frontiers | Frontiers in Arachnid Science

TYPE Brief Research Report
PUBLISHED 09 December 2025
DOI 10.3389/frchs.2025.1709631

OPEN ACCESS

EDITED BY
Volker Herzig,
University of the Sunshine Coast, Australia

REVIEWED BY
L. Paulina Maldonado-Ruiz,
University of Arizona, United States
Vipin Rana,
University of Maryland, College Park, United States

*CORRESPONDENCE
Shahid Karim
shahid.karim@usm.edu

RECEIVED 20 September 2025
REVISED 17 November 2025
ACCEPTED 24 November 2025
PUBLISHED 09 December 2025

CITATION
Oyediran O and Karim S (2025) Unusual paralytic response to *Amblyomma maculatum* nymphal bite in alpha-gal knockout mice. *Front. Arachn. Sci.* 4:1709631. doi: 10.3389/frchs.2025.1709631

Unusual paralytic response to *Amblyomma maculatum* nymphal bite in alpha-gal knockout mice

Olaoluwa Oyediran and Shahid Karim*

School of Biological, Environmental, and Earth Sciences, University of Southern Mississippi, Hattiesburg, MS, United States

The Gulf-Coast tick (*Amblyomma maculatum*) is an emerging species whose geographic range is expanding in the United States. Although tick bite-induced paralysis is uncommon, *Am. maculatum* has been implicated in cases affecting vertebrate hosts. We report a rare case of paralysis in α-Gal-deficient mice following nymphal tick attachment. Notably, the symptoms resolved rapidly after the nymph was removed.

KEYWORDS

ticks, *Amblyomma maculatum*, paralysis, alpha-gal syndrome, mice

1 Introduction

Although rare, tick paralysis is a potentially fatal condition caused by a neurotoxin transmitted in the saliva of an engorged female tick of a specific species (Paffenbarger, 1951). The toxin disrupts presynaptic acetylcholine release, leading to ascending flaccid paralysis (Edlow and McGillicuddy, 2008). Early signs often include malaise and generalized weakness, which can progress to muscle paralysis in an ascending pattern, and in severe cases, respiratory failure (Dehhaghi et al., 2019). Symptoms typically appear 4–7 days after tick attachment, progress rapidly, and are only reversible upon tick removal (Gerasimova et al., 2018). Prompt removal usually results in clinical improvement within hours and complete recovery within days.

While most cases occur in the United States, Canada, and Australia, tick paralysis has been reported worldwide, including rare cases in Europe and Africa (Deng et al., 2024). More than 75 tick species, primarily hard ticks, are capable of producing toxins that paralyze humans and animals (Edlow and McGillicuddy, 2008). In North America, most reported cases involve two species: *Dermacentor Andersoni* (Rocky Mountain wood tick), prevalent in the western regions, and *Dermacentor variabilis* (American dog tick), found mainly in the eastern and southern areas (Salman et al., 2023).

Toxins can be produced by both hard (Ixodid) and soft (Argasid) ticks. In Ixodids, toxins are secreted at all developmental stages except males, whereas in Argasids, only immature stages produce the toxin due to their prolonged feeding on the host (Mans et al., 2004). Tick paralysis is most often reported in the spring and summer months. Here, we

describe a rare case of paralysis in α-Gal-deficient mice following attachment by nymphal *Amblyomma maculatum*.

2 Materials and methods

2.1 Ethics statement

All animal procedures were conducted in strict accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, USA. The protocols for tick feeding on mice and sheep were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Southern Mississippi (protocol # 19041801.2, 15101501.6). All efforts were made to minimize animal distress and ensure their well-being throughout the study.

2.2 Ticks and other animals

The lone-star tick (*Amblyomma americanum*) and Gulf-Coast tick (*Amblyomma maculatum*) were originally obtained from the Oklahoma State University Tick rearing facility and maintained at the University of Southern Mississippi. Both immature and adult stages were maintained as previously described methods (Patrick and Hair, 1975; Sharma et al., 2024). Ticks were kept at room temperature under approximately 90% relative humidity, with a photo period of 14 hours light and 10 hours dark, before infestation on mice.

