

# Enfermedades Infecciosas y Microbiología Clínica



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### Letter to the Editor

Comments to the article "First reported case of imported scrub typhus in Spain: A disease to consider in travellers"



Comentarios sobre el artículo «Primer caso descrito de tifus de los matorrales en España: una enfermedad a considerar en los viaieros»

Dear Editor.

We have read with interest the Letter to the Editor from Arroyo-Andrés et al., 1 regarding the first reported case of imported scrub typhus in Spain: a disease to consider in travellers, and we would like to clarify three important points:

First, Arroyo-Andrés et al. only mention one neurological manifestation associated with scrub typhus, which is encephalitis in severe cases. 1 Scrub typhus can be a great imitator and may masquerade as a plethora of neurological manifestations in the so-called "neuro-scrub" spectrum. Although meningoencephalitis is one of the most common neurological manifestations, along with cranial nerve paresis, transverse myelitis, and polyneuropathy (including Guillain-Barré syndrome),<sup>2</sup> other neurological manifestations include diaphragmatic myoclonus, <sup>2</sup> limbic encephalitides,<sup>3</sup> pure alexia,<sup>4</sup> posterior reversible encephalopathy syndrome,<sup>2</sup> parkinsonism,<sup>2</sup> cerebellitis,<sup>2</sup> isolated opsoclonus and opsoclonus-myoclonus (with/without ataxia),2 myositides,2 polyradiculoneuropathies with cranial neuropathies,<sup>2</sup> acute transient behavioural changes,<sup>2</sup> post-scrub fibromyalgia,<sup>2</sup> cerebral venous sinus thrombosis,<sup>5</sup> seizures and/or status epilepticus.<sup>6</sup> Specifically, seizures have been reported in scrub typhus in 6.3–21.6% of patients. The outcome of scrub typhus patients with status epilepticus may be better than other central nervous system infections because of the good treatment response. 6 In a case series of 66 scrub typhus patients, all of them recovered completely with doxycycline by one month and antiseizure drugs (levetiracetam. phenytoin, and/or valproic acid) were withdrawn by eight months in all.6

Second, Arroyo-Andrés et al.<sup>1</sup> comment that classical manifestations are not always present like the black eschar in travellers compared to local cases. The eschar at the site of the mite bite is recognized as a pathognomonic diagnostic clue,<sup>2</sup> which is approximately present in up to 50% of scrub typhus patients. It may be found in obscure sites such as the pubis, axilla, or lower legs, so it is easily overlooked (this fact is of utmost importance and is not specified in the article by Arroyo-Andrés et al.<sup>1</sup>).

Third, Arroyo-Andrés et al.<sup>1</sup> argue that the treatment of choice is doxycycline twice daily for 3–7 days. Although true, there are situations such as pregnancy where azithromycin can be used.<sup>7</sup> For the treatment of severe scrub typhus, combination therapy with intravenous doxycycline and azithromycin is superior to monotherapy

with either antibiotic alone.<sup>8</sup> Regarding seizures/status epilepticus, these antibiotics (doxycycline and azithromycin) do not lower the seizure threshold.<sup>9</sup> In addition, minocycline, doxycycline, and tetracycline have antiseizure activity against focal seizures *in vivo*.<sup>10</sup>

In closing, we want to raise awareness among Spanish clinicians about the possible neurological manifestations of scrub typhus. Because this infection is treatable with antibiotics, it should be considered in the workup of febrile patients with acute neurological manifestations who travel from endemic areas.

Finally, further and more extensive prospective case series are warranted to shed light on the associated manifestations, evolution, and prognosis of the imported scrub typhus cases in Spain and the rest of the countries outside the "tsutsugamushi triangle".

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Nil.

### Conflict of interest

None

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# References

- Arroyo-Andrés J, Ferreiro López D, Oteo Revuelta JA, Zarco C. First reported case of imported scrub typhus in Spain: a disease to consider in travellers. Enferm Infecc Microbiol Clin (Engl Ed). 2023;41:132–4.
- Ghosh R, Mandal A, León-Ruiz M, Roy D, Das S, Dubey S, et al. Rare neurological and neuropsychiatric manifestations of scrub typhus: a case series of 10 cases. (Engl Ed). 2022;S2173-5808(22)00081-5, http://dx.doi.org/10.1016/j.nrleng.2022.07.001.
- 3. Biswas S, Ghosh R, Roy D, Ray A, De K, Biswas S, et al. Scrub typhus masquerading as limbic encephalitis. Neurohospitalist. 2022;12:105–10.
- 4. Ghosh R, Dubey S, Roy D, Benito-León J. Pure alexia as a presenting manifestation of scrub typhus. Neurologia (Engl Ed). 2023;38:307–9.
- 5. Biswas U, Ghosh R, Chakraborty A, Mondal SR, Roy D, Bhattacharjee A, et al. Cerebral venous sinus thrombosis following scrub typhus infection: a case report and a review of the literature. Med Res Arch. 2022;10, http://dx.doi.org/10.18103/mra.v10i10.3196.
- Kalita J, Mani VE, Bhoi SK, Misra UK. Status epilepticus in scrub typhus. Epilepsia. 2016:57:e125–8.

- 7. Rajan SJ, Sathyendra S, Mathuram AJ. Scrub typhus in pregnancy: maternal and fetal outcomes. Obstet Med. 2016;9:164–6.
- 8. Varghese GM, Dayanand D, Gunasekaran K, Kundu D, Wyawahare M, Sharma N, et al. Intravenous doxycycline, azithromycin, or both for severe scrub typhus. N Engl | Med. 2023;388:792–803.
- Wanleenuwat P, Suntharampillai N, Iwanowski P. Antibiotic-induced epileptic seizures: mechanisms of action and clinical considerations. Seizure. 2020;81:167–74.
- Wang DD, Englot DJ, Garcia PA, Lawton MT, Young WL. Minocycline- and tetracycline-class antibiotics are protective against partial seizures in vivo. Epilepsy Behav. 2012;24:314–8.

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