**TÍTULO:**

Hospitalizations due to Angioedema Without Urticaria in a Portuguese Center: 5-years Retrospective Study

Internamentos por Angioedema Sem Urticária num Centro Hospitalar Português: Revisão de 5 Anos

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**TÍTULO BREVE PARA CABEÇALHO:**

Hospitalizations due to angioedema without urticaria

**Hospitalizations due to Angioedema Without Urticaria in a Portuguese Center: 5-years Retrospective Study**

Abstract

Introduction: Hospitalizations due to angioedema are important especially in debilitating or life-threatening situations. Objective: To evaluate the frequency and aetiology of angioedema without urticaria in hospital admissions. Methods: The admissions between 2009 and 2013 in Centro Hospitalar Lisboa Norte with a diagnosis grouped under the ICD9 codes of angioedema were retrospectively analysed. Angioedema with urticaria was excluded. The admissions were categorized into 3 groups: A- hospitalizations motivated by the angioedema; B- hospitalizations in which the angioedema was an incidental finding; C- hospitalizations for prophylactic therapy in hereditary angioedema patients. Results: There were 201 hospitalizations (53% females, 96% adults, mean age 53.9±20.8 years), distributed by 23 hospital departments, 51% in the Immunoallergology Department. The mean annual angioedema admission rate was 86/100,000. In 55% of the cases, angioedema was the cause for the admission, in 29% an incidental finding and 16% were for prophylactic treatment of hereditary attacks. In 38% there was upper airway involvement. The aetiologies were: hereditary angioedema in 36%, angiotensin converting enzyme inhibitor induced angioedema in 26%, idiopathic angioedema in 17%, thrombolysis induced angioedema in 11%, nonsteroidal anti-inflammatory drug-induced angioedema in 4%. Discussion: The main aetiology was hereditary an HAE, followed by Angiotensin Converting Enzyme Inhibitor and thrombolysis induced angioedema, being this data similar to other international revisions. Conclusion: The mean annual angioedema admission rate was 86/100,000 and there was airway involvement in 38% of hospitalizations.

Key-words: Angioedema, Angioedema without Urticaria, Angiotensin Converting Enzyme Inhibitor, Hereditary Angioedema, Hospitalizations.

**Internamentos por Angioedema Sem Urticária num Centro Hospitalar Português: Revisão de 5 Anos**

Resumo

Introdução: Os internamentos por angioedema são importantes, sobretudo, nas situações incapacitantes ou de risco de vida. Objetivo: avaliar a frequência e etiologia dos internamentos por AE sem urticária. Metodologia: estudo retrospetivo dos internamentos com os códigos CID9 para angioedema, entre 2009 e 2013, no Centro Hospitalar Lisboa Norte. Excluídos os angioedema com urticária. Categorizaram-se os internamentos em 3 grupos: A- Internamentos motivados pela crise de angioedema; B- Internamentos em que o angioedema foi uma intercorrência; C- Internamentos para realização de terapêutica profilática de crise. Resultados: Incluídos 201 internamentos (53% mulheres, 96% adultos, idade média 53,9±20,8 anos), distribuídos por 23 Serviços hospitalares (51% na Imunoalergologia), com uma taxa média anual de internamentos de 86/ 100 000. Em 55% o angioedema foi o motivo de internamento, em 29% uma intercorrência e 16% destinaram-se a profilaxia de crise de angioedema hereditário. Em 38% houve envolvimento das vias aéreas superiores. As etiologias foram: em 36% angioedema hereditário, em 26% angioedema induzido por inibidores da enzima conversora da angiotensina, 17% foram idiopáticos, em 11% o angioedema surgiu após trombólise, em 4% induzido por anti-inflamatórios não esteroides e 6% outras etiologias. Em 63% dos 22 casos de trombólise, os inibidores da enzima conversora da angiotensina foram cofatores. Discussão: A principal etiologia o angioedema hereditário, seguido do angioedema induzido por inibidores da enzima conversora da angiotensina e trombólise, sendo estes dados semelhantes a outras revisões internacionais. Conclusões: A taxa media de internamentos por angioedema foi de 86/100 000 e a frequência de envolvimento das vias aéreas foi de 38%.

