

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

To the Editor,

Hen's egg (HE) is consumed worldwide and is one of the most frequent causes of food allergy.<sup>1,2</sup> In Japan, HE is the most commonly consumed avian egg, followed by quail's egg (QE). Quails (*Coturnix japonica*) belong to the same *Galliformes Phasianidae* family as the 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 are only one report on serological cross-reactivity between HE and QE,<sup>3</sup> and two reports on clinical cross-reactivity.<sup>4,5</sup> Therefore, whether all HE-allergic patients need to avoid QE consumption remains unclear. This study 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 clinical 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 a 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. 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™; Thermo Fisher Scientific/Phadia) were measured within 4 months of conducting QE-OFC. A skin prick test (SPT) was performed during the QE-OFC. The SPT procedure is described in Appendix S1. This study was approved by the ethics committee of Sagami Hospital (approval number: 2017-021) and was registered at the University Hospital Medical Information Network Clinical Trials Registry (no: UMIN000034820). Written informed consent was obtained from the guardians of all patients.

Among 870 patients who underwent HE-OFC, 183 failed the low-dose or medium-dose HE-OFC, 22 of whom underwent a QE-OFC. The threshold dose of HE was significantly higher in patients who received QE-OFC than in those who did not (Table S1). Two patients were excluded because of missing clinical data, and the remaining 20 were enrolled (Figure 1). The median patient age was

2.9 (range, 1.0–16.4) years, and 10 (50%) 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<sub>A</sub>/L, respectively (Table 1). There was a correlation between HEw-sIgE and QEw-sIgE levels (Figure S1). 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.

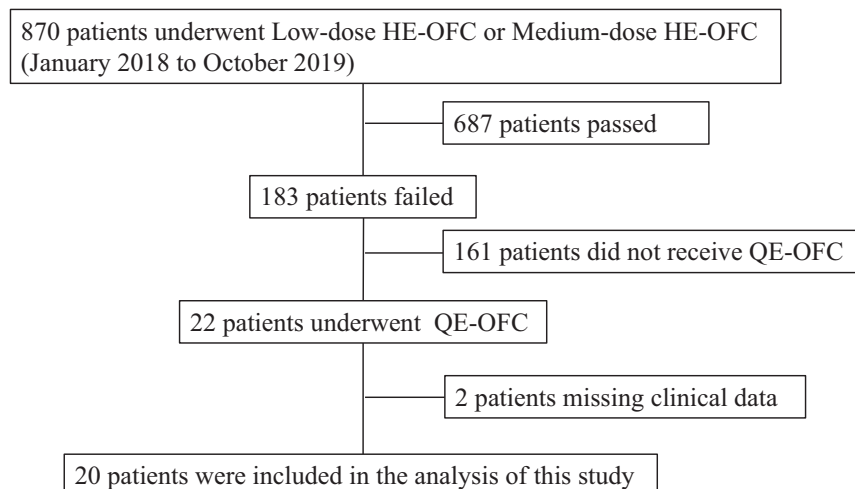
Among the 20 patients, four reacted to the low-dose HE-OFC (threshold dose,  $\leq 1/25$  of a heated HE), and 16 passed the low-dose but reacted to the medium-dose HE-OFC (threshold dose,  $>1/25$ – $1/8$  of a heated HE). Of the 20 patients, nine (45%) failed the QE-OFC. The median interval between 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  $\leq 1/25$  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],  $p = .026$ ; Figure 2). Patients' symptoms, severity, and treatment during the QE-OFC are described in Table S2. Three patients presented with symptoms in multiple organs; however, their symptoms improved after treatment with antihistamines, steroids, and/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).

In this study, some HE-allergic patients showed clinical cross-reactivity to QE, especially those with a low threshold of HE. In a previous report, approximately 70% of HE-allergic children had positive SPT results to raw QEw.<sup>6</sup> In another report, 33% (4/12) of HE-allergic children had positive SPT results to boiled QEw. Four of the remaining 8 patients with negative SPT results underwent OFC using boiled QEw, and one reacted.<sup>5</sup> In our study, 92% of HE-allergic patients had positive SPT results to raw QEw; all participants underwent QE-OFC, and 45% reacted.

The mean weight of HE and QE is 58 and 11.3 g, respectively.<sup>7</sup> Because the ratio of egg white to egg yolk mass in HE is almost equivalent to that in QE,<sup>7,8</sup> and the percentage of protein in HEw is also equivalent to that in QEw,<sup>7</sup> the amount of protein in the egg

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

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

**FIGURE 1** Flowchart of the study participation selection process. HE, hen's egg; QE, quail's egg; OFC, oral food challenge

