Original Article

Urological Manifestations in Pediatric Patients with Allergic Disorders: Associations or Manifestations.

Ahmed H Hassan[1], Ihab El-Hakim[1], Nada Elsoudy[1], Amani M.Abdel Ghani[2], Riham Ibrahim[3], Ghada Shousha[1]

1- Department of Pediatrics, Faculty of Medicine Ain Shams University, Egypt.
2- Department of Clinical Pathology, Faculty of Medicine Ain Shams University, Egypt.
3- Department of Pathology, Faculty of Medicine Ain Shams University, Egypt.

ABSTRACT

Introduction: The association between urinary abnormalities and allergic diseases was studied, but coincidence of allergy flare-ups with urological manifestations was seldomly discussed.
Aim of study: assess presence of urological manifestations in pediatric patients with various types of allergies and determine change in urological manifestations with allergic activity.
Methods: cross sectional pilot study with nested follow up, conducted in Allergy, Immunology and Rheumatology Clinic, Children's Hospital, our university over 6 months, March 2022 to September 2022. Patients diagnosed as allergy recruited consecutively during routine follow up. All patients screened at time of allergy flare-up for urological symptoms, 50 patients associated with urological symptoms were investigated at time of enrolment and at remission. Investigations included urine analysis, urinary eosinophils, and urinary eosinophilic cationic protein.
Results: Among 193 allergic children, 50 patients, aged 8.04 ± 2.97 years old, 28 (56%) boys and 22 (44%) girls, developed urological symptoms at time of allergy exacerbation (31.6%), 38% had combined forms of allergy. Statistically significant decline of urological manifestations found by time of allergy remission, on allergy controller therapies. Eosinophils were microscopically detectable in the urine of 18 (36%) of the studied patients during allergy flare-up, and not detected by remission. Urinary ECP median level was significantly higher at exacerbation than allergy convalescence.
Conclusion: Urological manifestations commonly associated with allergy flare-up, regardless type of allergy. Presence of urinary eosinophils and elevated levels of urinary ECP at allergy flare ups suggest that urinary system could be targeted by allergens, which needs more elucidation in further studies.

Keywords: Urological, Pediatric, Allergic

Corresponding author: Ahmed Hussein Hassan
Associate Professor of Pediatrics, Ain Shams University
Address: Villa 166 East Academy 3 First Settlement, New Cairo.
Email: ahmedkhattat@gmail.com
Phone: 01227956737/01069412333

INTRODUCTION

Allergic diseases such as bronchial asthma (BA), allergic rhinitis (AR), atopic dermatitis (AD), and food allergy (FA) are heterogeneous and multifactorial inflammatory diseases affecting people all around the world, and the clinical manifestations vary among allergic patients [1]. Allergic diseases are the most common chronic illness in children, followed by urinary incontinence. The association between urinary tract abnormalities and allergic diseases was studied **[2, 3, 4, 5].** Concerns were directed mainly to study the absurd connection between asthma and primary voiding dysfunction **[2, 6].**

The International Children's Continence Society (ICCS) has established standard definitions for urinary symptoms according to the phase of bladder function: storage or voiding. Therefore, symptoms include increased or decreased urinary frequency, urinary incontinence, urgency and nocturia. Voiding symptoms are classified as hesitation, straining, weak stream, and intermittency. Other symptoms involve holding manoeuvres, feeling of incomplete emptying, postmicturition dribble, and genital and lower urinary tract pain [7]. Studies were concerned with the possible association between presence of voiding dysfunction and allergic disorders **[3, 8].**

The similarity in the muscular and mucosal structure of the respiratory, gastrointestinal and urinary systems arouse the suggestion of the equal opportunity for the allergen to target any of these systems [9]. Functional bladder capacity was found to be significantly reduced after allergen exposure or at times of asthma exacerbations [10]. Disturbed sleep architecture and the negatively affected quality of life in asthmatic children were involved in augmenting the urological manifestations in those children.

Besides, kidney stone formation was 4-fold higher in asthmatic children compared to their healthy peers [11]. Monosymptomatic nocturnal enuresis has been reported to be correlated to the serum level of total IgE, absolute eosinophil count and allergen-specific IgE in allergic children **[6].** Moreover, allergic diseases were elicited in a group of adults with interstitial cystitis. Bladder biopsies of those patients showed infiltration with numerous eosinophils and mast cells, denoting the possibility of allergic impact on the urinary tract **[10].**

Therefore, the study aimed primarily to estimate the frequency of urological symptoms in association with childhood different forms of allergy during flare ups, followed by determination of however these symptoms were directly related to allergy or not through laboratory investigations at times of allergy flare ups and remissions.

METHODS:

Study design & settings: This study was a single arm cross sectional pilot study with nested prospective follow up. It was conducted at the Allergy, Immunology and Rheumatology Clinic, Children's Hospital, Ain Shams University, Cairo, Egypt, in the period from March 2022 to September 2022. Approval of the Research Ethics

Committee of Ain Shams University Hospitals number FMASU MS 138/2022 was accomplished, and participation in the study was done after obtaining the informed consent from the parents or caregivers and after explaining the nature, steps and benefits of the study.