2.3 Mice sensitization

Eight- to ten-week-old Alpha-1,3-galactosyltransferase knockout (AGKO) mice were bred and maintained in pathogen-free facilities under protocols approved by the University of Southern Mississippi's IACUC as described previously (Sharma et al., 2024). A total of 30 mice were randomly assigned to three groups: control (n=10), *Am. americanum*-infested (n=10), and *Am. maculatum*-infested (n=10).

For sensitization, mice were anesthetized by intraperitoneal injection of a ketamine/xylazine cocktail (10mg/kg), and 15 nymphal ticks (*Am. americanum* or *Am. maculatum*) were placed on each mouse ear. Ticks were allowed to attach freely before the mice were transferred to individual cages equipped with wire platforms positioned above water, allowing for the collection of engorged nymphs as previously described (Sharma et al., 2024).

3 Results and discussion

Five days after infestation, two mice in *Am. maculatum*-infested group were found weak and unresponsive. Both displayed stiffness and immobility in the hind limbs, attempting to move using only their forelimbs, and showed a marked loss of appetite. At this time, *Am. maculatum* nymphs remained attached to the ears of the affected mice. By day seven post-infestation, two additional mice in the same group developed similar symptoms. On day eight, the first two symptomatic mice were found dead in their cages, with tick bite-induced paralysis suspected as the cause of death.

The attached *Am. maculatum* nymphs were immediately removed from the remaining two symptomatic mice. Within 24 hours of tick removal, both animals recovered fully and returned to normal activity. The reported cases of tick paralysis in AGKO mice expand our limited understanding of this rare condition in laboratory animals and highlight the potential role of *Am. maculatum* nymphal saliva. This is especially important given that *Am. maculatum* is an emerging tick species expanding its range within the United States (Hecht et al., 2020; Molaei et al., 2021; Ramirez-Garofalo et al., 2022; Musnoff et al., 2024). Concerns about tick paralysis are justified, given the significant number of animals affected during the summer months, which can lead to substantial economic consequences.

Tick paralysis is not a new or emerging tick-borne condition; it has been recognized for decades. However, it has received limited attention because it's considered rare, a view that may need updating, given the numerous documented human cases (Matthews and Harfouch, 2023). In the United States, *Am. maculatum* is also known to parasitize humans, who may be at elevated risk for tick-induced paralysis. While tick paralysis is more common in small dogs, it has been reported in snakes, birds, ruminants, horses, bobcats, and domestic cats (Daniel et al., 2024). Unlike well-known TBDs that are primarily infectious or allergic in origin, tick paralysis is toxin-mediated, which makes it more complex and often overlooked.

In our experimental study, two tick species, *Am. americanum* and *Am. maculatum* originating from the same colony were infested in the same anatomical location (ear) in genetically modified AGKO mice. Notably, only mice infested with *Am. maculatum* developed signs of tick paralysis. This raises intriguing questions about whether the immune status of AGKO mice uniquely interacts with *Am. maculatum* saliva, or if *Am. maculatum* secretes a more potent paralytic toxin than *Am. americanum*. This observation aligns with the hypothesis that tick paralysis toxins vary among tick species (Borawski et al., 2018).

The discovery of paralysis five and seven days after infestation aligns with previous findings on tick paralysis, as the symptoms are known to show four to seven days after infestation (Gerasimova et al., 2018). Even though the precise mechanism is not fully understood, Pienaar et al. (2018) clarify that paralysis toxins are secreted just before the rapid engorgement phase, which typically takes 3–7 days post attachment. This is probably because hard ticks (Ixodidae) are the main culprit in tick paralysis, have a slow-fast feeding phase, which means that for the first few days, there will be low salivary output and minimal toxin delivery.

