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Anaphylaxis treated in a Canadian pediatric hospital: Incidence, clinical characteristics, triggers, and management

To the Editor:

Anaphylaxis is responsible for 0.18% of emergency department (ED) visits in the United States[1] and 150 to 200 fatalities annually.[2] However, the societal burden in Canada remains largely undefined.[3] Furthermore, it is unknown whether the knowledge gaps related to anaphylaxis management, which have been described elsewhere,[1,3] also exist in Canada.

Although studies[1,4-6] have examined anaphylaxis, these are limited by their reliance on review of medical charts, which are often incomplete and lack the information necessary to establish the diagnosis, identify triggers, and evaluate management. We aimed to overcome these limitations and provide Canadian data on the rate, triggers, and management of anaphylaxis by prospectively recruiting cases in the ED of the Montreal Children's Hospital (MCH), Quebec, Canada.

As part of the Cross-Canada Anaphylaxis Registry, MCH ED physicians recruited children with anaphylaxis (defined as involvement of 2 organ systems, hypotension in response to a potential allergen, or both)[7] between April 2011 and April 2012. After parents consented, the ED physician completed a 10-question survey on the clinical characteristics, potential triggers, comorbid conditions, and management of the anaphylactic reaction. Parents of children with moderate-to-severe reactions (Table I)[8] were contacted and queried on the use of epinephrine autoinjectors. Cases missed during prospective recruitment were identified through chart review of all patients presenting to the ED with *International Classification of Disease, 10th revision*, codes that are related to either anaphylaxis or an allergic reaction.[4]

Descriptive statistics were used to assess the incidence of anaphylaxis, triggers, frequency of inadvertent exposures, and epinephrine use. Univariate and multivariate logistic regression were used to estimate the association between severe anaphylaxis and age, sex, type of trigger, engagement in exercise, use of medications, and comorbid history. Analyses were performed with R version 2.12.0 software.

The study was approved by the McGill University Health Centre Ethic Review Board.

At the MCH, among 81,677 ED visits, 168 children presented with anaphylaxis (ie, 0.21%; 95% CI, 0.18% to 0.24%); 47.6% were recruited prospectively. Prospective and retrospective cases were comparable except for a higher percentage of reactions induced by insect stings, severe reactions, and admissions in prospective cases (Table I and see Table E1 in this article's Online

TABLE I. Demographics and comorbidities of prospectively and retrospectively recruited cases of anaphylaxis

	Prospective (n = 80)	Retrospective (n = 88)	All (n = 168)
Percentage of study population (95% CI)	47.6 (39.9-55.4)	52.4 (44.6-60.1)	
Age (y [interquartile range])	4.0 (1.8-10.1)	5.2 (3.0-10.1)	4.8 (2.3-10.1)
Sex (% male [95% CI])	52.2 (41.1-63.6)	51.1 (40.3-61.9)	51.8 (44.0-59.5)
Reaction to a known allergen (% [95% CI])	15.0 (8.3-25.1)	33.0 (23.5-43.9)	24.4 (18.3-31.7)
Reaction triggered by food (% [95% CI])	87.5 (77.8-93.6)	81.8 (71.9-88.9)	84.5 (78.0-89.5)
Reaction triggered by insect venom (% [95% CI])	5.0 (1.6-13.0)	2.3 (0.4-8.7)	3.6 (1.5-8.0)
Reaction triggered by drug (% [95% CI])	2.5 (0.4-9.57)	3.4 (0.9-10.3)	3.0 (1.1-7.2)
Reaction triggered by other* (% [95% CI])	1.2 (0.1-7.7)	3.4 (0.9-10.3)	2.4 (0.8-6.4)
Unknown trigger (% [95% CI])	3.8 (1.0-11.3)	9.1 (4.3-17.6)	6.6 (3.5-11.7)
Reaction severity (% [95% CI])			
Mild†	46.3 (35.2-57.7)	46.6 (36.0-57.5)	46.4 (38.8-54.3)
Moderate‡	41.3 (30.5-52.8)	51.1 (40.3-61.9)	46.4 (38.8-54.3)
Severe§	12.5 (6.5-22.2)	2.2 (0.4-8.7)	7.1 (3.9-12.4)
Reaction precipitated admission (% [95% CI])	3.8 (0.9-11.3)	0.0 (0.0-5.2)	1.8 (0.5-5.5)

*Including contrast material, exercise, topical cream, and cat.

