Clinical cross-reactivity to quail's egg in patients with hen's egg allergy

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To the Editor,

Hen's egg (HE) is consumed worldwide and is one of the most frequent causes of food allergy.[1,2] In Japan, HE is consumed most frequently among avian eggs, followed by quail's egg (QE). Quails (*Coturnix japonica*) belong to the same *Galliformes Phasianidae* family as chicken (*Gallus gallus domesticus*); therefore, cross-reactivity may occur between HE and QE. Consequently, HE allergic patients are generally advised to avoid QE consumption. However, there has been only one report on the serological cross-reactivity of HE and QE[3] and one case report on clinical cross-reactivity.[4] Moreover, whether all HE allergic patients need to avoid QE consumption remains unclear. This study, therefore, aimed to evaluate the clinical cross-reactivity between HE and QE by performing oral food challenge (OFC) tests.

We conducted a prospective study to determine whether HE allergic patients show cross-reactivity to QE. We performed QE-OFC in patients with HE allergy between January 2018 and October 2019. HE allergy was diagnosed through OFCs, which were performed stepwise, starting from a low-dose HE-OFC (containing 1/25 of a heated HE). Patients with negative results proceeded to a medium-dose HE-OFC (containing 1/8 of a heated HE). Patients with positive low-dose or medium-dose HE-OFC were included in this study. Patients with missing clinical data were excluded. QE-OFC was performed using one heated QE. All OFCs were performed in a single-dose or two-dose administration. In the two-dose OFCs, the challenged food was distributed at 60-min intervals. Symptom severity during OFCs was assessed according to the Japanese guidelines for food allergy.[2] Serum levels of total immunoglobulin E (IgE) and specific IgE to HE white (HEw-sIgE), HE ovomucoid (OVM-sIgE), and QE white (QEw-sIgE) (ImmunoCAP^{TM}; Thermo Fisher Scientific/Phadia, Uppsala, Sweden) were measured within four months of conducting QE-OFC, and skin prick test (SPT) was performed during QE-OFC. The SPT procedure is described in Supplemental Methods. This study was approved by the ethics committee of Sagamihara National Hospital (approval number: 2017-021), and was registered at the University Hospital Medical Information Network Clinical Trials Registry (no: UMIN000034820). The written informed consent was obtained from the guardians of all patients.

Among 870 patients who underwent HE-OFC, 183 failed in the low-dose or medium-dose HE-OFC, 22 of whom underwent a QE-OFC. Two patients were excluded because of missing clinical data, and the remaining 20 were enrolled (Figure 1). Median patient age was 2.9 (range, 1.0–16.4) years, and nine (45%) patients had a history of anaphylaxis to HE. The median HEw-sIgE, OVM-sIgE, and QEw-sIgE levels were 9.95 (2.67–365), 8.66 (<0.10–191), and 4.15 (0.73–>100) kU_A/L, respectively (Table 1). There was a correlation between HEw-sIgE and QEw-sIgE levels (Supplemental Figure 1). SPT was performed in 13 patients, and 12 (92%) were found to be sensitized to QE. The median SPT wheal diameters for HEw and QEw were 15 (3–32) and 12 (0–25) mm, respectively.

Among the 20 patients, four reacted to the low-dose HE-OFC (threshold dose, 1/25 of a heated HE or lower), and 16 passed the low-dose HE-OFC but reacted to the medium-dose HE-OFC (threshold dose, >1/25–1/8 of a heated HE). Of the 20 patients, 9 (45%) failed in the QE-OFC. The median interval between QE-OFC and HE-OFC was 2.8 months. The rate of positive QE-OFC results was significantly higher in patients with a threshold dose of [?]1/25 of a heated HE than in those with a threshold dose of >1/25–1/8 of a heated HE (100% [4/4] vs. 31% [5/16], $p = 0.026$; Figure 2). Patients' symptoms, severity, and treatment during the QE-OFC are described in Supplemental Table 1. Three patients presented with symptoms in multiple organs; however, their symptoms improved after treatment with antihistamine and steroid or inhalation of $\beta_2$stimulants. The HEw-sIgE, OVM-sIgE, and QEw-sIgE levels were significantly higher in patients with a positive QE-OFC result than in those with a negative QE-OFC result. There was no significant difference in the SPT wheal diameter to HEw and QEw between patients who reacted to QE-OFC and those who did not (Table 1).

To our knowledge, this is the first prospective study to evaluate the clinical cross-reactivity between HE and QE through OFC tests. In this study, clinical cross-reactivity to QE was observed in almost half of the patients who were allergic to HE.

In a previous case report, a patient with HE allergy showed cross-reactivity to QE.[4] Furthermore, approxi-

mately 70% of HE allergic children had a positive SPT result to QEw[5]; however, whether they showed clinical cross-reactivity to QE was not confirmed. In our study, 92% of the HE allergic patients had a positive SPT result to QEw, and 45% reacted to one QE.

The mean weight of HE and QE is 58g and 11.3g, respectively.[6] Because the ratio of egg white and egg yolk mass in HE is almost equivalent to that of QE[6,7]and the percentage of protein in HEw is also equivalent to that of QEw,[6] the amount of protein in the egg white of one QE would be equivalent to approximately 1/5 of that in one HE. Since the main antigen of immediate-type egg allergy is egg white, if the antigenicity of HEw and QEw is deemed to be identical, all HE allergic patients with a threshold dose of [?]1/8 of a heated HE would be expected to fail a QE-OFC. However, in this study, while all the patients with a threshold dose of [?]1/25 of a heated HE failed the QE-OFC, only 31% patients with a threshold dose of >1/25–1/8 of a heated HE failed. Therefore, QEw antigenicity seemed to be lower than that of HEw when comparing in terms of the same amount of protein, and whether HE allergic patients reacted to one QE appeared to depend on their threshold of HE.