Inclusion Criteria:

- Age between 1 and 16 years old.
- Both genders were involved.
- All types of allergy were represented, including allergic rhinitis (AR), bronchial asthma (BA), atopic dermatitis (AD) and food allergy (FA).
- Diagnosis of allergy was settled at least 6 months prior to enrolment.
- Patients with one form of allergy and those with combined allergies were included**.**

Criteria of allergy diagnosis, and determination of flare up and remission conditions:

Allergic rhinitis: AR is an immunoglobulin E (IgE)-mediated inflammatory nasal condition resulting from allergen introduction in a sensitized individual, with 3 cardinal symptoms: sneezing, nasal obstruction, and mucus discharge **[12]**. The Allergic Rhinitis and its Impact on Asthma (ARIA) proposals have categorized AR by presumed cause and seasonal vs perennial presentation **[13].**

Bronchial asthma: Diagnosis and severity of asthma followed the 2019 guidelines of The Global Initiative for Asthma (GINA) **[14]:**

Mild**:** Well-controlled with as-needed reliever medication alone or with low-intensity controller treatment such as low-dose inhaled corticosteroids (ICSs), leukotriene receptor antagonists, or chromones.

Moderate**:** Well-controlled with low-dose ICS/long-acting beta2-agonists (LABA).

Severe**:** Requires high-dose ICS/LABA, or asthma that remains uncontrolled despite this treatment.

Atopic dermatitis: In 2020, the European Task Force of Atopic Dermatitis (ETFAD) defined AD, severity, flare ups and remissions **[15]**. Flares are defined as disease worsening requiring escalation/intensification of treatment **[9]**. Description of AD lesions was illustrated by the American Academy of Dermatology (AAD). Acute lesions are itchy, red, small blisters or oozing. Chronic forms are dry, darkened, thickened skin. Each patient can have simultaneous acute, subacute and chronic forms **[17]**.

Food allergy: Flare up is defined as exposure to a food allergen that is followed by a rapid onset and evolution of symptoms over minutes to several hours. According to the European Academy of Allergy and Clinical Immunology (EACCI) guidelines **[18]**, food-induced anaphylaxis can have a milder course and resolve spontaneously and also can have severe course. FA can develop shortly after exposure to a culprit antigen, within minutes to few hours, in the form of mucocutaneous, respiratory, gastrointestinal, or more seriously, cardiovascular manifestations **[19]**.

Exclusion Criteria:

Patients associated with any of the following conditions were excluded:

- Acute or chronic renal diseases including congenital anomalies & metabolic disorders.

- Chronic diseases such as diabetes mellitus, celiac disease, and autoimmune diseases.
- Neurological or intellectual disorders.
- Chronic eczema, chronic urticaria or hereditary angioedema.

The end point of the first part of the study was to find 50 patients suffering from urological manifestations during allergy flare ups, in order to include them in the second part of the study to be investigated and followed up till full remission. Healthy control group was not involved as the aim of the study was to correlate the presence of urological manifestations at time of allergy flare ups with ECP and urinary eosinophils, in comparison to the remission status.

Study Tools:

All recruited patients were subjected to the following:

- Detailed history taking as regards socio-demographic data (age, gender and residency), family history of allergy or urological disorders and family history of primary or secondary voiding dysfunction.
- History of the allergic disease: type of allergy, duration of illness, disease controllability and adherence to treatment.
- Atopic status: through revising the medical records for the results of serum total IgE level and results of skin prick test if available. Positivity of any of them was considered sufficient to diagnose atopy **[20].**
- Screening for the presence of urological symptoms among children during allergy flare up, including dysuria, frequency, urgency, precipitancy, enuresis, loin or groin pain, oliguria (less than 0.5 mL/kg/hr), polyuria (more than 3 ml/kg/hr), change in color or odor of urine.
- Clinical examination: general and systemic examination including respiratory, cardiac and abdominal examinations were done to confirm the allergy flare up, and to examine for urological signs including loin pain, suprapubic tenderness, external genitalia affection, puffy eyelids or bilateral pitting lower limb edema.

All the recruited patients with concomitant urological manifestations and allergy flare ups were subjected to the following:

- Follow up till full remission of allergy.
- Clinical assessment for any urological manifestations during remission.
- Laboratory investigations during flare ups and remissions, as follows**:**
  - Complete blood count (CBC) with absolute eosinophil count (AEC).
  - Complete urine analysis including chemistry and cytology.
  - Eosinophil Cationic protein (ECP) in urine, using enzyme immunoassay **[21].**

Blood sampling: A 2 ml venous blood was withdrawn by a trained nurse under aseptic conditions. CBC was done using an automated cell counter (Coulter MicroDiff 18, Fullerton, CA, USA) and

differential counting was done manually. Measuring AEC needed multiplying the total white blood cells (WBC) count by the percentage of eosinophils [22].