†Defined as sudden itching of the eyes and nose, generalized pruritus, flushing, urticaria, angioedema, oral pruritus, oral tingling, mild lip swelling, nausea or emesis, mild abdominal pain, nasal congestion and/or sneezing, rhinorrhea, throat pruritus, throat tightness, mild wheezing, and tachycardia.[8]

‡Defined as crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, barky cough, difficulty swallowing, stridor, dyspnea, or moderate wheezing.[8]

§Defined as loss of bowel control, cyanosis or saturation of less than 92%, or respiratory arrest.[8]

TABLE II. Anaphylaxis management

	Either inside or outside the ED (% [95% CI])			
	Mild	Moderate	Severe	All
Epinephrine	64.1 (52.4-74.4)	76.9 (65.8-85.4)	100 (69.9-100.0)	72.6 (65.1-79.1)
Multiple epinephrine	5.1 (1.7-13.3)	1.3 (0.1-7.9)	41.7 (16.5-71.4)	6 (3.1-11.0)
Antihistamines	71.8 (60.3-81.1)	74.3 (63.0-83.3)	91.7 (59.8-99.56)	74.4 (67.0-80.7)
Steroids	24.3 (31.4-54.0)	33.3 (23.3-45.0)	75.0 (42.8-93.30)	40.5 (33.1-48.3)

Repository at www.jacionline.org). The median age was 4.8 years, and 51.8% were male.

Food was responsible for 84.5% of reactions, with peanut, tree nut, or both being the major culprit. Overall, 24.4% of all reactions were due to inadvertent exposure to a known allergen, and 75.6% were due to a new allergen (Table I). In 50% of cases of peanut- and milk-induced anaphylaxis and in 37.5% of cases of egg-induced and 22.7% of cases of tree nut–induced anaphylaxis, reactions occurred because of inadvertent exposure to a known food allergen.

Among all anaphylactic reactions, 12 (7.1%) were severe, 78 (46.4%) were moderate,[8] and 78 were mild (Table I).[8] All patients with severe reactions received epinephrine either outside (25.0%) or inside (83.3%) the ED. Twenty-three percent of patients with moderate reactions and 35.9% of patients with mild reactions did not receive epinephrine either outside or inside the ED (Table II). Of those with moderate-to-severe reactions, 18 had an autoinjector with them at the time of the reaction, but only 12 used it. Parents indicated that it was not used because they either "panicked," had a "fear of the needle," or "hesitated to use it." Five patients (1 with a severe, 1 with a moderate, and 3 with a mild reaction) received epinephrine both inside and outside the ED. Peanut or venom exposure and asthma were associated with experiencing a severe reaction (see Table E2 in this article's Online Repository at www.jacionline.org).

The incidence of anaphylaxis at the MCH is comparable with that seen in US studies,[1] but higher than that in Europe[4,5] and Australia.[6] Given that the major trigger of anaphylaxis in children is food and that studies suggest higher rates of peanut allergy in North America,[9] it is not surprising that North American rates of anaphylaxis exceed those in other countries (see Table E3 in this article's Online Repository at www.jacionline.org). Furthermore, our findings highlight that inadvertent exposures are frequent, especially in those with milk and peanut allergy, which is consistent with other reports.[10]

