Are children with food allergies more likely to have lower urinary tract symptoms? A case-control study

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Introduction: *There are multiple historic reports linking lower urinary tract symptoms (LUTS) in children with food allergies (FA), but contemporary studies are sparse. The objective of this study was to evaluate a potential link between FA and LUTS in the pediatric population. We hypothesized that children with FAs are more likely to have LUTS.*

Materials and methods: *After local IRB approval, pediatric patients (6-17 years [y]) with FAs proven by positive skin prick and/or serum IgE testing were invited to participate. A control group of pediatric patients without FAs was also recruited. All families/legal guardians signed informed consent, and all children signed written assent. Each participant filled out the Vancouver Symptom Score (VSS), a validated questionnaire for dysfunctional elimination syndrome, and the Pediatric Incontinence Questionnaire (PinQ), a validated quality of life assessment for children with bladder dysfunction. Demographic and clinical information were obtained retrospectively.*

Results: *From 2019-2020, 26 children with FAs and 57 without agreed to participate. Mean age was 9.3 y (IQR 7.9 y-13.5 y). There were no differences in gender, age, or race between the two cohorts. There were no significant differences between the two groups in mean VSS score or mean PinQ score. Four children with FAs (15%) and 15 children without (26%) had VSS score ≥ 11 ($p = 0.339$), indicating dysfunctional elimination. The median PinQ score was 0 (IQR 0-2) in both cohorts.*

Conclusions: *This study did not identify an association between FAs and LUTS in a population of pediatric patients with laboratory proven FAs.*

Key Words: lower urinary tract symptoms, pediatric, food allergies, quality of life

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Introduction

Food allergies (FAs) are very common in children, now affecting up to 5%-10% of children in certain regions of the world.[1,2] FA is often not an isolated condition, as other comorbidities including asthma and other atopic conditions are common in children with FAs.[3] Interestingly, an association between allergies and lower urinary tract symptoms (LUTS) have also been

questioned in both adults and children, dating back to reports in the literature as early as the 1920s.[4,5]

LUTS have been reported to comprise up to 30% of pediatric urology outpatient visits and are known to have a substantial impact on quality of life of both the child and their caregivers.[6-8] However, the population of children with non-neurogenic lower urinary tract dysfunction, or even just subjective LUTS, is heterogeneous, making treatment challenging. In many cases, symptom control is difficult with standard urotherapy and constipation management.[9] Increasing understanding of any underlying conditions predisposing patients to LUTS or differences in pathogenesis may help direct more patient-specific management over a global approach.

Despite multiple prior reports associating FAs and voiding symptoms, the relationship is not clearly defined, and recent literature is scarce.[5,10] The objective of this study is to explore the association between lower urinary tract symptoms and FAs in children and adolescents. We hypothesized that children with FAs are more likely to have LUTS, particularly irritative voiding symptoms.

Materials and methods

After obtaining local institutional review board approval (IRB #170978), children (6-17 years old) presenting to the university pediatric allergy clinic for FAs were invited to participate. To be included, the FA patients had to have documented positive skin prick and/or serum IgE tests confirming presence of one or more specific FAs. A control group without FAs was recruited from the pediatric general clinic for comparison. Written informed consent was obtained by parent or legal guardian for participation, and all children signed a written assent form. Two cohorts were identified: a FA cohort and a control group. Demographic and clinical information including age, gender, race, type of allergy and reaction, and prior genitourinary (GU) history were collected retrospectively from the electronic medical record. The Vancouver Symptom Score (VSS),[6] a validated 14-item questionnaire for diagnosing dysfunctional elimination syndrome in children, and the Pediatric Incontinence Questionnaire (PinQ),[7] a 20-item quality of life assessment tool for children with bladder dysfunction, were administered to participants. Both utilize Likert-based response formats.

Descriptive statistics were performed for baseline patient demographics. The FA group was compared to the control group using Fisher's exact test for categorical variables and Non-Paired Wilcoxon Rank Sum Test for continuous variables. To evaluate a potential association between the type of FA and symptom score, the FA

