

**LETTER TO THE EDITOR**

# Opsoclonus–Myoclonus Syndrome as a Heraldic Feature of Scrub Typhus: An Illustrative Case with a Video Vignette

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Dear Editor,

Scrub typhus, a rickettsial illness caused by *Orientia tsutsugamushi*, is transmitted by the bite of the larval form (chigger) of the trombiculid mite. Scrub typhus is prevalent in the 'tsutsugamushi triangle' which stretches from Pakistan and Afghanistan in the western to northern parts of Australia in the southern to northern Japan in the north, although there are reports from other regions.<sup>1</sup> The typical presentation is a short febrile illness associated with a pathognomonic cutaneous 'cigarette burn' eschar, but neuropsychological features are increasingly being described.<sup>2</sup> Commonly, these include seizures and aseptic meningitis. Rarer neurological syndromes include extrapyramidal features, hearing loss, and opsoclonus.<sup>2</sup> We present a patient with opsoclonus-myoclonus syndrome (OMS) as an initial manifestation of scrub typhus.

A 23-year-old pregnant female, in the 36th week of gestation, presented to the emergency room with high-grade fever for one week along with abnormal movements of her eyes and limbs from day two of fever onset. There was no history of drug or toxin intake. She had been well otherwise and had no significant past medical history. On examination, she was restless and appeared sick. Her blood pressure was 90/50 mm Hg, pulse rate 120 beats/minute, respiratory rate 32 breaths/minute and oxygen saturation 96% on room air. She had bilateral basal crepitations. She was also noted to have a typical 'cigarette burn' eschar of scrub typhus in the left submammary region (Figure 1). On neurological examination, she was conscious and oriented to

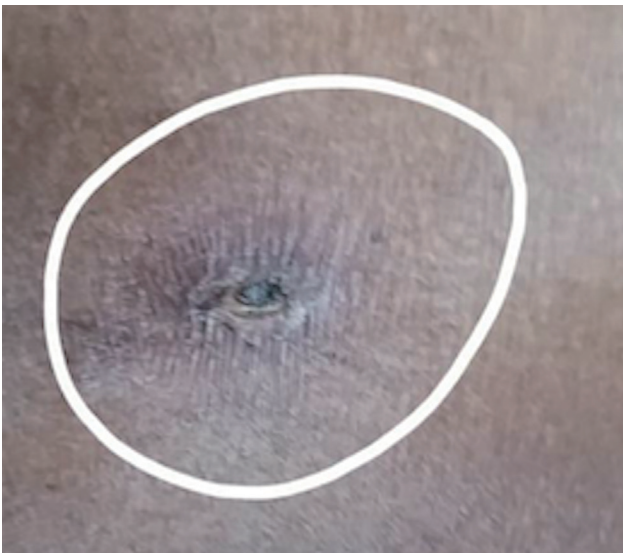
time, place and person. She was observed to have conjugate, chaotic, multidirectional eye movements consistent with opsoclonus, as well as myoclonic jerks involving all four limbs (Supplementary Video 1 in the online-only Data Supplement). Motor examination revealed normal tone, power and deep tendon reflexes. There were no features of parkinsonism, such as bradykinesia or rigidity. There were no features of cerebellar dysfunction, and she was able to perform the finger-nose test, the heel-knee-shin test and the tandem gait test normally. Laboratory evaluation showed elevated leukocyte count (13,000 cells/mm<sup>3</sup>), thrombocytopenia (platelet count 90,000 cells/mm<sup>3</sup>), deranged renal function (blood urea nitrogen = 64 mg/dL, serum creatinine = 1.4 mg/dL) and deranged hepatic function (elevated total bilirubin = 2.0 mg/dL, aspartate amino transferase = 11 IU/L, alanine transaminase = 121 IU/L), suggestive of multiorgan dysfunction. Serum electrolyte levels, including sodium (138 mEq/L), potassium (3.8 mEq/L), magnesium (2.1 mg/dL) and calcium (9.8 mg/dL), were normal. She underwent emergency cesarean section followed by intensive care admission. She was treated with injectable azithromycin for a period of 10 days, along with supportive management. The diagnosis of scrub typhus was confirmed by IgM ELISA. Vasculitis markers (anti-nuclear antigen, rheumatoid factor, anti-neutrophilic cytoplasmic antibodies) were negative. A detailed serum autoimmune (antibodies to NMDA receptor, LGI1, CASPR2, AMPA receptor, GluR1/GluR2, GABA-B, GAD, anti-thyroid peroxidase) and paraneoplastic antibody profile (anti-Hu, anti-Yo, anti-Ri, anti-CV2, anti-Ma2, anti-amphiphysin) was nonrevela-