Use of epinephrine in children treated in the MCH was substantially higher than in many other centers,[5,6] although similar to US estimates.[1] In contrast to what might be expected, of those who had an autoinjector available, a higher percentage of those experiencing moderate versus severe reactions actually used the autoinjector (76.9% vs 40%). It is possible that parents of children experiencing severe reactions are more anxious and unable to cope with using the autoinjector. Although all severe reactions were treated with epinephrine, a considerable proportion of mild and moderate reactions were not. Anaphylaxis guidelines recommend prompt administration of epinephrine regardless of severity.[7] It is possible that ED physicians who do not administer epinephrine are making decisions based on the patient's milder presentation on ED arrival. Epinephrine should not be delayed by the use of antihistamines and corticosteroids, which do not relieve upper airway obstruction.[3,8] However, in our study 23.6% of patients were treated only with steroids or antihistamines; a recent European study reported similar findings.[11]

Our results are consistent with those of other studies reporting greater severity in those with known asthma and in cases induced by peanut and venom.[3] It is suggested that there are greater levels of the anaphylatoxin receptors C3aR and C5aR in the lungs of patients with severe or uncontrolled asthma that render them more sensitive to the effects of systemic anaphylaxis.[12]

Given that our data are collected from 1 hospital, they might not be representative of the entire population. Furthermore, the percentage of cases presenting to the ED with anaphylaxis is an indirect measure of anaphylaxis incidence in the entire population. Differences in the catchment population might account for higher rates of anaphylaxis in our center. However, among industrialized countries, Canada has the highest rate of ED use, and a high proportion of Canadians report using the ED for nonemergency services.[13] Thus we anticipate that our estimates would have been even higher (ie, our denominator would be smaller) had our health system been more similar to that of the United States or Europe, where fewer patients visit the ED for less urgent problems. There is also a potential for misclassification bias because almost 50% of the data are acquired retrospectively. However, given that the characteristics of children recruited prospectively and retrospectively are similar, this bias is likely to be minimal. Finally, there is a potential for misclassification in blood pressure in children. However, we anticipate that misclassification will be nondifferential between cases of anaphylaxis and other diagnoses.

Our results highlight that anaphylaxis is a substantial health problem, inadvertent exposures to known food allergens are common culprits, and epinephrine is underused. As part of a larger initiative within the Cross-Canada Anaphylaxis Registry, our group is examining anaphylaxis rates, precipitants, and management in other Canadian centers.

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TABLE II. *(Continued)*

Outside the ED (% [95% CI])			Inside the ED (% [95% CI])		
Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
25.6 (16.7-37.0)	33.3 (23.3-45.0)	25.0 (6.7-57.2)	42.3 (31.4-54.0)	52.6 (10.1-63.9)	83.3 (50.9-97.1)
0 (0.0-5.8)	0 (0.0-5.8)	0 (0.0-30.1)	1.3 (0.1-7.9)	0 (0.0-5.8)	33.3 (11.3-64.6)
39.7 (29.0-51.5)	37.2 (26.7-48.9)	25.0 (6.7-57.2)	42.3 (31.4-54.0)	48.7 (37.3-60.2)	83.3 (50.9-97.1)
1.3 (0.1-7.9)	0 (0.0-5.8)	0 (0.0-30.1)	41.0 (30.2-52.7)	33.3 (23.3-45.0)	75 (42.8-93.3)

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Massively parallel sequencing reveals maternal somatic *IL2RG* mosaicism in an X-linked severe combined immunodeficiency family

To the Editor:

Severe combined immunodeficiency (SCID) is characterized by a near-absence of T cells that provokes a marked failure of cellular and humoral immune responses. Patients with SCID are at a high risk of severe infections early in life, and the course of the disease is usually fatal unless the immune system can be reconstituted.[1] Different forms of SCID can be recognized by their inheritance pattern, the immunophenotype of circulating lymphocytes, and the underlying genetic defect. The X-linked T^- B^+ NK^- SCID (X-SCID) is the most frequent type (44%-46%) and is a consequence of *IL2RG* mutations, which encode the common gamma chain of interleukin receptors.[1] Around 13% to 56% of patients with X-SCID are carrying *de novo IL2RG* mutations.[2,3] From these, an unknown proportion could actually be a consequence of unidentified somatic *IL2RG* mosaicism occurring in the mother and vertically transmitted to the child.

