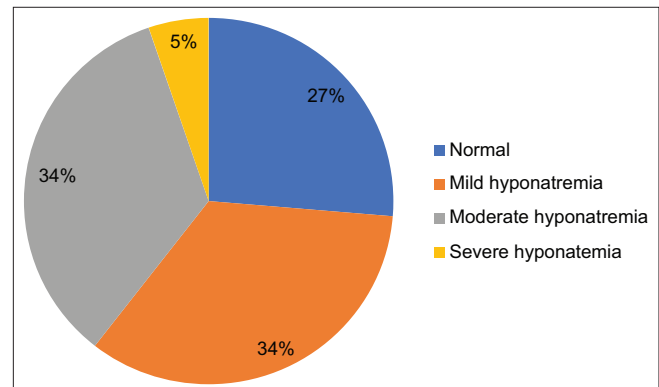


Figure 3: Proportion of study subjects with altered serum sodium levels

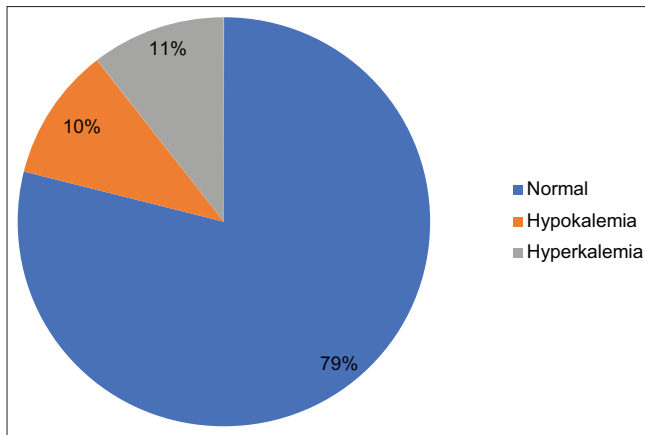


Figure 4: Proportion of study subjects with altered serum potassium levels

subjects, but it did not have any correlation with AKI among the patients.

Discussion

Scrub typhus is a mite-borne disease caused by a gram-negative intracellular bacterium called *Orientia tsutsugamushi*. AKI is known to occur as a complication of this disease. A lot of mechanisms regarding AKI have been proposed explaining its occurrence in this disease, which includes pre-renal failure, interstitial nephritis, and sepsis as the most accepted causes.

In our study, the incidence of AKI as a complication in subjects with scrub typhus was observed to be 13.16%. KDIGO guidelines were used in our study to define AKI in the study subjects.^[4] A study done in North India showed that AKI is a much more common complication among patients with scrub typhus. According to this study, AKI was seen in 53% of the study subjects.^[3]

In a study conducted in Shimla, scrub typhus was found to be a leading cause (18.5%) of sepsis associated with AKI.^[5] Another study from Himachal Pradesh showed the incidence of AKI to be 35% in patients with scrub typhus.^[6] A prospective study from a tertiary care hospital in south India showed the incidence of AKI to be 22.3% and also suggested that the possibility of AKI should be considered in patients with thrombocytopenia and in those requiring intensive care treatment.^[7] One study has shown that occurrence of scrub typhus outbreaks is very common in Puducherry and Tamil Nadu during the cooler months of the year.^[1]

According to previous studies conducted in various regions by using either KDIGO guidelines or RIFLE criterion, a variable incidence of occurrence of AKI among patients with scrub typhus was observed. In a study done by Sun *et al.*, using RIFLE criteria, the incidence of AKI was found to be 21%.^[8] Another similar study done by Basu *et al.* showed the incidence of AKI to be 40%. Also, the risk of mortality among their study subjects was noted to be high.^[9]

Other studies done in India have shown the incidence of AKI to be 23.2%, 31.9%, and 35% by Attur *et al.*, Singh *et al.* and Vikrant *et al.* respectively.^[6,7,10] The highest incidence of AKI was observed in a study done by Kumar *et al.*, where the incidence was found to be 53% among patients with scrub typhus.^[3] A study done in Nepal showed the incidence of AKI among the subjects to be 35.8%.^[11]

In a similar study done recently in south India by Jayaprakash *et al.* and Premraj *et al.*, the incidence of AKI in patients with scrub typhus was found to be 18.7% and 16%, respectively.^[2,12] In a review done by John R and Varghese GM, the incidence of AKI among patients with scrub typhus admitted to a tertiary care teaching hospital in south India was found to be 18%.^[13] The incidence of AKI in our study is close to these studies. Electrolyte abnormalities in the form of hyponatremia and hypokalemia are seen in some patients with AKI. But the present study could not identify any significant impact of these variables on AKI.

AKI is a common complication that can occur in patients with scrub typhus. It may be associated with electrolyte abnormalities like hyponatremia and hypokalemia. However, our study did not find a correlation between electrolyte abnormalities and AKI in patients with scrub typhus.

Limitations of the study

1. This study has shown a lower incidence of AKI among patients with scrub typhus as compared with other studies. It may have been due to administration of empirical antibiotics like doxycycline or azithromycin, which are highly effective against the causative organism. The empirical treatment could have reduced the occurrence of complications among study subjects with scrub typhus.
2. This is a single center study with a limited number of subjects being studied for complications of scrub typhus. Increased awareness among clinicians about this tropical disease and prompt administration of treatment and early referral of patients to a tertiary care center may have reduced the occurrence of AKI in the study subjects.

Conclusion

The incidence of AKI among patients with scrub typhus was 13.16%. Electrolyte abnormalities like hyponatremia, hypokalemia, and hyperkalemia were seen among the affected patients, but there was no significant correlation of these variables with the presence or absence of AKI.

Acknowledgement

The authors gratefully acknowledge the logistic support provided by JIPMER, Puducherry for conducting this study. The authors also thankfully acknowledge the contributory role of ICMR in approving this study as a short-term student (STS) project for MBBS students.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Indian Council of Medical Research (ICMR), New Delhi and JIPMER, Puducherry.

Conflicts of interest

All the authors declare that they have no conflict of interest regarding this study.

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