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Review

Alpha-Gal Syndrome

Mine Ün[1], Selen Dağaşan[2]

ABSTRACT

Galactose-alpha-1,3-galactose (alpha-gal) is a typical glycoprotein found in mammals except humans and primates. Since humans and primates have lost the galactosyltransferase enzyme in the evolutionary process, the immune system perceives the α-gal glycoprotein as a foreign body and creates an immune response. In recent years, it has been identified that this mammalian oligosaccharide epitope triggers a newly discovered IgE - mediated antibody response in the body and the associated disease is called Alpha-gal Syndrome. Alpha-gal syndrome is observed in 3 types of cases in the clinic: It presents as the observation of a delayed type-1 allergic reaction within 3-6 hours after the consumption of mammalian products rich in alpha gal, after drug use, and as a result of a tick bite. In this review, alpha Gal syndrome was examined in detail and the possible relationship between the Bourbon virus associated with the lone star tick (A. americanum) and alpha Gal syndrome is described.

Keywords: Allergy, alpha-gal syndrome, bourbon virüs, red meat.

IMMUNOGLOBINS

Immunoglobins are a type of glycoprotein, developed by the immune systems of some multicellular organisms that act against organic structures they encounter, that they perceive as foreign bodies. B lymphocytes turn into plasma cells and synthesize these antigen-specific molecules which help the human body mediate its response.[1]

Immunoglobins consist of 4 polypeptide chains, two heavy (H) and two light (L) chains. The Fab section of the molecule, composed of L and H chains is involved in antigen binding and presents with a modifiable structure. On the other hand, the Fc section consists only of heavy (H) chain and fulfills biological functions. There are 5 main immunoglobin types; IgG, IgM, IgA, IgD, and IgE, whose differences are only presented by the differences of amino acid sequences in their heavy and light chains.[1]

ALPHA-GAL SYNDROME

Landstreiner,[2] while defining the ABO blood group system, reported that there is a substance similar to the blood group antigen B on mammalian cells and that antibodies are formed against this substance in individuals with immune system deficiencies. It was later determined that this substance is the alpha-gal glycoprotein.[3-6]

Galactose-alpha-1,3-galactose (alpha-gal) is a typical glycoprotein found in certain mammals[7] but humans and primates seem to have lost the galactosyltransferase enzyme required for α-Gal production in the evolutionary process. Therefore, the immune system perceives the α-gal glycoprotein as a foreign body and creates an immune response. This is a well recognized obstacle in xenotransplantation where xenoreactive native antibodies directed against alpha gal molecules induce a process of organ rejection. Antibody response to alpha-gal is mediated by around 1% of the total immunoglobulin reserve of the body and recent studies show that IgG antibodies are observed in relatively low amounts during this reaction.[5,8]

In recent years, it has been identified that this mammalian oligosaccharide epitope triggers a rather

[1]Istanbul Aydın University, Faculty of Medicine Istanbul, Turkey
[2]Trakya University, Faculty of Nutrition and Dietetics, Edirne, Turkey

Correspondence: Mine Ün. İstanbul Aydın Üniversitesi Tıp Fakültesi, 34295 Sefaköy, Küçükçekmece, İstanbul, Türkiye.

E-mail: unmine13@gmail.com

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IgE-mediated antibody response and the disease associated with this condition is called alpha-gal syndrome. According to the WHO/IUIS data, it has been found that, even though the reaction is mostly instigated against the epitope of the molecule that is in protein structure, rather than against its carbohydrate portions, Alpha gal Syndrome is made unique in a way that it involves a rare type-1 hypersensitivity against a carbohydrate. Cases have been identified in the Southeast USA, in Europe, Asia, Scandinavia and Austria with an increasing prevalence seen in immunology clinics.[5,9-11]

Alpha-gal Syndrome is clinically observed in three types of cases involving delayed type 1 allergic reactions that usually occur within 3-6 hours after exposure: first and most commonly, after the consumption of a food product rich in alpha-gal; secondly, after drug use, and lastly, against a tick bite.[7,12,13]

