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Profile of Urticaria and Angioedema Patients at Dr. Moewardi General Hospital Surakarta, Indonesia

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ABSTRACT

Background: Urticaria is a heterogeneous inflammatory skin disease that results from the activation and degranulation of cutaneous mast cells, followed by the release of histamine and other mediators that cause sensory nerve activation, vasodilation, plasma extravasation, and recruitment of immune cells. The prevalence and incidence of urticaria and angioedema have been extensively studied worldwide, but there is still limited data in Indonesia, especially regarding the profile of urticaria and angioedema patients. The purpose of this study was to determine the profile of urticaria and angioedema patients at Dr. Moewardi General Hospital for the period January 1st, 2020 - December 31st, 2022. **Methods:** This study is a cross-sectional retrospective study with secondary data derived from medical records of urticaria and angioedema patients. **Results:** There were 152 patients with urticaria, most of whom were in the age group >60 years (20.39%), female with a male to female ratio of 1:1.92, and worked as housewives (17.76%) and students (16.45%). Most cases were diagnosed with urticaria (86.84%) with some patients having angioedema (13.16%). The most common comorbidities rhinoconjunctivitis (2.63%), atopic dermatitis (1.97%) and asthma (1.32%). The dominant symptoms were itching and bumps (100%). The main treatment received by patients was single AH1 (71.71%) followed by combination therapy of AH1 and systemic corticosteroids (14.47%), combination therapy of AH1 and topical corticosteroids (10.53%), and the rest received combination therapy of AH1, topical corticosteroids, and systemic corticosteroids (3.29%). The skin prick test was positive in 16 patients (35.56%), with the most common allergens found being peanut (37.5%), egg yolk (37.5%), and tomato (37.5%). **Conclusion:** The characteristics of urticaria patients were dominated by elderly patients, female gender, and working as housewives or not working. Patients were predominantly diagnosed with urticaria with the most common comorbidities being diabetes mellitus. The main treatment received was AH1 class drugs. The most common types of allergens identified were peanuts, egg yolks, and tomatoes.

1. Introduction

Urticaria is a heterogeneous inflammatory skin disease and occurs due to the activation and degranulation of skin mast cells, followed by the release of histamine and other mediators that cause sensory nerve activation, vasodilation, plasma extravasation, and recruitment of immune cells.¹ This process causes signs and symptoms such as urticaria

lesions, angioedema, or both.^{2,3} Urticaria is classified based on the onset of the disease into acute urticaria (AU) lasting ≤6 weeks and chronic urticaria (CU) lasting >6 weeks.³ Urticaria is further classified into induced urticaria and spontaneous urticaria based on the cause. In induced urticaria, signs and symptoms are induced by specific and definite triggers in certain subtypes, such as urticaria, which is triggered by cold

temperatures or food. In spontaneous urticaria, signs and symptoms appear unexpectedly and without a definite trigger. Spontaneous urticaria is more common than induced urticaria, and both can occur simultaneously.^{4,5}

The prevalence of urticaria is estimated at 86 million cases worldwide.⁶ The prevalence of AU in the United States is reported to be 0.13%, and the CU is at 0.08%. Asian countries such as China and South Korea have a CU prevalence of 2.6% and 0.38%, respectively.⁷ The prevalence of urticaria, both acute and chronic, has never been reported before in Indonesia. However, several hospital-based studies in several large cities in Indonesia, such as at the Dr. Soetomo General Hospital Surabaya, reported the number of urticaria cases as many as 463 patients since 2015-2017.⁸ Some risk factors for urticaria include densely populated residential populations, family history of allergic diseases, low socioeconomic status and genetic factors.^{9,10} A study involving twins revealed that genetic factors may partially explain susceptibility to urticaria. The role of polymorphisms of several genes, such as TNFRS11A, TBXA2R, and PLA2G4A37, is thought to have an important role in susceptibility to urticaria and/or angioedema induced by several types of non-steroid anti-inflammatory drugs (NSAIDs). Cutaneous mast cells have a central role in the pathogenesis of urticaria and are found in the upper papillary dermis as well as the deep dermis and subcutis, mostly around the skin, blood vessels, and sensory nerves.¹¹

