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Scrub Typhus as an Etiology of Acute Febrile Illness in Gorakhpur, Uttar Pradesh, India, 2016

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Abstract. Seasonal outbreaks of acute encephalitis syndrome (AES) with high mortality occur every year in Gorakhpur region of Uttar Pradesh, India. Earlier studies indicated the role of scrub typhus as the important etiology of AES in the region. AES cases were hospitalized late in the course of their illness. We established surveillance for acute febrile illness (AFI) (fever \geq 4 days duration) in peripheral health facilities in Gorakhpur district to understand the relative contribution of scrub typhus. Of the 224 patients enrolled during the 3-month period corresponding to the peak of AES cases in the region, about one-fifth had immunoglobulin M (IgM) antibodies against *Orientia tsutsugamushi*. Dengue and leptospira accounted for 8% and 3% of febrile illness cases. Treating patients with AFI attending the peripheral health facilities with doxycycline could prevent development of AES and thereby reduce deaths due to AES in Gorakhpur region.

Gorakhpur and the adjoining districts of Indian state of Uttar Pradesh have been witnessing seasonal outbreaks of acute encephalitis syndrome (AES) since 1978, causing high morbidity and mortality especially among children.^{1–3} Japanese Encephalitis (JE) was considered to be the major cause of AES in eastern Uttar Pradesh of India till 2005.⁴ With the mass vaccination campaigns against JE as well as introduction of the vaccine in the Universal immunization program, the proportion of AES attributable to JE has declined to less than 10%.³ However non-JE cases with CNS as well as multiorgan involvement continue to occur every year during the rainy season.³ Investigations conducted during the 2014 and 2015 outbreaks revealed presence of immunoglobulin M (IgM) antibodies against scrub typhus in more than 60% of AES cases, suggesting a role for scrub typhus among the etiological agents of AES.⁵ Based on these findings, intravenous azithromycin was recommended for all hospitalized AES patients (ICMR, unpublished data, 2014). The response to azithromycin, however, was not dramatic, and the case fatality remained high.⁵ Addition of doxycycline or chloramphenicol did not improve the outcomes (M. Mittal et al., unpublished data). Studies also indicate that AES cases were hospitalized late (median reported duration between fever onset and hospitalization: 7 days, interquartile range; IQR: 5–10 days) during the course of illness and this could be the reason for the lack of a dramatic response to antibiotics.⁵ Administration of appropriate antibiotics to febrile patients early in the course of illness, before CNS manifestations develop, is crucial. With this background, we conducted a study to estimate the proportion of fever cases attending peripheral health facilities because of scrub typhus.

We established fever surveillance in three health facilities (Community Health Center, Campierganj; Community Health Center, Pipraich; and Primary Health Center, Bhatat) from Gorakhpur district during August 2016 to October 2016. This period corresponds to the peak of AES cases in the district. Children aged \leq 15 years attending these health facilities with a history of fever for 4 days or more were enrolled. All the

children were clinically examined and 3 mL of blood was collected in clot activator test tubes. Sera were tested for IgM antibodies against *Orientia tsutsugamushi* (Scrub Typhus Detect; Inbios International Inc., Seattle, WA), dengue (Panbio Dengue IgM capture ELISA, Brisbane, Australia), and leptospira (Panbio Leptospira IgM ELISA, Brisbane, Australia) using commercial enzyme-linked immunosorbent assays (ELISAs). For InBios ELISA, an optical density (OD) value of 0.5 was considered as positive.⁶ The patients were also evaluated for malaria using microscopy. The patients were followed up telephonically for ten days for any sequelae.

