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EGG-INDUCED ADULT FOOD PROTEIN-INDUCED ENTEROCOLITIS: CLINICAL PHENOTYPES, NATURAL HISTORY AND IMMUNOLOGICAL CHARACTERISTICS

Purificación Gonzalez-Delgado, MD, PhD, Sara Anvari, MD, MSc, Jordi Barrachina, PhD, Ana I. Jimenez Portillo, MD, Teodorikez Jimenez, MD, PhD, Francisco M. Marco de la Calle, MD, PhD, Javier Fernandez, MD, PhD

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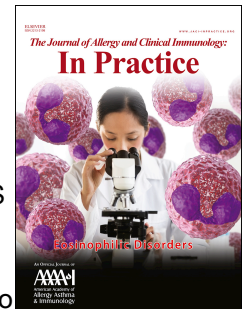
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3 **CHARACTERISTICS**

4

5 **Purificación Gonzalez-Delgado** MD, PhD^{1,2}, **Sara Anvari** MD, MSc^{3,4}, **Jordi**
6 **Barrachina** PhD², **Ana I. Jimenez Portillo** MD⁵, **Teodorikez Jimenez** MD,
7 PhD¹, **Francisco M Marco de la Calle** MD, PhD⁵, **Javier Fernandez** MD,
8 PhD^{1,2}.

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10 ¹ Allergy Service, Alicante General University Hospital, Alicante Institute for Health and
11 Biomedical Research (ISABIAL), Alicante, Spain.

12 ² Clinical Medicine Department, University Miguel Hernández, San Juan, Alicante, Spain

13 ³ Baylor College of Medicine, Texas Children's Hospital, Department of Pediatrics,
14 Division of Immunology, Allergy and Retrovirology, Houston, TX

15 ⁴ Texas Children's Hospital, William T. Shearer Center for Human Immunobiology,
16 Houston, TX

17 ⁵ Immunology Service. Alicante General University Hospital, Alicante Institute for Health
18 and Biomedical Research (ISABIAL), Alicante, Spain

19 **Correspondence**

20 Purificación González-Delgado

21 Servicio de Alergia. Hospital General Universitario Dr. Balmis de Alicante.

22 C/ Pintor Baeza 11, Alicante. Spain 03010

23 +34 965913771

24 purifica60@gmail.com

25 Purificación González-Delgado purifica60@gmail.com ORCID: 0000-0002-1192-8475

26 Jordi Barrachina jordibernabeu15@gmail.com ORCID: 0000-0002-4697-2783

27 Ana Jiménez-Portillo anajimenezportillo@gmail.com ORCID: 0000-0002-6439-4948

28 Francisco Marco de la Torre marco_fradela@gva.es ORCID: 0000-0001-5113-3637

29 Teodorikez Jiménez teodorikez@gmail.com ORCID: 0000-0002-4341-0507

30 Javier Fernández fj.fernandez@umh.es ORCID: 0000-0003-1065-7199

31 Sara Anvari Sara.Anvari@bcm.edu ORCID 0000-0002-9942-6188

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41 **Statement of Ethics**

42 This study was approved by the Ethics Committee of Alicante and was conducted

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**EGG-INDUCED ADULT FOOD PROTEIN-INDUCED ENTEROCOLITIS:
CLINICAL PHENOTYPES, NATURAL HISTORY AND IMMUNOLOGICAL
CHARACTERISTICS**

Clinical Implications:

Egg is an important FPIES food trigger in adults. Diagnosis requires a high index of suspicion when adult patients present with recurrent delayed gastrointestinal symptoms. Similar to pediatric FPIES, we observed an increase in IL-17 following a positive oral food challenge.

KEY WORDS

Food allergy, FPIES, adult FPIES, Food protein–induced enterocolitis syndrome, egg FPIES, irritable bowel syndrome, non-IgE food allergy.

56 In the initial reports of adult food protein-induced enterocolitis (FPIES), seafood
57 was the most common food implicated.^{1,2} However, in the last few years, egg has
58 been increasingly recognized as an FPIES food trigger in adults.^{3,4,5} We examine
59 the clinical characteristics and natural evolution of adults with egg FPIES and
60 examine the immunological changes during oral food challenges (OFCs).

61 We conducted an 8-year prospective study in adults diagnosed with acute FPIES
62 to egg who were admitted to the Allergy Unit of the Alicante General Hospital.
63 Inclusion criteria for adult egg FPIES was based on previously proposed criteria.⁴
64 Informed consent was obtained prior to study enrollment.