Symptoms that can be caused by urticaria include urtica lesions, which are characterized by limited superficial edema of the skin and are mostly surrounded by erythema accompanied by itching or a burning sensation. Urtics develop within minutes and are temporary as the skin returns to its normal appearance within 1-24 hours.¹² Angioedema appears as edema that feels painful or a burning sensation, is not itchy, and is not too severe in the dermis and deep subcutis or mucosa. Angioedema manifests as skin-colored or slightly reddened inflammation, and when compared with urtica, angioedema develops slowly

and can last for days.¹³ The diagnosis of urticaria and angioedema can be made based on a clinical approach. The clinical manifestations of urticaria are very similar across different age groups, ethnicities, and genders. Urtica and angioedema have the same anatomical distribution in all races, but erythema associated with urtica is more difficult to detect in people with darker skin tones. A detailed history and physical examination are important first steps in establishing a diagnosis of urticaria. Diagnosis of urticaria is easy regardless of type or subtype.¹⁴ Management of urticaria and angioedema is based on the identification and preventive action of trigger factors as well as the provision of pharmacological therapy, especially second-generation antihistamine 1 (AH1) drugs. Severe urticaria or angioedema requires pharmacological therapy with corticosteroid drugs.¹⁵ This research was conducted to determine the profile of urticaria and angioedema patients at Dr. Moewardi General Hospital Surakarta in the last 3 years, namely the period January 1st, 2020, to December 31st, 2022. This research is expected to provide an overview of the characteristics of urticaria and angioedema based on age, gender, occupation, risk factors, clinical manifestations, and management of both urticaria and angioedema. Better knowledge of urticaria and angioedema is expected to improve diagnosis and increase awareness and appropriate management in clinical practice.

2. Methods

This research is a retrospective cross-sectional study with secondary data originating from medical records of patients with urticaria and angioedema at Dr. Moewardi General Hospital in the period January 1st, 2020, to December 31st, 2022. Basic patient data was taken using filters according to diagnosis from International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD 10), namely L.50 which is used to code urticaria and T.78.3 which is used to code angioedema with urticaria using total sampling technique. The data taken is in the form of patient characteristics, consisting of age, gender,

occupation, history which includes the main complaint, symptoms, clinical manifestations, history of other diseases, management and supporting examinations.

3. Results

In a period of 3 years during the 2020-2022 period, there were 152 patients with urticaria and/or angioedema, most of whom were 135 outpatients, and 17 other patients were inpatients. Patients in this study were assessed for their characteristics consisting of age, gender, occupation, history which included main complaints, symptoms, clinical

manifestations, history of other diseases and management. In this study, the largest number of patients were in the age group >60 years, which covered 20.39% of the total patients. The youngest patient was 1 year old, and the oldest patient was 87 years old. The mean age of patients was 41.74 years. The gender distribution is dominated by women, with a sex ratio between men and women of 1: 1.92. The most common occupation was non-working, which included 20.39% of patients, followed by housewives, which included 17.76%, and students, which included 16.45% of patients. Data on patient demographic characteristics is in (Table 1).

Table 1. Demographic characteristics of urticaria and angioedema patients.

Parameter	Total (n=152)	Percentage
Age		
1-10 years	15	9,87%
11-20 years	12	7,89%
21-30 years	17	11,18%
31-40 years	27	17,76%
41-50 years	20	13,16%
51-60 years	30	19,74%
>60 years	31	20,39%
Gender		
Male	52	34,21%
Female	100	65,79%
Occupation		
Civil servants	9	5,92%
Housewife	27	17,76%
Self-employed	18	11,84%
Employee	24	15,79%
Teacher	1	0,66%
Student	25	16,45%
Laborer	5	3,29%
Farmer	4	2,63%
Nurse	1	0,66%
Retired	7	4,61%
Doesn't work	31	20,39%

In this study, the division was also carried out based on diagnosis, namely urticaria, angioedema, or both. Most of the patients were diagnosed with urticaria alone, which accounted for 86.84%, while

urticaria and angioedema accounted for 13.16%. There were no patients diagnosed with angioedema alone. The distribution of patient diagnoses is listed in (Table 2).

