Original article

Screening for allergic disorders among adults and children with kidney disease

Background: *Patients with kidney disease may exhibit various allergic disorders and allergy mimickers. Recognition of these reactions is essential to establish correct diagnosis and initiate the proper treatment. We sought to assess the frequency of different allergic disorders among adults and children with kidney disease* ***Methods:*** *We conducted a cross-sectional study focusing on screening for allergic manifestations among 170 patients (130 adults and 40 pediatric) with different renal diseases. All cases were screened using an allergy questions checklist including allergy type, trigger, duration, associated symptoms, and use of anti-allergic medications. Patients were subjected to laboratory assessment including renal function tests, serum electrolytes, parathormone and complete blood picture.* ***Results****: We enrolled 55 patients with acute and 115 patients with chronic renal disease including 41 patients on regular hemodialysis. Thirty-nine percent of patients complained of one or more allergic manifestations, with the bronchial asthma most prevalent (19.4%) followed by allergic rhinitis (7.1%). In the adult group, 40% of patients had allergic diseases; 21.5% had asthma followed by allergic rhinitis (6.9%), while 9.2% had chronic kidney disease-associated pruritus (CKDaP). In the pediatric group, 37.5% had allergic diseases including asthma (12.8%), allergic rhinitis (7.5%), while 10% of patients had CKDaP. Allergic and non-allergic patients were comparable in terms of their clinicodemographic data and laboratory assessment except for higher platelet count among allergic patients (p=0.022). Urea and parathormone hormone (PTH) levels were higher among patients with CKDaP (p-value <0.05).* ***Conclusion:*** *Kidney diseases are associated with a complex array of allergic manifestations. Awareness of allergy disorders and differentiation from allergy mimickers would help in proper direction of the management plan, decreasing comorbidities and improving quality of life.*

Keywords: Allergic diseases, Adults, Children, kidney disease

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INTRODUCTION

Allergy is an exaggerated response from the immune system to inert substances present in the environment. Allergy symptoms range from mild to life-threatening reactions, the usual symptoms are pruritus, rash, urticaria, angioedema, vomiting, abdominal cramping, shortness of breath, wheezing and bronchospasm, stridor, syncope or collapse.[1] Allergy is a class of hypersensitivity reactions, while Atopy is a genetic predisposition to allergic

diseases and every atopic reaction is considered an allergy.[2]

Risk factors associated with allergic diseases include familial or personal atopy, female sex, personal or passive smoking at home, pet ownership in childhood, and living in a rural area.[3] The allergic reaction involves different target tissues including conjunctiva, upper and lower airways, skin, gastrointestinal system, and kidney leading to the development of different allergic diseases such as allergic conjunctivitis (AC), allergic rhinitis (AR), allergic asthma, atopic dermatitis/eczema, allergic enteritis and nephropathy.[4]

Hypersensitivity nephropathy is an allergic interstitial nephritis (AIN), which is the most common form of acute interstitial nephritis. It is most often caused by exposure to a drug. AIN is often associated with an acute decline in renal function and may be associated with permanent renal insufficiency. The hallmark histopathologic finding of AIN is a marked inflammatory infiltrate of the renal interstitium.[5]

Pruritus is a common symptom among patients on dialysis, less frequently, pruritus occurs in non-dialysis chronic kidney disease patients. Pathophysiology is incompletely understood; however, non-allergic theories are dominant in this issue including uremia, neuropathy, and hyperparathyroidism, the preferred term is chronic kidney disease–associated pruritus (CKD-aP).[6]

Allergy in renal patients has not been extensively studied in medical research, it could be categorized into four groups; first, the allergic kidney diseases as allergic interstitial nephritis, second; the primary allergy disorders in renal patients, third; the reactions to dialyzers, fourth, the allergy mimickers as uremic pruritis. Hence, this study is aimed to assess clinico-epidemiological aspects of allergic diseases among adults and children with kidney disease.

METHODS

A cross-sectional hospital-based study was conducted on patients with kidney diseases in the in-patient ward and out-patient nephrology, pediatric nephrology, immunology and allergy clinics in Menoufia University and the nearby hospitals in Menoufia, Egypt. Adults and children above 2 years of both genders were included. Patients with acute or chronic kidney diseases diagnosed according to kidney disease Improving Global Outcomes (KDIGO) criteria [7, 8] were included in the study. A cluster sample of renal patients was recruited from September 2022 to February 2024.

