ABSTRACT

Background: The prevalence of peanut allergy (PA) among children has increased significantly over the past decade. Even though the prevalence of PA in Singapore is considered low, peanut is the top trigger for food-induced anaphylaxis in Singaporean children.

Objective: To describe the demographic characteristics and clinical features of children with PA.

Methods: This is a 5-year retrospective review of children diagnosed with PA based on clinical history coupled with a positive skin prick test to peanut or positive oral food challenge results.

Results: There were 269 patients (53.9% males) with a clinical diagnosis of PA. The median age at first allergic presentation for the PA group was 24 months old, with interquartile range of 13–39 months. The most common form of peanut introduced was roasted peanut. The rate of peanut anaphylaxis was 7.1%. Concomitant tree nut sensitization was found in 32.3% of this cohort, predominantly to cashew nut. Majority of them have a personal history of atopy—75.8% with eczema, 63.6% with allergic rhinitis, and 19.7% with asthma.

Conclusion: This is the first large review of peanut-allergic children in Singapore. Prospective population-based studies are needed to establish the true prevalence and risk factors associated with the development of this potentially life-threatening condition.

Keywords: Peanut allergy; Children; Singapore; Asia

INTRODUCTION

The prevalence of peanut allergy (PA) among children has risen significantly over the past decade [1, 2]. However, in Asia, the prevalence of PA has remained relatively low in comparison to Western countries—0.22% in Korea, 0.1%–0.3% in Singapore, 0.43% in the Philippines versus 1.50% in the UK, 1.40% in the US, and 3% in Australia [3-7]. The reason for this difference is unknown but hypotheses include early exposure to peanut and differences in the methods of peanut preparation [3, 8]. In Asia, peanuts are traditionally consumed as boiled, braised, fried or roasted whole nuts. Peanuts may be crushed into powder, made into sauce or spread and incorporated as a culinary ingredient in many dishes. The Asian cooking method of boiling and frying peanuts results in lower allergenicity compared with the Western method of roasting [9].
To date, published data on the demographic and clinical profile of children with PA in Singapore is scarce. Even though the prevalence of PA in Singapore had been reported to be low [4], there is evidence of an increasing trend [10] and a change in the pattern of food anaphylaxis. Within 2 decades, peanut anaphylaxis had risen from a rare entity to the commonest trigger of food anaphylaxis in Singapore [11]. Hence, this retrospective study aims to describe the demographic and clinical characteristics of PA in Singaporean children. Peanut skin prick test (SPT) wheal size and peanut-specific IgE of this cohort have been published separately [12].

MATERIALS AND METHODS

Children ≤ 16 years old who had a positive SPT to peanut between 2012 to 2016 were identified from our departmental electronic database at KK Women’s and Children’s Hospital, the largest tertiary paediatric hospital in Singapore. Clinical documents were reviewed. Data on demographic characteristics, age at initial presentation, clinical reactions to peanut, personal or family history of atopy and associations with tree nuts (almond, brazil nut, hazelnut, pecan, walnut, and pistachio) were collected.

Diagnosis of PA was made based on a history of clinical reaction within 2 hours of peanut exposure (either by ingestion or contact) with evidence of peanut sensitization (either positive SPT and/or positive IgE), or a positive oral food challenge (OFC) to peanut. A group of children whom had positive SPT but tolerant to regular peanut ingestion, was identified for comparison (peanut tolerant [PT] group).

SPT was performed using Stallergenes Greer Laboratories (Lenoir, NC, USA) commercial extracts and Duotip-Test II (Lincoln Diagnostics Inc., Decatur, IL, USA) disposable skin applicator. Positive SPT was defined as mean wheal diameter of ≥3 mm in comparison to the negative control. Positive peanut-specific IgE (ImmunoCAP, Thermo Fisher, Uppsala, Sweden) was defined as ≥0.35 kU/L.

OFC using peanut butter or roasted peanuts was performed at the Allergy Outpatient Specialist Clinic in our unit following the recommendations set out by the PRACTALL Consensus Report [13]. The diagnosis of anaphylaxis was in accordance to the definition by the World Allergy Organization [14].

Data were extracted for statistical analysis using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline demographic and clinical features were compared between PA and PT groups using 2-sided 2 independent sample t test and chi-square/Fisher exact test for continuous and categorical variables, respectively. The association between demographics, atopic history and the measures of SPT wheal size and food-specific IgE concentrations with the risk of PA were tested using univariate and multivariable logistic regression analysis.