Palavras chave: Angioedema, Angioedema Hereditário, Angioedema sem Urticária, Inibidores da Enzima Conversora da Angiotensina, Internamentos.

**Introduction**

Angioedema (AE) is a self-limited, localized swelling of deep dermis, subcutaneous or submucosal tissues due to vascular leakage1. It was first described in 1876 by John Laws Milton, who, at the time, called it "giant urticaria" 2. Later, in 1882, Heinriche Quincke defined this condition as angioneurotic edema3.

AE classification according to endotypes4,5 and phenotypes6,7 is crucial for a correct diagnosis and therapeutic approach. Based on these, AE is classified as occurring "with” or “without” wheals6. Angioedema with wheals is a hallmark of urticaria8,9 and can be acute or chronic, spontaneous or inducible. AE without wheals, on the other hand, may occur as a distinct entity and can be classified as histaminergic or non-histaminergic4,7. In the first group are included the acute allergic, the pseudo-allergic and the recurrent AE forms. Within the non-histaminergic AE group there are included the AE induced by angiotensin-converting-enzyme inhibitor (ACEi), the AE induced by nonsteroidal anti-inflammatory drugs (NSAID) and the hereditary angioedema (HAE)10 either with quantitative and/or qualitative complement deficiency (type I and type II HAE) or without complement deficiency (HAE with normal complement)11.

Clinically, AE without urticaria can be acute or recurrent, have a spontaneous resolution or can be a life-threatening condition, if there is upper airway involvement and risk of asphyxia11,12,13,14. Thus, hospital admission and subsequent inpatient hospitalization may be important for monitoring a potentially life-threatening situation and its response to treatment.

Additionally, abdominal attacks in HAE patients may also require special monitorization. They are caused by edema of the gastrointestinal wall, which can be very painful, simulating an “acute abdomen”15,16. In these circumstances, hospital admissions are important for clinical surveillance and to evaluate patients’ response to specific and non-specific therapy.

AE can be the cause of an emergency department admission and lead to an inpatient hospitalization or can be an incidental situation during a hospitalization, as an adverse reaction to drugs such as ACEi, recombinant tissue plasminogen activator (rtPA), or NSAID. Besides this, HAE patients may need to be admitted for prophylactic therapy to prevent acute HAE attacks with plasma-derived C1-inhibitor (pdC1-INH), 1-2h before an invasive procedure. These hospitalizations generally have a mean duration of 24 hours to allow a proper patient monitorization after the procedure.

There are international consensus for the diagnosis and approach of AE without wheals15. However, in Portugal, the epidemiological characteristics of the inpatient hospitalizations for this type of AE are unknown.

Thus, the objective of the present study is to evaluate the frequency of these hospitalizations and the aetiology and clinical characteristics of the hospitalized patients with AE without wheals in the Centro Hospital Universitário de Lisboa Norte.

**Methods**

*Study design*

Retrospective analysis of the hospital inpatient admissions that happened between 2009 and 2013 with a diagnosis grouped under the broad categories of AE (ICD-9-CM codes 995.1: angioneurotic oedema and 277.6: other deficiencies of circulating enzymes) in the Centro Hospitalar Universitário de Lisboa Norte (CHULN). CHULN is a Portuguese public medical center that incorporates two university hospitals, Hospital de Santa Maria and Hospital Pulido Valente, both located in Lisbon. Clinical data from the patients from these two hospitals under these codes was reviewed. We only included the situations of AE without associated wheals.

We excluded all the admissions coded with ICD9-codes 708 (urticaria) and 698.2 (pruritus and other associated conditions), all AE that were part of an anaphylactic episode and all situations that were incorrectly diagnosed as AE. Hereditary Angioedema patients that needed to be hospitalized for prophylactic treatment administration before an invasive procedure were not included in this revision.

The following data was recorded from patients’ files: demographics (age, ethnicity and gender), AE characteristics (location, probable causal agent and other associated conditions), patients’ previous therapy, hospitalization duration (number of days) and destination after discharge. According to the information described in the patients’ file the existence or not of upper airway involvement (tongue or pharyngo-laryngeal AE) was also considered. If the patient had clinical and/or laboratorial criteria of infection it was classified as having concomitant infection. Types 1 and 2 HAE diagnoses were made based on biochemical and functional levels of C1INH found in patients’ files. More than one episode of hospitalization was allowed per patient. Hospitalizations with at least 24-hour duration were considered.