Study tools

The main study tools included an investigator-constructed checklist of questions related to allergic and renal diseases together with laboratory assessment. All participants were subjected to screening for allergic manifestations by an English written checklist of questions that was expert-revised, pilot studied and reformatted before finally being administered to patients/legal guardians by the investigators (supplementary file 1). The check list questions included the following:

Questions related to the underlying renal disease: Patients were checked for the underlying renal disease, physician diagnosis, renal disease duration, whether acute or chronic, renal disease related treatment (e.g. dialysis, antihypertensives, hormonal therapy ...etc.) and the associated comorbidities. The distinction between acute and chronic kidney injury was done according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria [7, 8] which is based mainly on the duration of the injury. Specifically, kidney injury is classified as acute if it lasts for less than three months and as chronic if it persists for three months or longer. All available documents for the underlying renal disease and their related medications were examined.

Questions related to screening for allergic manifestations: Using the allergy check list questions, the patients/parents were investigated for the following items:

1. Type and pattern of allergic disease: Different allergic diseases were screened for, including atopic dermatitis, allergic rhinitis, allergic asthma, allergic conjunctivitis, urticaria, - angioedema, food allergy and severe allergic reactions (anaphylaxis). 2. Allergic disease onset, course, duration, and seasonal variation. 3. Possible triggers for allergic manifestations: food, drug, inhalation, insects, contacts, physical stimuli, infections, stress, latex, detergents, pet ownership, and any other environmental exposure. 4. Associated symptoms including: fever, stridor, wheeze, or any systemic features. 5. Associated any underlying immunological disease (e.g. autoimmune, immunodeficiency...etc.). 6. Family history of allergic diseases. 7. Use of anti-allergy medications including systemic and local antihistamines, mast cell stabilizers, topical/local and systemic corticosteroids, short and long acting B2 agonists, moisturizer ointments, antileukotrienes and nasal lavages.

We defined major allergic diseases according to the international consensus of diagnostics or expert consensus including Allergic Rhinitis,[9] asthma,[10] Atopic Dermatitis/eczema,[11] urticaria,[12] Allergic Conjunctivitis,[13] and anaphylaxis.[14] Specific Allergy-related conditions and allergy mimics in renal patients were defined according to reference criteria for each condition; including allergy to dialyzers and Chronic pruritus related to CKD.[15,16]

Patients with other inflammatory, malignancy, or infectious dermatoses were excluded as seborrheic dermatitis, psoriasis, pompholyx, napkin dermatitis, lichen simplex, dermatitis herpetiformis, scabies, tinea corporis, pityriasis lichenoides, pityriasis alba and HIV.

Laboratory assessment

All recruited subjects were subjected to the following laboratory assessment: Complete blood count (CBC) with differential (Sysmex XN-1000 Hematology Analyzer, Tokyo, Japan), erythrocyte sedimentation rate (Westergren method), C-reactive protein (a high-sensitivity immunoturbidimetric analysis (Modular PP analyzer, Roche, Basel, Switzerland), thyroid stimulating hormone (TSH) (Immulite 2000 third generation.), serum total IgE (solid phase enzyme-linked immunosorbent assay), Anti-nuclear antibody (ANA) (IIF, HEp 20-10, Euroimmun, Germany), liver and kidney functions, calcium, phosphorus (enzymatic colorimetric technique) and serum parathormone (PTH) (electrochemiluminescence immunoassay on the fully automated VIDAS (Biomerieux, Marcy l'Etoile, France).

Measurements and outcomes

Our primary outcome was to assess allergy type and prevalence among patients with kidney disease. Secondary outcomes included comparing allergy and non-allergic patients in their clinical and laboratory parameters and assessing risk factors in adults and children.

Ethical considerations

The present study was performed in concordance with international ethical standards and applicable local regulatory guidelines. Informed consent was obtained from adult patients and caregivers of the pediatric patients before enrolment in the study after explanation of the study objectives, methodology, risks, and benefits. The study's protocol was reviewed and approved by the ethics committee of the Faculty of Medicine Menoufia University, approval number 10/2022INTM6.