We enrolled 224 patients from the three health facilities. Most patients (53%) were male and 45% were aged 5 years or less (Table 1). The reported median duration between fever onset and visiting the health facility was 7 days (IQR: 5–10). Besides fever, the common presenting symptoms included body ache ($N = 110$, 49.1%), cough ($N = 82$, 36.6%), headache ($N = 57$, 25.4%), abdominal pain ($N = 44$, 19.6%), and vomiting ($N = 32$, 14.3%). The salient findings on clinical examination included lymphadenopathy ($N = 33$, 14.7%), hepatomegaly ($N = 29$, 12.9%), conjunctival congestion ($N = 10$, 4.5%), periorbital edema ($N = 5$, 2.2%), and splenomegaly ($N = 6$, 2.7%). Ten (4.5%) patients had maculopapular rash and three had an eschar (1.3%).

Before seeking care from the surveillance health facilities, 42 (19%) had taken antibiotics, whereas another 58 (26%) had taken some medications, the nature of which could not be ascertained. None of these health facilities had doxycycline available in their stock. One hundred fifty (67%) patients were followed up telephonically; all patients followed up telephonically had recovered. Most (70%) were treated with antibiotics; cephalosporins, amoxicillin, and ciprofloxacin being the common antibiotics. None of these patients were prescribed doxycycline at the health facilities. The three patients with eschar were given doxycycline (5 mg/kg/day in two divided doses for 5 days), purchased from pharmacies outside the health facilities by the surveillance team. Fever subsided in two, but persisted in one patient who did not take the prescribed doxycycline. On later history-taking, it was found that the patient developed irritability and had upward rolling of eyes for which she was admitted in a private hospital. Laboratory investigations revealed thrombocytopenia and elevated liver enzymes. Ultrasonogram of the abdomen revealed mild

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TABLE 1
Age and sex distribution of patients with acute febrile illness, Gorakhpur district, 2016

	Number	IgM scrub typhus antibodies (%)	IgG scrub typhus antibodies (%)	IgM dengue antibodies (%)	IgM leptospira antibodies (%)
Age group (years)					
≤ 5	100	15 (15)	36 (36)	12 (12)	2 (2)
6–10	83	19 (22.9)	53 (63.9)	3 (3.6)	1 (1.2)
11–15	41	6 (14.6)	32 (78)	2 (4.9)	4 (9.8)
Sex					
Male	118	14 (11.8)	61 (51.7)	12 (10.2)	4 (3.4)
Female	106	26 (24.5)	60 (56.6)	5 (4.7)	3 (2.8)
Total	224	40 (17.9)	121 (54.0)	17 (7.6)	7 (3.1)

hepatomegaly, mild bilateral pleural effusion, and minimal ascites. Patient was started on third generation cephalosporins. The patient did not recover and got discharged because of financial reasons. The patient was again given doxycycline during her follow-up visit and became afebrile after three days of doxycycline treatment. On serology, this patient was positive for IgM antibodies against scrub typhus.

Of the 224 patients, 40 (17.9%, 95% confidence interval [CI]: 13.3–23.3) and 121 (54.0%, 95% CI: 47.5–60.5) had IgM and IgG antibodies against scrub typhus, respectively. Thirty-six of the 40 IgM-positive patients were also positive for IgG antibodies against scrub typhus. The median OD value among IgM- and IgG-positive patients was 2.208 (IQR: 1.069–3.229) and 2.823 (IQR: 1.627–3.492), respectively. IgM antibody positivity was not different in different age groups ($\chi^2 = 2.28$, $P = 0.319$) but was significantly higher among girls ($\chi^2 = 5.27$, $P = 0.02$). On the other hand, IgG antibody positivity was not different by sex ($\chi^2 = 0.54$, $P = 0.462$) but was different by age group ($\chi^2 = 25.8$, $P = 0.000$). None of the patients tested positive for malaria, whereas 17 (7.6%) and 7 (3.1%) had IgM antibodies against dengue and leptospira, respectively (Table 1). Five patients with scrub typhus IgM positivity were also positive for IgM antibodies against dengue, whereas another two IgM scrub typhus positive patients were positive for IgM antibodies against leptospira.