The study is approved by SingHealth Centralised Institutional Review Board (reference number: 2016/2346).
RESULTS

A total of 269 patients were diagnosed as PA and 59 patients as PT. Their demographics is shown in Table 1. The ethnic distribution of the PA group was Chinese (68.4%), Malay (12.6%), Indian (4.1%), and other races (14.9%) with Caucasians making up 4.5%. Rhinitis was a more common comorbidity in the PA group compared to the PT group (odds ratio [OR], 2.52; 95% confidence interval [CI], 1.42–4.47) (Table 2).

The median age of peanut introduction and first allergic presentation for the PA group were both 24 months old, with interquartile range (IQR) of 15–41.8 months and 13–39 months respectively. The age of peanut introduction for the PT group could not be analysed as they

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Table 1. Demographic and clinical characteristics of peanut allergy and peanut tolerant groups

| Variable                      | Peanut allergy (PA) (n = 269) | Peanut tolerant (PT) (n = 59) | p value† |
|-------------------------------|--------------------------------|------------------------------|----------|
| Demographics                  |                                |                              |          |
| Male sex                      | 145 (53.9)†                    | 37 (62.7)                    | 0.218    |
| Age (yr)                      | 3.9 ± 3.2                      | 3.7 ± 3.3                    | 0.633    |
| Race, Chinese                 | 184 (68.4)                     | 39 (66.1)                    | 0.732    |
| History of atopy              |                                |                              |          |
| Rhinitis†                     | 171 (63.6)                     | 24 (40.7)                    | <0.01    |
| Atopic dermatitis‡            | 204 (75.8)                     | 47 (79.7)                    | 0.330    |
| Asthma§                       | 53 (19.7)                      | 9 (15.3)                     | 0.429    |
| Drug allergy∥                 | 14 (5.2)                       | 4 (6.8)                      | 0.630    |
| Urticaria/angioedema∥         | 27 (10.1)                      | 9 (15.3)                     | 0.550    |
| Tree nut sensitisation∥       | 87 (32.3)                      | 15 (25.4)                    | 0.299    |
| Other food allergies**        | 149 (55.4)                     | 26 (44.1)                    | 0.114    |
| Investigation results         |                                |                              |          |
| SPT wheal size (mm)           | 10.2 ± 5.5                     | 5.2 ± 3.3                    | <0.01    |
| IgE to peanut (kU/L)          | 22.8 ± 30.7                    | 7.6 ± 19.3                   | <0.05    |

Values are presented as number (%) or mean ± standard deviation.

SPT, skin prick test.

†Comparing the 2 groups (PA and PT); 2-sided 2 independent sample t test for continuous variables and chi-square/Fisher exact test for categorical variables.

‡Parental report of patient’s history of rhinitis, atopic dermatitis, drug allergy and urticaria/angioedema.

§Physician-diagnosed asthma.

**Clinical diagnosis of food allergy based on clinical history and positive SPT/IgE.

Table 2. Univariate and multivariable analysis of demographics, atopic history, and investigation parameters with peanut allergy

| Variable                  | Unadjusted OR (95% CI)* | p value | Adjusted OR (95% CI)† | p value |
|---------------------------|-------------------------|---------|-----------------------|---------|
| Demographics              |                         |         |                       |         |
| Male sex                  | 0.70 (0.39–1.25)        | 0.228   | 0.68 (0.38–1.23)      | 0.200   |
| Age (yr)                  | 1.57 (0.89–2.78)        | 0.122   | 1.18 (0.64–2.18)      | 0.598   |
| Race, Chinese             | 1.12 (0.62–2.03)        | 0.709   | 1.03 (0.56–1.88)      | 0.936   |
| History of atopy          |                         |         |                       |         |
| Rhinitis§                 | 2.52 (1.42–4.47)        | <0.01   | 2.39 (1.30–4.48)      | <0.01   |
| Atopic dermatitis‡        | 0.82 (0.41–1.63)        | 0.575   | 0.80 (0.40–1.62)      | 0.541   |
| Asthma§                   | 1.31 (0.61–2.81)        | 0.482   | 0.90 (0.40–2.02)      | 0.792   |
| Drug allergy∥             | 0.70 (0.23–2.16)        | 0.534   | 0.45 (0.14–1.46)      | 0.182   |
| Urticaria/angioedema∥     | 0.61 (0.27–1.36)        | 0.223   | 0.67 (0.29–1.53)      | 0.345   |
| Tree nut sensitisation∥   | 1.38 (0.73–2.60)        | 0.324   | 1.33 (0.70–2.54)      | 0.378   |
| Other food allergies**    | 1.57 (0.89–2.76)        | 0.118   | 1.57 (0.87–2.84)      | 0.132   |
| Investigation results     |                         |         |                       |         |
| SPT wheal size (mm)†      | 4.68 (2.32–9.41)        | <0.01   | 1.32 (1.20–1.45)      | <0.01   |
| IgE to peanut (kU/L)†     | 1.96 (0.63–6.11)        | 0.244   | 1.09 (1.02–1.17)      | <0.05   |

OR, odds ratio; CI, confidence interval; SPT, skin prick test.

