Oncology
and Radiotherapy©
18(4) 2024: 001-005 • RESEARCH ARTICLE

Prevalence of anaphylaxis in the emergency department at the university clinical center of Kosovo

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ABSTRACT

Background: Allergic Diseases (AD) are the most common chronic diseases in Europe. AD diagnosis poses a significant challenge due to the variety of definitions, diversity of symptoms, and the heterogeneous involvement of organs as well as the lack of diagnostic methods in our country. These problems in diagnosis, specifically in the Emergency Department (ED), occur even when differentiation is made of anaphylaxis with Anaphylactic Reactions (AR). Do you mean adverse reactions instead of anaphylactic reaction?

Purpose of the study: Prevalence of allergic diseases and anaphylaxis in ED in University Clinical Center of Kosovo (UCCK), determination of the main causes that induce these reactions, the relation of the allergy trigger, and the time of symptoms' manifestation, observation of the correct approach and appropriate treatment of these cases.

Materials and methods: The research is a cross-sectional study of patients over the age of 15 who presented in our center between January 1st 2020 and April 30th 2020. In the cases obtained from the recorded data, patients with a diagnosis of "Reactio allergica" (urticaria, angioedema, erythema, etc.) were selected. The data were obtained based on the anamnesis and present clinical status of the patient, where a questionnaire with 8 questions based on the questionnaire of "Agana Heights Elementary School, General Allergy and Anaphylaxis Questionnaire, Jan 2013" was used. Statistical analysis was done with SPSS program, data were not normally distributed therefore non-parametric tests were used with a confidence interval of 95% and 99%.

Results: Out of 15,131 persons presented at the ED in Prishtina in UCCK for various emergency health problems, 74 allergic reactions were registered that required emergency medical assistance; gender ratio f/m=53/21 ($p<0.001$) with a predominance of 15 years-30 years of age (39 of them). Dominant symptoms in our patients were skin changes in the form of urticarial changes (36 of them), erythematous changes (51 of them), and angioedema manifested in 27 patients. Fortunately, during the research period 41 (55.4%) cases had mild forms of generalized reaction, 23 (31.0%) moderate and only 10 (13.6%) cases had severe form, according to Brown's classification. Of these, 18 (24.3%) cases were in anaphylaxis according to the criteria of the "Second symposium on the definition and management of anaphylaxis"; this incidence would be 0.1% of all visits in the ED, even though no patient was diagnosed with anaphylaxis by emergency doctors. The most commonly known causes were medications (44.6%). The most common causative drugs were the NSAIDs group (48.3%), ketoprofen lysine (brand name, OKI) leading the way with 25.8% of all cases of allergic reactions to the drugs. The second group of drugs was β-lactam antibiotics with 7 (22.6%) cases, led by cephalosporins and followed by penicillin. The second most common cause was food in 12.1% of cases.

Conclusion: Due to the lack of a unique protocol for anaphylaxis and AR, in our study we managed to identify 18 cases of anaphylaxis, which were not recorded with this diagnosis in the patient's medical history. Therefore, we consider that health care professionals would benefit from better education on setting criteria to distinguish an allergic reaction from an anaphylactic reaction or anaphylaxis and vice versa.

Keywords: anaphylaxis, emergency department, university clinical center of kosovo, cancer, radiology, allergic reactions, healthcare, incidence

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Word count: 3597 **Tables:** 00 **Figures:** 03 **References:** 18

Received: 9 January, 2024, Manuscript No. OAR-24-124777
Editor Assigned: 18 January, 2024, Pre-QC No. OAR-24-124777(PQ)
Reviewed: 23 January, 2024, QC No. OAR-24-124777(Q)
Revised: 26 January, 2024, Manuscript No. OAR-24-124777(R)
Published: 15 February, 2024, Invoice No. J-124777