Statistical analysis

All the obtained data were statistically analyzed and presented in tables, graphs, and charts using the IBM Statistical Package for Social Science (SPSS) software version 23.0. Data were expressed in the form of mean, standard deviation, median, range, or percentages where appropriate. For continuous variables, independent t-test was performed to compare the means of normally distributed data, while Mann–Whitney U test was used to compare the median differences of the data that were not normally distributed, and the chi-square test was used for categorical data. Logistic regression was performed to assess risk factors of allergy in the studied renal patients. A p-value below 0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical data are demonstrated in **(table 1).** Participants of the study included 130 (76.5%) adult patients while the remaining 40 (23.5%) were in the pediatric age group. The age of adult patients ranged from 19-92 years while the age of children ranged from 3-17 years. In the adult group 118 (90.8%) patients had comorbidities, 107 patients (82.3%) had hypertension followed by diabetes mellitus in 46 (35.4%) while in the pediatric group, 25 (62.5%) of patients had comorbidities where 18 patients (45%) had hypertension followed by other comorbidities in 9 (22.5%). In the adult group, 9 (7%) of patients had a family history of allergy while in the pediatric group, one patient (2.5%) had a family history of allergy. In the adult group, 63 patients (48.5%) had chronic kidney disease followed by acute kidney injury (47; 36.2%) while in the pediatric group, 24 patients (60%) had end-stage renal disease followed by acute kidney injury (8; 20%) and chronic kidney disease (8 (20%). Nephrotic syndrome was found in 12 patients (8 adults and 4 children). There were 41 patients on regular hemodialysis including17 adults and 24 children. Ten patients (all of them were adults) had clinical and laboratory features suggestive of allergic interstitial nephritis. Drug allergy was reported as in 4.7 % of our patients mainly induced by antibiotics (ceftriaxone, meropenem, vancomycin) in 7 patients, while allergy to parenteral iron was reported in only one adult patient.

Figure 1 demonstrates the frequencies of different allergic disorders in the whole studied sample. In the adult group, 52 (40%) of patients had allergic diseases. Asthma was the most frequent allergic disorder in this group, where it was reported in 28 patients (21.5%) followed by allergic

rhinitis in 9 (6.9%), while 12 patients had chronic pruritus related to CKD followed by allergic interstitial nephritis 10 (7.7%). The main suspected triggers were indoor pets in 15 (11.5%) followed by other aeroallergens in 5 (3.8%). In the pediatric group, 15 (37.5%) of patients had allergic diseases and the major type of allergy was asthma (5; 12.8%) followed by allergic rhinitis (3; 7.5%). Five pediatric patients had chronic pruritus related to CKD. The main suspected triggers in children were food and indoor pets, each in 2 (5%) followed by transfusion related allergy (2.5%) **(Table 2).**

In the adult group, 43 (33.1%) of participants used anti-allergic medications and most of them used systemic corticosteroids (30; 23.1%) for allergic symptoms followed by topical therapy in 25 (19.2%) while in the pediatric group 10 (25%) used anti-allergic medications; 7 of them were topical therapy followed by systemic corticosteroid in 3 patients **(Table 3).**

Family history of allergy was significantly more frequent among patients with allergy in comparison to non-allergic patients (p-value <0.001*), while there was no significant difference between allergic and non-allergic patients regarding sex, age, occupation, residence, smoking, and comorbidities (p-value>0.05) **(Table 4).**

Hemoglobin, WBCs, urea, eosinophils count, ESR, CRP, TSH, serum calcium and phosphorous, PTH levels, ANA, and HCV positivity were comparable among allergic and non-allergic patients (p-value>0.05) while platelet counts were higher among allergic versus non-allergic patients (p-value =0.022) **(Table 5).**

In multivariate analysis for the detection of risk factors of allergy among studied participants based on family history and the suspected triggers, there was no significant association of family history of allergy, aeroallergens, and platelets among allergic patients (p-value>0.05), while food allergens and indoor pets were significantly associated with allergy (odds ratio: 10.605 and 3.252 and p-value: 0.035 and 0.042, respectively), with 95% confidence interval. Urea and parathormone hormone (PTH) levels were significantly higher among patients with chronic uremic pruritus (p-value <0.05), while calcium, and phosphorus levels were comparable to those without (p-value>0.05) **(Table 6).**

DISCUSSION

The present study covered different allergy subsets among renal patients, it demonstrates that 39% of total studied renal patients had symptoms suggestive of one or more of an allergic manifestation. In the adult group, 21.5% had asthma while allergic rhinitis was reported in 6.9% and 9.2% had chronic pruritus related to CKD. In the pediatric group, 37.5% of patients had allergic diseases and the major type was asthma (12.8%) followed by allergic rhinitis (7.5%), 10% of patients had chronic pruritus related to CKD and food allergens were suspected in 3.5%.

