Are The Proton Pump Inhibitor-Responsive And Non-Responsive Phenotypes Of Eosinophilic Esophagitis Exactly The Same?

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A new conceptual definition of eosinophilic esophagitis (EoE) was proposed in the 2011 consensus and a new potential disease phenotype, the proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) was also recognized [1]. EoE was defined as a clinicopathological condition, antigen driven, characterized clinically by symptoms of esophageal dysfunction and histologically by ≥15 eosinophils per high power field (eos/hpf), and after a comprehensive assessment of non-EoE disorders that could cause esophageal eosinophilia [2]

EoE and PPI-REE were considered separate clinical entities as they showed a different response to the PPI trial. Later, the experts proposed not to include the responsiveness to a PPI as a diagnostic criterion and, consequently, avoiding the term PPI-REE for those subjects that have an EoE phenotype with both histological and clinical response to PPI therapy [3]. Currently, they advise to call these two phenotypes as responding EoE (R-EoE) and not responding EoE to PPI (NR-EoE).

Although not all experts agree, recent and evolving evidence, mostly from adults, shows that PPI-REE and EoE patients are clinically, endoscopically and histologically indistinguishable, with features of Th2 immune-mediated inflammation and gene expression [3].A Spanish study concludes that, both phenotypes of EoE share sensitization profiles with only slight differences [4]

There are few any studies on whether both phenotypes (R-EoE and NR-EoE), are identical in allergic characteristics (ACh) and atopic comorbidities (AC). The objectives of this study were to study the similarities and differences between both phenotypes regarding the ACh and AC.

This was a prospective observational study that included patients diagnosed with EoE (symptoms of esophageal dysfunction and ≥ 15 eos / hpf in at least one esophageal biopsy), from 2013-2018. All completed a 2 months treatment with omeprazole 40 mgs b.i.d. Subsequently, an esophagoscopy with sectional biopsies was performed to each patient to see if the EoE had remitted with PPI therapy.

In both subgroups (R-EoE and NR-EoE), the following variables were studied and compared: skin prick tests (SPT) for aeroallergens (mites, fungi, epithelia and pollens) and foods (wheat, cow´s milk (CM), eggs, lentils, peanuts, hake and shrimp), total IgE (tIgE), specific Ig E (sIgE) to the mentioned foods, eosinophils in peripheral blood (EPB), eosinophil cationic protein (ECP), atopy (at least 1 positive allergological test (SPT> 3.3 mm or sIg E> 0.35 kU / L) and atopic

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comorbidities(AC) such as atopic dermatitis (AD), rhinoconjunctivitis (RC), bronquial asthma (BA) and IgE-mediated food allergy (Ig E-FA).

Statistical study: Comparison between the two groups were made using the Student's t-test for quantitative variables and the Chi square test for qualitative variables, since patient samples from both phenotypes followed a normal distribution. Statisticsstudy were performed using a SPSS package.

Treatment with omeprazole was prescribed to 203 patients diagnosed with EoE, but 27 left the study for breach or refusing ofesophagoscopies. EoE remitted only in 55 patients (31.25%)

Significant differences were found between both groups in the following variables: tests to animal dander:(p:0.025), sIgE to CM:(p:0.045)IgE-FA:(p:0.024), EPB: (p:0.021), atopy:(p:0.002, 50% and AC:(p:0.001) (Table 1). We did not find significant differences between both phenotypes in sensitization to the rest of aeroallergens or other foods except to egg that was at the limit of statistical significance.

Although most experts in EoE agree that the management of this disease should be multidisciplinary [5] but there is hardly any scientific study on allergological characteristics in both EoE phenotypes, probably, because the experts did not consider it relevant, but it is known that AC (DA, RC, BA and IgE-FA) are positively associated with EoE diagnosis and, possibly, it might be a late manifestation of the allergic march [6]

There were no significant differences between the patients with R-EoE and NR-EoE regarding total IgE or sensitizations to aeroallergens except for sensitization to epithelia and CM; if we compare our results with those of a study in a Japanese population [7], where they compared total IgE level in both EoE phenotypes, they found differences in the levels of this biomarker, being higher in NR-EoE; This difference with our results could be explained because the number of patients in our study is much smaller and because the authors do not specify whether they were sensitized to seasonal/perennial aeroallergens.

Pollen sensitization is the most frequent one in our EoE patients, but we did not find differences between both subgroups in this variable. These results agree with those of other published studies [8]; which could be explained because in the area where the patients in our study live, the levels of grass pollens and olive trees in spring are very high.

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The results of the differences in sIgE levels to CM support a higher atopic burden in patients with R-EoE; in addition, in a study found that BA and IgE-FA, were independently and cumulatively associated with more EoE diagnoses [6]

In a study done in the US several years ago, there were no differences for total IgE level (9); On the other hand, the authors of this same study did find significant statistical differences in the EPB count which was greater in the NR-EoE subgroup; these results agree with those obtained in our study and with those of the Japanese study previously mentioned [7].

IgE-FA is more frequent in patients with NR-EoE both in our study and in the Japanese one. Our patients have more AC also in this subgroup, while in the Japanese study, they only found that the NR-EoE subgroup had more BA [7]

In studies carried out by allergists, the percentage of patients with R-EoE is lower than in other studies carried out by gastroenterologists (10); these differences could be explained because patients referred from Primary Care to Allergologyhave more atopy than those referred to other specialties such as pediatrics and / or gastroenterology.

This study compares the atopic characteristics and comorbidities between the two populations, the R-EoE and NR EoE. The results suggest that both phenotypes may not exactly be the same; the NR-EoE phenotype seem to have a greater number of allergic sensitizations and comorbidities. Although more studies with a greater number of patients are needed to confirm these results.

We conclude that NR-EoE may represent a phenotype with a higher degree of atopy.

Conflict of interest
All authors declare no conflict of interests.

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Table 1. Variables with significant estatisticaldifferences between both subgroups of Eosinophilic esophagitis

EoE unresponsive to PPI	EoE responsive to PPI	P
Skin prick test (positive to epitelia)	43.8%	25% 0.025
sIg E-Cow´milk (kU/L)	0.54	0.24 0.045
Foof Allergy 29.6%	12%	0.024
Eosinophils in Peripheral blood/µL	323.66(X)	250.75(X) 0.021
Atopic	75%	50% 0.002
Atopic Comorbidities	77.6%	52,2% 0.001

PPI: Protom pump inhibitors drugs
P<0.05 (statisticalsignificance)
X: Arithmetic mean

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