The authors distinguished 2 groups: A- patients in which AE motivated the patient hospitalization; B- patients that had an AE as an incidental situation that appeared during a hospitalization due to another clinical condition.

The study protocol was approved by the ethics committee of CHULN and the confidentiality of all data was assured.

*Statistical analysis*

Statistical analysis was performed using a software SPSS version 24 for Windows. Absolute frequencies and percentage were used to characterize categorical variables while mean and standard deviation were used to describe continuous variables. The rate of hospitalizations per year was determined by dividing the number of hospitalizations due to AE without urticaria by the total number of hospitalizations that occurred in the CHULN in the same year. The authors also determined the mean hospitalization rate for angioedema between 2009 and 2013 as the average of the 5-year rates. Monte Carlo estimate of Fisher’s exact test was used for statistical analysis, except for comparisons between the means where we used the Kruskal-Wallis test. A p value <0.05 was considered statistically significant.

**Results**

Between 2009 and 2013 there were 209 hospitalizations in the CHULN that received an angioedema ICD9 code. Only 169 episodes were included. There were excluded 8 miscoded episodes and 32 hospitalizations that were made for prophylactic therapy in hereditary angioedema patients. Table 1 summarizes the clinical and demographic characteristics from the inpatient hospital admissions. Eighty-seven (51.5%) patients were female, 162 (96%) were adults and the mean age was 52 years old. Regarding ethnicity 114 (67.5%) were Caucasian, 35 (20.7%) had an African origin and in 20 (11.8%) other ethnicities or no information regarding ethnicity in the patients’ files.

The mean hospitalizations duration was of 5.9 days (max 69 days, min 1 day), there were no fatalities and 62% were referred to the allergy unit outpatient clinic after hospital discharge. Eighty-seven (51.5%) of the inpatient admissions took place in the Immunoallergology Department hospitalization ward, being the remaining distributed by 23 different CHULN departments/units.

**Inserir “Table 1” aqui**

Table 2 shows the number of inpatient hospital admissions per year for AE as well as the overall number of CHULN inpatient admissions, between 2009 and 2013. According to this data, in 2009 the rate of hospitalized patients for AE in the CHULN was 53.9 per 100,000 and in 2013 reached 70.5 per 100,000, being the mean value of hospitalizations for angioedema of 71.6 per 100,000 hospitalizations in CHULN in the 5-year period of the study.

**Inserir “Table 2” aqui**

In 111 (55%) inpatient admissions, AE was the main reason for the patient admission; in 58 (29%) AE was an incidental situation that happened during the admission (Table 3).

**Inserir “Table 3” aqui**

The most common reason for AE inpatient admissions was ACEi induced AE in 52 (30.8%) followed by HAE (n=40;23.7%), AE associated with thrombolysis in 22 (13%) hospitalized patients, AE induced by NSAID in 8 (4.7%) of hospitalizations, AE induced by other less frequent situations (antibiotics or antifungal drugs or infection) in 12 (7.1%) and in 35 (20.7%) hospitalizations episodes the AE was classified as idiopathic (p=0.58). In all the hospital inpatient admission that occurred in children (4%), the AE aetiology was HAE. The number of hospitalizations due to HAE slightly increased over the years, while the number of idiopathic AE hospitalizations decreased from 2012 to 2013. For the remaining aetiologies the number of hospitalizations over the years was similar.

**Inserir “Figure 1” aqui**

There were no statistically significant differences regarding age (p=0.07) between all causes of AE. In general, a predominance of females (p=0,01) and a predominance of Caucasian patients (p<0,0001) was observed in almost all aetiologies, with few exceptions– table 4.

**Inserir “Table 4” aqui**

Regarding the AE location, there was upper airway (tongue, pharynx, larynx) involvement in 64 cases (38%), either as an isolated location or associated with another AE site involvement (table 5). In only two hospitalization, both due to rtPA induced AE, it was necessary to do airway intubation In HAE admissions, the abdominal location was the most frequent site involved, whether in ACEi induced AE or in the rtPA induced the face, the lips and the upper airway (tongue or pharyngo-laryngeal) were the most frequent locations (table 5).