Table 2. Distribution of patient diagnoses of urticaria and angioedema.

Diagnosis	Total (n=152)	Percentage
Urticaria	132	86,84%
Angioedema	0	00,00%
Urticaria and angioedema	20	13,16%

Some patients in this study also had very diverse comorbid diseases such as atopic dermatitis, rhinoconjunctivitis, and asthma. The most common comorbidity was rhinoconjunctivitis at 2.63%, followed by atopic dermatitis at 1.97% and asthma at 1.32%. The dominant symptoms in this study consisted of itching, bumps, and swelling, either alone or in a combination of the three. Symptoms of itching and bumps were found in all patients, while symptoms of swelling were only found in 11.18% of patients. The treatment received by urticaria patients in this study consisted of administering AH1 class drugs and corticosteroids consisting of topical and systemic corticosteroids. The types of drugs in the AH1 group that were given to the majority were cetirizine and

loratadine, while a small number received Rutadine, fexofenadine, ketotifen, cyproheptadine, chlorpheniramine maleate, and mebhydroline. The types of topical corticosteroids given to patients in this study consisted of desoxymetasone, mometasone, and hydrocortisone. The types of corticosteroids given include dexamethasone and methylprednisolone. Most patients received AH1 therapy alone, accounting for 71.71% of patients. A total of 10.53% of patients received combination therapy of AH1 and topical corticosteroids, 14.47% received combination therapy of AH1 and systemic corticosteroids, and the remaining 3.29% received combination therapy of AH1, topical corticosteroids, and systemic corticosteroids (Table 3).

Table 3. Distribution of comorbid diseases, symptoms and management of patients with urticaria and angioedema.

Information	Total (n=152)	Percentage
Comorbid disease		
Atopic dermatitis	3	1,97%
Rhinoconjunctivitis	4	2,63%
Asthma	2	1,32%
Complaint*		
Itching	152	100%
Bumps	152	100%
Swollen	17	11,18%
Management		
AH1 single	109	71,71%
AH1 + topical corticosteroid	16	10,53%
AH1 + corticosteroid systemic	22	14,47%
AH1 + corticosteroid topical + corticosteroid systemic	5	3,29%

*Note: 1 patient can have >1 lesion in a different location, so the total percentage is more than 100%.

Patients in this study also underwent supporting examinations in the form of a skin prick test (SPT). SPT examination was positive in 16 patients (10.53%). The types of allergens that were most frequently identified from the 16 patients who were

positive on the SPT examination were peanuts, egg yolks, and tomatoes, each with a percentage of 37.5%. The most common non-food allergens found were dog dander in 5 patients (31.25%) and house dust in 4 patients (25.00%) (Table 4).

Table 4. Results of skin prick test and allergen type of urticaria and angioedema patients.

Information	Total (n=152)	Percentage
SPT examination results		
Positive results	16	35,56%
Unchecked	136	64,44%
Type of Allergen*		
House dust	4	25,00%
Dog fur	5	31,25%
Wheat	2	12,50%
Chocolate	3	18,75%
Cashew nuts	3	18,75%
Coffee	1	6,25%
Tea	4	25,00%
Tomato	6	37,50%
Carrot	4	25,00%
Pineapple	2	12,50%
Groundnut	6	37,50%
Cow's milk	2	12,50%
Egg whites	3	18,75%
Egg yolk	6	37,50%
Tuna	3	18,75%
Squid	5	31,25%
Milkfish	2	12,50%
Shrimp	1	6,25%
Snapper	5	11,11%
Crab	3	6,67%
Shell	4	8,89%

*Note: 1 patient can have >1 allergy, so the total percentage is more than 100%.