We compared the signs and symptoms of AFI patients who had IgM antibodies against scrub typhus with those who were IgM negative. On multivariable logistic regression analysis, IgM scrub typhus-positive patients were more likely to have hepatomegaly (adjusted odds ratio, AOR = 3.2, 95% CI: 1.3–7.8), or lymphadenopathy (AOR: 2.9, 95% CI: 1.3–7.3) and did not have cough (AOR: 2.5, 95% CI: 1.1–6.9) (Table 2).

Compared with those who were positive only for IgG antibodies against scrub typhus, AFI patients positive for IgM antibodies were more likely to have hepatomegaly (AOR: 3.6, 95% CI: 1.3–9.9) (data not shown).

Studies conducted earlier identified scrub typhus as one of the important etiologies of AES in Gorakhpur. Most of the AES patients had a history of fever for about a week, before developing CNS symptoms such as altered sensorium and seizures.⁵ Our surveillance data indicated that scrub typhus is an important etiology of acute febrile illness in the region, accounting for nearly one-fifth of patients with fever attending peripheral health facilities in Gorakhpur. The use of doxycycline in these facilities, however, was low.

Our study had certain limitations. As the primary objective of the study was to estimate the proportion of febrile cases due to scrub typhus, we did not investigate for other etiologies such as influenza. Second, because of logistic reasons, the surveillance was conducted only during the 3-month period of peak AES incidence.

Although, most IgM scrub typhus-positive patients recovered without documented specific therapy for scrub typhus suggesting that the majority had mild illness, there remains the risk of some with delayed diagnosis and treatment developing multiorgan dysfunction, CNS manifestations and progression to AES, as documented elsewhere.⁷ Data on AES from Gorakhpur region have shown that scrub typhus contributes to a large proportion of the cases with AES with considerable mortality.⁵ AES cases were hospitalized late and had fever for about a week before CNS manifestations developed.⁵ With the finding from this study that 17.9% of AFI could be attributed to scrub typhus, it may be worth treating those with AFI with doxycycline to prevent development of

TABLE 2
Common clinical manifestations of IgM scrub typhus-positive patients, Gorakhpur, 2016

	IgM+ve (N = 40)	IgM-ve (N = 184)	Odds ratio (OR)	95% CI	Adjusted OR	95% CI
Symptoms						
Cough	9	73	2.3*	1.0–5.0	2.5*	1.1–6.9
Headache	15	42	2	0.98–4.2	–	–
Vomiting	7	25	1.3	0.5–3.4	–	–
Diarrhea	2	2	4.8	0.7–35.1	–	–
Abdominal pain	12	32	2	0.9–4.4	–	–
Myalgia	20	90	1	0.5–2.1	–	–
Signs						
Conjunctival congestion	1	9	0.5	0.1–4.0	–	–
Hepatomegaly	12	17	4.2	1.8–9.8	3.2	1.3–7.8
Rash	2	8	1.15	0.2–5.7	–	–
Eschar	2	1	9.6	0.9–108.9	8.2	0.7–100.9
Lymphadenopathy	11	22	2.8	1.2–6.4	2.9	1.2–7.3
Splenomegaly	1	5	0.9	0.1–8.0	–	–

* OR for absence of cough.

AES and thereby reduce deaths due to AES. The Indian Council of Medical Research guidelines for diagnosis and management of rickettsial diseases also recommends treating all cases of suspected rickettsial infection with doxycycline at a primary care setting without waiting for laboratory confirmation.⁸ Doxycycline is one of the most effective antibiotics for the treatment of suspected rickettsial infections.⁸ Studies also indicate that a short course (< 10 days) of doxycycline treatment is not associated with any increased risk of dental staining, enamel hypoplasia, or tooth color differences.⁹ Implementing this strategy in public as well as peripheral health facilities during the months of July to October, when nearly 80% of AES cases are reported, could reduce the burden of AES in the region.

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