**Inserir “Table 5” aqui**

*Angiotensin converting enzyme inhibitor induced angioedema*

Considering the 169 AE hospitalizations, ACEi induced AE was the most frequent aetiology.

Fifty-two inpatient hospital admissions were due to ACEi induced AE (65% females, 27% were Caucasian and 73% had an African origin, mean age±SD 67±15.2 years).

In patients with ACEi induced AE the timing in which the patient started being treated with an ACEi was revised. One patient was on ACEi for more than 10 years, 11 (21.2%) were taking an ACEi between 10 years to 6 months and 10 (19.2%) were taking ACEi for less than 6 months. Two cases (3.8%) corresponded to situations of patients with previous indication for ACEi avoidance that had a subsequent ACEi administration in the emergency department for a hypertensive crisis. In 28 hospitalizations (53.8%) there was no data in the clinical file regarding the period during which patients were taking ACEi. According to the data in the clinical file, the most commonly involved ACEi was captopril (29%), followed by perindopril (25%), enalapril (19%), lisinopril (17%), ramipril (6%) and cilazapril (4%).

*Hereditary angioedema*

HAE was the second most frequent aetiology. Within the 40 hospitalization episodes 82.5% were adults, 57.5% were females, 98 % Caucasians, mean age±SD was 37±15 years. Seventeen (42.5%) of the hospitalizations were of type I HAE, while 23 (57.5%) of type II HAE and there were no patients with HAE with normal complement.

In 39 (97.5%) of these hospitalizations the AE attack was the cause of hospitalization. The reported triggers for the HAE crises were: stress (26%), therapeutic non-adherence (10%), infection (8%), extreme physical exercise (3%), ACEi therapy (3%). In 21% there was no reported trigger. Abdomen was the most frequent location for HAE attacks. All patients were submitted to an abdominal ultrasonography but only in 6 the abdominal involvement was documented by abdominal ultrasonography (ascites and intestinal wall oedema were found in 5 patients and in 1 patient only minimal peritoneal fluid was identified).

~~There were 32 hospitalizations for prophylaxis of HAE. The procedures that required pdC1-INH prophylaxis were: dental extraction (63%), elective caesarean (13%), other gynaecological procedures (6%), appendectomy (6%), adenoidectomy/ amygdalectomy (6%), ophthalmological surgery (3%) and cutaneous surgery (3%).~~

*Thrombolysis induced angioedema*

There were 22 cases with rtPA induced AE (36% females, 77% Caucasian, mean age±SD 68.5±12.8 years) and all episodes corresponded to patients that were hospitalized due to an acute stroke. In these, three subset of patients were found: the first (37 %) in which AE appeared within the first 8 hours after rtPA in patients with no previous history of ACEi intake, the second (37 %) that corresponded to the situations of hypertensive patients previously medicated with ACEi who underwent rtPA and developed AE; and the third group (26 %) in which patients were submitted to rtPA and were prescribed with ACEi concomitantly during the procedure due to a hypertensive crisis. The most frequent location was the tongue with a unilateral angioedema of the tongue (ipsilateral to the stroke site).

There was upper airway involvement in 13 patients and 2 of these required airway intubation. These 2 patients that needed intubation were prescribed with an ACEi for a hypertensive crisis, during the thrombolysis procedure and had no previous history ACEi intake.

*Nonsteroidal anti-inflammatory drug induced angioedema*

In 8 admissions NSAID was the aetiological factor considered (50% females, 75% caucasian, mean age±SD 52.5±11.5 years). Ibuprofen was involved in 4 (50%), naproxen in 2 (25%), diclofenac in 1 (25%) and etoricoxib in 1 (12.5%). No infection criteria were established in these admissions.

*Other aetiologies and idiopathic angioedema*

In the group named “other aetiologies” we included 12 hospitalizations episodes (75% females, 100% Caucasian, mean age±SD 56±18.5 years) probably associated with antibiotics or antifungal drugs (75%) and probably due to infection (25%) without any associated drug.

In 35 hospitalizations (43% females, 77% Caucasian, mean age±SD 58.6±20.8 years), no aetiology for angioedema was established in the patients’ medical record and were classified in this revision as idiopathic AE attacks.