We report a family with an only male child diagnosed as suffering from X-SCID on the basis of clinical and immunologic data (see Fig 1, *A*, for familial pedigree; detailed clinical case described in the Online Repository available at www.jacionline.org). After obtaining signed informed consent and in accordance with the Helsinki Declaration, genetic studies were performed. These showed a hemyzygous C-to-T transition at c.690 position (GenBank RefSeq: NM_000206.2) in the patient, causing the cysteine-for-arginine substitution at residue 226 (p.R226C) of the common gamma chain. This variant was previously detected in several unrelated patients with X-SCID and represents a mutational hot spot of the *IL2RG* gene.[4] To establish the intrafamilial pattern of mutational segregation, genetic analyses were performed on the patient's parents by using Sanger-based sequencing. As expected, the mutation was not detected in the patient's father. Instead, a possible heterozygous genotype was detected in the patient's healthy mother, with a marked difference in the fluorescence intensity of the 2 alleles. The intensity of the wild-type allele was near normal, whereas that of the mutant allele was severely diminished and close to background (see Fig 1, *B*). To exclude potential selective amplification of the wild-type allele versus the mutant, 2 additional primer pairs were designed (see Fig 1, *C*). The results obtained were similar to those obtained previously, supporting the observation that the 2 maternal *IL2RG* alleles were equally amplified. Altogether, these data pointed to the possibility of a somatic *IL2RG* mosaicism in the patient's mother. To verify this hypothesis, massively parallel sequencing of DNA extracted from different tissues from the patient's mother was performed in a GS Junior 454 platform. These studies revealed the presence of the p.R226C *IL2RG* mutation in all analyzed samples, with frequencies for the mutated allele oscillating from 7.7% to 20% depending on the respective cell's origin (Table I). Moreover, *IL2RG* mutation was not detected in the patient's maternal grandparents, supporting the *de novo* nature of the mother's somatic mosaicism.

This evidence supports the vertical transmission of the somatic p.R226C *IL2RG* mutation from the mother to the child as the genetic mechanism underlying the patient with X-SCID described here. The frequency of the mutated *IL2RG* allele in the mother's peripheral blood (~15%) is notably different from that observed in females carrying germ line *IL2RG* mutations (~50%) and in