It is difficult to accurately compare childhood and adult-onset allergic disorders, especially in renal patients due to existing gaps in the literature. Asthma varies considerably across the life course. Childhood asthma is known for its overall high prevalence with a male predominance before puberty, common remission, and rare mortality. Adult asthma is known for its female predominance, uncommon remission, and unusual mortality. Both childhood and adult asthma have variable presentations. Adult asthma severity is associated with increased IgE, eosinophilia, obesity, smoking, and low socioeconomic status. Adult-onset disease is associated with more respiratory symptoms and asthma medication use. [17]

Patients with chronic kidney disease are known to have a higher prevalence of lung dysfunction regardless of the disease's stage, including sleep apnea syndrome, pulmonary hypertension, and chronic obstructive pulmonary disease (COPD). Asthma was reported on 19.4. % of patients in our study, and efforts should be made to differentiate preexisting allergic asthma from uremic asthma, as both can present with wheezing and dyspnea, however the tools that might help to differentiate them include the onset of asthma, history of atopy, the relation to uremia, and improvement with dialysis. Uremic lung is a severe pulmonary complication observed in patients with uremia owing to fluid overload, increased lung vascular permeability and inflammation induced by chemokines and leucocytes. Radiology as well can be a helpful tool as it usually shows a pattern suggestive of lung oedema with central distribution of pulmonary opacities in patients with uremic lungs.[18,19]

Eczema was reported in only 2.4% of participants, (2 adults and 2 children). In an epidemiological study of cutaneous manifestations in patients with chronic kidney disease on hemodialysis, xerosis was the commonest finding, and pruritus was the commonest symptom. An association between atopic dermatitis and chronic kidney disease has been reported in observational studies, but the connection of this association was uncertain.[20]

Table 1. Baseline characteristics of the studied participants with renal diseases (n=170)

Variable		Total (n=170)		Adults (n=130)		Pediatrics (n=40)	
		No.	**%**	**No.**	**%**	**No.**	**%**
Age groups	Adults	130	76.5	130	100	0	0
	Paediatrics	40	23.5	0	0	40	100
Age (Years)	Median (IQR)/ Mean ±SD	56 (23.25-65)		58.42 ±14.34		10 (7-13.25)	
	Range	3-92		19-92		3-17	
Sex	Male	96	56.5	71	54.6	25	62.5
	Female	74	43.5	59	45.5	15	37.5
Residence	Rural	132	77.6	96	73.8	36	90
	Urban	38	22.4	34	26.2	4	10
Occupation	Working	43	25.3	43	33.1	0	0
	Not working	127	74.7	87	66.9	40	100
Smoking	Smoker	34	20	34	26.2	0	0
	Non-smoker	136	80	96	73.8	40	100
Comorbidities	Present	143	84.1	118	90.8	25	62.5
	Absent	27	15.9	12	9.2	15	37.5
Comorbidities type #	Stress& Anxiety	4	2.4	4	3.1	0	0
	Depression	1	0.6	1	0.8	0	0
	Heart disease	38	22.4	36	27.7	2	5
	SLE	10	5.9	9	6.9	1	2.5
	Hypertension	125	73.5	107	82.3	18	45
	Epilepsy	8	4.7	8	6.2	0	0
	Liver disease	18	10.6	17	13.1	1	2.5
	musculoskeletal disease	11	6.5	11	8.5	0	0
	Hypothyroidism	7	4.1	7	5.4	0	0
	DM	46	27.1	46	35.4	0	0
	Malignancy	6	3.5	6	4.6	0	0
	Others	26	15.3	17	13.1	9	22.5
Family history of allergy	Present	10	5.9	9	7	1	2.5
	Absent	159	94.1	120	93	39	97.5
Type of kidney disease	AKI	55	32.4	47	36.2	8	20
	CKD	71	41.8	63	48.5	8	20
	Nephrotic syndrome	12	7	8	6.2	4	10
	ESRD On regular dialysis	41	24.1	17	13.1	24	60
	Transplantation	3	1.8	3	2.3	0	0

AKI: acute kidney injury, CKD: chronic kidney disease, DM: diabetes mellitus, ESRD: end stage renal disease IQR: Interquartile range, SD: Standard deviation

