

# Ovomucoid-specific IgD increases in children who naturally outgrow egg allergy.

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January 12, 2021

## Letter to Editor

To the Editor

Egg-allergic children have higher ovomucoid (OVM)-specific IgD (sIgD) levels compared to the atopic controls.<sup>1</sup> Within the egg-allergic group, children with higher levels of OVM-sIgD have a decreased risk of anaphylactic reactions. Ovalbumin (OVA)-sIgD increases in egg-allergic children desensitized by oral immunotherapy (OIT) but not in children unresponsive to OIT or with sustained unresponsiveness to OVA challenge.<sup>2</sup> The natural development of tolerance and the acquisition of sustained unresponsiveness by OIT in egg-allergic children are associated with an increase in OVM-specific IgG4 (sIgG4) levels and a decrease in OVM-specific IgE (sIgE) levels.<sup>3</sup> To elucidate the potential role of IgD in the outgrowing of egg allergy, we analyzed levels of egg white (EW)-, OVM-, and OVA-sIgD and sIgG4 in sera from 57 egg-allergic children (28 avoided all forms of egg in the diet (complete avoidance of egg: CAE), 18 were able to ingest at least 1/32 cooked whole egg but not one cooked whole egg (partial avoidance of egg: PAE), and 11 outgrew egg allergy (OGE)) and 23 healthy non-egg allergic children (non-egg allergy: NEA) (Table S1). The study was approved by The Research Ethics Committee of University of Fukui (#20110052), and written informed consent was obtained from the parent or guardians.

EW-, and OVM-sIgE levels measured using ImmunoCAP (Thermo-Fisher Inc., MA) were higher in the CAE group, followed by the PAE, OGE, and NEA groups (Fig 1, Fig S1). The CAE group exhibited lower serum levels of EW- and OVA-sIgD compared to the NEA group and the PAE group, respectively, and had the lowest OVM-sIgD serum levels among all groups, suggesting that OVM-sIgD levels are associated with outgrowing egg allergy. We observed the lowest serum levels of EW-, OVA-, and OVM-sIgG4 in the CAE group, followed by the PAE and OGE groups. The ratio of OVM-sIgD to OVA-sIgD increased as children outgrew egg allergy, whereas the ratio of OVM-sIgG4 to OVA-sIgG4 did not change. Thus, the production of OVM-sIgD differs from OVM-sIgG4 as children naturally outgrow egg allergy.

High-affinity, but not low-affinity, IgE is known to cause anaphylaxis.<sup>4</sup> High-affinity IgE is derived from memory IgG1<sup>+</sup> B cells, whereas low-affinity IgE is derived from naïve IgM<sup>+</sup>IgD<sup>+</sup> B cells. Considering class switching pathways, switching direction from IgM to IgD, and from IgG1 to IgE or IgG4, elevated OVM-sIgD levels might be associated with low-affinity OVM-sIgE levels as children outgrow egg allergy, resulting in hypo-responsiveness to OVM.

A recent study found that OVM-sIgE avidity was more effective at differentiating clinically reactive egg-

allergic patients from those tolerant of heated egg compared to EW-sIgE.<sup>5</sup> The ratio of OVM-sIgE to OVM-sIgD or sIgG4 in the CAE group was significantly higher compared to the PAE, OGE, and NEA groups (Fig 2). Receiver operating analysis revealed that the ratio of OVM-sIgE to OVM-sIgD discriminated non-tolerant from partially-tolerant egg-allergic patients with the largest area under the curve (AUC = 0.965) compared with levels of OVM-sIgE or the ratio of OVM-sIgE to OVM-sIgG4. The optimal cutoff for the ratio of OVM-sIgE to OVM-sIgD had 86.5% sensitivity and 96.4% specificity to identify high-risk subjects (Table S2).

There are several limitations to this study. First, there was a small number of patients. Second, all children were only challenged with heated egg and were instructed to avoid egg of any form if they tested positive with less than 1/32 cooked whole egg. Finally, there was a lack of trajectory of sIgD levels during natural tolerance development.

In conclusion, the ratio of OVM-sIgE to OVM-sIgD is a useful marker to identify high-risk egg-allergic patients capable of ingesting a low-dose of cooked whole egg who might be a good candidate for low-dose OIT.

## REFERENCES

1. Suprun M, Getts R, Grishina G, et al. Ovomuroid epitope-specific repertoire of IgE, IgG4 , IgG1 , IgA1 , and IgD antibodies in egg-allergic children. *Allergy*. 2020;75:2633-2643. 2. Shan M, Carrillo J, Yeste A, et al. Secreted IgD Amplifies Humoral T Helper 2 Cell Responses by Binding Basophils via Galectin-9 and CD44. *Immunity*. 2018;49:709-724. 3. Caubet JC, Lin J, Ahrens B, et al. Natural tolerance development in cow's milk allergic children: IgE and IgG4 epitope binding. *Allergy*. 2017;72:1677-1685. 4. Gowthaman U, Chen JS, Eisenbarth SC. Regulation of IgE by T follicular helper cells. *J Leukoc Biol*. 2020;107:409-418. 5. Sato M, Yamamoto-Hanada K, Tada H, et al. Diagnostic performance of IgE avidity for hen's egg allergy in young infants. *J Allergy Clin Immunol Pract*. 2020;8:2417-2420.

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**Short title:** Ovomuroid-specific IgD in egg-allergic children

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## Key words:

egg white, food allergy, IgD, IgG4, ovomucoid

## Conflict of interest:

The authors declare that they have no conflicts of interest.

## Acknowledgements

We thank Ms. Michiyo Toyooka and Ms. Yuki Mori for their assistance in carrying out Ig measurement.

### Author contribution:

NI, MY, AK, HM, EN, YH, and KO collected the samples. NI wrote the manuscript and YO organized the study. All authors read and approved the final manuscript. This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (to YO).

### Figure legends

**Figure 1** Egg allergen-specific IgE, IgD, and IgG4 levels in egg-allergic and non-egg allergic patients (NEA). Ovomucoid (OVM)-specific IgE (sIgE)(A), specific IgD (sIgD)(B), and specific IgG4 (sIgG4)(C), and relationship between ovalbumin (OVA) and OVM-sIgD (D) or sIgG4 (E) in the complete avoidance of egg (CAE), partial avoidance of egg (PAE), outgrown egg allergy (OGE), and NEA groups. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

**Figure 2** Relationship between ovomucoid-specific IgD, IgG4, and IgE in egg-allergic and non-egg allergic patients (NEA), and Receiver-operating characteristic predicting tolerance to cooked egg white ingestion. The logarithms of the ratio of OVM-sIgE to OVM-sIgD (A), OVM-sIgE to OVM-sIgG4 (B), and OVM-sIgD to OVM-sIgG4 in the complete avoidance of egg (CAE), partial avoidance of egg (PAE), outgrown egg allergy (OGE), and NEA groups. Receiver-operating characteristic curves (C) of OVM-sIgE (long dashed double-dotted line), sIgE/sIgG4 (dotted line), sIgD (broken line), and sIgE/sIgD (bold line).

\* $p < 0.001$

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