INTRODUCTION

Allergic Diseases (AD) are the most common chronic diseases in Europe. Although allergies were not very popular in the early twentieth century, in recent years we have seen an increase in the incidence of these diseases. There are over 150 million people with chronic AD in Europe, according to research by The European Academy of Allergy and Clinical Immunology (EAACI); by the year 2025 half of the European Union population will suffer from some type of AD [1]. AD present a serious problem for diagnosis due to the variety of definitions, the different appearance of symptoms, and heterogeneous involvement of organs, as well as the lack of diagnostic methods in our country [2, 3]. No criteria can be used to diagnose anaphylaxis with 100% sensitivity and specificity, but it is thought that the criteria set on the Second Symposium on the definition and management of anaphylaxis from the Second National Institute of Allergy and Infectious Disease (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) may cover more than 95% of anaphylactic cases [4]. These problems in diagnosis, specifically in the Emergency Department (ED), occur even when differentiation is made of anaphylaxis with Anaphylactic Reactions (AR). This is due to the lack of a globally accepted guideline, the atypical presentation of signs and symptoms, and in most cases because the stimulus is unknown. This problem is an obstacle for the adequate form and time to treat anaphylaxis with epinephrine [5, 6].

According to the time of onset of symptoms, AR are divided into Immediate Reactions (IR), ≤ 1 hour, and Non-Immediate Reactions (NIR)>1 hour, whereas according to Brown's classification, the severity of systemic hypersensitivity reactions is divided into mild, moderate, and severe [7, 8].

Due to the more detailed analysis of anaphylaxis and new therapeutic discoveries in the medical field, there are changes in the clinical manifestation of anaphylaxis, as well as in its pathophysiology. To make the diagnosis faster and more efficient, based on the clinical signs, we divided anaphylaxis into four phenotypes: Type-I reactions (most common), cytokine-release mediated reactions, mixed reactions, reactions mediated by bradykinin, and complement. Endotypes are based on the cellular and molecular mechanism of the hypersensitivity reaction, responding to the respective above-mentioned phenotypes; they are classified as Ig-E and non-Ig-E mediated, mediated by cytokines, mixed processes, and direct activation of immune cells from complement or bradykinin [9].

According to a meta-analysis, the incidence of anaphylaxis in Europe varies between 1.5 per 100,000 person-years and 32 per 100,000 person-years, but due to the heterogeneity of data and the variety of incidence reporting pooled analysis cannot be done. Prevalence of allergic reactions to food in children in Germany has been 4.2% while drug allergies in London's hospitals have shown a prevalence of 44.5%, according to patient history 12. In terms of the most severe forms, such as anaphylaxis have a prevalence of 0.3% in Europe [10, 11].

PURPOSE OF THE STUDY

Prevalence of AD and anaphylaxis in ED in University Clinical Center of Kosovo (UCCK), determination of the main causes that induce these reactions, the relation of the allergy trigger and the time of symptoms' manifestation, observation of the right approach, and appropriate treatment of these cases.

The research is a cross-sectional study. The research was done in 3 months from January 1st 2020 to April 30th 2020. Patients over the age of 15 are included in the study. Patients under this age are treated in the Emergency Department of the Paediatric Clinic, and they were not included in this study. The cases included in the research are the ones that have shown symptoms of allergic reactions in the ED of UCCK, Prishtina. In the cases obtained from the recorded data, patients with a diagnosis of "Reactio allergica" (urticaria, angioedema, erythema) were selected and vital parameters were measured. Because the research was done during the seasonal flu period, patients with skin symptoms and other allergy-like symptoms and no history of allergies or any contact with allergens, as well as laboratory changes for infections were excluded from the study. At the end of our study, our country faced the pandemic from the Coronavirus Disease 2019 (COVID-19); this made the health system in Kosovo take strict measures in ED on March 13th 2020; as a result, the number of visits dropped significantly - zero for allergic reactions. Due to the possibility of altering the final results with the cases of the last days during the pandemic, we have excluded the data obtained during this period. The data were obtained based on the anamnesis and present clinical status of the patient, where a questionnaire with 8 questions based on the questionnaire of "Agana Heights Elementary School, General Allergy and Anaphylaxis Questionnaire, Jan 2013" was used. Some of the data were retrospectively obtained from patient reports submitted overnight to the ED.

Statistical analysis

Statistical analysis was done with SPSS program, data were not normally distributed therefore we used non-parametric tests such as Binomial, Fisher's Exact, Cramer's V, Kruskal Wallis Test, Pearson X2 with confidence interval of 95% $p<0.05$ and 99% $p<0.01$. Results are presented in the form of intervals, percentages, or averages.

RESULTS

From the total population of Kosovo ≈ 1,795,666, we identified a total of 74 cases of AD in the ED of UCCK out of 15,131 persons who presented in this department for any problem during the 3-months research period.