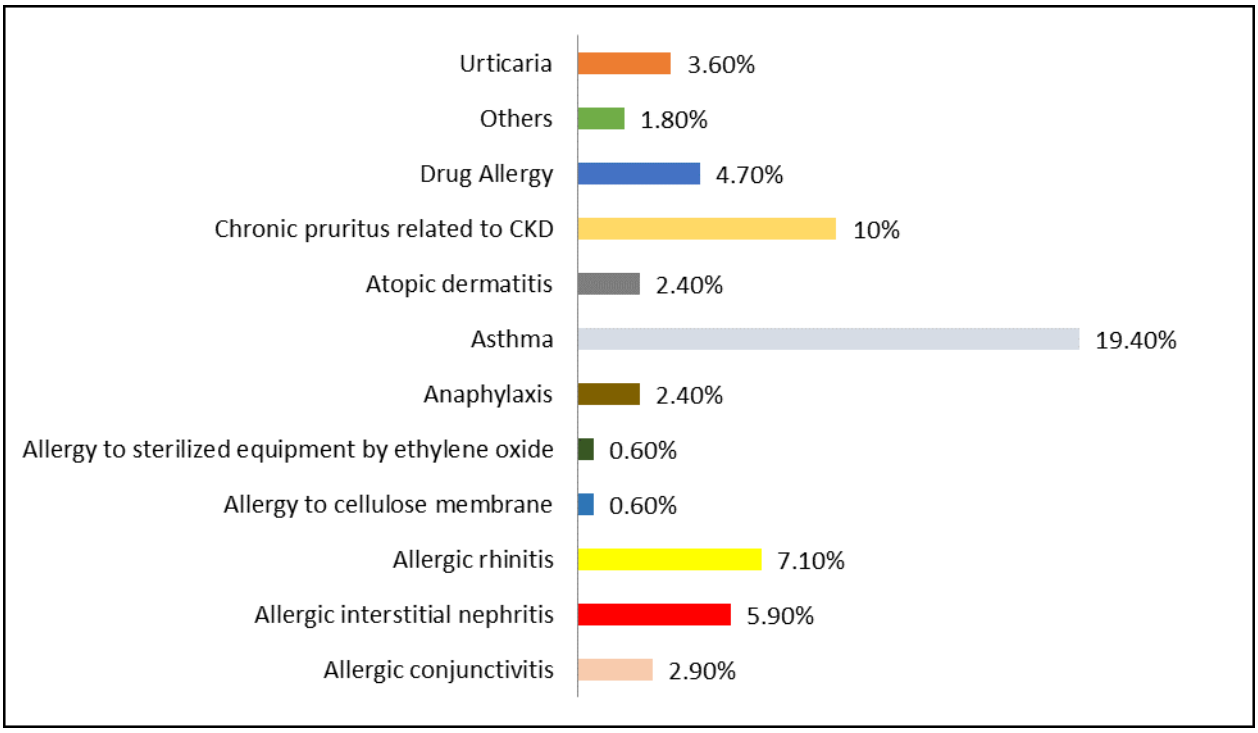

Figure 1. Types of allergic diseases among the total studied participants

Table 2. Prevalence and patterns of allergy among studied participants (n=170)

Variable		**Total (n=170**		**Adults (n=130)**		**Children (n=40)**	
		No	**%**	**No**	**%**	**No**	**%**
Allergic diseases	Present	67	39.4	52	40	15	37.5
	Absent	103	60.6	78	60	25	62.5
Type of allergic disease	Asthma	33	19.4	28	21.5	5	12.8
	Eczema	4	2.4	2	1.5	2	5
	Urticaria	6	3.6	5	3.9	1	2.5
	Allergic rhinitis	12	7.1	9	6.9	3	7.5
	Allergic conjunctivitis	5	2.9	3	2.3	2	5
	Others	3	1.8	2	1.5	1	2.5
	Anaphylaxis	4	2.4	3	2.3	1	2.5
	Drug Allergy	8	4.7	6	4.6	2	5
Renal- specific allergic manifestations	Allergic interstitial nephritis	10	5.9	10	7.7	0	0
	Allergy to sterilized equipment byethylene oxide	1	0.6	1	0.8	0	0
	Allergy to cellulose membrane	1	0.6	1	0.8	0	0
Allergy mimics	Chronic pruritus related to CKD	17	10	12	9.2	5	12.5
Possible triggers	Food	6	3.5	4	3.1	2	5
	Aeroallergens	5	3	5	3.8	0	0
	Insect stings	1	0.6	1	0.8	0	0
	Transfusion-related allergy	2	1.2	1	0.8	1	2.5
	Indoor pets	17	10	15	11.5	2	5
	Antibiotics	7	4.1	5	3.8	2	5
	Parenteral Iron	1	0.6	1	0.8	0	0

#: The participant may have more than one type of allergy, CKD: chronic kidney disease. CKD: chronic kidney disease

Table 3. Anti-allergic medications use among the studied participants (n=170)