**Discussion**

This study describes the results of the first retrospective analysis, carried out in Portugal, regarding hospitalizations due to AE without associated urticaria. Over the last few years, interest in the pathophysiology and clinical manifestations of this form of AE has increased. However, little is known about the epidemiology and characteristics of the hospitalizations for this form of AE.

Between 2009 and 2013, there were 169 inpatient hospitalization episodes due to AE without urticaria and in 65.7% of these the AE attack was the reason for the hospitalization, in 34.3% AE was an incidental condition during the hospitalization. Overall, we documented an annual average hospitalization rate of 46.9 per 100,000 for the hospitalizations motivated by the AE attack and a rate of 24.6 per 100,000 for the hospitalizations in which the AE attack occurred in patients hospitalized for other reasons. The number of hospitalizations for AE slightly increased between 2011 and 2012 mainly due to HAE hospitalizations. This aspect can be justified by the fact that CHULN is a reference Center for HAE.

Regarding the 111 hospitalizations that were motivated by the AE attack, the most frequent reason was HAE (n = 39; 35%) followed by ACEi induced AE (n = 34; 31%) and by idiopathic AE episodes (n=35,17%). Mansi et al15 in a review of 1058 hospitalizations episodes due to AE without urticaria, between 1993 and 2012, in a tertiary hospital, found a frequency of hospitalizations due to HAE similar to ours (36%). However, in Mansi et al 15 study the most frequent aetiology was idiopathic AE (42%) and ACEi induced AE was the third most frequent aetiology (27%). This data is also in line with the one published by Malbrán et al 16, that characterized 280 hospitalizations episodes due to AE without urticaria and found that idiopathic AE was the most frequent aetiology (55.7%) followed by drug induced AE episodes (24.3%) and by HAE in 15.7% of the cases. In our opinion the high frequency HAE in our population may be explained by the fact that CHULN is a national reference center for the follow-up of patients with this disease.

Considering the hospitalizations that were motivated by other conditions and in which AE occurred as an incidental situation, 33.8% corresponded to idiopathic AE, 31% to rtPA induced AE and 25% to ACEi induced AE.

rtPA is a therapeutic option after an acute stroke17. However, about 1.3 to 5% of patients treated with rt-PA after a stroke may develop AE18. AE associated with the administration of rtPA generally appears as unilateral and painless edema of the lips, tongue and face, 30 to 120 minutes after the beginning of rt-PA administration18.

An aspect to be emphasized in our study is that in 63% of the patients with rtPA induced AE there was a history of concomitant prescription of ACEi. It is estimated that AE occurs in 0.1-2.2% of patients treated with ACEi19 but this frequency may rise given that these drugs are increasingly being used. ACEi induced angioedema is more common in females and in patients with a black origin19,20 as it is pointed out in our revision. Studies prior to ours describe a frequency of 30-38% of emergency admissions due to ACEi induced AE20. However, only few of these cases require inpatient hospitalization for surveillance and therapy21. Bonner et al22 recently proposed an ACEi induced AE classification scale and clinical discharge criteria based on the symptoms of airway involvement. In this classification the main criteria for hospitalization is the existence of airway edema or the evidence of edema rapid progression to the airways23. Banerji et al21, however, consider advisable to monitor elderly patients with ACEi induced AE in order to improve their comfort. In our study, we found that patients with ACEi induced AE were older compared to patients with other aetiologies such as patients with HAE or NSAID-induced AE. Thus, we believe that the fact that elderly patients have more co-morbidities and a higher risk of serious adverse drug reactions may justify the high number of hospitalizations for ACEi induced AE in our population.

Emergency admissions and inpatient hospitalizations may be important for monitorization of symptoms and treatment response, especially in life-threatening conditions such as upper airway edema. In our study, tongue, pharynx or larynx involvement was found in 38% of the AE episodes. Javaud et al24 reviewed all the hospitalizations motivated by HAE that happened in France, between January 2011 and December 2013 (29 patients, 50 attacks) and found that the main risk factors for AE hospitalization were face and larynx involvement and less frequently abdominal crisis. In our study, abdominal attacks had a similar frequency (32.5%) to face and upper airway attacks (35%), within HAE hospitalized patients.