Hematophagy in ixodid ticks can be divided into three main phase: attachment, slow feeding, and "big sip". Both immature and mature ticks insert their hypostome deep into the host's skin and secrete cement that anchors them securely. As pool feeders, ticks secrete saliva during slow feeding to modulate and evade host immune defenses. In some species, once feeding is established

and before full engorgement, the tick's adhesion to the host skin loosens. This loose attachment is followed by the release of neurotoxins that can paralyze the host, allowing the tick to take a large blood meal before detachment (Karim et al., 2021).

Stone et al. (1983) investigated the cells responsible for toxin production and described the feeding and salivation patterns associated with paralysis. Their work showed that it typically takes about 4–7 days before the toxin exerts its effect. The longer a female tick remains attached, the more the composition of its saliva changes, with toxin levels gradually increasing. As a result, saliva becomes progressively more potent and, if uninterrupted, may ultimately cause host death. The observed stiffness and immobility in the hind limbs are due to the blockage of acetylcholine from the presynaptic vesicle because, without the release of acetylcholine, muscles cannot contract (Stone and Neish, 1984). It was also observed that for all mice, paralysis started in the hind limbs. The reason for this is still a subject of research, but this could be due to the toxin's impact on the neuromuscular junction, which disrupts the communication between nerves and muscles, which are necessary for coordinated movement (Simon et al., 2023).

Two main hypotheses have been proposed to explain the weakness and loss of appetite associated with tick paralysis. Stone and Neish (1984) reported that the condition interferes with acetylcholine release not only at limb motor endplates but also at neuromuscular junctions of cranial nerves. This disruption impairs the muscles of mastication, swallowing, and tongue movement, making chewing and swallowing difficult and leading animals or experimental hosts to refuse food. In addition, because the neurotoxins can affect the autonomic nervous system, including the vagus nerve, disruption of vagal signaling may impair gastrointestinal motility and alter satiety pathways (Browning et al., 2017). This provides a plausible mechanism for the anorexia observed. Our findings also align with the literature, with the complete reversal of paralysis after 24 hours of tick removal from the affected mice. This is because, unlike degenerative neuropathies, which are also progressive, once the tick has been removed and toxin exposure ceases, the synaptic acetylcholine is released, and recovery occurs (Simon et al., 2023).

In North America, tick paralysis has traditionally been associated with *Dermacentor andersoni* and *Dermacentor variabilis*, although other species, including *Am. americanum*, *Am. maculatum*, and *Ixodes scapularis* have also been implicated (Pienaar et al., 2018). Some tick species secrete salivary neurotoxins that trigger paralysis, while others do not, and the identity, size and molecular class of these toxins vary across genera. To date, no single, unified "tick paralysis toxin" has been identified. The best-characterized paralytic factors are the holocyclotoxins produced by *Ixodes holocyclus*. These are small, cystine-rich secreted proteins that cause presynaptic failure of neurotransmitter release (Rodriguez-Valle et al., 2018). Functional and biochemical studies show that holocyclotoxins interfere with calcium-dependent acetylcholine release at motor nerve terminals. Similar findings in Dermcentor species, including reduced motor nerve conduction and diminished acetylcholine release, support a comparable presynaptic mechanism in that genus as well (Murnaghan, 1960). In contrast, the molecular identity of paralysis-associated factors in *Amblyomma* ticks remain poorly defined. Sporadic clinical and experimental reports, however, link *A. maculatum* and *A. americanum* to paralytic illness (Dworkin et al., 1999). A 2011 human case definitively associated *Amblyomma maculatum* with ascending flaccid paralysis that resolved following tick removal, demonstrating that this species can produce clinically significant paralytic effects (Espinoza-Gomez et al., 2011). Overall, the diversity of candidate salivary toxins across tick genera suggests convergent evolution of paralytic mechanisms rather than a single toxin family. Different tick lineages appear to have independently evolved salivary molecules with venom-like neurotoxic activity that impair host motor function and support prolonged feeding (Cabezas-Cruz and Valdés, 2014).