4. Discussion

In this study, 152 patients were diagnosed with urticaria and/or angioedema during the 2020-2022 period. The highest prevalence of AU is found in children aged <5 years, while the CU, especially the spontaneous type, occurs most often in women aged >30 years. Adult patients with spontaneous CU range in age from 30-70 years. In adults, all types of urticaria are more common in women than men, except cholinergic urticaria, which is more prominent in adult men and children.¹⁶ Sex hormones can modulate the function of immune cells and inflammatory cells, including mast cell secretion. This is the reason why women are more susceptible to suffering from several autoimmune and inflammatory diseases, including urticaria than men. Hypersensitivity reactions to endogenous or exogenous female sex hormones are also involved in the pathogenesis of urticarial lesions associated with dermatitis caused by the hormones progesterone and estrogen and the process of autoimmunity. Hormonal fluctuations during the menstrual cycle can also influence urticaria exacerbations.¹⁷ In this study, there was no division of

urticaria into acute or chronic types. The patients in this study were predominantly patients with chronic spontaneous CU. The patients in this study were also predominantly female, with a male-to-female ratio of 1:1.92 (Table 1).

Urticaria and angioedema can be triggered by various factors such as food, stress, or weather. Weather and food are trigger factors related to induced urticaria, while stress is more related to spontaneous urticaria.¹⁷ The stress experienced by patients can cause an imbalance in the nervous system-immune system-skin circuit. The complex nervous system-immune system-skin circuit involves various neuropeptides and neurokines, mediators and inflammatory cells, hormones in the hypothalamic-pituitary-adrenal axis, and skin that contribute to the emergence of urticaria.¹⁸ In this study, it was found that the most types of work were housewives and students. These two professions are types of work with a fairly high-stress load, making it possible to trigger urticaria and angioedema (Table 1).

The clinical manifestation of urticaria can be pink or white, well-defined urticarial lesions with a raised

surface surrounded by an erythematous base and pale in the center. Urticarial lesions can coalesce and form large plaques. Urticarial lesions can vary in size and shape from a few millimeters to several centimeters. Urticarial lesions may be accompanied by angioedema, which is asymmetric non-pitting edema of the lips, cheeks, legs, genital organs, and periorbital area.¹⁹ Research by Kaplan in the United States (2017) reported that angioedema was only found in around 16% of patients with urticaria.²⁰ In this study, urticaria patients with angioedema were only found in 13.16% of patients (Table 2).

The pathophysiology of urticaria involves a systemic type 1 hypersensitivity reaction, so urticaria is often accompanied by comorbidities. Urticaria patients are more at risk of suffering from other autoimmune diseases than patients without a history of urticaria. Research by Kolkhir et al in the United States (2020) shows that there is an increase in the prevalence of atopic diseases in urticaria sufferers such as atopic dermatitis, rhinoconjunctivitis and asthma.²¹ Research by Ghazanfar et al in Denmark (2020) reported that the most common comorbidities found in chronic urticaria sufferers were depression, diabetes mellitus type 2, rheumatoid arthritis, rhinoconjunctivitis and atopic dermatitis.²² In this study, the most common comorbidity found was rhinoconjunctivitis (Table 3).

The main symptom of urticaria is the presence of urticar plaques accompanied by itching. Urtic plaques can appear in a short period of time, namely within a few minutes. The itching sensation suffered by urticaria patients can be so disturbing that it can hinder daily activities, including rest and sleep.²³ Research by Atmaja et al. in Bali (2019) reported that the most common symptoms suffered by urticaria patients were itching and bumps.²⁴ In this study, it was found that all patients suffered from itching and bumps, while 11.18% suffered from swelling (Table 3).