This study has some limitations. First, OFCs were not double-blind and placebo-controlled. However, as most patients exhibited objective symptoms during OFCs, the number of false-positive OFC results would be low. Second, some patients may have achieved tolerance during the interval between the OFCs. However, the interval between QE-OFC and HE-OFC was relatively short, with a median of 2.8 months. Moreover, the median age of the subjects in this study was 2.9 years, and since it has been reported that only 30% of Japanese HE allergic patients achieve tolerance between 3 and 6 years old,[8] the influence of the interval between the OFCs is considered minimal. Third, we did not evaluate whether patients with negative QE-OFC results were reactive to amounts larger than one QE. Therefore, our study may have underestimated the rate of patients who had true clinical cross-reactivity to QE. Further studies with a larger number of patients, including those with a higher HE threshold, are necessary.

In conclusion, this study showed that some HE allergic patients are clinically cross-reactive to QE. Furthermore, patients with a lower threshold of HE were more likely to react to QE. Therefore, HE allergic patients, especially those with a low threshold, should consider avoiding QE consumption.

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vi. Impact statement

Some patients with allergy to hen's egg are also clinically reactive to quail's egg. Therefore, such patients, especially those with a low threshold dose, should consider avoiding the consumption of quail's egg.

vii. References

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viii. Tables

Table 1. Characteristics of the study patients and comparison of patients with QE-OFC positive and negative results

Characteristics	**All patients n = 20**	**QE-OFC positive n = 9**	**QE-OFC negative n = 11**	p **value***
Age (years)	2.9 (1.0–16.4)	2.6 (1.0–11.1)	3.2 (1.0–16.4)	0.656
Sex (male)	14 (70)	7 (78)	7 (64)	0.642
History of anaphylaxis to HE	9 (45)	5 (56)	4 (36)	0.653
Food allergy other than HE, current	9 (45)	3 (33)	6 (55)	0.406
Atopic dermatitis, current	16 (80)	8 (89)	8 (73)	0.591
Bronchial asthma, current	3 (15)	1 (11)	2 (18)	> 0.999
Allergic rhino-conjunctivitis, current	3 (15)	0 (0)	3 (27)	0.218
Total IgE (kIU/L)	322 (31.1–4040)	526 (58.4–1170)	280 (31.1–4040)	> 0.999
HEw-sIgE (kU_A/L)	9.95 (2.67–365)	62.3 (5.43–365)	8.22 (2.67–33.5)	0.025
OVM-sIgE (kU_A/L)	8.66 (< 0.10–191)	53.2 (3.22–191)	4.57 (< 0.10–18.7)	0.004
QEw-sIgE (kU_A/L)	4.15 (0.73–> 100)¶	36.8 (2.75–> 100)¶	3.28 (0.73–14.2)$^{+}$	0.019
SPT wheal diameter to HEw (mm)	15 (3–32)	23 (11–32)$^{++}$	14 (3–22)§	0.101
SPT wheal diameter to QEw (mm)	12 (0–25)	13 (10–25)$^{++}$	11 (0–24)§	0.295

Values are reported as median (range) or number (%).

* Comparisons between subjects with QE-OFC positive and negative results were conducted using Mann-Whitney U test for continuous variables or using chi-square or Fisher's exact test for categorical variables.

$^{+}$In 2 patients, QEw sIgE data were missing

$^{++}$In 3 patients, SPT data were missing.

§In 4 patients, SPT data were missing.

¶QEw-sIgE concentrations exceeding 100 kU_A/L were not evaluated by dilution.

Abbreviations: QE-OFC, quail's egg oral food challenge; HE, hen's egg; HEw, hen's egg white; OVM, hen's egg ovomucoid; QEw, quail's egg white; IgE, immunoglobulin E; sIgE, specific IgE; SPT, skin prick test

ix. Figure legends

Figure 1. Flowchart of the study participation selection process

Abbreviations: HE, hen's egg; QE, quail's egg; OFC, oral food challenge

Figure 2. Positive rates in quail's egg oral food challenge.

Abbreviations: HE, hen's egg; QE, quail's egg; OFC, oral food challenge

Author Contributions

Masatoshi Mitomori: Conceptualization (equal); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (equal); supervision (equal); validation (supporting); visualization (supporting); writing-original draft (lead); writing-review and editing (equal). Noriyuki Yanagida: Conceptualization (lead); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (lead); validation (lead); visualization (lead); writing-original draft (equal); writing -review and editing (lead). Mari Takei; Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (supporting); project administration (supporting); resources (supporting); software (supporting); supervision (supporting); validation (supporting); visualization (supporting); writing-original draft (supporting); writing-review and editing (supporting). Kinji Tada: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (supporting); project administration (supporting); resources (supporting); software (supporting); supervision (supporting); validation (supporting); visualization (supporting); writing-original draft (supporting); writing-review and editing (supporting). Makoto Nishino: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (supporting); project administration (supporting); resources (supporting); software (supporting); supervision (supporting); validation (supporting); visualization (supporting); writing-original draft (lead); writing-review and editing (equal). Sakura Sato: Conceptualization (lead); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (lead); validation (lead); visualization (lead); writing-original draft (equal); writing-review and editing (lead). Motohiro Ebisawa: Conceptualization (lead); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (lead); validation (lead); visualization (equal); writing-original draft (equal); writing-review and editing (lead).

Key Message

This study showed that some hen's egg allergic patients are also clinically reactive to quail's egg. Therefore, such patients, especially those with a low threshold dose, should consider avoiding the consumption of quail's egg.