Variable		Total (n=170)		Adults (n=130)		Children (n=40)	
		No.	**%**	**No.**	**%**	**No.**	**%**
Anti- allergic medications	Used	53	31.2	43	33.1	10	25
	Not used	117	68.8	87	66.9	30	75
Type of anti-allergic medications#	Antihistamines	15	8.8	14	10.8	1	2.5
	Mast cell stabilizers	1	0.6	1	0.8	0	0
	Topical therapy	32	18.8	25	19.2	7	17.5
	Systemic CS	34	20	30	23.1	4	10
	Anti-leukotriene	3	1.8	3	2.3	0	0
	ICS Inhalers	9	5.3	6	4.6	3	7.5
	Anti lgE (biologic)	0	0	0	0	0	0
	Immuno-suppressants	4	2.4	4	3.1	0	0

The participant may use more than one type of anti-allergic medications. CS: corticosteroids

Table 4: Demographic characteristics in the studied allergic and non-allergic participants with renal disease

Variable		Patients with Allergy (n=67)		Patients without Allergy (n=103)		Test	p-value
		No.	**%**	**No.**	**%**		
Sex	Male Female	37 30	55.2 44.8	59 44	57.3 42.7	$\chi2$=0.07	0.791
Age (Years)	Mean ±SD. Range	48.76 ±25.02 4-92		45.96 ±23.58 3-85		U=0.96	0.338
Occupation	Working Not working	13 54	19.4 80.6	30 73	29.1 70.9	$\chi2$=2.03	0.154
Residence	Rural Urban	49 18	73.1 26.9	83 20	80.6 19.4	$\chi2$=1.30	0.255
Smoking	Smoker Non-smoker	12 55	17.9 82.1	22 81	21.4 78.6	$\chi2$=0.30	0.583
Comorbidities	Present Absent	56 11	83.6 16.4	87 16	84.5 15.5	$\chi2$=0.02	0.878
Family history of allergy	Present Absent	10 57	14.9 85.1	0 103	0 100	FE=16.33	**<0.001***

*Statistically significant, $\chi2$: Chi-squared test, FE: Fisher exact test, U:Mann-Whitney U test

Table 5. Variation of the laboratory findings among allergic and non-allergic participants with renal disease (n=170)

Variable		Allergic patients (n=67)		Non-allergic patients (n=103)		Test of significance	p-value
		Mean ±SD		Mean ±SD			
Haemoglobin (gm/dl)		9.84 ±1.72		9.70 ±1.94		t=0.35	0.723
Platelets (x10^3/ mm^3)		269.21 ±80.12		241.59 ±82.35		U=2.30	0.022*
WBCs (x10^3/ mm^3)		8.06 ±5.85		7.79 ±5.56		U=0.21	0.838
Urea		191.48 ±62.09		187.29 ±54.84		t=0.45	0.655
Eosinophils (/ mm3)		210.96± 162.87		187.09 ±107.41		U=0.92	0.358
ESR (mm/hour)		50.52 ±43.17		37.67 ±38.76		U=0.58	0.564
CRP (mg/dl)		64.63 ±92.33		34.49 ±62.85		U=0.52	0.602
TSH (uIU/ml)		3.21 ±1.71		4.10 ±1.52		U=1.08	0.280
Ca+ (mg/dl)		8.44 ±1.57		8.39 ±1.51		t=0.17	0.865
PO4+ (mg/dl)		4.58 ±1.29		4.52 ±1.15		t=0.36	0.720
PTH (pg/mL)		302.30 ±308.21		270.39 ±171.33		U=0.24	0.812
ANA (N and %)	Not done Negative Positive	55 8 4	82.1 11.9 6	83 15 5	80.6 14.6 4.9	$\chi2$=0.31	0.866
HCV (N and %)	Negative Positive	3 64	4.5 95.5	14 89	13.6 86.4	$\chi2$=3.78	0.053

*: Statistically significant, $\chi2$: Chi-squared test, t: Student t test, U: Mann-Whitney U test

ANA: antinuclear antibodies, Ca+ calcium, CRP: C- reactive protein, ESR: erythrocyte sedimentation rate, HCV: hepatitis C virus, PO4+ phosphorus, PTH: parathormone hormone, TSH: thyroid stimulating hormone, WBCs: White blood cells

Table (6): Major renal laboratory tests among patients with and without Chronic pruritus related to CKD.