TABLE E1. Reaction characteristics

	Prospective* (% [95% CI])	Retrospective† (% [95% CI])	All (% [95% CI])
Known comorbidity			
Asthma	21.3 (13.2-32.1)	17.0 (10.2-26.9)	19.0 (13.6-26.0)
Eczema	23.8 (15.2-34.8)	9.0 (4.3-17.6)	16.1 (11.0-22.7)
Peanut allergy	17.6 (10.2-28.0)	29.5 (20.5-40.4)	23.8 (17.7-31.1)
Tree nut allergy	10.0 (4.7-19.2)	9.0 (4.3-17.6)	9.5 (5.7-15.3)
Peanut and tree nut allergy	3.8 (1.0-11.3)	1.1 (0.1-7.1)	2.4 (0.8-6.4)
Fish allergy	3.8 (1.0-11.3)	3.4 (0.9-10.3)	3.6 (1.5-8.0)
Shellfish allergy	3.8 (1.0-11.3)	6.8 (2.8-14.8)	5.3 (2.6-10.2)
Milk allergy	6.3 (2.3-14.6)	10.2 (5.1-19.0)	8.9 (5.3-14.6)
Egg allergy	10.0 (4.7-19.2)	12.5 (6.7-21.7)	11.3 (7.1-17.3)
Sesame allergy	5.0 (1.6-13.0)	4.5 (1.5-11.8)	4.8 (2.2-9.5)
Reaction triggered by food			
Peanut‡	30.0 (20.0-42.3)	29.2 (19.3-41.2)	29.5 (22.4-37.9)
Tree nut‡	17.1 (9.5-28.4)	14.0 (7.2-24.5)	15.5 (10.2-22.7)
Peanut or tree nut‡	47.1 (35.2-59.4)	43.1 (31.6-55.2)	45.0 (36.8-53.6)
Nuts§	1.4 (0.07-8.8)	12.5 (6.2-22.9)	7.0 (3.6-12.9)
Milk‡	7.1 (2.7-16.6)	6.9 (2.6-16.1)	7.0 (3.6-12.9)
Egg‡	2.9 (0.5-10.9)	8.3 (3.4-17.9)	5.6 (2.6-11.2)
Fish‡	8.6 (3.5-18.4)	2.8 (0.5-10.8)	5.6 (2.6-11.2)
Shellfish‡	5.7 (1.8-14.7)	4.2 (1.1-12.5)	4.1 (1.8-8.7)
Sesame‡	2.9 (0.5-10.9)	2.8 (0.5-10.8)	2.8 (0.9-7.5)
Kiwi‡	1.4 (0.07-8.8)	1.3 (0.07-8.5)	1.4 (0.2-5.5)
Soy‡	1.4 (0.07-8.8)	0.0 (0.0-6.3)	0.7 (0.04-4.4)
Wheat‡	1.4 (0.07-8.8)	0.0 (0.0-6.3)	0.7 (0.04-4.4)
Reaction at home	66.2 (54.5-76.4)	46.1 (34.7-57.8)	56.2 (48.0-64.1)
Reaction at school/day care	13.0 (7.7-23.0)	6.6 (2.4-15.3)	9.8 (5.8-15.9)
Reaction during exercise	8.5 (3.5-18.1)	5.2 (1.3-15.2)	7.0 (3.4-13.2)‖
Reaction during exercise in the context of food exposure	4.4 (1.1-13.2)	3.4 (0.6-12.9)	3.9 (1.4-9.3)‖

*Among 64 prospective reactions for foods, 4 for venom, and 2 for drugs, the self-reported trigger was confirmed (based on follow-up visits in the allergy clinic and use of skin prick test responses, specific IgE levels, or both) in 89%, 75%, and 50%, respectively.

†Among 68 retrospective reactions for foods, 2 for venom, and 2 for drugs for which information was available through chart review, the self-reported trigger was confirmed in 97.1%, 50%, and 50%, respectively.

‡Of all food-triggered reactions.

§Not clear whether the trigger was peanut or tree nut.

‖Among those for which full data exist (n = 129 and n = 125).

TABLE E2. Predictors of reaction severity

Predictor	Univariate (OR [95% CI])	Multivariate* (OR [95% CI])
Peanut exposure	11.2 (2.9-43.6)	18.8 (3.3-107.4)
Venom exposure	7.6 (1.2-46.6)	95.5 (7.7-1182.3)
Asthma	3.4 (1.0-11.6)	8.3 (1.7-40.4)

OR, Odds ratio.
*Adjusting for age; sex; type of trigger; level of activity; use of nonsteroidal anti-inflammatory drugs, β-blockers, monoaminoxidase inhibitors, tricyclic antidepressants, or angiotensin-converting enzyme inhibitors; and comorbid history.

TABLE E3. Comparison of anaphylaxis rates across countries

Country	Numerator/denominator	Study	Rate (%)	Canada vs comparator country (% difference [95% CI])
Canada (Montreal)	168/81,677	Ben-Shoshan et al	0.21	
United States (New York City)	213/118,680	Huang et al[1]	0.18	0.026 (−0.01 to 0.07)
Sweden (Stockholm)	140/447,739	Vetander et al[4]	0.031	0.17 (0.14 to 0.20)
Spain (San Sebastián)	64/133,591	Arroabarren et al[5]	0.047	0.16 (0.12 to 0.19)
Australia (Brisbane)	57/56,655	Braganza et al[6]	0.10	0.11 (0.06 to 0.15)