TABLE 1. **Demographics**

	Total	**Food allergy**	**Control**	**p value**
N	83	26	57	
Gender				0.473
Male	50 (60%)	14 (54%)	36 (63%)	
Female	33 (40%)	12 (46%)	21 (37%)	
Age, years (median [IQR])		8.6 [7.4-12.3]	11.1 [8.1-13.714]	W = 560; 0.076
Race				0.261
White	40 (48%)	15 (58%)	25 (44%)	
African American	27 (33%)	7 (27%)	20 (35%)	
Asian	7 (8%)	1 (4%)	6 (11%)	
Hispanic	1 (1%)	1 (4%)	0 (0%)	
Multiracial	4 (5%)	2 (8%)	2 (4%)	
Unknown	4 (5%)	0 (0%)	4 (7%)	
Prior GU symptoms?				0.717
Yes	10 (12%)	4 (15%)	6 (11%)	
No	73 (88%)	22 (85%)	51 (89%)	
Previously seen by a urologist?				1
Yes	6 (7%)	2 (8%)	4 (7%)	
No	4 (5%)	2 (8%)	2 (4%)	
Missing	73 (88%)	22 (84%)	51 (89%)	

group was divided into children with nut allergies, seafood allergies, and multiple allergies. These groups were compared using Pearson's chi-squared test for categorical variables and Non-paired Wilcoxon Rank Sum Test for continuous variables. A similar analysis was done to investigate the association between different types of reactions (i.e. rash, swelling, anaphylaxis, gastrointestinal distress, etc.) and symptoms scores. Statistical significance was set at a p value of < 0.05.

Results

Between 2019-2020, 26 children with FAs and 57 without agreed to participate. Median age of the entire cohort was 9.3 years (IQR 7.9-13.5 years). There were no significant differences between groups in gender, age, or race, Table 1. The most common food allergy was peanut allergy in 58% of children with FA. Fifty-eight percent of children in the FA group were allergic to multiple foods. Fifteen percent of the FA group and 11% of the control group reported prior GU symptoms, most commonly bedwetting. Only two patients reported history of urinary tract infection (one FA, one control). No patients reported history of irritative LUTS. Only 8% of children with FA and 7% of children without had previously seen a urologist.

Comparison of VSS and PinQ score is summarized in Figure 1. The mean VSS among the FA group and control group were 7.7 and 8.3, respectively ($p = 0.828$). Using the validated VSS cut off score of 11 indicating dysfunctional elimination, four children (15%) with FAs and 15 controls (26%) had a score ≥ 11, which was not statistically significant ($p = 0.399$). There were also no significant differences between the two groups with regards to individual responses to the VSS questions, including questions regarding irritative symptoms such as frequency, urgency, and dysuria, Table 2. In terms of quality-of-life assessment, there was no difference in PinQ scores. Both groups had a median score of 0, indicating no significant overall bother. Mean scores PinQ scores were 2.15 and 2.2 in the FA and control groups respectively ($p = 0.633$). For the two children with UTI history, the patient with FA reported a VSS of 13 and the control patient reported a VSS of 11, both higher than the average VSS score of either cohort. For PinQ, the FA patient reported a score of 5, while the control patient reported a score of 0.

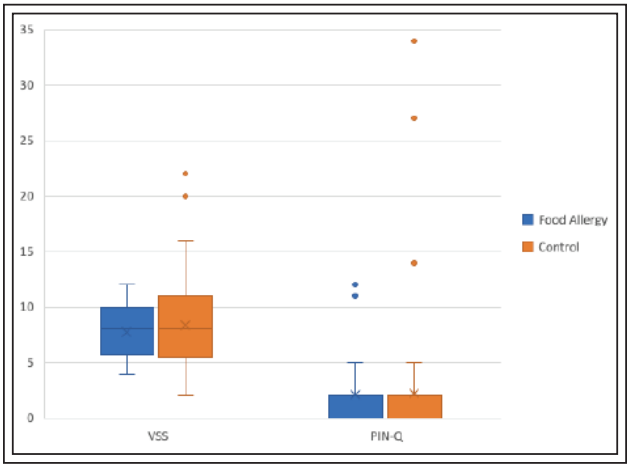

Figure 1. Symptom scores. VSS = Vancouver Symptom Score; PinQ = Pediatric Incontinence Questionnaire

Among the FA cohort, 17 had nut allergies alone, 3 had shellfish allergies, and 6 had multiple allergies. There was no significant difference in VSS or PinQ scores among the different types of food allergies ($p = 0.582$ and $p = 0.399$, respectively). Additionally, there was no significant association between type of reaction and VSS or PinQ score ($p > 0.05$ for each reaction).

Discussion

In this study, we investigated a potential relationship between laboratory-proven FAs and LUTS in pediatric patients. Using a validated symptom questionnaire, children with FAs did not report more LUTS compared to children without. Our results suggest that the relationship between FAs and lower urinary tract conditions is not substantial.