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**Figure 1.** The typical 'cigarette burn' eschar, as seen in our patient inside the white circle, consisted of an erythematous papule with a cap of blackish scab and surrounding desquamation.

tory. Serology for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C and the Venereal Diseases Research Laboratory (VDRL) test were negative. Brain MRI with contrast was normal (Supplementary Figure 1 in the online-only Data Supplement). Cerebrospinal fluid examination and electroencephalography were also normal. Positron emission tomography-computed tomography (PET-CT) of the whole body to screen for malignancy was normal. The OMS observed at presentation gradually resolved over the next two weeks without any specific treatment or immunotherapy.

OMS commonly manifests a paraneoplastic syndrome. Pediatric OMS is described prominently in association with neuroblastomas in children below the age of two years, with nearly 50% of pediatric cases associated with neuroblastomas. In adult OMS, malignancies commonly associated with paraneoplastic OMS include small cell lung cancer and breast and gynecological malignancies. However, non-paraneoplastic conditions associated with OMS are being increasingly observed. Parainfectious OMS has been described together with streptococcal infection and viral infections such as HIV, Epstein-Barr virus and cytomegalovirus.<sup>3</sup> We have summarized the case reports and case series of opsoclonus and/or myoclonus in association with scrub typhus in Supplementary Table 1 (in the online-only Data Supplement). The largest is a retrospective case series of 18 patients with opsoclonus, most in association with myoclonus, cerebellar dysfunction or extrapyramidal syndrome.<sup>4</sup> However, opsoclonus or OMS is usually observed as a transient phenomenon that presents several days after the onset of the febrile illness, unlike our patient, in whom the onset of OMS was nearly simultaneous with the fever. Paraneoplastic OMS is immune-mediated. Pathological an-

tibodies targeted to shared epitopes that are expressed by the tumor, but otherwise found exclusively in the nervous system, are putatively responsible. However, a majority of patients may be negative for these antibodies, suggesting yet unknown target antigens or alternate pathogenetic mechanisms.<sup>5</sup> Antibodies have been shown to bind to cerebellar antigens, particularly cerebellar nuclei. However, the exact pathogenesis of the disorder is far from clear.

The underlying pathogenetic mechanism of OMS in scrub typhus is thought to be immune mediated, led by type 2 hypersensitivity against self-antigens due to the usual lag between fever onset and OMS onset.<sup>4</sup> Although this lag was very small in our patient (one day), pregnancy may have accelerated the usual class switch from an IgM to an IgG titer against *O. tsutsugamushi*, the latter gaining access to target tissues in the central nervous system after traversing the blood-brain barrier. Her rapid recovery suggests that autoantibodies probably exhibited weak and/or transient binding to the self-antigen and will not lead to lasting neuronal injury.<sup>5</sup> This temporal course may differentiate postinfectious syndrome from parainfectious syndrome. This is significant in light of the observations that parainfectious OMS in scrub typhus is usually transient and may resolve spontaneously. Postinfectious syndromes may, in contrast, necessitate immune therapy of some kind. Paraneoplastic OMS in children responds well to steroids, adrenocorticotrophic hormone (ACTH) and other immunosuppressive measures, unlike adult cases. In the cases related to an infective etiology, symptoms subside over 6 to 8 weeks, so specific therapy is not required. However, the use of high-dose intravenous immunoglobulin has been described for parainfectious OMS.<sup>6</sup>

This case report highlights the increasingly variable and complex neurological presentation of scrub typhus. OMS is typically a well-characterized paraneoplastic syndrome with a likely antibody-mediated mechanism. Parainfectious OMS, unlike its paraneoplastic counterpart, seems to have a good prognosis when the underlying infection is treated.