According to Wikel (1996), species that feed on small mammals or birds which can easily remove ticks by grooming or preening tends to benefit from secreting toxins that immobilize host while ticks specializing on large ungulates or reptiles which are less agile groomers may not require such toxins and instead invests in other salivary strategies such as anticoagulants and immunomodulators. Previous studies have noted that ticks causing paralysis are often attached to locations near the head, such as the scalp, neck, behind the ears, or groin. This is consistent with our findings, as ticks were infested on the ears of the mice.

While the diversity of the compounds used by hematophagous arthropods is impressive and the biological functions of many of the salivary compounds secreted remain unknown, there is a hypothesis regarding the biological relevance of knocking down a host with their toxin, Mans et al. (2004) hypothesized that paralysis improves feeding success by reducing host grooming and mobility, allowing ticks to maintain attachment. Therefore, it serves as an adaptive mechanism to suppress defenses like grooming in the mice. This hypothesis was also further corroborated by studies from Akinyi et al. (2013) and Jones et al. (2015), whose studies reported respectively that baboons receiving higher amounts of grooming had significantly fewer ticks, and impalas restricted from grooming harbored nine times more ticks than those permitted to groom.

It is important to note that these observations were made in α-galactosyltransferase knockout mice, which lack α-gal epitopes. Because these mice do not express α-gal on these cells and tissues. Their immune system recognizes α-gal as a foreign molecule. This makes them useful humanized model for study α-gal immune responses and for investigating immune pathways, tick salivary components, and potential vaccine strategies for Alpha-Gal Syndrome (LaTemple and Galili, 1998). Although they were chosen to explore α-gal related mechanisms, the genetic absence of α-gal containing glycans could theoretically influence the host response to tick feeding or toxin exposure. Altered glycan profiles may affect immune regulation or the clearance of salivary proteins and neurotoxins. Despite these considerations, the clinical signs observed, including marked loss of appetite, progressive hind limb paralysis, and recovery after tick removal, are consistent with tick paralysis.

Our study provides the first reported case of tick paralysis caused by the nymphal stage of *Am. maculatum* in either experimental or natural settings. Although this appears to be a novel finding, undocumented cases may have occurred, as tick paralysis is considered rare and most reports focused on more common species such as Dermacentor and the Ixodes. Moreover, *Am. maculatum* is primarily recognized as a vector of *Rickettsia parkeri*, which may have further limited attention to its role in paralysis.

This finding expands our understanding of tick salivary biology by highlighting paralysis and host-immune modulation as important components, and it identifies salivary toxins as potential targets for anti-tick vaccines or inhibitors. Because such molecules are essential for tick feeding, they represent valuable tools for disrupting tick survival. These findings also underscore the need for greater vigilance toward this underrecognized toxin-mediated disease, with important implications for both human and animal health. Increased public and scientific awareness will be critical to preventing cases, clarifying pathogenesis, and identifying the molecular mechanisms involved.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by The University of Southern Mississippi. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

OO: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SK: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This research was principally supported by the NIH NIAID Awards #R21AI175885, and #R21AI190957.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

Akinyi, M. Y., Tung, J., Jeneby, M., Patel, N. B., Altmann, J., and Alberts, S. C. (2013). Role of grooming in reducing tick load in wild baboons (Papio cynocephalus). *Anim. Behav.* 85, 559–568. doi: 10.1016/j.anbehav.2012.12.012

Borawski, K., Pancewicz, S., Czupryna, P., Zajkowska, J., and Moniuszko-Malinowska, A. (2018). Tick paralysis. *Przegl Epidemiol.* 72, 17–24.