Complete urine analysis:

- Urine sample collection: Samples were collected after cleaning the urinary opening with a sterile wipe to remove bacteria. Male children wiped the tip of the penis. Female children cleaned their labia from front to back. Samples were collected from the midstream.
- Chemical examination [23]**:** reagent strips were impregnated with reactive chemicals. Each strip was dipped into the urine. Any abnormality in the urine composition triggers a color change within seconds or minutes. The 10 performed reagent were bilirubin, erythrocytes, glucose, ketones, leukocytes, nitrites, pH, protein, specific gravity and urobilinogen.
- Microscopic examination [24]**:** the urine sample was centrifuged and spined at a rapid speed to precipitate the sediment. A drop or two of the sediment was then placed on a slide under the microscope. Cells, crystals and other substances were counted and reported as "per high power field" (HPF). In this test, the followings were screened: Bacteria, yeast or parasites, casts, crystals, epithelial cells, red cells, pus cells and urinary casts.

Urinary eosinophil count: Urine was tested for the presence of eosinophils using Hematoxylin and Eosin (H and E) stain. Twenty millilitres of freshly voided urine were collected from each patient and 12 ml was centrifuged at 1400 rpm for 5 minutes. The supernatant was discarded and the remaining specimen was examined microscopically. The slide was stained by H and E stain, then magnified to 400 and examined for the presence of eosinophils for every 100 white cells present, and the results were expressed as a percentage. Urinary eosinophils were considered positive when eosinophils were at least 1% of all urinary white cells. H and E stain easily identifies eosinophils depending on its morphology, red or pink appearance with bi-lobed nucleus and the cytoplasm was stained pink with its characteristic eosinophilic granules [25].

The testing of urine for eosinophils was conducted by a consultant pathologist in a blinded manner to the clinical data and laboratory investigations of the cases. As it was difficult for eosinophils to sustain centrifugation, this examination is considered a good positive test for urinary eosinophils. Normally, eosinophils are not detectable in urine.

Eosinophil Cationic protein (ECP) in urine:

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human ECP in samples. Specimens were preserved in -80ºc in sterile container, centrifuged 20 min at the speed of 2000-3000 rpm, then the supernatant was removed. ECP solution was added to monoclonal antibody enzyme well which was pre-coated with Human ECP monoclonal antibody and incubated. Then, we added ECP antibodies labelled with biotin reacting 60 minutes at 37 ℃. and combined with Streptavidin-HRP to form immune complex; then we carried out incubation and washing again to remove the uncombined enzyme. Then Chromogen Solution A, B, were added reacting 10 minutes at 37 ℃, the color of

the liquid was changed into the blue, and at the effect of acid, the color finally became yellow. The chroma of color and the concenthumanion of the Human Substance ECP of sample were positively correlated then the OD value was measured within 10 min and we calculated out the standard curve linear regression equation. The levels of urinary ECP were compared at time of flare up and remission, not to the reference of the kit [21].

STATISTICAL ANALYSIS

Statistical analysis was performed with statistical package for social science (SPSS 27). Numerical data were summarized using mean and standard deviation or median and range. Comparison between variables were evaluated by chi-square test, Wilcoxon Ranks test, Mann-Whitney test, independent t-test. P-value <0.005 was considered significant.

RESULTS

The ages of the 193 allergic participants ranged between 1-16 years (7.83+4.22); 114 (59%) males and 79 (40.9%) females. Type of their allergy was distributed as follows: bronchial asthma (BA) in 50.2 % of patients (62 males, 35 females), allergic rhinitis (AR) among 25.9% (29 males, 21 females), atopic dermatitis (AD) in 13.9% (13 males, 14 females) and food allergy (FA) in another 9.8% of patients (10 males, 9 females).

Urological symptoms were reported by 31.6% (50/193) of patients in association with their allergy flare ups. The mean age of those 50 patients was 8.04 ± 2.97 years old (range 3-15 years old), being 28 (56%) boys and 22 (44%) girls, with 62% of them were living in urban areas. The type of their allergic disease was distributed as follows: 50% with BA, 40% with AR, 32% with AD and 20% with FA, taking into consideration that 38% of the patients had more than one allergic manifestation **Table 1**.

Atopy was defined among 26 (52%) patients and non-atopic status was defined in the residual 4 (8%) patients depending on the results of SPT and total IgE results. Atopy was undetermined among 20 (40%) patients, who lack the results of total IgE, skin prick test (SPT) or serum specific IgE in their medical records **Table 2**.

The urological manifestations detected at time of the allergy flare ups were, from more to less frequently encountered: frequency in 32 (64%) children, change of urine color and change of urine odor in 20 (40%) patients each, urgency in 15 (30%) children, enuresis in 9 (18%) patients, loin pain in 6 (12%) patients, dysuria in 3 (6%) patients and polyuria in only one (2%) patient **Figure 1**.

Clinical and laboratory assessments were done at times of flare ups and remissions. All the studied children reported complete disappearance of the urological manifestations at times of allergy remissions without receiving any medications other than the specific allergy controllers **Table 3**. Therefore, urological manifestations at time of allergy flare ups are likely related to the allergy itself.

