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EDITORIAL

Diarrhoea due to allergy to egg: Is there a role for specific IgG?

Food allergy is the reproducible clinical manifestation after ingestion, contact or inhalation of a food allergen and caused by an anomalous immunological response. Depending on the principal immunological mechanism involved, food allergy is subdivided into that mediated by IgE, that mediated by cells (T-lymphocytes), and that with a mixed, humoural and cellular component.[1,2]

The most frequent food allergy in children is allergy to egg, mostly IgE mediated.[3] Its estimated prevalence varies according to age and population, in the first two years of life it is 1% in the USA[4] and 1.6% in Norway,[5] reaching 9% in an Australian population study[6] in the first year of life. The natural evolution of egg allergy is to resolution: in a study in the Spanish population this was 66% at 60 months of age,[7] although somewhat less, 49% at 72 months, in a recent study[8] in the USA. Moreover, up to two of every three patients who are allergic to egg will tolerate extensively cooked egg,[9] with this acquired tolerance being observed up to the age of 13 years.[10]

Depending on the immunological pathways implicated, egg allergy presents in different clinical forms or syndromes, which are not always well delimited, and many of them involve a digestive pathology.[1] IgE-mediated reactions appear rapidly, generally within the first hour after ingestion, and may include gastrointestinal affectation, generally manifested by vomiting and abdominalgia, above all when a multisystemic or anaphylactic reaction occurs.

Non-IgE-mediated reactions occur later and more frequently affect the digestive system, with egg allergy being the cause of up to 11% of food protein-induced enterocolitis syndromes (FPIES),[11] in the majority of cases with a low incidence and a favourable resolution,[12] but references to it are on the rise and are of great importance due to its seriousness and the difficulty to diagnose, given its low suspicion index. However, egg allergy is not associated to food protein-induced coloproctitis, which is more common at ages prior to the habitual introduction of this food. Enteropathy induced by food proteins is the most frequent manifestation within this non-IgE group, but is infrequent for egg allergy.

There is also a group with clinical manifestations which are predominately gastrointestinal and of slow presentation, in which there are alterations in cell and on occasions also humoural immunity, with an increase of specific IgE, such as eosinophilic oesophagitis, in which egg allergy has been established as the cause in 16%of the cases in children[13] and 26% in adults[14], and eosinophilic gastroenteritis, a rare cause of diarrhoea which is accompanied by eosinophilia in peripheral blood in 20–80% of cases,[15] although without a clear relationship with egg allergy.

The altered immunological response in each clinical entity is what orients towards the best route to follow for its diagnosis.[3] When an IgE-mediated reaction to egg is suspected, the diagnosis is based on its detection in the patient, using skin tests or serology, which will only indicate sensitisation. The evidence of repeated and recent reactions with this food or by checking using the controlled oral provocation test, habitually open and in the cases where it is advised, or in studies using the double-blind placebo-controlled technique[16]; positivity will assure it is that food which caused the referred pathology. A new generation of tests for specific IgE, which detect the allergenic components of the food allergy sources has opened a new way of focusing the diagnosis, prognosis and therapeutical management of IgE-mediated food allergy, the so-called component-resolved diagnostics (CRD),[17] whose application for egg allergy has been revised[18]; microarray techniques are available for a personalised focus for food allergy.[19]

In non-IgE mediated food allergy, the use of skin tests with foods is controversial in eosinophilic oesophagitis,[13] with their diagnostic performance in FPIES not being shown, according to a recent study.[20] In eosinophilic pathologies the diagnosis is based on biopsy and detecting the increase in eosinophiles at local level (more than 15 per field at great magnification, ×400), and although specific IgE can be found against certain foods, orienting towards the implicated food, only the exclusion of the suspected food and more frequently by means of an elimination diet and the reappearance of the alterations following its reintroduction

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will be of use for the aetiological diagnosis in up to 74% of paediatric cases.