**TABLE 1** Characteristics of the study patients and comparison of patients with QE-OFC positive and negative results

| Characteristics                       | All patients<br><i>n</i> = 20 | QE-OFC positive<br><i>n</i> = 9 | QE-OFC negative<br><i>n</i> = 11 | <i>p</i> Value <sup>a</sup> |
|---------------------------------------|-------------------------------|---------------------------------|----------------------------------|-----------------------------|
| Age (years)                           | 2.9 (1.0–16.4)                | 2.6 (1.0–11.1)                  | 3.2 (1.0–16.4)                   | .656                        |
| Sex (male)                            | 14 (70)                       | 7 (78)                          | 7 (64)                           | .642                        |
| History of anaphylaxis to HE          | 10 (50)                       | 5 (56)                          | 5 (45)                           | >.999                       |
| Food allergy other than HE, current   | 10 (50)                       | 4 (44)                          | 6 (55)                           | >.999                       |
| History of previous consumption of QE | 0 (0)                         | 0 (0)                           | 0 (0)                            | –                           |
| Atopic dermatitis, current            | 16 (80)                       | 8 (89)                          | 8 (73)                           | .591                        |
| Bronchial asthma, current             | 3 (15)                        | 1 (11)                          | 2 (18)                           | >.999                       |
| Allergic rhinoconjunctivitis, current | 3 (15)                        | 0 (0)                           | 3 (27)                           | .218                        |
| Total IgE (kIU/L)                     | 322 (31.1–4040)               | 526 (58.4–1170)                 | 280 (31.1–4040)                  | >.999                       |
| HEw-sIgE (kU <sub>A</sub> /L)         | 9.95 (2.67–365)               | 62.3 (5.43–365)                 | 8.22 (2.67–33.5)                 | .025                        |
| OVM-sIgE (kU <sub>A</sub> /L)         | 8.66 (<0.10–191)              | 53.2 (3.22–191)                 | 4.57 (<0.10–18.7)                | .004                        |
| QEW-sIgE (kU <sub>A</sub> /L)         | 4.15 (0.73–>100) <sup>e</sup> | 36.8 (2.75–>100) <sup>e</sup>   | 3.28 (0.73–14.2) <sup>b</sup>    | .019                        |
| SPT wheal diameter to HEw (mm)        | 15 (3–32)                     | 23 (11–32) <sup>c</sup>         | 14 (3–22) <sup>d</sup>           | .101                        |
| SPT wheal diameter to QEW (mm)        | 12 (0–25)                     | 13 (10–25) <sup>c</sup>         | 11 (0–24) <sup>d</sup>           | .295                        |

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

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

<sup>b</sup>In 2 patients, QEW-sIgE data were missing.

<sup>c</sup>In 3 patients, SPT data were missing.

<sup>d</sup>In 4 patients, SPT data were missing.

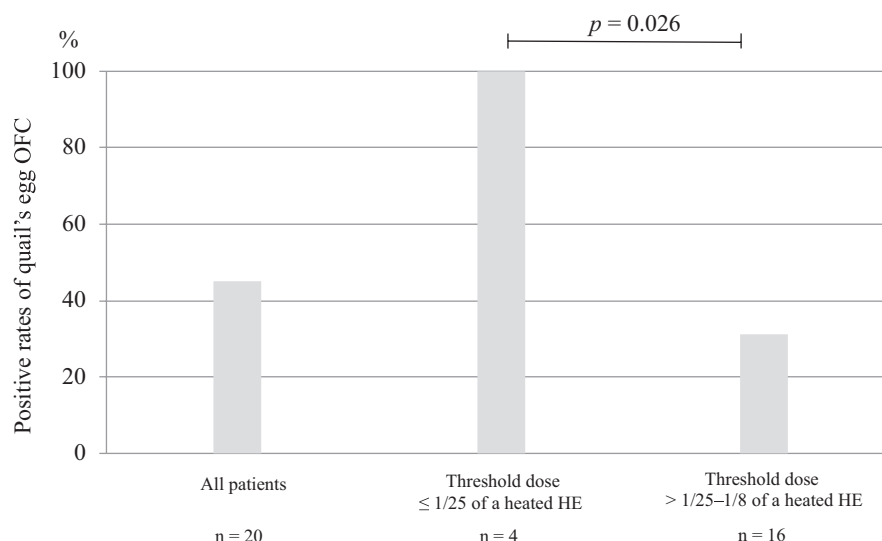
<sup>e</sup>QEW-sIgE concentrations exceeding 100 kU<sub>A</sub>/L were not evaluated by dilution.

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  $\leq 1/8$  of a heated HE would be expected to fail a QE-OFC. However, in this study, while all patients with a threshold dose of  $\leq 1/25$  of a heated HE failed the QE-OFC, only 31% of 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. Therefore, HE-allergic patients with a higher threshold may consume QE to provide nutritional benefits and perhaps also to enhance the development of immune tolerance.

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

**FIGURE 2** Positive rates in quail's egg oral food challenge. HE, hen's egg; QE, quail's egg; OFC, oral food challenge



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,<sup>9</sup> the influence of the interval is considered minimal. Third, as many of the parents were reluctant of allowing their child to consume QE after a positive HE-OFC, QE-OFC was performed for a limited number of participants. Owing to this selection bias, the threshold dose of HE in patients who received QE-OFC was higher than that in those who did not. Fourth, 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 clinical cross-reactivity to QE. However, these limitations would not affect the fact that HE-allergic patients with a lower threshold dose were more likely to react to QE.

In conclusion, HE-allergic patients, especially those with a lower threshold, may show clinical cross-reactivity to QE, and therefore should consider avoiding QE consumption. Further studies are needed to safely recommend whether, for patients with a higher threshold, QE could be a useful constituent of a hypoallergenic alternative diet to HE.

## KEYWORDS

child, cross-reactivity, food allergy, hen's egg, oral food challenge, pediatrics, quail's egg

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## CONFLICT OF INTERESTS

Motohiro Ebisawa received lecture fees from Mylan EPD. Sato Sakura received lecture fees from Mylan EPD. The other authors declare that they have no conflicts of interest.

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## PEER REVIEW

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