Variable	Chronic pruritus related to CKD		Test of significance	p-value
	Positive (n=17)	Negative (n=153)		
	Mean ±SD	Mean ±SD		
Urea (mg/dl)	214.67 ±45.61	180.48 ±66.95	U=2.70	0.007*
Ca+ (mg/dl)	7.60 ±0.99	8.29 ±1.47	t=1.05	0.309
PO4+ (mg/dl)	5.48 ±1.83	4.63 ±1.33	t=1.44	0.153
PTH (pg/mL)	393.00 ±125.08	251.71 ±129.24	U=3.34	0.001*

***:** Statistically significant**, t:** Student t test**, U:** Mann-Whitney U test
Ca+ calcium **IgE** immunoglobulin E, **PO4+** phosphorus, **PTH**: parathormone hormone

Urticaria was reported in 3.6% of total participants in our study with features suggestive of allergic urticaria. This should be differentiated from urticarial vasculitis (HUVs) as occurs in hypocomplementemia urticarial vasculitis that is characterized by urticaria, hypocomplementemia and positivity of anti-C1q antibodies together with immune-complex mediated glomerulonephritis that might be associated as well with severe angioedema, laryngeal edema and pulmonary involvement. The urticaria in HUVs usually presents with painful, persistent urticarial plaques that last more than 24 hours and resolve with bruising of the skin unlike the allergic urticaria that are itchy and rapidly resolves within hours. Urticaria with autoinflammatory disorders and renal involvement is another mimicker of allergic urticaria. Every effort should be done to reach the accurate diagnosis in order to provide the proper management plan and avoid morbidities. [21]

Allergic conjunctivitis (AC) results from an airborne allergen and the symptoms include itching, excessive lacrimation, ophthalmic discharge, and conjunctival hyperemia. This study found that AC in 2.9 % of total participants. The diagnosis of this condition is primarily clinical, and the management is usually through topical antihistamines and mast cell stabilizers. [22]

Allergic rhinitis (AR) AR was found in 7.1 % of total participants. It usually manifests with nasal symptoms such as nasal congestion, rhinorrhea, itching, sneezing, and ocular symptoms like redness, and puffy lids. It also causes itching of the palate and pharynx and post-nasal discharge.[23] Allergic Rhinitis has certain differences between children and adults; AR in children is more intermittent, and severe, with fewer symptoms but with more comorbidities than in adults. Furthermore, AR has important comorbidities such as sinusitis, asthma, nasal polyposis, otitis media, and respiratory infections. The cornerstones of AR treatment are local nasal irrigation, intranasal steroids, allergen-specific immunotherapy and environmental control measures. [24]

Pruritus is common among patients with end-stage kidney disease and is often an annoying symptom. Multiple mechanisms contribute to chronic kidney disease-associated pruritus (CKDaP), categorized into the following factors: local skin changes, metabolic alterations, neuropathy and dysregulation of opioid pathways, and psychological factors. Uremic pruritus is largely a clinical diagnosis, based on the onset of pruritis and a history of chronic kidney disease; The onset of pruritus with commencement of dialysis, persistence of symptoms, or elevated blood urea levels is consistent with a diagnosis of CKDaP. [25] Patients with uremic pruritus often have pruritus without a primary skin eruption. However, because of scratching behaviors, secondary cutaneous changes developed; including excoriations, prurigo nodularis, or nonspecific eczema.[26] Chronic pruritus related to CKD was reported in 10 % of total participants in the present study and is considered the most important allergy mimicker in renal patients. Patients with chronic pruritis related to CKD in our study had significantly higher parathormone and urea levels compared to those without ($p<0.001$). A longitudinal Study of uremic pruritus in hemodialysis patients found that in most patients, pruritus was symmetric and generalized pruritus. The pruritus was persistent and recurrent, and most patients suffered from daily itching. There were no typical cutaneous lesions; however, xerosis was commonly present. The heat was found to aggravate itching. [27]

In our study, 4 patients had history suggestive of anaphylaxis: 3 adults and a child. There are several causes of severe allergic hypersensitivity reactions among patients with renal disease particularly those on dialysis, ranging from anaphylactic reactions to ethylene oxide or medications (such as erythropoiesis-stimulating agents or iron) to reactions in response to dialyzer membranes or

heparin. Once anaphylaxis developed, it is important to stop hemodialysis therapy and immediately return blood together with management of anaphylaxis. Patients also might have serum tryptase levels testing, specific IgE testing and consideration of a challenge test in selected cases.[28] A historical case report of Asthma developed in an adult patient after 1 year of hemodialysis. The attack was exclusively associated with each hemodialysis. Skin test for the usual allergens such as house dust or pollens was negative. The provocation test by inhaling acetate solution or oral intake of acetic acid was positive resulting in an increase in the pulmonary resistance, or asthmatic attack. This asthma disappeared completely after the substitution of acetate in the dialysate using bicarbonate.[29]

Dialysis-associated hypersensitivity reactions refer to all abnormal events (allergic and nonallergic) resulting from the interaction between blood and hemodialysis membrane. Reactions generally present as acute events such as flushing, pruritus, angioedema, and pain, more severe reactions lead to dyspnea, a sense of impending doom, and hypotension. The differential diagnosis of dialyzer reactions includes other acute complications of dialysis such as hemolysis, air embolism, dialysis-associated episodic hypotension, dialysis-induced hypoxemia, and disequilibrium.[30] In this study, we had only two cases with presumed dialyzer reactions; this low incidence could be explained by proper rinsing of the dialyzer, adequate sterilization techniques for the dialysis machine, and advances in the used materials.