Browning, K. N., Verheijden, S., and Boeckxstaens, G. E. (2017). The vagus nerve in appetite regulation, mood, and intestinal inflammation. *Gastroenterology* 152, 730–744. doi: 10.1053/j.gastro.2016.10.046

Cabezas-Cruz, A., and Valdés, J. J. (2014). Are ticks venomous animals? *Frontiers in Zoology* 11, 47. doi: 10.1186/1742-9994-11-47

Daniel, I. K., Ramos, R. A. N., Luksovsky, J. L., Galindo, M. A., Saleh, M. N., and Verocai, G. G. (2024). Apparent tick paralysis by Otobius megnini in a cat. *Veterinary Parasitol: Regional Stud. Rep.* 48, 100972. doi: 10.1016/j.vprsr.2023.100972

Dehhaghi, M., Kazemi Shariat Panahi, H., Holmes, E. C., Hudson, B. J., Schloeffel, R., and Guillemin, G. J. (2019). Human tick-borne diseases in Australia. *Front. Cell. Infection Microbiol.* 9. doi: 10.3389/fcimb.2019.00003

Deng, Y.-P., Fu, Y.-T., Elsheikha, H. M., Cao, M.-L., Zhu, X.-Q., Wang, J.-L., et al. (2024). Comprehensive analysis of the global impact and distribution of tick paralysis, a deadly neurological yet fully reversible condition. *Clin. Microbiol. Rev.* 37, e0007424. doi: 10.1128/cmr.00074-24

Dworkin, M. S., Shoemaker, P. C., and Anderson, D. E. (1999). Tick paralysis: 33 human cases in Washington State 1946-1996. *Clin. Infect. Dis.* 29, 1435–1439. doi: 10.1086/313502

Edlow, J. A., and McGillicuddy, D. C. (2008). Tick paralysis. *Infect. Dis. Clinics North America* 22, 397–413. doi: 10.1016/j.idc.2008.03.001

Espinoza-Gomez, F., Newton-Sanchez, O., Flores-Cazares, G., de la Cruz-Ruiz, M., Melnikov, V., Austria-Tejeda, J., et al. (2011). Tick paralysis caused by Amblyomma

maculatum on the Mexican Pacific Coast. *Vector borne zoonotic Dis. (Larchmont N.Y.)* 11, 945–946. doi: 10.1089/vbz.2010.0154

Gerasimova, M., Kelman, M., and Ward, M. P. (2018). Are recreational areas a risk factor for tick paralysis in urban environments? *Veterinary Parasitol.* 254, 72–77. doi: 10.1016/j.vetpar.2018.02.044

Hecht, J. A., Allerdice, M. E. J., Karpathy, S. E., Yaglom, H. D., Casal, M., Lash, R. R., et al. (2020). Distribution and occurrence of Amblyomma maculatum sensu lato (Acari: Ixodidae) and Rickettsia parkeri (Rickettsiales: Rickettsiaceae), Arizona and New Mexico 2017–2019. *J. Med. Entomol.* 57, 2030–2034. doi: 10.1093/jme/tjaa130

Jones, C. R., Brunner, J. L., Scoles, G. A., and Owen, J. P. (2015). Factors affecting larval tick feeding success: Host, density and time. *Parasites Vectors* 8, 340. doi: 10.1186/s13071-015-0955-6

Karim, S., Kumar, D., and Budachetri, K. (2021). Recent advances in understanding tick and rickettsiae interactions. *Parasite Immunol.* 43, e12830. doi: 10.1111/pim.12830

LaTemple, D. C., and Galili, U. (1998). Adult and neonatal anti-Gal response in knock-out mice for alpha1,3galactosyltransferase. *Xenotransplantation* 5, 191–196. doi: 10.1111/j.1399-3089.1998.tb00027.x

Mans, B. J., Gothe, R., and Neitz, A. W. (2004). Biochemical perspectives on paralysis and other forms of toxicoses caused by ticks. *Parasitology* 129, S95–S111. doi: 10.1017/s0031182003004670