With resemblances to the respiratory and gastrointestinal tracts histologically, it has been theorized that the bladder may also be affected by the same inflammatory mediators in response to allergen exposure.[5] The activation and hyperplasia of mucosal mast cells in the intestine is known to be a key mediator in the development of IgE-related FAs and to play an important role in the immediate allergic reaction via release of chemical mediators including histamines and inflammatory cytokines.[11] Mast cells in the respiratory tract play a similar role in triggering a response to airway allergens.[12] However, mast cells are not unique to the respiratory and gastrointestinal lining and are also found within the mucosal surface of the bladder, where increased amounts of these cells have been associated with bladder conditions including interstitial cystitis (IC) and overactive bladder (OAB) in the adult population.13 In fact, increased levels of urinary histamines have been seen in patients with FAs.[14]

Considering the manifestations of FAs vary greatly, from bloating and stomach upset to more severe somatic reactions such as gastroenteritis,

TABLE 2. **Responses to VSS questions**[6]

	N	Food allergy (26)	Control (57)	p value
I pee in my underwear during the day:				1
Never	89% (74)	92% (24)	88% (50)	
One day/week	10% (8)	8% (2)	11% (6)	
2-3 days/week	1% (1)	0% (0)	2% (1)	
When I pee in my underwear they are:				0.718
I do not pee in my underwear	84% (70)	92% (24)	81% (46)	
Almost dry	7% (6)	4% (1)	9% (5)	
Damp	4% (3)	0% (0)	5% (3)	
Wet	5% (4)	4% (1)	5% (3)	
In a normal day I go to the washroom to pee:				0.292
1-2 times	19% (16)	23% (6)	18% (10)	
3-4 times	51% (42)	46% (12)	53% (30)	
5-6 times	22% (18)	15% (4)	25% (14)	
7-8 times	7% (6)	15% (4)	4% (2)	
More than 8 times	1% (1)	0% (0)	2% (1)	
I feel that I have to rush to the washroom to pee:				0.871
Never	31% (24)	32% (8)	30% (16)	
Less than half the time	54% (42)	60% (15)	51% (27)	
Half the time	10% (8)	8% (2)	11% (6)	
More than half the time	4% (3)	0% (0)	6% (3)	
Every day	1% (1)	0% (0)	2% (1)	
I hold my pee by crossing my legs or sitting down:				0.843
Never	49% (40)	54% (14)	47% (26)	
Less than half the time	33% (27)	31% (8)	35% (19)	
Half the time	15% (12)	12% (3)	16% (9)	
More than half the time	2% (2)	4% (1)	2% (1)	
It hurts when I pee:				0.526
Never	92% (76)	88% (23)	93% (53)	
Less than half the time	6% (5)	12% (3)	4% (2)	
Half the time	1% (1)	0% (0)	2% (1)	
More than half the time	1% (1)	0% (0)	2% (1)	
I wet my bed at night:				0.410
Never	87% (72)	88% (23)	86% (49)	
3-4 nights/month	8% (7)	4% (1)	11% (6)	
1-2 nights/week	2% (2)	4% (1)	2% (1)	
4-5 nights/week	1% (1)	4% (1)	0% (0)	
Every night	1% (1)	0% (0)	2% (1)	
I wake up to pee at night:				0.617
Never	47% (39)	50% (13)	46% (26)	
Less than half the time	35% (29)	42% (11)	32% (18)	
Half the time	10% (8)	4% (1)	12% (7)	
More than half the time	4% (3)	0% (0)	5% (3)	
Every day	5% (4)	4% (1)	5% (3)	

TABLE 2 (cont'd). **Responses to VSS questions**[6]

	N	Food allergy (26)	Control (57)	p value
When I pee, it stops and starts:				0.746
Never	81% (67)	81% (21)	81% (46)	
Less than half the time	16% (13)	15% (4)	16% (9)	
Half the time	1% (1)	0% (0)	2% (1)	
More than half the time	1% (1)	0% (0)	2% (1)	
Every day	1% (1)	4% (1)	0% (0)	
I have to push or wait for my pee to start:				0.385
Never	72% (60)	65% (17)	75% (43)	
Less than half the time	20% (17)	31% (8)	16% (9)	
Half the time	5% (4)	4% (1)	5% (3)	
More than half the time	2% (2)	0% (0)	4% (2)	
I have bowel movements (poop):				1
More than once a day	14% (12)	15% (4)	14% (8)	
Every day	53% (44)	54% (14)	53% (30)	
Every other day	30% (25)	31% (8)	30% (17)	
Every 3 days	2% (2)	0% (0)	4% (2)	
My stool (poop) is hard:				0.829
Never	37% (31)	42% (11)	35% (20)	
Less than half the time	36% (30)	35% (9)	37% (21)	
Half the time	12% (10)	8% (2)	14% (8)	
More than half the time	10% (8)	8% (2)	11% (6)	
Every day	5% (4)	8% (2)	4% (2)	
I have bowel (poop) accidents in my underwear:				1
Never	96% (80)	96% (25)	96% (55)	
1-2 times/week	4% (3)	4% (1)	4% (2)	