In patients with food allergy which is not by an IgE mechanism, there is no analytical determination technique or any other type of complementary examination for use in clinical practice which indicates that a suspected food caused the disease, only following the removal and subsequent reintroduction with an exposure test, can we be sure what the causal factor is. Attempts to resolve this difficulty in diagnosis have been made using the assessment of different components of the immune system implicated in allergy: basophile activation test, products from cellular activation (calprotectin, interleukins, etc.), as well as other immunoglobulins which detect food antigens, particularly those of the different subclasses of IgG.

The humoural response to the food antigen involves antibodies of the isotypes IgE, IgA and IgG and their subclasses, with differing functions and evolution, responding differently depending on the food antigen. The production of IgG is a normal response in the face of food antigens; a great number of people who tolerate them can be detected.[21]

Children with cow's milk allergy have lower levels of IgA and IgG than non-allergic children probably when they cease to ingest cow's milk after its initial introduction. On the other hand infants with higher levels of IgG1 against ovalbumin (OVA) and lower levels in the relationship IgG4/IgE are at greater risk from atopic diseases.[22] Patients whose allergy to egg white was persistent had a higher level of specific IgG against OVA compared to those whose allergy was transitory.[23]

Conversely, one study[24] concluded that the determination of IgG and specific IgG4 for egg did not provide additional information for the diagnosis of egg allergy in children, and did not advise routine determination. In another study[25] the levels of specific IgG4 against OVA and against ovomucoid were not related with the response to cooked egg in allergic patients, with the tolerance not being predictive; thus, the determination of specific IgG4 levels for egg was not advisable in clinical practice. The low diagnostic performance of this technique has led to the guides from different scientific societies[2,26,27] not recommending its use in clinical practice.

The current issue of Allergologia et Immunopathologia presents a study[28] in which the levels in blood of eosinophiles; total IgE; IgE; and specific IgG against egg white are determined in 89 patients diagnosed with egg allergy with diarrhoea following ingestion, comparing the results with a group of 45 healthy individuals. The principal results were that the control group had IgG against egg white below 50 U/mL (value established as negative or the lower limit), a statistically significant 54% increase in total IgE, in specific IgE of 28% and in specific IgG of 100% of those patients who had been diagnosed with egg allergy, without the existence of differences regarding the frequency of peripheral eosinophilia, with respect to the healthy group. The younger the age of the patients the higher the level of specific IgE was. Correlation was also found between the levels of total and specific IgE and of eosinophiles with the level of specific IgG.

Having grouped the patients by the symptom of diarrhoea, information is not available related to which nosological group each patient belonged to, although it groups together both immediate and late reactions, which implies different immunological pathogen mechanisms.

However, the determination of total specific IgG and not its subclasses impedes distinguishing between those with elevated IgG4, associated to food tolerance, in particular in the case of egg this has been checked in induction to tolerance tests, and other subclasses, in particular IgG1, which on occasions has been associated to extradigestive pathologies.

In IgE-mediated allergies the patient may even tolerate cooked egg, which will produce an IgG4 protective response and in non-IgE mediated patients, in their different forms, they may tolerate different amounts of egg without clinical manifestation; this means that high levels of IgG may appear which are not indicative of allergy but of low tolerance.

Some patients could even be cases of irritable intestine syndrome, since although they are not allergic on occasions their symptoms are associated to certain foods, but significant differences have not been found in the levels of IgG and specific IgG4 against egg white and yolk in this type of patients with respect to healthy controls.[29] The eosinophilia may have other causes, the most frequent of which are parasites and atopic dermatitis, associated to patients who are allergic to egg.

From the above, the results, although different to the control group, are not conclusive regarding the usefulness of pre-testing to determine specific IgG against egg white. Until further data are available the recommendation that different scientific groups indicate is maintained until new research can provide evidence of its usefulness and therefore, IgG to foods: a test not ready for prime time.[30]

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José Manuel Lucas Moreno*
Sección Alergia Pediátrica, Servicio de Pediatría, Hospital Clínico Universitario Virgen Arrixaca, Murcia, Spain

* Corresponding author.
E-mail address: jm-lucas@telefonica.net