As regards the laboratory investigations **Table 4**, AEC levels were

significantly decreased at times of remission (median 0, IQR 0 – 120 cells/cm^3) compared to flare ups (median 260, IQR 120 – 500 cells/cm^3) (p= 0.000). AEC level was elevated in 27 (54%) patients. Urine chemistry was positive for crystals, WBCs or bacteria in 15 (30%) patients, and negative in the other 35 (70%) patients at time of flare ups, whereas by remission, urine chemistry was abnormal in 17 (34%) patients and normal in the other 33 (66%) of patients (p= 0.668). Crystals were the only found abnormality in the urine of patients at time of remission.

Eosinophils were microscopically detectable in the urine of 18 (36%) of the studied patients during allergy flare up, and not detected in the urine of all patients by remission (p=0.000) **Figure 2**. ECP median level in urine of the studied patients was 43 (IQR: 30 – 53) ng/ml at time of flare up with extremely high level up to 120 ng/ml in one patient. The median level of urinary ECP decreased significantly during remission (median: 12.75, IQR:11–22.5) (p= 0.000) **Figure 3.**

Table 1: Demographic data and characteristics of the studied patients

		Total = 50
Age (years)	Mean ± SD	8.04 ± 2.97
	Range	3 – 15
Gender	Male	28 (56%)
	Female	22 (44%)
Residency	Rural	19 (38%)
	Urban	31 (62%)
Combined	No	31 (62%)
	Yes	19 (38%)
Type of allergy	BA	25 (50%)
	AR	20 (40%)
	AD	16 (32%)
	FA	10 (20%)
Age of diagnosis (years)	Median (IQR)	3 (1 – 5)
	Range	0 – 11
Family history of allergy	Negative	19 (38%)
	Positive	31 (62%)

AD: atopic dermatitis, AR: allergic rhinitis, BA: bronchial asthma, FA:food allergy, IQR: interquartile range, No.: number.

Table 2: Atopy status of the studied patients based on the results of total IgE levels and SPT

		Total =50
SPT	Positive	18 (36%)
	Negative	2 (4%)
	Not done	30 (60%)
Total IgE	High	15 (30%)
	Low	8 (16%)
	Not done	27 (54%)
Total IgE (mg/dl)	Median (IQR)	176.9 (52 – 363)
	Range	15.3 – 1448
Atopy	Atopic	26 (52%)
	Non atopic	4 (8%)
	Undetermined	20 (40%)

SPT: skin prick test, IgE: immunoglobulin E, IQR: interquartile range

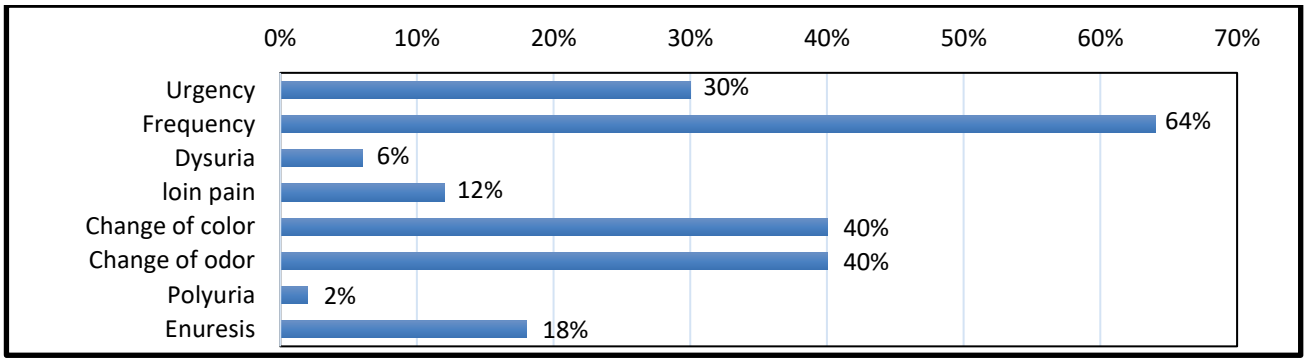

Figure 1: Distribution of the urological manifestations among all the studied patients

Table 3: Comparison between urological manifestations at activity and at remission among all the studied patients

Urological manifestations		At activity	At remission	P-value	Sig.
Urgency	No	35 (70%)	50 (100%)	**0.000**	**HS**
	Yes	15 (30%)	0 (0%)		
Frequency	No	18 (36%)	50 (100%)	**0.000**	**HS**
	Yes	32 (64%)	0 (0%)		
Dysuria	No	47 (94%)	50 (100%)	0.079	NS
	Yes	3 (6%)	0 (0%)		
loin pain	No	44 (88%)	50 (100%)	**0.012**	**S**
	Yes	6 (12%)	0 (0%)		
Change of color	No	30 (60%)	50 (100%)	**0.000**	**HS**
	Yes	20 (40%)	0 (0%)		
Change of odor	No	30 (60%)	50 (100%)	**0.000**	**HS**
	Yes	20 (40%)	0 (0%)		
Polyuria	No	49 (98%)	50 (100%)	0.315	NS
	Yes	1 (2%)	0 (0%)		
Enuresis	No	41 (82%)	50 (100%)	**0.002**	**HS**
	Yes	9 (18%)	0 (0%)		