Hypersensitivity nephropathy was reported in adults only in our study and not reported in any child which could be attributed to the misuse of over-the-counter drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. Although drugs are the most common type of hypersensitivity nephropathy, other causes of acute interstitial nephritis should be kept in mind including tubulointerstitial nephritis with uveitis syndrome, IgG4-related disease, drug reaction with eosinophilia and systemic symptom syndrome.[31]

Nephrotic syndrome was reported in 10% of children in this study and 6.5 % of adults. A longitudinal cohort of children with nephrotic syndrome found that two-thirds of children with nephrotic syndrome (NS) at presentation have allergic symptoms and asthma; however, neither are associated with an increased frequency of relapses. In the study by Riar and colleagues, among 277 participants, the majority were male (65%) with a median age of 3.7 years at presentation. A total of 64% reported lifetime allergies with 20% having asthma, 33% wheezing, 27% eczema, and 24% had rhinitis. Over 3.3 years of follow-up, the presence of asthma and allergies was not associated with frequently relapsing NS, higher relapse rates, or risk of first relapse compared with those with no history of allergic diseases.[32] Although NS and pediatric atopic diseases have different pathological positions and clinical manifestations, similar pathogenesis was reported in children some of them were complaining of NS and atopic disease simultaneously or soon after the onset of the other.[33] Also, the existence of allergen sensitization in children with renal tubular acidosis was evident by allergen-specific IgE that was positive in 25.6%, mainly for milk, wheat and egg white.[34]

Drug allergy was reported in 4.7 % of our patients mainly induced by various antibiotics (ceftriaxone, meropenem, vancomycin) and parenteral iron. Drugs are identifiable causes of hypersensitivity reactions in patients receiving hemodialysis. These include iron, erythropoietin, heparin, and topical antibiotics or anesthetics, which lead to allergy or other hypersensitivity reactions.[35] In a study, serum IgE levels in 120 patients with different types of glomerulonephritis were found to be significantly elevated in cases of minimal change glomerulonephritis compared with membranous or membranoproliferative glomerulonephritis.[36]

Anti-allergic medications should be used with caution in patients with impaired renal function. Hypertension, cardiovascular disease, urinary retention, and increased ocular pressure are relative contraindications to the use of antihistamines. [37] Regarding allergy biological therapy, omalizumab is used with the same dose as normal kidney functions, although acute interstitial nephritis was reported as an unusual side effect of omalizumab.[38] Dupilumab has a good safety profile and is less likely to cause renal adverse events. However, a case has been reported with decreased renal function after starting dupilumab therapy, with exacerbation of a preexisting IgA nephropathy.[39]

In conclusion, different allergic disorders are common among patients with renal disease of different ages exceeding one-third of patients with renal diseases. Asthma was the most prevalent allergic disease in both pediatric and adult populations. Allergy mimickers should be kept in consideration as well, particularly CKDaP. The detection of allergic manifestation and

differentiation between true allergy and allergy mimickers are of outmost importance to initiate the proper treatment and decrease morbidity. The limitations of this study include the small sample size, the lack of allergy specific investigations like testing for allergen specific IgE whether in serum or by skin testing, the inadequate representation of different renal disorders and certain forms of allergy and the lack of healthy control group. Data on hemodialysis machine-related allergies and differential diagnosis of allergy mimics were limited as well.

We recommend that future research should include multicenter prospective studies to validate our findings, investigate the underlying pathogenesis and to accurately assess the impact on long-term outcomes of both allergic and renal diseases.

AUTHORS CONTRIBUTION

EME: proposed the research idea, design of the study and contributed to writing the main text and conclusion of the manuscript. **WAH:** contributed to data collection and results analysis. **HBA:** shared in data collection especially pediatrics and revised the manuscript, **ESA:** was responsible for the allergy checklist design, data collection and revision**, MEE:** participated in data collection and revision, **ASE**: participated in manuscript writing and revision. All authors read and approved the final manuscript.

CONFLICTS Of INTEREST

The authors declare no conflict of interest.

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