

Galactose- α -1,3-Galactose Allergy Is Not a Hitherto Unrecognized Cause of Chronic Spontaneous Urticaria

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Key Words

Galactose- α -1,3-galactose · Chronic spontaneous urticaria · Tick bite

Abstract

Background: Tick bite-induced galactose- α -1,3-galactose (α -Gal) IgE and subsequent ingestion of red meat may cause delayed severe allergic reactions including urticaria, gastrointestinal symptoms or anaphylaxis. We tested the hypothesis that increased levels of IgE to α -Gal due to tick bites and the subsequent ingestion of red meat or meat products may possibly be an un(der)recognized cause of chronic spontaneous urticaria (CSU). **Methods:** Levels of IgE to α -Gal and total IgE were measured (ImmunoCAP, Phadia AB/Thermo Fisher Scientific) in 83 patients (61 female and 22 male, median age 43 years, range 18–82) from the Department of Dermatology and Allergy, Charité – Universitätsmedizin, Berlin, Germany. All had been clinically diagnosed with moderate-to-severe CSU of a median duration of 2.9 years (range 0.1–50). **Results:** Eighty of the 83 patients (96%) had undetect-

able (<0.1 kU_A/l) serum levels of IgE against α -Gal. The levels in the remaining 3 were all low (0.25, 0.4 and 3.1 kU_A/l). In no patient, including those with measurable serum levels of IgE against α -Gal, was eating red meat associated with the development of symptoms of urticaria. **Conclusion:** Our results indicate that an allergic response to α -Gal is highly unlikely to be a hitherto unrecognized common cause of CSU.

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Galactose- α -1,3-galactose (α -Gal) is an oligosaccharide ubiquitously expressed in glycoproteins and glycolipids of non-primate mammals. IgE to α -Gal has recently been shown to cause a severe form of food allergy after consumption of red meat (beef, pork or lamb) [1, 2]. In such patients, eating red meat or drinking milk may cause generalized urticaria as well as angio-oedema, gastrointestinal symptoms or anaphylaxis 3–6 h later. Because of the delay in the onset of symptoms neither the patients nor their treating physicians make a ready association with meat ingestion.

Chronic spontaneous urticaria (CSU) has an incidence approaching 1% in the population [3]. Although its mechanism is far from clear, the clinical effectiveness of omalizumab (anti-IgE) suggests that it has an IgE-dependent component. Clearly the allergen involved is not one of the major plant or animal allergens leading to the speculation that it is either an auto-allergen or a minor, as yet unidentified, allergen [4]. Could this allergen be α -Gal? The appearance of delayed symptoms, of which urticaria was dominant, was demonstrated in 37/39 (95%) of Swedish patients with a history of red meat allergy and a median IgE against α -Gal of 20 kU_A/l (range 1.3–130 kU_A/l) [2].

There have been several reports suggesting a relationship between tick bites and red meat allergy [1, 2, 5, 6]. Although the ticks previously associated with this response were *Ixodes holocyclus* in Australia [6] and *Amblyomma americanum* predominantly in the USA [1], the European tick *Ixodes ricinus* has recently been identified as a carrier when α -Gal was identified in its gastrointestinal tract [7]. This suggests ticks to be potential worldwide initiators of red meat allergy. In a recent case report from the Eastern USA, a patient with a 2-year history of urticaria was reported to have IgE to α -Gal. Upon discontinuing the consumption of trigger meats, his symptoms resolved [8]. The authors concluded that in tick endemic areas patients with chronic urticaria should be questioned about tick bites and their symptoms in relation to meat ingestion.

Against this background, we tested the hypothesis that increased levels of IgE to α -Gal due to tick bites and the subsequent ingestion of red meat or meat products may possibly be an un(der)recognized cause of CSU.

Methods

Patients

A total of 83 patients (61 female and 22 male, median age 43 years, range 18–82 years) from the Department of Dermatology and Allergy, Charité-Universitätsmedizin, Berlin, Germany, were included in this study. All had been clinically diagnosed with moderate-to-severe CSU urticaria of a median duration of 2.9 years (range 0.1–50 years). None of the patients reported gastrointestinal symptoms or had a documented history of red meat allergy. The median 7-day urticaria activity score was 17 (range 7–38) the week before blood was taken for measurements of IgE against α -Gal and total IgE.

IgE Assays

IgE to α -Gal and total IgE were measured using ImmunoCAP (Phadia AB/Thermo Fisher Scientific, Uppsala, Sweden). The limit of detection was 0.1 kU_A/l for α -Gal and 2 kU/l for total IgE.

Results

We found that 80 of the 83 patients (96%) had undetectable (<0.1 kU_A/l) serum levels of IgE against α -Gal. The levels of the remaining 3 were all low, being 0.25, 0.4 and 3.1 kU_A/l. There was wide variability in total IgE levels of the 83 patients, the median being 110 kU/l (range <2 –2,337). The total IgE levels of the 3 patients with measurable IgE against α -Gal were 279, 117 and 164 kU/l, respectively, giving fractional α -Gal IgE levels of 0.09, 0.34 and 1.89%. Upon questioning these individuals revealed that all of them ate red meat without any acute or delayed consequences.

Discussion

We show here for the first time that IgE antibodies against α -Gal seem not to be the underlying cause of CSU. The 3 patients with IgE against α -Gal all ate red meat without having any acute or delayed symptoms. Commins et al. [9] have reported that α -Gal titres among anaphylaxis-urticaria patients with red meat allergy make up at least 10% (or 30%) of total serum IgE. Upon investigating the fraction of α -Gal IgE to total IgE among our 3 patients, we found that it was less than 2%, supporting that the low titres we observed are not related to red meat allergy. Furthermore, red meat-allergic patients in Sweden suffer from intermittent urticaria, and they also report gastrointestinal symptoms, which was not the case with the CSU patients. Even though CSU seems to have an IgE-dependent mechanism, α -Gal seems not to be the target of IgE, which is an important message in the management of CSU patients.

Furthermore, 4% of the CSU patients had IgE to α -Gal which is in line with the incidence of IgE antibodies to α -Gal in the general population, where 10% (15/143) of healthy Swedish blood donors were shown to be sensitized to α -Gal [2]. This was also noted in a recent study among 2,297 Danish and 444 Spanish randomly selected adults who showed a frequency of α -Gal IgE of 5.5 and 8.1%, respectively [10]. Interestingly, the authors concluded that presence of α -Gal IgE antibodies is associated with a history of tick bites, atopy and cat ownership. The latter observation probably reflects sensitization to cat IgA which carries α -Gal [11].

Conclusions

Our results indicate that an allergic response to α -Gal is highly unlikely to be a hitherto unrecognized common cause of CSU.

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Disclosure Statement

None of the authors disclose a conflict of interest.

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