1- Red meat consumption and Alpha-gal Syndrome

Alpha Gal Syndrome first emerged among patients who presented to the clinic with general urticaria, angioedema and recurrent anaphylactic attacks between 2006-2008. Most of these patients in the US reported from Georgia, South Carolina, Mississippi, Kentucky, Oklahoma, Texas, and West Virginia with a common point in their medical histories: They were all found to have consumed beef, pork or lamb 3-6 hours before their symptoms presented and they could all consume meat without any problem before.[11,14] Micro-punctures were made in the skin by prick test and commercial beef, pork or lamb extracts were applied in layers. After an average of 10-20 minutes, the reactions on the skin were tested but the results turned out negative. The syndrome was then only confirmed by applying specific IgE Ab and red meat blood tests.[14]

Alpha Gal Syndrome is also commonly referred as some sort of red meat allergy as well and the characteristics of such a red meat allergy are different from some other typical allergic reactions we see in the clinic in a way that it presents with additional gastrointestinal complaints and urticaria and the patients are usually found to experience symptoms 3-5 hours after consuming red meat. But the fact that symptoms don't occur every time after allergen consumption, indicates a dose-dependent nature to the syndrome.[15]

At first, a large number of researchers investigated the source of the syndrome, in the form of a common allergen that was supposed to be present in beef, pork and lamb, but investigations yielded no useful results. 7 different types of alpha-gal structures containing glycoproteins that were found to be heat - resistant had been identified in beef, only.[11,16] a Not only that the common structure of alpha-gal on various types of red meat is still unknown, it is also not clear whether these structural variations affect IgE binding on the patient.[11]

As the challenges of this syndrome is still persistent, individual counseling for allergens and oral food challenges (ingesting high doses of a suspected allergen in a controlled manner) have diagnostic significance for the patients' prognoses. These diagnostic procedures should be overseen by healthcare professionals working in the emergency department, since the reactions to the allergens develop only in time. Associated factors of the syndrome like physical exercise, alcohol consumption, non-steroidal anti-inflammatory drug usage etc. should also be taken under consideration to see if they contribute to the development of the allergic reaction after the consumption of the red meat product. The type of red meat consumed plays a huge role in the severity of the reaction, too: In a study conducted in France, it was reported that kidney tissue contains higher amounts a-gal compared to muscle tissue when eaten and α-Gal is absorbed more rapidly from the intestines, compared to the other components of the meal, too.[7,17]

2- Drug use and Alpha-gal Syndrome

Alpha Gal Syndrome has also been observed to be induced as a result of IV administration of certain drugs like Cetuximab and gelatin-based colloids, since these drugs were derived from mammalian tissues that contain alpha gal as well.[7]

Cetuximab is a chimeric mouse - human IgG monoclonal antibody designed against the epidermal growth factor receptor (EGFR).[7] It has been approved for use in the treatment of metastatic colorectal cancer and in the squamous cell carcinomas of the head & neck.[18-20] During clinical trials of cetuximab, the antibody was found to cause hypersensitivity reactions and patients developed symptoms within 20 minutes following the first infusion of the antibody. It has been observed that patients reacting to drugs had IgE antibodies developed before even starting the treatment.[19,21] In subsequent studies, as a result of the glycosylation characteristic of cetuximab, 21 separate oligosaccharide structures, out of which approximately 30% had 1 or more alpha-1,3-linked galactosyl residues, emerged, which lead

to the establishment of a correlation between IgE antibodies and alpha gal epitopes.[13]

Some common vaccines typically include gelatin as a product derived from mammalian tissues. The highest concentration of gelatin found in vaccines is belong to the MMR and live attenuated herpes zoster. Case reports emphasize that the herpes zoster vaccine is found to be more reactive in patients with alpha-gal allergy.[5]