Abdominal symptoms occur in about 70% to 80% of HAE patients25,26. Abdominal AE attacks are generally associated with severe abdominal pain, nausea, vomiting and diarrhea. Ascites may also occur due to the existence of intestinal wall edema and increased vascular permeability that leads to extravasation of plasma in the peritoneal cavity 26,27. In rare cases, these attacks may also be associated with hypovolemia26. For this reason, hospitalizations are important for a faster symptomatic relief through the administration of specific and non-specific therapies and for clinical monitorization. In our population, patients with abdominal AE crisis performed abdominal and pelvic ultrasound and in 50% of these patients’ intestinal wall edema was documented. Pedrosa et al28 considered that abdominal ultrasound is a cost-effective, reliable and reproducible diagnostic method and important for a correct diagnosis.

Our study has, however, some limitations. The first is related to its retrospective design. As we retrospectively reviewed all the hospitalizations coded with the ICD9 codes for AE during a 5-year period, it is not possible to establish, with a great precision, an evolutionary curve of hospitalizations given the short period of time considered. Secondly, our analysis may be limited to the fact that we only considered data from patients' clinical files as there is undoubtedly some variability in the records, especially concerning AE location. We attempted to overcome this limitation by independently analyzing the data by two authors of our study. Thirdly, no information about the treatment used for the different AE aetiologies was analyzed. In our opinion, this information may be necessary for further studies, in order to establish precise hospitalization and clinical discharge criteria to be adopted in national guidelines.

**Conclusion**

This is the first review carried out in Portugal that analyzes the frequency of hospitalizations for AE without associated urticaria, having documented an average annual rate of AE inpatient hospitalizations of 71.6 per 100,000 hospitalizations, with upper airway (tongue, larynx and pharynx) involvement in 38% of the episodes.

We found that in the majority of the hospitalizations, the AE attack was the reason that led to hospitalization, which highlights the nature of this clinical condition. The main aetiology of AE attacks was HAE, followed by ACEi induced AE and idiopathic AE. The AE also occurred as an incidental condition in hospitalizations motivated by other causes, in these patients AE attacks occurred mainly associated with administration of ACEi and rtPA.

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**Conflitos de Interesse**

The authors declare that they have no conflicts of interest related with the present work.

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**Tables and Figures**

Table 1 - Demographic and clinical characteristics of the population

Legenda: SD – Standad deviation

Table 2 - Total of hospitalizations and angioedema without urticaria hospitalizations, between 2009 and 2013

Legenda: AE-angioedema; HAE- Hereditary angioedema

Table 3 - Distribution of hospitalization episodes

Legenda: AE- angioedema, ACEi-AE - angiotensin-converting-enzyme inhibitor induced angioedema; HAE - Hereditary angioedema; rTPA-AE – recombinant tissue plasminogen activator induced angioedema; NSAID-AE - nonsteroidal anti-inflammatory drugs induced angioedema; Other- other aetiologies.

Table 4 - Demographic characteristics of hospitalizations according to aetiology

Legenda: AE – angioedema, ACEi-AE - angiotensin-converting-enzyme inhibitor induced angioedema; HAE - Hereditary angioedema; rTPA-AE - recombinant tissue plasminogen activator induced angioedema; NSAID-AE - nonsteroidal anti-inflammatory drugs induced angioedema; Other- other aetiologies

Table 5 - Angioedema without urticaria attacks location

Legenda: \*In 6 (50%) the abdominal AE was documented by ultrasonography; \*\*The 32 hospitalizations for AE prophylaxis are not included in these as there were no AE crisis. ● Airway intubation was required. Abbreviations: HAE - Hereditary angioedema; ACEi-AE - angiotensin-converting-enzyme inhibitor induced angioedema; rTPA-AE - Thrombolysis induced angioedema; NSAID-AE - Nonsteroidal anti-inflammatory drugs induced angioedema; Other- other aetiologies

Figure 1 - Number of hospitalizations per year according to angioedema aetiology between 2009 to 2013

Legenda: AE – angioedema, ACEi-AE - angiotensin-converting-enzyme inhibitor induced angioedema; HAE - Hereditary angioedema; rTPA-AE - recombinant tissue plasminogen activator induced angioedema; NSAID-AE - nonsteroidal anti-inflammatory drugs induced angioedema; Other- other aetiologies