

# Angioedema - Our Experience Focused On Socio-Demographic, Etiological and Clinical Characteristics of the Condition and Its Management

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## Abstract

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**BACKGROUND:** Angioedema (AE) is acute oedema of the skin and mucous surfaces, involving the respiratory and gastrointestinal tracts. AE could be a life-threatening medical condition. Regardless of its growing clinical importance, many aspects of its aetiology and pathogenesis remain poorly understood. Its incidence, demographic characteristics, diagnosis and therapy, need further investigation.

**AIM:** This study reports our experience with angioedema concerning its social and demographic characteristics, aetiology, clinical features, diagnosis and treatment outcomes. Study design: Eighty-eight patients with AE were enrolled. The study is a retrospective analysis of patients treated in our Clinics.

**METHODS:** All participants were asked on a voluntary basis to fill out a specially designed questionnaire on the day of their discharge. Other important data sources included: patients' history and notes during the hospital stay, information from previous admissions, etc. Parametric and non-parametric statistical methods were used for data processing. Data analysis was performed using SPSS (SPSS Inc., IBM SPSS Statistica) version 20.0

**RESULTS:** Based on our results, AE affects more frequently patients over 50 years of age, regardless of their sex. Urban residents prevail, among them - more commonly working women. Non-steroidal anti-inflammatory drugs (NSAIDs), hormones and antibiotics were among the most common triggers – in 8%, 4.5% and 11.4% of the cases respectively. In 9.09% of the patients, food-induced AE was seen, the most common foods reported, were – nuts, eggs and egg products. The common sites of involvement were periorbital area and lips. In only 9.1% of the patients, oedema progressed to spread to the upper respiratory tract. Cardiac conditions were the most frequent underlying disorders – 33%, of the patients, auto-immune thyroiditis was the second most common-14.8%, followed by musculo- skeletal disorders (10.2%) and diabetes (4.5%) Family history of allergy was seen in 8.4% of the patients, the most frequent allergic disorder, reported, was asthma. In patients with HAE, family history was present in 2.9% of the patients.

**CONCLUSIONS:** All patients received therapy with steroids and antihistamines, resulting in resolution of symptoms and no invasive procedures were necessary. Based on our results, the diagnosis of AE is often difficult and delayed and requires specialist evaluation. If recognised on time and adequately treated, the outcomes are favourable.

## Introduction

Angioedema (AE) usually presents with oedema of the deep layers of the skin, located predominantly on the eyelids, lips, tongue, pharynx and larynx. However, it may also affect other parts of the body, including the extremities. Regardless of its growing clinical importance, many aspects of its aetiology and pathogenesis remain poorly understood. It is the objective of this study to present a detailed

picture of the incidence, aetiology, triggering factors and pathology of AE. An attempt is made to describe the complexity and the many different aspects of the clinical presentation, the sociodemographic and clinical characteristics, the causal factors and the current diagnostic criteria as well as the therapeutic approaches. The analysis is made, based on our more than 5-years experience with the condition. A comparison is drawn between our diagnostic and therapeutic approach to these patients against the established criteria, based on data in the available

literature.