Tick bite and Alpha-gal Syndrome

The relationship between tick bites and red meat allergy was first proposed in Australia but the involvement of a-gal molecule in this had not yet been fully established. Since Rocky Mountain Spotted Fever (RMSF) is found linked with the syndrome, and is very common in Australia, associated tick vectors like Dermacentor variabilis (brown dog tick) and Amblyomma americanum (lone star tick) have been under the spotlight as prime suspects of this correlation.[6]

A relationship was found between increased a - gal IgE levels associated with extracts of the lone star tick (Amblyomma americanum) in an individual with red meat allergy which led to the establishment of a correlation between the history of tick bites and α-gal IgE levels. In addition, it has been reported that IgE titers increasee 4-10 times against a-gal in individuals who receive consecutive tick bites.[22,23]

Similarly, another tick thought to be associated with alpha-gal is Ixodes scapularis. It contains the pathogen responsible for Lyme disease and the a-gal sensitivity. In a study conducted in Sweden, a-gal IgE titers were evaluated in people with Lyme disease, but sensitivity to the allergen was found minimal compared to the control group and related titers were found to be within normal parameters.[24]

The connection between ticks and α-gal was originally identified with A.americanum in the USA, while cases associated with the discovery were reported in Australia, Europe, Japan, South Korea and Central America.[16,25,26] Even though species vary among regions, tick – borne infections were found endemic in all of the aforementioned locations. For instance, α-gal IgE sensitivity in southern Sweden is commonly associated with bites of Ixodes ricinus and the presence of a-gal in I.ricinus has been proven in later studies as well.[27,28]

There were certain theories suggested on how tick bites can lead to an IgE response and a prominent explanation has been about the components of the saliva produced by the tick causing the reaction. This suggestion was backed up by alpha-gal molecules being identified in the saliva of A.Americanum.[23,29] Some of the other hypothesized theories were on mammalian glycoproteins or glycolipids present in the tick triggering the reaction independently from the tick's own materials and the reaction being induced by another organism present in the tick, like the strains of Rickettsia or B.burgdorpheri found in A.americanum.[23]

Bourbon Virus and Alpha-Gal Syndrome

Bourbon virus (BRBV) was first isolated from a febrile patient with a history of tick bites in Bourbon County in the USA in 2014, and the patient died in the following days.[30] Later, BRBV infection was reported in various parts of the USA.[31] In 2015, a patient living in Oklahoma was tested positive for BRBV antibodies before fully recovering.[32]

Bourbon virus is an RNA virus belonging to the genus Thagotovirus from the Orthomyxoviridae family.[32] Thogoto and dhori viruses of the Thagotovirus genus have been associated with human diseases. Viruses of this category are associated with and disseminated by hard or soft ticks. Recent studies show that the lone aster tick (A.Americanum), associated with Alpha-gal syndrome, carries BRBV. These ticks feed on mammals that may play a role in their BRBV transmission.[31-33] The direct relationship of the Bourbon virus with Alpha-gal syndrome has not yet been completely identified and adequate amount of studies have not yet been performed. Given the role of lone star ticks (A. Americanum) in transmitting and spreading the bourbon virus, it is possible that they may also play a role in inducing alpha-gal syndrome.[31-33]

Conclusions

Alpha-gal syndrome is a recently identified food allergy with an Ig E-mediated antibody response to alpha-gal (galactose-1,3-galactose), a typical mammalian glycoprotein. The alpha-gal glycoprotein, found in all mammals except humans and primates, due to the absence of the galactosyltransferase enzyme, creates an immune response in the human body. It is characterized by a type-1 hypersensitivity reaction to the protein and the carbohydrate epitopes of the allergen in a delayed (3-6 hours) manner. Alpha-gal Syndrome is clinically observed upon consumption of a food product rich in alpha-gal (mammalian meat, organs and blood), after drug use (cetuximab and gelatin-based colloids) and associated with a tick bite (such as A. americanum).

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