65 Open OFCs were performed to confirm diagnosis or resolution of egg FPIES if
66 no accidental exposures with subsequent reactions had occurred in the last 18
67 months. At initial diagnosis and prior to all OFCs, we performed skin prick test
68 and/or specific IgE to egg, as the presence of specific IgE has been associated
69 with a protracted course, in the pediatric FPIES population.⁶ OFCs with IV
70 placement were performed in the day hospital unit. The total serving size (one
71 egg; 7g protein) was divided into 2 doses. The first dose was 25% of the total
72 amount followed by a 2-hour observation and the remaining dose was given
73 followed by a 4-hour observation period. OFCs were carried out with the same
74 form of egg that triggered symptoms (fried egg, boiled egg, scrambled egg and
75 baked egg). An egg OFC was also carried out in a control population who
76 consumed egg regularly but had FPIES to other foods. A complete blood count
77 with differential was obtained before the OFC (T1) and 2-hours after symptom
78 onset (T2).

Cytokine and chemokine variations were analysed in patients with positive OFC and in the control population at T1 and T2 (in controls prior to discharge, 4 hours post-challenge). Cytokine and chemokine were measured by flow cytometry (D Biosciences Kit) and included: IL-12p70, TNF- α , IL-10, IL-6, IL-1 β , IL-8, IL-17, IFN- γ and IL-4. Patients who passed the OFC were contacted 24-hours and 30-days post-challenge to determine if they had delayed symptoms and whether they were regularly consuming egg.

A total of 30 adults with egg FPIES were enrolled. Demographic and clinical history are outlined in Table 1. Sixty-three percent reported FPIES symptoms only to egg, 37% reported symptoms with egg and other foods or food groups. Sixty percent of patients were referred from primary care and 40% from the gastroenterology service, of which 5 patients had been initially diagnosed with irritable bowel syndrome (IBS). These 5 individuals had undergone extensive studies for their symptoms (including endoscopy and colonoscopy with biopsy) but after an exhaustive clinical history, patients related the possible implication of foods, and were referred to our Allergy section. Patients kept a dietetic diary and excluded egg and in some cases also avoided other foods from the diet which led to resolution of symptoms. An OFC confirmed egg as the triggering food in these 5 patients. A diagnostic OFC also confirmed implication of other foods different to egg.

A total of 22 OFCs with egg were conducted, 17 in egg FPIES patients and 5 in controls. OFCs were negative in the control group. In the egg FPIES group, 13 OFCs were performed to confirm diagnosis and 4 OFCs were to assess for egg tolerance (a prior diagnosis was made based on clinical history with multiple episodes of egg FPIES reactions and remission of symptoms with avoidance). For

patients who were not challenged, this was due to a recent egg FPIES reaction. Fourteen OFCs were positive. Symptoms included colicky abdominal pain (100%), nausea (78%), vomiting (43%), and diarrhea (71%). Six patients reported weakness, and 4 were noted to have bradycardia and hypotension. No immediate symptoms were observed in patients with detectable egg-specific IgE.

Pre- and post-OFC serum samples were available for 11 egg OFC reactors, and 5 patients with non-egg FPIES diagnosis (controls). Patients with a positive OFC, showed a statistically significant increase in IL-17 at T2 compared to baseline levels (T1); an elevation in IL-6 and IL-10 was also observed but not statistically significant in T2 compared to T1. Samples obtained from controls (T1 and T2) did not demonstrate significant cytokine elevation (Figure 1). An increase in neutrophil count of more than 1000 cells/mL above baseline was observed in 7 OFC reactors at T2.

Patients were followed up for a median of 5 years [IQR: 3-8 years]. Five patients (17%) developed resolution of their egg FPIES and were able to consume eggs on a regular basis after a median duration of 3.5 years [IQR: 2-8]. Tolerance was confirmed by OFC in 3 patients, the other 2, by accidental or deliberate egg intake at home.

Vomiting, the main criterion for FPIES according to the international guidelines⁶ was absent in up to 50% of adult patients with egg FPIES. Abdominal pain was the most common manifestation, in positive OFC, followed by nausea and diarrhea, findings common to other adult series of FPIES.^{4,7}

Several clinical profiles have been observed, from patients who cannot tolerate small traces of well-cooked egg to others that have symptoms only with raw or

undercooked egg. This observation would suggest that the same proteins that trigger an IgE-mediated egg allergy could be implicated in triggering egg FPIES symptoms.