Henrich Quinke [1] first described the clinical picture of AE in 1882. Though it is known that there had been some earlier descriptions – by Marcelo Donatti in 1586 [2] and by John Milton [3] in 1876. In 1888, W. Osler [4] reported the first cases of the hereditary form of the disease; he coined the term "hereditary angioneurotic oedema. In 1961, Lepou et al. discovered the C1 esterase inhibitor (C1-INH) and demonstrated that it increases vascular permeability in guinea pigs. In 1962, Landerman [5] suggested that the reduced levels of kallikrein could trigger the formation of oedema. Donaldson and Evans [6], [7] were the first to describe family members of AE patients with reduced C1-INH levels and respective elevation of C1 esterase concentration. In our country, the first case of AE was reported at the first National Allergy Conference in 1976 [8]. Throughout 30 years, at the National Allergy Clinical Center, a database was developed, including approximately 39 affected families – 120 patients [8]. In the last decades, new forms of acquired AE have been described, and significant progress has been made in clarifying the aetiology, pathogenetic mechanisms, and the genetics of the disease. Serious advances have been achieved in the management of AE. Due to accumulated knowledge, current diagnosis of AE requires the definition of its type. Attempts to classify AE types have been made after it was first described. At present, there is an international consensus that AE could be hereditary (HAE) or acquired (AAE). However, the international task group [9] on AE, analysing and summarising the data, introduced a new classification of AE in 2014. Based on this classification if AAE responds to antihistamines, it is termed histaminergic AE – (IH-AAE). In this case, exposure to allergens should be sought. Another form is the idiopathic non- histaminergic AAE (InH-AAE). It responds well to prophylaxis with tranexamic acid. It was first described by Cicardi et al., [10]. There is an AAE form related to the use of angiotensin-converting enzyme inhibitors (ACEI-AAE). This enzyme plays a crucial role in the metabolism of bradykinin. It is seen in < 0.5% of hypertensive patients and is more common in Africans [11]. Acquired AE with C1INH (C1-INH-AAE) deficiency has also been defined. In this form, there is no family history or established gene mutations. It seems related to depletion of C1INH and is seen mainly in lymphoproliferative disorders. In hereditary AE-two phenotypes are described – type I with quantitative reduction of C1-INH (C1-INH-HAE type I), and type II – with normal C1-INH level, but it is non – functional-(C1-INH-HAE type II) [12]. Another form of HAE is characterized by normal C1INH level and accompanying mutation of factor XII (FXII-HAE). The likely etiology in this case is a missense mutation of the factor XII gene [13]. However, there are patients, non – carriers of this mutation who exhibit AE. This form is of unknown aetiology and is termed U-HAE [14]. AE, as seen from the classification as mentioned above, has many

subtypes. The key to its understanding is that fact, that histamine and bradykinin are the most recognized vaso-active mediators known to be critical in the pathological process; most cases of AE are primarily mediated by 1 of these 2 mediators. The final result is increased capillary permeability, leading to plasma extravasation and accumulation in the deeper layers of the skin and submucosa Figure 1.

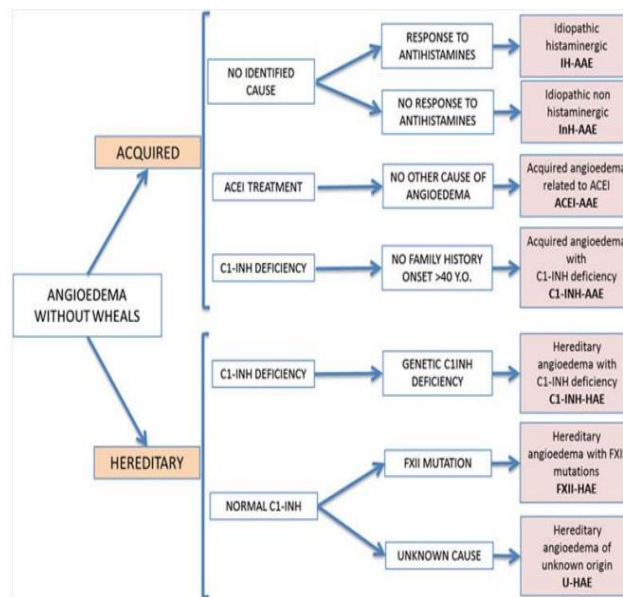


Figure 1: Classification of angioedema

## Material and Methods

The study was conducted at a Clinic of Allergy and Occupational Diseases. It encompassed all patients with AE, admitted and treated at the Clinics from January 1, 2010, to December 31, 2014.

Analyzed variables were categorized as 1. factorial – age, sex, place and district of residence, social status, occupation; 2. resultative – diagnosis at admission and discharge, disease outcome, previous admissions, etiology, other underlying medical conditions, family history, location of the edema and its dynamics, diagnostic criteria, laboratory tests, treatment and therapeutic outcomes.

Two basic methods of medical sociology were applied during data collection: medical interview and analysis of documents.

The study medical questionnaire was developed before the conduction of the study. The first variant was initially tested with 20 patients. This allowed further detailization and clarification of the content of questions. Some questions were added, and others were deleted from the questionnaire.