The mean age was 38.3 years Standard Deviation (SD): 18.35, interval: 15 years-83 years. The most common age group was 28 years, with a total of 6 (8.1%) cases. We have a significant difference of age groups: 53% are 15 years-30 years old compared to other age groups with 15-year intervals.

The distribution of AD between the genders has significant differences (Confidence Interval, CI: 99%, $p<0.001$): 72% of those presented in ED due to AD were female, while 28% were male. There was also a significant difference in the question "Have you ever been to ED for any reaction?" due to AD. Out of 61 patients, 77% (CI: 95%, $p<0.001$) answered "no", while 23% answered "yes". The previous diagnosis with any of the AD has a strong statistically significant correlation with the gender of the cases, where 63% of men were previously diagnosed with at least one AD, while 73% of women were never diagnosed with any AD (CI: 95%, $p<0.05$; Cramer's V> 0.3).

Even though female cases were more than the double of male cases in the age group of 45 years-60 years the cases with AD were the same; respectively, in the age group of 75-90 there was one more male with reactions than in the other group.

According to the presentation of patients in ED, skin symptoms and signs were the most common: 19% Erythema (Figure 1), 15% Pruritus (Itching), 13% Urticaria (Figure 2A and 2B), followed by 11% Sensation of heat, 10% Angioedema (Figure 3A and 3B), 7% Dyspnea, as well as other symptoms in fewer cases . Erythema was the most common symptom, present in almost all 67 cases with symptoms from all allergy triggers; it appeared in 25 (75.8%) cases with drug allergy, 1 (100%) case with symptoms triggered by pet dander allergy, 6 (100%) cases with irritative dermatitis, 8 (88.9%) cases with food allergy, and 10 (58.8%) cases with unknown allergy trigger.

According to the anaphylaxis criteria shown for the possible diagnosis of anaphylaxis, and data obtained from patients, we concluded that 18 (24.3%) cases out of 74 patients most likely had symptoms and signs of anaphylaxis; despite this they were released from ED with a diagnosis of any allergic diseases. Not a single patient, including these 18 cases, has been treated with Adrenaline (Epinephrine).

A total of 38 (63%) cases out of 60 have claimed that that was their first reaction ever. Of the patients treated in the past for AD, 8 (42%) denied having ever been treated in ED but said they had been treated in primary care centers.

According to the time of onset of symptoms, out of 55 valid cases, 36 (66%) had an Immediate Reaction (IR) ≤ 1 hour; this was a significant difference compared to 19 (34%) cases that had a Non-Immediate Reaction (NIR)>1 hour. Unlike other allergy triggers where IR dominated, in skin irritants, the distribution was the same (1:1). If we test the relationship between gender and the time of onset of symptoms, we see that 13 (93%) males had IR, while only 23 (56%) females had IR. This indicates that there is a strong significant association between gender and IR (Fisher's Exact Test 0.02; Cramer's V> 0.3).

Based on Brown's classification for the severity of the generalized hypersensitivity reaction, we have the following forms of reaction in our cases: mild 41 (55%) cases, moderate 23 (31%) cases, and severe 10 (14%) cases.

Based on the anamnesis taken and the data obtained from the 74

cases, we concluded that the main cause with the most cases for allergic reaction were medications with 33 (44.6%) patients, while twenty-four (32.4%) cases had unknown allergy triggers.

The main drug to trigger allergic reactions has been the group of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), with 48% of all 31 cases with drug allergies. Within this group, ketoprofen lysine (brand name, Oki) has caused the largest number of cases (26%). The other most common group of drugs is that of β-lactam antibiotics with 29% of cases, while cephalosporins lead this group with 7 (78%) cases .

Fig. 1. SH. J. 66 years, Generalized erythema from skin irritants

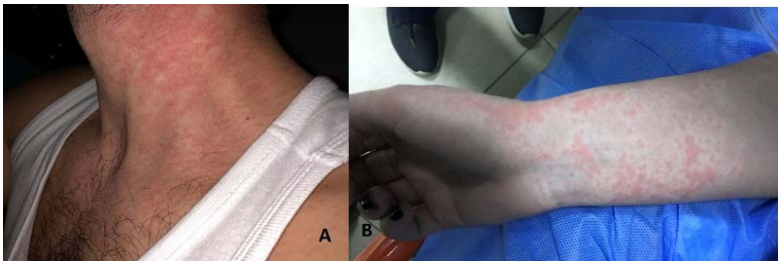

Fig. 2. (A) A. H. 25 years, contact allergies and (B) V. T. 22 years, food allergies