A lot European Academy of Allergy and Clinical Immunology in 2018 recommended second-generation AH1 single therapy as first-line therapy and if it cannot be controlled within 2-4 weeks, second-line therapy

can be given in the form of second-generation AH1 with an increased dose of up to 4x the initial dose. Pharmacological therapy is also accompanied by patient education to avoid factors that trigger urticaria. Third-line therapy with omalizumab may be considered if urticaria remains uncontrolled after increasing the dose of second-generation AH1. Fourth-line therapy with cyclosporine may be considered if third-line therapy does not achieve controlled urticaria.²⁵ This recommendation will be updated in 2023, where administration of second-generation AH1 will remain first-line therapy; however, increasing the dose to a maximum of 4x the initial dose does not need to wait for evaluation for 2-4 weeks and can be given directly if deemed necessary. Second-line therapy can be given after 2-4 weeks of evaluation, and the urticaria cannot be controlled. The second line therapy that can be given is omalizumab at a dose of 400 mg every 4 weeks, and if deemed necessary, the dose can be increased, and/or the duration of administration can be shortened to 600 mg every 2 weeks. Evaluation is then carried out for 2-4 weeks and if urticaria control has not been achieved, third-line therapy can be given in the form of cyclophorine with a maximum dose of 5mg/kgbb. Second and third-line therapy is only given in CU conditions.²⁶ In cases of unavailability of omalizumab or cyclophorine, administration of corticosteroids can be an effective therapy, especially for UA cases.²⁷ In this study, the majority of patients received single therapy with AH1, namely 71.71%, 10.53% of patients received combination therapy with AH1 and topical corticosteroids, 14.47% received combination therapy with AH1 and systemic corticosteroids, and the remaining 3.29% received combination therapy of AH1, topical corticosteroids, and systemic corticosteroids (Table 3).

Urticaria can be triggered by food, food additives, inhalants (pollen, fungus, animal fur, and house dust mites), and so on. The etiology of urticaria remains largely unidentified in the majority of cases. The diagnosis of urticaria can be made based on the patient's clinical picture. However, in certain

conditions such as chronic, prolonged urticaria, supporting examinations such as SPT, autologous serum skin test (ASST) and basophil test (BT) for needs screening, detecting certain types of allergens, diagnosis or possible autoimmune reactions. The skin prick test can be an important diagnostic procedure to identify allergens that trigger urticaria because it is easy to perform and widely available in various healthcare facilities compared to other supporting examinations such as ASST and BT.²⁸⁻³⁰ Research by Koirala et al. in Nepal (2020) reported that SPT was found positive in 71% of urticaria sufferers. The study also reported that the most common allergen found in positive SPT patients was Dermatophagoid meal (50%), dust (17.7%), mosquitoes (16%), straw dust (14.5%), *Cladosporium herbs* (14,5%), *Candida albicans* (12,9%), *Parthenium hysterophorus* (9.6%), flies (9.6%), soybeans (9.6%) and canned fish (8%).²⁹ In this study, positive SPT examinations were found in 35.56%, with the most common types of allergens found being peanuts, egg yolks, and tomatoes, each with a percentage of 37.5%. The most common non-food allergens found were dog dander in 5 patients (31.25%) and house dust in 4 patients (25.00%) (Table 4).

5. Conclusion

For the period January 1st, 2020, to December 31st, 2022, within 3 years, there were 152 patients with urticaria and angioedema at Dr. Moewardi General Hospital Surakarta. The largest age group is dominated by the age group >60 years, with an average age of 41.74 years. Urticaria patients are dominated by women, with a male-to-female ratio of 1:1.92. The most common type of work held by urticaria patients is not working, followed by housewives and students. The most common diagnosis is urticaria, with the most complaints being itching and bumps. In this study, it was found that the majority of urticaria patients had comorbid diseases, where rhinoconjunctivitis is found most frequently. The treatment often given is a single administration of AH1, with others receiving combination therapy with topical or systemic

corticosteroids. The SPT examination was positive in a small number of patients, with the most common allergens found being peanuts, egg yolks, and tomatoes.

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