NS: Non-significant; S: Significant; HS: Highly significant *: Chi-square test

Table 4: Comparison between laboratory data at activity and at remission among all the studied patients

		At activity	At remission	Test value	P-value	Sig.
AEC	Median (IQR)	260 (120 – 500)	0 (0 – 120)	-5.91≠	0.000	HS
	Range	0 – 3900	0 – 200			
AEC for age	Normal	19 (38%)	23 (46%)	44.45*	0.000	HS
	Low	4 (8%)	27 (54%)			
	High	27 (54%)	0 (0%)			
Urine chemistry	Negative	35 (70%)	33 (66%)	0.18*	0.668	NS
	Positive	15 (30%)	17 (34%)			
Urine eosinophils	Negative	32 (64%)	50 (100%)	21.95*	0.000	HS
	Positive	18 (36%)	0 (0%)			
ECP in urine	Median (IQR)	43 (30 – 53)	12.75 (11 – 22.5)	-5.91≠	0.000	HS
	Range	8 – 120	7.5 – 30			

NS: Non-significant; S: Significant; HS: Highly significant *: Chi-square test; ≠: Wilcoxon Ranks test

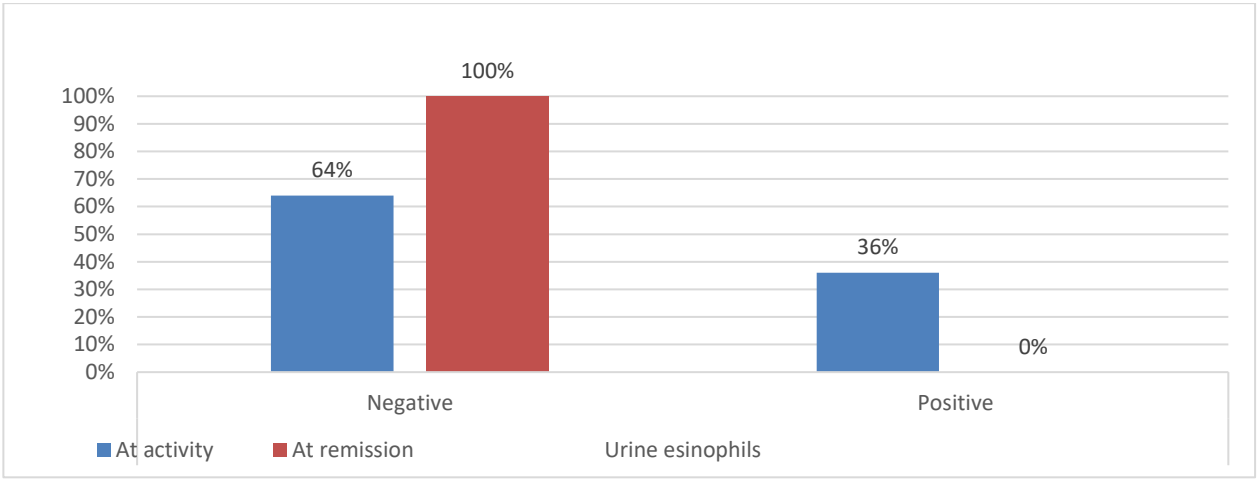

Figure 2: Comparison between urine eosinophils in allergy flare up and remission among all the studied patients.

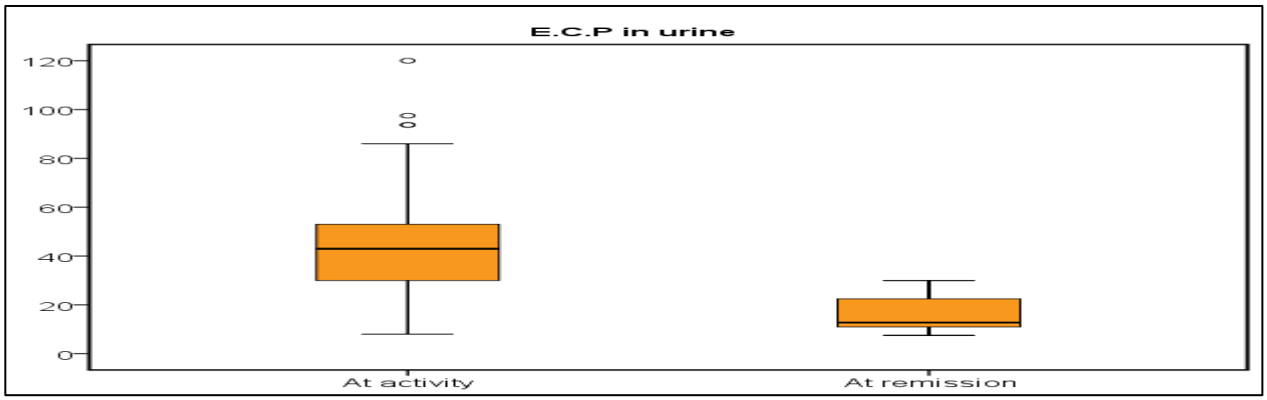

Figure 3: Comparison between ECP in urine in allergy flare up and remission among all the studied patients.

