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LETTER TO THE EDITOR

The alpha-Gal Syndrome is Underdiagnosed

El síndrome de alfa-Gal está infradiagnosticado

To the Editor,

Recently, Fernández de la Fuente et al.¹ published an interesting case associated with reactions to *Dermacentor marginatus* tick bite. Forty-eight hours after tick bite the case presented an indurated lesion around the bite and a bad bounded erythematous edematous plaque accompanied by a very painful bilateral palpable cervical adenopathy, elevated levels of some hepatic enzymes and several peaks of low-grade fever (37.8 °C). The patients tested negative for tick-borne pathogens *Rickettsia conorii* and *Borrelia burgdorferi*.¹ Accordingly, the patient was diagnosed with the spotted fever group disease tick-borne lymphadenopathy (TIBOLA).¹

The alpha-Gal syndrome (AGS) is associated with IgE antibodies and allergic reactions to tick bites, mammalian meat consumption and pharmaceuticals containing glycan galactose-alpha-1,3-galactose (α -Gal) modification in proteins and lipids.^{2–5} Multiple tick species with different α -Gal content are associated with the AGS worldwide.⁶

Hominids evolved with multiple events of catastrophic selection including losing the synthesis of α -Gal and thus developing the capacity to produce IgM/IgG antibodies and activate immune mechanisms in response to this molecule with protective capacity against pathogens containing or not this glycan modification.^{2,3,7} Accordingly, immunization with α -Gal and probiotics with α -Gal content can bust protective immune responses against pathogen infection (e.g., Ref. 8).

According to Centers for Disease Control and Prevention (CDC; <https://www.cdc.gov/ticks/alpha-gal/index.html>), AGS reactions can include hives or itchy rash, nausea or vomiting, heartburn or indigestion, diarrhea, cough, shortness of breath, or difficulty breathing, drop in blood pressure, swelling of the lips, throat, tongue, or eye lids, dizziness or faintness, and severe stomach pain. The most common symptoms include urticaria and angioedema, respiratory distress, cardiovascular/heart disease, gastrointestinal symptoms, diarrhea, abdominal pain, reflux, and emesis.⁵ These symptoms can be different from person-to-person and commonly appear 2–6 h after eating meat or



dairy products, or after exposure to products containing α -Gal such as gelatin-coated medications.⁵ In some cases, mortality is associated with AGS while some people may not have allergic reactions after every exposure to tick bites or α -Gal.⁵ In Spain, some cases have presented anaphylaxis to tick bites associated with anti- α -Gal IgE antibody levels and tick proteins.⁹

Despite recent advances in the diagnosis and treatment of AGS,^{4,6} tick proteins and immune mechanisms triggering the AGS have not been fully characterized,¹⁰ and only preliminary evidence on tick alphagalactome have been recently published.⁶ Furthermore, the variety in AGS symptomatology and case-to-case differences together with limited knowledge in health care practitioners and general population makes it difficult to diagnose and treat AGS.

Considering these facts and even if the identified tick species have not been previously associated with AGS, it is recommended for cases with reactions to tick bite like the one described by Fernández de la Fuente et al.¹ to detail patient history and test serum anti- α -Gal IgE antibody levels.⁴ Allergy skin testing may be also considered.⁴

Note

For information on AGS in Spanish: Mazuecos, L., de la Fuente, J., Villar, M., 2023. Las garrapatas y la alergia a la carne roja. Notas de divulgación del IREC No. 3. Instituto de investigación en Recursos Cinegéticos, Ciudad Real, España. 4 pp. <https://www.irec.es/divulgacion-cientifica/nota-divulgativa-garrapatas-y-alergia-carne-roja/>.

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Conflict of interest

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

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