The questionnaire included 56 open-ended, semi-open-ended and closed questions. They were

grouped into 5 categories as follows:

- social and demographic characteristics of the patients;
- hospital treatment;
- aetiology;
- clinical features and diagnosis;
- laboratory diagnosis.

Document analysis was performed based on patients' hospital papers. Data were entered in a specialised database.

All participants were asked on a voluntary basis to fill out the questionnaire on the day of their discharge. Other important data sources included: patients history and notes during the hospital stay, information from previous admissions, etc.

Primary information was translated, coded and entered into a specialised data base. At a second stage, data were grouped, aggregating factorial and resultative variables to allow summarisation and analysis, thus meeting the study objective. The following statistical methods were used:

- Descriptive statistical methods: extensive variable analysis and graphic analysis

- Analysis of variance – for quantitative data processing. To test the normality of the distribution, Kolmogorov-Smirnov  $\lambda$  criterion was applied. U criterion was used to compare the two sample means. Statistical significance and evidence in support of the null hypothesis were assumed at  $p = 0.05$ .

- Parametrical tests were applied for quantitative variables. Depending on the parameters of interest both the classic and Fisher's exact tests were used. To calculate percentages, Van der Waerden test was applied.

- Correlation analysis was used to test the relationships between factorial and resultative variables. Regression analysis was applied to assess quantitative relationships.

- Non- parametric tests – non-parametrical tests were used to test hypothesis not meeting the criteria for normal distribution. Used tests included: Pearson's squared test, Kolmogorov-Smirnov test, Wilcoxon- Mann – Whitney and Kruskal-Wallis tests.

- Dispersion analysis (Tukey's) tests were applied to allow comparison among multiple pairs of means.

- The method of the least squares was used to equalise dynamic data lines (for the period January 1, 2010, and February 1, 2017) and find the best fit for the data sets.

- The graphic analysis allowed

visualisation of the observed relationships and processes.

Data procession was performed using SPSS (SPSS Inc., IBM SPSS Statistica) version 20.0 and Microsoft Office 2010 platform.

## Results

In the studied period, 88 patients with suspected AE on admission were treated at the Clinics of Allergy and Occupational Disorders. Regarding their socio-demographic characteristics, it was found out that: most patients with AE were over 50 years of age, the condition affected equally males and females, the sex differences being statistically insignificant in all age groups. Results are presented in Table 1.

**Table 1: Distribution of the studied contingent according to age group and sex in AE**

| Age group                  | Males  |        |      | Females |        |      | Total  |        |
|----------------------------|--------|--------|------|---------|--------|------|--------|--------|
|                            | Number | %      | Sp   | Number  | %      | Sp   | Number | %      |
| Up to 30 years of age      | 7      | 20.00  | 6.40 | 4       | 7.55   | 4.15 | 11     | 12.50  |
| Between 30-40 years of age | 9      | 25.71  | 7.39 | 9       | 16.98  | 5.16 | 18     | 20.45  |
| Between 40-50 years of age | 3      | 8.57   | 4.74 | 11      | 20.75  | 5.58 | 14     | 15.91  |
| Over 50 years of age       | 16     | 45.71  | 8.42 | 29      | 54.72  | 6.84 | 45     | 51.14  |
| Total                      | 35     | 100.00 | -    | 53      | 100.00 | -    | 88     | 100.00 |

Regarding the place of residence, most patients were urban residents, however, among urban residents; females were predominant (61.7%). Regarding socio-economic status, working females were prevailing (53.6%), the percentage of students was least-0.9%. The occupational characteristics of the study population were also addressed as occupational exposure could play a role as a trigger in AE. Of the study contingent, 9 patients were medical professionals. Of them, women, assistant nurses were predominant (30.5%), most of the men worked in the hospital administration (70.8%). Finally, some seasonal distribution of the cases was established – the number of admitted patients with AE peaked in early spring and autumn.