Interestingly, 37% of our cohort of patients with egg FPIES, also experienced FPIES to other unrelated foods, such as seafood, dairy, nuts, or fruit. The coexistence of FPIES to foods other than egg, has led to some of these patients experiencing almost daily gastrointestinal symptoms with chronic abdominal pain, diarrhea, and sporadic emesis and were previously misdiagnosed with IBS.

A tendency of disease persistence has been reported in adult FPIES.¹ However, 17% of patients in our series, developed resolution of their egg FPIES, with total tolerance to egg. Moreover, 10% of our cohort demonstrated a trend towards symptom improvement, with tolerance to some forms of eggs that were not previously tolerated. These findings are in accordance to recent reports of adult FPIES.^{4,7}

A significant elevation in IL-17 was detected in patients experiencing a positive OFC, at T2, compared to baseline. In a study of children and adolescents up to 16 years, Berin et al.⁸ reported that FPIES OFCs were associated with significant elevation of cytokines and chemokines including IL-17, markers of T-cell activation (IL-2), and innate inflammatory markers (IL-8, oncostatin M, LIF, TNF α , IL-10, IL-6). In our patients, a slight increase in IL-6 and IL-10 were also observed but this was not statistically significant. Our findings would suggest the same mechanism that is observed in the pediatric FPIES population.

Open OFCs were performed, as previously reported.^{6,9} However, in patients with recurrent symptoms where more than one implicated FPIES food trigger exists, a placebo-controlled challenge should be considered.

In conclusion, egg is an important FPIES food trigger in adults. Our work is the first to demonstrate an elevation of IL-17 following a positive OFC in adult FPIES patients. This is similar to findings seen in pediatric FPIES patients. Our findings support the potential pathological mechanism implicated in FPIES. However, larger studies are needed to identify biomarkers to aid in the diagnosis or resolution of FPIES.

This work emphasizes the importance of suspecting FPIES in adults with recurrent symptoms after ingestion of foods containing the same ingredient. A diagnosis of egg FPIES may be difficult to obtain initially, as egg is a ubiquitous ingredient and individuals may react to either the baked and/or unbaked forms of egg. Thus, clinicians should have a high index of suspicion when an adult patient presents with recurrent delayed gastrointestinal symptoms following the ingestion of foods containing egg.

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196 **Figure 1.-** Differences in interleukin concentrations in cases and controls at T1 (baseline) and
197 T2 (2 hours after symptom onset). In controls, blood was taken at baseline (T1) and 4 hours
198 after challenge (T2). IL: Interleukin; ** means p-value <0.001

199 **Table 1: Clinical data in adult patients with egg FPIES**

Characteristics	Cohort
Sex n (%)	
Male	3 (10)
Female	27 (90)
Age at first reaction (y), median (IQ ₂₅₋₇₅)	33 (23-40)
Age at diagnosis (y), median (IQ ₂₅₋₇₅)	34 (24-43)
Delay to diagnosis (y), median (IQ ₂₅₋₇₅)	2 (1-3)
Time of follow-up (y), median (IQ ₂₅₋₇₅)	5 (3-8)
Number of episodes, median (IQ ₂₅₋₇₅)	7 (5-10)
Latency period (min), median (IQ ₂₅₋₇₅)	60 (45-120)
Patients referred from (n, %)	
Primary care	18 (60)
Gastroenterology	12 (40)
Manifestations (n, %)	
Abdominal pain	29 (97)
Diarrhea	26 (87)
Nausea	21 (70)
Vomiting	18 (60)
Weakness	10 (33)
Lethargy	10 (33)
Chills	8 (27)
Emergency department, n (%)	5 (17)
FPIES to egg only	19 (63)
FPIES to egg and 1 food/food group	8 (27)
FPIES to egg and 2+ food /food group	3 (10)
Egg Sensitization Testing	
Positive egg skin prick testing n (%)	0 (0)
Positive egg specific IgE testing n (%)	4 (13)
Egg IgE values kU/L (Q ₂₅₋₇₅)	1.01 (0.74-2.05)
Atopy (n, %)	17 (63)
Allergic rhinitis	15 (50)
Asthma	7 (23)

Atopic dermatitis	2 (7)
IgE mediated food allergy to other foods	5 (17)
Eosinophilic esophagitis	1(3)
Intestinal associated conditions (n, %)	
Celiac disease	1 (3)
Helicobacter pylori	7 (23)

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201

202

Figure 1