### Ethics Statement

Written informed consent was obtained from the patient.

### Supplementary Video Legends

Video 1. The patient has rapid, conjugate, multidirectional, chaotic movements of both eyes, typical of opsoclonus. Associated sudden, jerk-like movements involving all four limbs are seen, exacerbated by tactile contact, suggestive of myoclonus. The patient has consented to the submission of this article to this journal.

### Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.14802/jmd.20148>.

## Conflicts of Interest

The authors have no financial conflicts of interest.

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## Author Contributions

Conceptualization: all authors. Investigation: all authors. Writing—original draft: Divyani Garg. Writing—review & editing: all authors.

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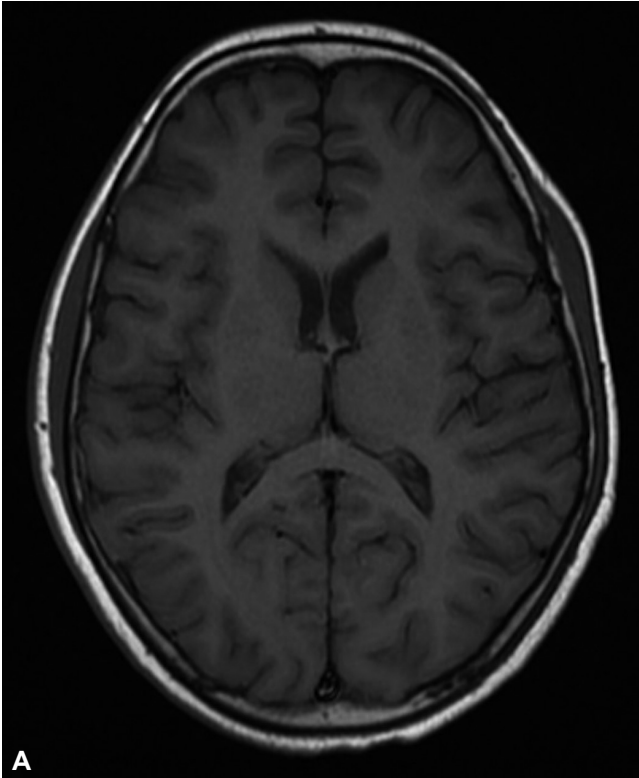
**Supplementary Table 1.** Summary table of case reports/series of scrub typhus with opsoclonus and/or myoclonus syndrome