DISCUSSION

It has been suggested that allergic diseases may be associated with urinary tract disorders. Some authors proposed that food allergy, asthma and allergic rhinitis may result in nocturnal enuresis **[10, 5, 26].**

Patients with urological manifestations in association with allergy flare ups were followed up till remission. Interestingly, the urological manifestations regressed with the control of allergic symptoms in all patients. The most frequently encountered urological manifestations were urinary frequency, followed by change in urine color and odor, enuresis and loin pain. Dysuria and polyuria were the least reported manifestations. The connection between enuresis, particularly nocturnal enuresis (NE), and allergy was observed and studied by many authors. Commonly, enuresis was associated with increased estimates of AR and asthma **[10, 26, 27]**. It was demonstrated in one study that children with NE had higher incidence of AD and allergic conjunctivitis as well as AR **[5].** It has been suggested that allergic disease and the bladder may share a common allergic response pathway. The bladder acts as a target organ for allergens in triggering NE onset. Moreover, excessive parasympathetic nervous system activation after cycles of allergic responses

detrusor instability and overactive bladder [5]. Higher estimates of AR and asthma (54.3%) were reported in children with complicated dysfunctional bladder disorders [28]. Close to our results, ***Dahan et al.*** [29] demonstrated that asthma increased odds for nocturnal enuresis in children to 1.9. On the other hand, frequency of asthma was higher among children with NE compared to their continent peers. Another retrospective study conducted on children with bladder dysfunction showed presence of history of variable allergic manifestations, respiratory, conjunctival and cutaneous, with significantly elevated serum levels of total IgE [8]. ***Soyer et al.*** [2] denoted that asthma children had a higher incidence of frequency and urgency.

Median absolute eosinophilic count (AEC) of the studied patients at time of flare ups was 260 cells/mm^3 (ranged from 120 to 3900 cells/mm^3), which decreased significantly at time of remission ($p< 0.001$). In hand with these results, ***Mudhusudanet al.*** [30] reported high AEC at time of allergic disease activity with mean values 440 cells/mm^3 and ***Surana et al.*** [31] reported AEC mean levels of 450 ± 210 cells/mm^3 at flare ups, with significant decrease in the levels by remission. Mean values of AEC were comparable between different types of allergies at time of activity and remission. In concordance to our results, ***Surana et al.*** [31] did not report significant differences between variable allergic diseases regarding AEC.

Notably, urinary eosinophils were detectable among the studied allergic patients with urological manifestations at time of flare ups and disappeared by time of remission ($p< 0.001$). Urinary eosinophilic cationic protein (ECP) was estimated in significantly higher levels at time of allergy exacerbation compared to remission ($p< 0.001$). In concordance to our findings, there were significant elevated urinary eosinophils and ECP among asthmatic children compared to control group ($p= 0.03$) [32]. Also, *Shah et al.* [33] reported that allergic flare ups were associated with significantly increased levels of serum and urinary ECP in comparison to remission status. Similarly, *Gore et al.* [38] showed that patients in exacerbation of allergic diseases had higher urinary ECP, and many authors agreed on the positive correlation between urinary ECP levels and asthma activity [34,35,36,37]. Based on our findings and the results of the previously mentioned studies, presence of urinary eosinophils and ECP at times of allergy exacerbation, parallel with the occurrence of urological symptoms, followed by regression of both the clinical and laboratory abnormalities by the control of allergy would support our suggestion that allergy can target the urinary tract and show up with variable urological manifestations.

Our studied patients were comparable as regards types of allergy in one arm, and the different urological manifestations. On the contrary, *Tsai et al.* [5] found higher incidence of enuresis among children with AR and AD than asthmatics. However, *Ozkaya et al.* [6] reported higher incidence of NE among children with asthma and AR than AD. Moreover, no statistically significant difference was found among different types of allergy as regards urinary ECP.

This was not the situation in *Gore et al.* [38] who reported higher estimates of urinary ECP among children with asthma and AD compared to AR. However, in the latter study, urinary ECP was measured to all allergic children regardless the presence or absence of urological manifestations in association. This can explain the elevated levels of urinary ECP in our studied allergic children with urological symptoms at time of flare up, therefore, this supports our suggestion that urinary ECP is not only related to the atopic status, but also to the urinary tract affection during allergy exacerbation, regardless the type of allergy.

Urinary ECP did not correlate to the age or gender of our studied children. Unlikely, ***Gore et al.*** [38] found that allergic boys had significantly higher urinary ECP than girls, which needs to be verified on wider samples of allergic children, and in different age groups. Surprisingly, urinary ECP did not correlate to AEC levels, serum IgE levels or urinary eosinophils. Unfortunately, we could not trace such a correlation in the published studies, as they were concerned with serum rather than urinary ECP as biomarker of atopy [39, 40]**.** However, urinary ECP was significantly correlated to the incidence of urgency (p= 0.04) and enuresis (p= 0.04) in the studied population. Such correlations were not referred to in the literature as per our knowledge. This is because there is lack in the area of research as regards the associated urological manifestations with allergy flare ups and the possible underlying common immunopathological ground. The research work focused on the correlations between eosinophilic biomarkers and allergy rather than allergy flare ups in association with urological symptoms.