*Odds ratio (OR) using univariate logistic regression analysis.

†Odds ratio using multivariable logistic regression analysis; adjusted for age and rhinitis.

‡Parental report of patient’s history of rhinitis, atopic dermatitis, drug allergy, and urticaria/angioedema.

§Physician-diagnosed asthma.

¶Clinical diagnosis of food allergy based on clinical history and positive SPT/IgE.

∥Odds ratio is reported for the risk of SPT ≥ 3 mm, and serum IgE ≥ 0.35 kU/L.
were not routinely documented. In the PA group, the commonest form of peanut that was first introduced was roasted peanut such as peanut butter, peanut kernel, peanut snack, peanut sauce, or crushed peanut topping (80.3%). This was followed by boiled peanut such as peanut soup or porridge (6.3%). In 36 PA children (13.4%), the form of peanut that was introduced was not specified.

The onset of symptoms was within 1 hour of exposure in 93.3% of the PA group and the commonest clinical features were mucocutaneous signs (86.6%) (Table 3). The rate of peanut anaphylaxis in our study population was 7.1%. There was no reported mortality in these patients who develop anaphylaxis in this study.

Amongst the PA group, 32.3% were also sensitized to tree nuts; predominantly to cashew nut (17.1%), followed by almond (15.6%), hazelnut (15.6%), and walnut (14.1%). With regards to atopic tendencies, 75.8% had eczema, 63.6% had allergic rhinitis, and 19.7% had physician-diagnosed asthma. About half of the children (44.6%) with PA had other food allergies, of which 29% were allergic to egg, 13% to cow’s milk and 2.6% to soy. Family history of atopy was present in 45% of PA children, including a family history of PA in 3.3%.

**DISCUSSION**

Singapore is a multiethnic country with a total population of 5.64 million, comprising of Chinese (74.1%), Malays (13.4%), Indians (9.2%), and Others (3.3%) [15]. In the PA cohort, there was a higher percentage patient of “other” ethnicity (14.9%) with the majority (57.5%) originating from the Philippines and Indonesia, whilst 42.5% of them were Eurasians or Caucasians. A population-based questionnaire survey by Shek et al. [16] reported a higher prevalence of PA in Singapore expatriate children (1.2%) versus local Singaporean children (0.47%–0.64%), albeit a relatively small number. At the same time, there is also evidence of increasing prevalence of food allergy in rapidly developing countries such as Thailand [17] and China [18]. Hence we postulate that a rising trend of PA in Singapore could be a result.
of a true rising incidence or in part, contributed by a larger migrant population from high prevalence regions [15].

It is noteworthy that the median age at presentation of PA in our study was 24 months old compared to the median age of 12 to 14 months reported in Western countries [19, 20]. This is possibly due to delayed peanut introduction in our cohort whose mean age was 30.4 ± 22.4 months. A recent local study by Tham et al. [4] (GUSTO Cohort) demonstrated similar pattern of late introduction of peanut (beyond 1 year old) at a mean age of 19 ± 7.87 months. Delay in peanut introduction has been attributed to multiple reasons including fear of choking, concerns of possible PA, lack of knowledge on the types of peanut-containing food suitable for young children or the perception that peanut butter is too sweet for toddlers. This is of particular concern as delayed introduction of peanut in a subset of atopic patients with moderate to severe atopic dermatitis has been shown to contribute to the rising rates of PA [21, 22]. Furthermore, it is noted that the most common form of peanut introduced in this cohort was roasted peanut compared to the more traditional practice of giving boiled peanut in soups/porridge as one of the first weaning foods [11]. Both the shift in age of peanut introduction as well as the increased consumption of roasted peanuts highlighted the “Westernisation” of diet and lifestyle in parts of Asia such as Singapore, which may have an impact on the incidence of PA.