Matthews, S. N., and Harfouch, C. (2023). A meta-analysis of tick paralysis in humans globally. *Open Forum Infect. Dis.* 10, ofad500.694. doi: 10.1093/ofid/ofad500.694

Molaei, G., Little, E. A. H., Khalil, N., Ayres, B. N., Nicholson, W. L., and Paddock, C. D. (2021). Established population of the Gulf Coast tick, Amblyomma maculatum (Acari: Ixodidae), infected with Rickettsia parkeri (Rickettsiales: Rickettsiaceae), in Connecticut. *J. Med. Entomol.* 58, 1459–1462. doi: 10.1093/jme/tjaa299

Murnaghan, M. F. (1960). Site and mechanism of tick paralysis. *Sci. (New York N.Y.)* 131, 418–419. doi: 10.1126/science.131.3398.418

Musnoff, B. L., Cuadera, M. K. Q., Birney, M. R., Zipper, L., Nicholson, W., Ayres, B., et al. (2024). The first record of an established population of Amblyomma maculatum (Acari: Ixodidae) in New Jersey, USA. *J. Med. Entomol.* 61, 1081–1085. doi: 10.1093/jme/tjae056

Paffenbarger, R. S. Jr. (1951). Tick paralysis; implicating Amblyomma maculatum. *New Orleans Med. Surg. J.* 103, 329–332.

Patrick, C. D., and Hair, J. A. (1975). Laboratory rearing procedures and equipment for multi-host ticks (Acarina: Ixodidae). *J. Med. Entomol.* 12, 389–390. doi: 10.1093/jmedent/12.3.389

Pienaar, R., Neitz, A. W. H., and Mans, B. J. (2018). Tick paralysis: Solving an enigma. *Veterinary Sci.* 5, 53. doi: 10.3390/vetsci5020053

Ramírez-Garofalo, J. R., Curley, S. R., Field, C. E., Hart, C. E., and Thangamani, S. (2022). Established populations of Rickettsia parkeri-infected Amblyomma maculatum ticks in New York City, New York, USA. *Vector-Borne Zoonotic Dis.* 22, 184–187. doi: 10.1089/vbz.2021.0085

Rodriguez-Valle, M., Moolhuijzen, P., Barrero, R. A., Ong, C. T., Busch, G., Karbanowicz, T., et al. (2018). Transcriptome and toxin family analysis of the paralysis tick, Ixodes holocyclus. *Int. J. Parasitol.* 48, 71–82. doi: 10.1016/j.ijpara.2017.07.007

Salman, F., Atlantawi, A., and Maraqa, N. (2023). Tick paralysis: A thorough examination may prevent unnecessary harm. *Cureus* 15, e43932. doi: 10.7759/cureus.43932

Sharma, S. R., Choudhary, S. K., Vorobiov, J., Commins, S. P., and Karim, S. (2024). Tick bite-induced alpha-gal syndrome and immunologic responses in an alpha-gal deficient murine model. *Front. Immunol.* 14. doi: 10.3389/fimmu.2023.1336883

Simon, L. V., West, B., and McKinney, W. P. (2023). "Tick paralysis," in *StatPearls* (Treasure Island, Florida: StatPearls Publishing).

Stone, B. F., Commins, M. A., and Kemp, D. H. (1983). Artificial feeding of the Australian paralysis tick, Ixodes holocyclus, and collection of paralysing toxin. *Int. J. Parasitol.* 13, 447–454. doi: 10.1016/s0020-7519(83)80007-1

Stone, B. F., and Neish, A. L. (1984). Tick-paralysis toxoid: An effective immunizing agent against the toxin of Ixodes holocyclus. *Aust. J. Exp. Biol. Med. Sci.* 62, 189–191. doi: 10.1038/icb.1984.18

Wikel, S. K. (1996). Host immunity to ticks. *Annu. Rev. Entomol.* 41, 1–22. doi: 10.1146/annurev.en.41.010196.000245