| Author/year of publication       | Age (years)/gender   | Presenting features   | Course of opsoclonus+/myoclonus   | Evaluation  | Treatment                                      | Outcomes  |
|----------------------------------|--|---|---|---|--|---|
| Nam et al. <sup>1</sup> (2010)   | 64/female  | Not mentioned<br>[Drowsiness and nuchal rigidity noted in both]   | Not mentioned   | CSF cells = 49 cells/mm <sup>3</sup><br>CSF protein = 102 mg/dL   | Not mentioned                                  | Not mentioned   |
|                                  | 40/male  |   |   | CSF cells = 28 cells/mm <sup>3</sup><br>CSF protein = 91 mg/dL<br>MRI brain normal in both  |  |   |
| D'sa et al. <sup>2</sup> (2012)  | 54/male  | Fever for 7 days,<br>headache for 2 days,<br>opsoclonus for 2 days  | Onset of opsoclonus on day 5 of fever   | MRI brain and CSF normal<br>IgM ELISA in serum positive for scrub typhus  | Doxycycline                                    | Complete recovery at 2 weeks  |
| Koti et al. <sup>3</sup> (2015)  | 26/male  | Fever for 5 days  | Onset of opsoclonus and myoclonus on day 6 of fever   | MRI brain and CSF normal<br>IgM scrub typhus ELISA positive   | Doxycycline                                    | Opsoclonus subsided on day 3, 4 of treatment and 9th and 10th day of illness  |
| Sahu et al. <sup>4</sup> (2017)  | 60/male  | Fever for 2 weeks   | Onset of opsoclonus not mentioned   | IgM scrub typhus ELISA positive   | Doxycycline and azithromycin                   | Opsoclonus decreased 2 days after initiation of therapy and resolved by day 3   |
| Choi et al. <sup>5</sup> (2017)  | 59/male  | Decreased mentation, ataxia   | Onset 8 days following 'scrub typhus infection'   | Imaging normal  | Doxycycline and steroid IV MP pulse for 5 days | 'Good' outcome  |
| Ralph et al. <sup>6</sup> (2019) | 18 patients in a retrospective series had opsoclonus, of which 9 (50%) had myoclonus associated                          | Fever, headache, nausea, vomiting<br>Eight had concomitant cerebellar signs, and six had extrapyramidal dysfunction | Onset of opsoclonus was mean 11 days (range 7–18 days) from onset of fever<br>In one patient, opsoclonus noted one day post-defervescence | Scrub typhus ELISA positive in all patients<br>14/18 patients had abnormal CSF (2 were not tested)<br>Normal MRI in 9/12 patients | Doxycycline +/- azithromycin                   | 13/17 followed up at 6 weeks; myoclonus completely resolved in all, opsoclonus persisted in nine. At 3 months, 12 were followed up. Complete resolution of myoclonus in all |
| Saini et al. <sup>7</sup> (2020) | One child in a retrospective case series of children with 'infection-associated opsoclonus' had scrub typhus<br>7/female | Fever for 7 days  | Opsoclonus noted on day 5 of fever  | IgM scrub typhus ELISA positive<br>MRI brain normal<br>CSF showed 30 cells/m <sup>3</sup> , 55 mg/dL protein                      | Doxycycline                                    | Resolved completely over 7 days   |

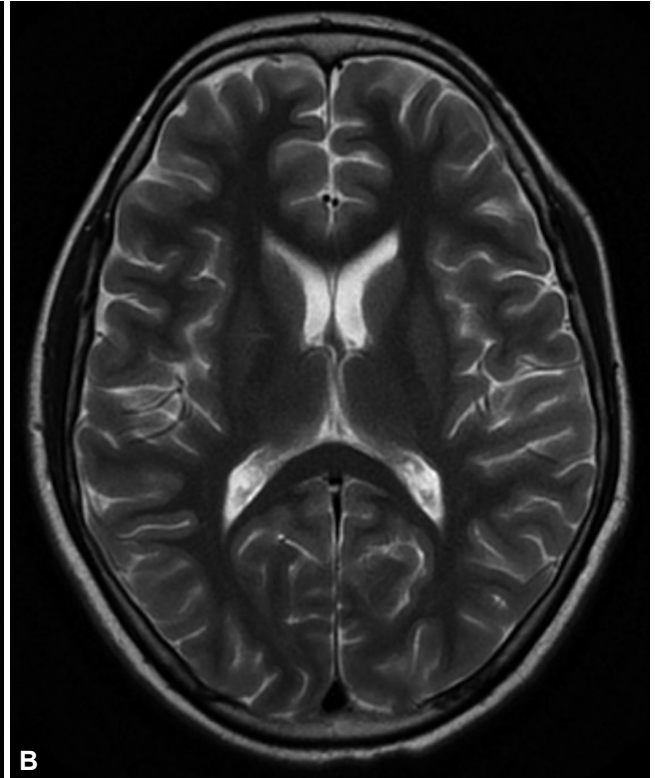
CSF: cerebrospinal fluid

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A



B

**Supplementary Figure 1.** Brain MRI showing normal axial T1 (A) and T2 (B) sequences.