The most common clinical feature of peanut-allergic reaction in our cohort was mucocutaneous signs (86.6%), similar to that in the Western countries (58.2%–89%) [19, 23]. However, the rate of anaphylaxis in our study is significantly lower (7.1%) in comparison to the West (US – 23.7% to 34.9%) [19, 24]. Even though, the rate of peanut anaphylaxis was low in our cohort, a study by Liew et al. [11] showed that there is a recent change in the pattern of food anaphylaxis in Singapore. Peanut, which used to be a nonexistent food trigger 2 decades ago, is currently the top trigger for food-induced anaphylaxis in Singaporean children (19%). This is similar to the findings reported in Korea, the US, the UK, and Australia [3, 11, 25-27].

Many studies have shown the association between tree nut allergy and PA [28, 29]. A study in the US by Anagnostou [28] showed high cross-sensitization of 80% to tree nut in peanut-allergic children, mainly to cashew nut and walnut (50% and 49%, respectively). Another US study conducted by Maloney et al. [30] also showed a high proportion of peanut-allergic children (86%) with cross-sensitization to tree nut, and 34% with cross-allergy, mainly to walnut and almond. A retrospective cohort study in the UK showed 23.4% of children with PA had cross-reactivity to tree nuts and 7.4% of them had concomitant tree nut allergy, predominantly to almond [31]. Several studies have shown an in vitro cross-reactivity between peanut and tree nut IgE binding epitopes which could explain the association between peanut and tree nut allergy, but whether this translates to clinical cross-reactivity remains controversial [24, 32, 33]. In our study cohort, 32.3% of children with PA were also sensitized to tree nuts, predominantly to cashew nut (17.1%). While an OFC would have been necessary to confirm allergy, most subjects in this cohort did not proceed to OFC. The rate of tree nut cross-sensitization in our cohort of children with PA appears to be much lower than in the US. This may be related to the low prevalence of tree nut allergy in Singapore (0.3%), in comparison to the West (1.1% US, 1.14%–1.7% Canada, 0.5%–1.3% Europe, and 2.3% Australia) [16, 34].

In vitro cross-reactivity between peanut, soy and other legumes was previously reported [35]. However, recent studies have demonstrated that this is unlikely to translate into clinical cross-reactivity and thus, it is not recommended for children with PA to routinely eliminate legumes
in their diet [36, 37]. A study in the US by Bock and Atkins [37] showed that the prevalence of \textit{in vivo} cross-reactivity between peanut and soy allergy in children was low (3%). Similar rate was seen in our study cohort, where 2.6% of children with PA had concomitant soy allergy.

Eczema is a strong predictor for the development of food allergy [38]. The presence of Filaggrin gene mutation in patients with eczema leads to epithelial barrier dysfunction, which ultimately results in allergen sensitization and the development of PA [39, 40]. Overall, the prevalence of eczema in Singaporean children was high (>20%) and similar rates were reported in other Asian countries [4, 41-44]. In our study, 75.8% of our patients with PA had underlying eczema. The absence of statistically significant association between eczema and PA in our cohort (adjusted OR, 0.80; 95% CI, 0.40–1.62; \(p = 0.541\)) is likely due to the fact that the comparison was made with atopic children.

Instead, we found an association between allergic rhinitis and PA (adjusted OR, 2.39; 95% CI, 1.30-4.38; \(p = <0.01\)). Wang et al. [45] reported a high prevalence rate of allergic rhinitis in Singaporean children with 25.5% in 6- to 7-year-olds and 42.1% in 12- to 15-year-olds. Although the overall high prevalence of allergic rhinitis in our population may have confounded the finding of an association between allergic rhinitis and PA, the coexistence of primary food allergies and allergic rhinitis in children has been described in a few cohort studies [46-48]. In a prospective longitudinal birth cohort study in Sweden, it concluded that 40% of children with food allergies in infancy had allergic rhinitis by the time they were 8 years old [46]. In a retrospective cohort study by Hill et al. [48], 35% of paediatric patients with established food allergies went on to develop allergic rhinitis (adjusted OR, 2.72; 95% CI, 2.45–3.03).

This is the first largest study in this region to evaluate the demographic pattern and clinical manifestations of PA in children. Our study findings suggest that changing dietary practices with regards to peanut introduction may have an impact on the prevalence of PA in Singapore and this warrants further investigation with prospective population-based studies. Limitations of this study include its retrospective design, and the limited use of OFCs to confirm PA in the majority of patients.

In conclusion, PA is an important cause of food-induced anaphylaxis and possibly underestimated health burden in developing countries including Singapore. In particular, the paucity of data from South East Asian countries necessitates prospective population-based studies to establish the true prevalence and the risk factors associated with the development of PA in the region.

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