colitis, and anaphylaxis, physicians have questioned if an additional manifestation may include cystitis.[10,14] Allergic manifestations in the genitourinary tract, although rare, have been cited in the literature for many years. For example, in 1961, Powell described a severe edema of the bladder resulting in urinary obstruction as a result of food allergy.[15] Ammann and Rossi in 1966 described the case of a 3-year-old boy with multiple other allergic conditions who presented with periodic hematuria only related to eating pineapple, which resolved once pineapple was removed from the diet.[16] In 1971, Harrison noted that many patients were presenting to clinic for both allergy desensitization shots and for assessment of bladder symptoms, theorizing that a link may be present between the two conditions.[10] Further, Horesh presented 50 pediatric patients with recurrent urinary tract infections as well as allergic conditions such as asthma, allergic bronchitis, atopic dermatitis, and urticaria in 1976.[17] After being treated for their allergic conditions, recurrent urinary tract infections improved in the majority of cases, suggesting a link between the two conditions.[17]

Over time, we have increased our understanding of the pathogenesis of allergies, contributing to our understanding of their potential relationship to urologic conditions. It seems unusual that the large mucosal membrane surface of the bladder would be immune to allergy when allergy is so well described in the mucosal surfaces of the respiratory and gastrointestinal tracts.[5] However, the bladder theoretically does not have a high level of environmental exposure unlike the lungs, intestine, and skin, potentially explaining the rarity of allergic bladder conditions. Since those early reports, the true relationship between LUTS and allergies in children has not been well reported.

This study aimed to further investigate this idea, though we did not find a meaningful relationship

between patients with proven FAs and urinary symptoms as hypothesized. In fact, only 8% of patients with FAs had seen a urologist, compared to 7% in the control group. It is possible that perhaps the correlation between allergy and urinary symptoms may be more common in patients with other atopic conditions, including atopic dermatitis, asthma, or allergic rhinitis, but these patients were not captured by this study. Additionally, there may be an association between reported or subjective, but not proven, food allergy/sensitivity complaints and urinary symptoms resulting in frequent clinic visits. However, these patients were also not within the scope this study as our FA cohort was limited to only those with a diagnosis proven by skin prick or serum IgE testing. Further, the children included in the FA cohort were identified via the pediatric allergy clinic at our institution, and thus may have allergic symptoms under good control, or at least under active treatment. One potential question not captured by this study would be if these children had significant LUTS prior to their FA diagnosis and treatment.

Bladder symptoms and lower urinary tract dysfunction in children have also been related to many high-stress conditions, including school anxiety, bullying, abuse, and attention-deficit/hyperactive disorders.[18,19] Similarly, LUTS, including IC and OAB, in the adult population have also been associated with a variety of high-stress conditions, including not only anxiety and environmental stress, but also allergies.[20,21] IC, known to be affected by dietary intake, is also thought to at least partially be mediated by mast cells, raising the question of a potential relationship between food allergy and LUTS in both adults and children.[20,22,23] Although allergies can be considered a stressful condition, our results suggest true FAs are not correlated with LUTS. Again, children with undocumented subjective "allergy" symptoms resulting in stress and associated LUTS may not have been captured by this study.

Limitations

Limitations of this study include the small sample size and single institution basis of our study. Additionally, it is possible that with well-controlled allergies in our patient population, whether by avoidance of foods or medical treatment, urinary symptoms may be generally suppressed. Surveys reflected current symptoms, potentially excluding LUTS present prior to patients seeking medical treatment for their allergies. Although we did not identify a substantial relationship between FAs and urinary symptoms, we studied only patients with confirmed allergy testing, potentially excluding those with more subjective allergic complaints, or food intolerances instead of laboratory proven allergy. We also did not obtain information regarding subjective allergies in the control group, further complicating analysis. Future work is needed to better understand potential genitourinary manifestations of allergies in children.

Conclusions

Despite historic reports of associations between allergies and urinary symptoms, based on our sample, children with FAs documented via skin prick or serum IgE testing were not more likely to report lower urinary tract symptoms than children without. Although we did not find a significant relationship between the two conditions, limitations of our sample population leave room for further investigation. □

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