In conclusion, urological manifestations in association with allergy flare ups were associated with high estimates of urinary eosinophils and urinary ECP, which supports our theory that the urinary tract can be targeted by allergy**.** Wider scaled studies are needed to elucidate the possible common immunopathogenesis between allergy and the urinary tract. This study was limited by the lack of healthy control group for comparison.

ABBREVIATIONS

AAD	The American Academy of Dermatology	**GINA**	The Global Initiative for Asthma
AD	Atopic dermatitis	**HPF**	High power field
AEC	Absolute eosinophil count	**ICCS**	International Children's continence society
AR	Allergic rhinitis	**ICS**	Inhaled corticosteroids
ARIA	Allergic Rhinitis and its Impact on Asthma	**IgE**	Immunoglobulin E
BA	Bronchial asthma	**LABA**	Long acting beta2 agonist
CBC	Complete blood count	**LPF**	Low power field
EACCI	European Academy of Allergy and Clinical	**SABA**	Short acting beta2 agonist
ECP	Immunology	**SPSS**	Satistical package for social science
ETFA	Eosinophilic cationic protein	**SPT**	Skin prick test
D	The European Task Force of Atopic Dermatitis	**WBC**	White blood cells
FA	Food allergy		
FEIA	Fluoro-enzyme immunoassay		

REFERENCES

1. Bieber T, Angelo MD, Akdis CA, Traidl-Hoffmann C, Lauener R, Schäppi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go?. J Allergy Clin Immunol 2017; 139(4):S58-64.
2. Soyer OU, Kilincoglu B, Senyucel MF, Aslan MK, Cakmak M, Dallar Y, et al. Dysfunctional voiding in children with asthma. Arch Dis Child 2013; 98(4):312-4.
3. Karakas HB, Mazlumoglu MR, Simsek E. The role of upper airway obstruction and snoring in the etiology of monosymptomatic nocturnal enuresis in children. Eur Arch Otorhinolaryngol 2017; 274:2959–63
4. Yılmaz-Durmuş S, Alaygut D, Soylu A, Alparslan C, Köse SŞ, Anal Ö. The association between monosymptomatic enuresis and allergic diseases in children. Turk J Pediatr 2018; 60(4):415-20.
5. Tsai JD, Chen HJ, Ku MS, Chen SM, Hsu CC, Tung MC, et al. Association between allergic disease, sleep-disordered breathing, and childhood nocturnal enuresis: a population-based case-control study. Pediatr Nephrol 2017; 32(12):2293-301.
6. Ozkaya E, Aydın SC, Yazıcı M, Dundaröz R. Enuresis Nocturna in children with asthma: prevalence and associated risk factors. Ital J Pediatr 2016; 42:1-6.
7. Linde JM, Nijman RJM, Trzpis M, Broens PMA. Prevalence of urinary incontinence and other lower urinary tract symptoms in children in the Netherlands. J Pediatr Urol 2019; 15(2): 164-e1.
8. Zheng Y, Zhang Z, Hou L, Wang X, Jiang K, Zhang S, et al. Clinical Observation of the Correlation Between Overactive Bladder and Atopic Constitution in Children. Front Pediatr 2021; 9:646118.
9. Zaleski A, Shokeir MK, Gerrard JW. Enuresis: familial incidence and relationship to allergic disorders. Can Med Assoc J 1972; 106:30-1.
10. Mungan NA, Seckiner I, Yesilli C, Akduman B, Tekin IO. Nocturnal enuresis and allergy. Scand J Urol Nephrol 2005; 39(3):237-41.
11. Kartha GK, Li I, Comhair S, Erzurum SC, Monga M. Co-Occurrence of Asthma and Nephrolithiasis in Children. PLoS ONE 2017; 12.1:e0168813.
12. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. Int Forum Allergy Rhinol 2018; 8(2):108-352.
13. Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol. 2019; 143(3):864-79.
14. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. Available from: www.ginasthma.org
15. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, et al. European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy. J Eur Acad Dermatol Venereol 2022; 36(9):1409-31.
16. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020; 396(10247): 345-60.
17. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis. Section 1: Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014; 70(2):338-51.
18. Halken S, Muraro A, de Silva D, Khaleva E, Angier E, Arasi S, et al. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol 2021; 32(5):843-58.
19. Li X, Ma Q, Yin J, Zheng Y, Chen R, Chen Y, et al. A Clinical Practice Guideline for the Emergency Management of Anaphylaxis (2020). Front Pharmacol 2022;13:845689.
20. Justiz Vaillant AA, Modi P, Jan A. Atopy. [Updated 2022 Jul 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls 2023.

