

学位論文の要旨

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学位論文名 Cohort Study of Subclinical Sensitization Against Galactose- α -1,3-galactose in Japan: Prevalence and Regional Variations

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論文内容の要旨

INTRODUCTION

Sensitization to galactose- α -1,3-galactose (α -Gal) leads to the development of α -Gal syndrome, which includes red meat allergy and cetuximab-induced anaphylaxis. Cetuximab contains glycosylation sites, including the α -Gal site in the Fab region. The late-onset urticaria and anaphylaxis that occurred 3–6 h after red meat consumption are mediated by IgE specific to the α -Gal carbohydrate structure, similar to that in cetuximab allergy. Several studies showed that tick bites are involved in the development of red-meat allergy via sensitization to α -Gal, because the salivary gland or the gastrointestinal tract of tick contains α -Gal-bearing proteins. Since tick bites represent the main cause of α -Gal sensitization, it was speculated that sensitization to α -Gal occurs throughout Japan. However, few cohort studies have investigated α -Gal sensitization in Japan. Since we have identified certain cases of cetuximab allergy even without a previous history of red meat allergy, it is of clinical interest to determine the prevalence of sensitization to α -Gal for predicting the risk of allergic reactions before cetuximab administration. Therefore, we aimed to elucidate the subclinical sensitization rate to α -Gal in Japan.

MATERIALS AND METHODS

We randomly recruited 100 participants each from Shimane University Hospital (Shimane prefecture), Tokyo Medical and Dental University Hospital (Tokyo metropolis), and Tohoku

University Hospital (Miyagi prefecture), for a total of 300 participants. Clinical information from the participants was collected using a questionnaire. ImmunoCAP-bovine thyroglobulin (BTG) with cetuximab immunoblotting and ImmunoCAP-beef were used to quantify α -Gal-specific and beef-specific IgE, respectively. One-way analysis of variance and the post hoc Tukey multiple comparison or Games–Howell test were used to compare the positive rates among hospitals. The chi-square test was used to investigate the association of clinical factors with positivity for α -Gal-specific IgE and/or beef-specific IgE. Pearson’s correlation analysis was used to confirm the correlation between the two parameters. The study protocol was approved by the Ethics Committee of Shimane University (approval nos. 1788 and 4278). The purpose and procedures of the study were explained to eligible participants and written informed consent was obtained from each participant.

RESULTS AND DISCUSSION

We employed three different tests to clarify the subclinical sensitization to α -Gal; BTG-specific IgE test, beef-specific IgE test, and cetuximab IgE immunoblotting. As a result, we demonstrated that the prevalence of sensitization to α -Gal is 4.0% in Japan using BTG-specific IgE test in the investigation of three institutes covering Shimane Prefecture (western part), Tokyo Metropolis (central part), and Miyagi Prefecture (northern part) of Japan. True sensitization to α -Gal seems to be lower than 4.0%, since positive rate using cetuximab IgE immunoblotting was 2.7% and rate for both positive BTG-specific IgE and positive cetuximab-immunoblotting was 2.0%. Namely, overall sensitization rate to α -Gal is calculated to be 2.0-4.0% in Japan. This overall positive rate is comparable to the α -Gal-sensitization rates in the previous reports which were 1.8% in Denmark and 2.2% in Spain. These results indicate that α -Gal sensitization has worldwide distribution, although the rates vary among different regions. The difference became obvious when the sensitization was evaluated using ImmunoCAP-BTG combined with cetuximab-immunoblotting. In our study, the sensitization rate was the highest in Shimane Prefecture (5.0%) and lowest in Tohoku Region (0.0%). Sensitization to α -Gal is thought to be caused mainly by tick bites and, thus, the higher sensitization rate may be due to the higher chance of tick bites. The participants examined at Shimane University Hospital possibly had a higher incidence of tick bites, because forest area constitutes more than 80% of the Shimane Prefecture.

In contrast, ImmunoCAP-beef positivity rates were 4.0%, 19.0%, and 6.0% in Shimane University Hospital, Tokyo Medical and Dental University Hospital, and Tohoku University Hospital, respectively, with significant inter-institute differences. The discrepancy in these results between the two tests may be attributed to different sensitization routes and different causative allergens; tick bites might be the main cause of sensitization in the Shimane area, whereas

gastrointestinal absorption of beef allergens might be the predominant route for beef-sensitization in the Tokyo and Miyagi areas.

The other aspect of our study was the association between positive beef-specific IgE and male sex, although no association was found between positive BTG-specific IgE test and sex. Although there is no evidence of an association of α -Gal syndrome with difference in sex, a primary beef allergy can occur more frequently in males.

CONCLUSION

the prevalence of subclinical sensitization to α -Gal is likely to be 2.0-4.0% in Japan and high in Shimane prefecture. The risk of hypersensitivity reactions to cetuximab and/or red meat should be carefully evaluated, even in subjects without a history of red meat allergy, especially in rural areas, such as Shimane prefecture. By contrast, the prevalence of IgE sensitization to beef is high in the Tokyo Metropolis, suggesting an association with gastrointestinal sensitization against beef, predominantly in male participants and regardless of tick bites.