Fig. 3. (A) Q. F. 48 years, Angioedema from ketoprofen lysine and (B) D. K. 40 years, periorbital edema from hair dye allergy

DISCUSSION

With 74 cases out of 15,131 visits, respectively one case with AD for 204 visits (0.5%) made to the ED, it is clear that allergic diseases have a relatively high incidence. This is similar to other countries in the world, such as Australia where the incidence was of one patient with an acute allergic reaction or anaphylaxis in 205 visits to the ED13, in Lebanon 1 case in 105 visits14, while in the United States (US) there was one case in 250 visits to the ED.

The mean age of the cases is 38.3 years, which is similar to the ages reported in other studies [12-18].

The sex of the patients had significant differences, where the ratio of females to males was 5:2, the same was true for Australia, but at a lower rate 3:2. 13 Opposite to these, in Lebanon the incidence was slightly higher in males ≈ 1. 4:1, whereas in Italy the ratio was the same. But the highest difference was in the research done in the Paediatrics ED, where the ratio of males to females was 3:2.

Skin and mucosal changes were present in 56.6% of cases, with erythema accounting for 18.8% of the cases. These were the most common changes in another research as well.

The incidence of anaphylaxis in Europe is very heterogeneous, due to which it responds to misdiagnosis. Errors in the diagnosis of anaphylaxis are common in 80% of cases worldwide, the ED fails to diagnose it right. In Minnesota in a 4-months period from 17 patients who met the criteria for anaphylaxis, only 4 were correctly diagnosed, 13 others were diagnosed as having an "allergic reaction" and no anaphylaxis. This problem is a concern in the health community, as the relation of anaphylaxis with epinephrine creates confusion in treatment; if the patient is not diagnosed with anaphylaxis then usually the lifesaving treatment is not given. In the study done for three months, although there were cases with systolic blood pressure <60 mm Hg and other accompanying symptoms, epinephrine was not administered even once.

A smaller number of cases 22 (36.7%) had a history of earlier allergic reactions in their life, similar to the research done in Lebanon,

Italy, and Australia, where there were ≈30% such cases [13,14,16]. In the US study there were differences within the research, where the majority of women 72.2% had not been previously diagnosed with any AD, unlike 62% of men who had previous histories of AD. Of the 61 cases, 47 (77%) had never been treated in the ED for AD. Of the patients who had previously been treated for an allergy, 8 (42%) patients had never been treated in the ED, but had been treated in a primary care center. According to the time of onset of symptoms from the moment of contact with the allergen, 36 (65%) cases had immediate reactions (≤ 1 hour), almost all men (93%) and slightly more than half of the females (56%); the other cases were had NIR.

Fortunately, during the research period, 41 (55%) cases were mild with generalized reaction forms, 23 (31%) were moderate and only 10 (14%) cases had severe forms as shown in Brown's classification. According to NIAID and FAAN's second symposium's criteria for anaphylaxis 4, 18 (24%) cases had anaphylaxis; this incidence would be 0.1% of all ED visits, but no patient was diagnosed with anaphylaxis at the time of the study by the ED doctors. The most commonly known causes to trigger AD were medications (45%). The NSAIDs group was the main cause with 48% of cases, led by ketoprofen lysine (brand name, OKI) with 26% of all cases of allergic reactions to drugs. The second group of drugs was β-lactam antibiotics with 7 (23%) cases, led by cephalosporins and followed by penicillin. The second most common cause was food in 12% of cases. The same was valid in research done in Australia (28%), Lebanon (24%), and Italy (27%): the most common causes were drugs, but there they were led by antibiotics. In Lebanon and Italy, the most common antibiotics were the penicillin group, while in Lebanon the most common triggers were cephalosporins [13,14,16]. In 32% of cases, the cause was unknown, while in a study in Lebanon it was unknown in more than half of the cases (53%) [14].

CONCLUSION

Based on the criteria for diagnosing anaphylaxis, the research revealed 18 cases of anaphylaxis, whereas in patients' medical histories this diagnosis did not appear. For this reason, health care professionals should be more informed about these diseases, so that these cases can be correctly diagnosed and adequately treated. All this is due to the lack of a unique protocol for anaphylaxis and anaphylactic reactions.

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