21. Frandsen B, Lose G. Determination of eosinophil cationic protein in urine by an enzyme immunoassay. Scand J Clin Lab Invest 1986; 46(7):629-34

22. Klion AD, Ackerman SJ, Bochner BS. Contributions of eosinophils to human health and disease. Ann Rev Pathol: Mechan Dis 2020; 15:179-209.

23. Ko DH, Jeong TD, Kim S, Chung HJ, Lee W, Chun S, et al. Influence of Vitamin C on Urine Dipstick Test Results. Ann Clin Lab Sci 2015; 45(4):391-5.

24. Riley RS, McPherson RA. Basic examination of urine. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Philadelphia, PA: Elsevier.2022; chap 29.

25. Song Y, Yin J, Chang H, Zhou Q, Peng H, Ji W, et al. Comparison of four staining methods for detecting eosinophils in nasal polyps. Sci Rep 2018; 8(1):17718.

26. Lai PH, Yang PS, Lai WY, Lin CL, Hsu CY, Wei CC. Allergic rhinitis and the associated risk of nocturnal enuresis in children: a population-based cohort study. Intern Forum Allergy Rhinol 2018; 8(11):1260-6.

27. Ziaei E, Dorreh F, Yousefichaijan P, Sarmadian R, Sajjadi N, Kahbazi M. Evaluation of the association between asthma and non-neurogenic urinary incontinence in children; a case-control study. BMC Pediatr 2023; 23(1):1-7.

28. De Jesus LE, Tomé A, Cobe D, Camelier P. Psychosocial and respiratory disease related to severe bladder dysfunction and non-monosymptomatic enuresis. J Pediatr Urol 2016; 12(2):126-e1.

29. Dahan P, de Bessa J, de Oliveira DM, Gomes CC, Cardoso JC, Macedo IT, et al. Association between asthma and primary nocturnal enuresis in children. J Urol 2016; 195(4):1221-6.

30. Madhusudan SR, Prabhavathi R, Sandhya V, Ranganath, KR. Comparative Study Between Nasal Smear Eosinophilia And Absolute Eosinophilic Count In Children With Allergic Rhinitis. Europ J Mol Clin Med 2022; 9(4):1617-21.

31. Surana M, Pande V, Agarkhedkar S, Teegala A. Correlation between Total Serum Immunoglobulin E (IgE) and Absolute Eosinophil Count (AEC) in Allergic Diseases In Children. VIMS Health Sci J 2020; 7(1):5-9.

32. Oh JW, Shin SA, Lee HB. Urine leukotriene E4 and eosinophil cationic protein in nasopharyngeal aspiration from young wheezy children. Pediatr Allergy Immunol 2005; 16(5):416-21.

33. Shah SN, Grunwell JR, Mohammad AF, Stephenson ST, Lee GB, Vickery BP et al. Performance of eosinophil cationic protein as a biomarker in asthmatic children. J Allergy Clin Immunol: In Pract 2021; 9(7):2761-9.

34. Storm Van'S Gravesande K, Mattes J, Gruntjens T, Kopp M, Seydewitz HH, Moseler M, et al. Circadian variation of urinary eosinophil protein X in asthmatic and healthy children. Clin Exp Allergy 1999; 29(11):1497–501.

35. Hoekstra MO, Hovenga H, Gerritsen J, Kauffman HF. Eosinophils and eosinophil-derived proteins in children with moderate asthma. Eur Respir J 1996; 9(11):2231-5.

36. Khalil Kalaajieh W, Hoilat R. Asthma attack severity and urinary concentration of eosinophil X protein in children. Allergol Immunopathol (Madr) 2002; 30(4):225-31.

37. Nuijsink M, Hop WC, Sterk PJ, Duiverman EJ, Hiemstra PS, de Jongste JC, et al. Urinary eosinophil protein X in children with atopic asthma. Mediators Inflamm 2007; 2007:49240.

38. Gore C, Peterson CG, Kissen P, Simpson BM, Lowe LA, Woodcock A, et al. Urinary eosinophilic protein X, atopy, and symptoms suggestive of allergic disease at 3 years of age. J Allergy Clin Immunol 2003; 112(4):702-8.

39. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Europ Respir J 2018; 51:5.

40. Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol: In Prac 2019; 7(1):156-64.

AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.

All authors have contributed to authorship, have read and approved the manuscript.

Conception and design of study: AH, IEH, GS.

Acquisition of data: NES

Analysis and/or interpretation of data: AH, IEH, GS, NES, RI, AAG.

Drafting the manuscript: AH, GS.

Revising the manuscript critically for important intellectual content: AH, IEh, GS.

Approval of the version of the manuscript to be published: AH, IEH, GS, NES, RI, AAG.

STATEMENTS

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Ain Shams University Hospitals number FMASU MS 138/2022 and informed written consent was obtained in every case from their legal guardians.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material

"Not applicable"

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors declare that this research work did not revise any fund.

Acknowledgements

Authors would like to thank all patients and their family members for their valuable contributions to the study.

Submission Date: **16/08/2023**
Acceptance Date: **15/11/2023**
Publication Date: **31/12/2023**