Among cases with HAE, emergency hospital admissions predominate, whereas other AE cases, attended as either emergency patients or as planned admissions. (46% and 54% respectively) This fact illustrated the need for detailed diagnostic work up, laboratory tests and planned long term treatment necessary in AE as well as the need to manage acute attacks of AE. The median duration of the hospital stay was 3 days.

Our study demonstrates that 34.1% of our patients have no history of taking medication before the onset of AE, however, drug-induced AE could be

suspected in 42.05% of the cases. Based on our data the most common therapeutic agents implicated in the aetiology of AE were: NSAID, including aspirin (8% and 3.9%) hormones (estrogen – 4.5) and antibiotics – 11.4% Table 2.

**Table 2: Etiology of drug-induced AE**

| Medication  | Based on the patient's history |      |      |        |      |      | Total  |     |
|---|--------------------------------|------|------|--------|------|------|--------|-----|
|   | No                             |      |      | Yes    |      |      | Number | %   |
|   | Number                         | %    | Sp   | Number | %    | Sp   |        |     |
| NSAID   | 81                             | 92.0 | 2.89 | 7      | 8.0  | 2.89 | 88     | 100 |
| Acetyl-salicylic acid and derivatives                           | 74                             | 84.1 | 2.51 | 14     | 15.9 | 3.90 | 88     | 100 |
| Analgesics, anti-pyretics, anaesthetics                         | 81                             | 92.0 | 2.89 | 7      | 8.0  | 2.89 | 88     | 100 |
| Anti-platelet agents  | 86                             | 97.7 | 1.60 | 2      | 2.3  | 1.60 | 88     | 100 |
| Antibiotics   | 78                             | 88.6 | 3.39 | 10     | 11.4 | 3.39 | 88     | 100 |
| Radio-contrast dyes   | 88                             | 100  | -    | 0      | 0    | 0.0  | 88     | 100 |
| Psychoactive agents   | 86                             | 97.7 | 1.60 | 2      | 2.3  | 1.60 | 88     | 100 |
| Beta-blocking agents  | 87                             | 98.9 | 1.11 | 1      | 1.1  | 1.11 | 88     | 100 |
| Herbs   | 87                             | 98.9 | 1.11 | 1      | 1.1  | 1.11 | 88     | 100 |
| Cytostatics   | 87                             | 98.9 | 1.11 | 1      | 1.1  | 1.11 | 88     | 100 |
| Hormones  | 84                             | 95.5 | 2.21 | 4      | 4.5  | 2.21 | 88     | 100 |
| Transfusion of plasma, plasma substitutes and colloid solutions | 88                             | 100  | -    | 0      | 0    | 0    | 88     | 100 |
| Local therapeutic agents  | 82                             | 93.2 | 2.68 | 6      | 6.8  | 2.68 | 88     | 100 |
| Homeopathic agents  | 88                             | 100  | -    | 0      | 0    | 0    | 88     | 100 |
| Vitamins  | 88                             | 100  | -    | 0      | 0    | 0    | 88     | 100 |
| Latex products  | 88                             | 100  | -    | 0      | 0    | 0    | 88     | 100 |
| Synthetic polymers and plastics                                 | 84                             | 95.5 | 2.21 | 4      | 4.5  | 2.21 | 88     | 100 |
| Other   | 62                             | 70.5 | 4.86 | 26     | 29.5 | 4.86 | 88     | 100 |

It is worth noting that in some cases, the triggering medication could not be identified.

Based on the results from our study, food-induced AE could be suspected in 9.09% of the cases. Nuts, eggs and egg products, as well as sea foods, were most frequently involved. Insect bites, radio contract dyes and physical agents were not commonly implicated in the aetiology of AE, based on the results of our study. Interestingly, stress and sustained trauma as triggers of AE, in our research were identified in 30% of the cases. However, repeated trauma did not result in an increased frequency of edemas. The relationship of AE with other underlying medical conditions, especially allergic and auto-immune have been addressed in other research works. Our study demonstrated that in AE patients, most frequently cardiac conditions were identified (33%). Auto-immune thyroiditis was the second most common-14.8%, followed by musculo-skeletal disorders (10.2%) and diabetes (4.5%) Family history of allergy was seen in 8.4% of the patients, the most frequent allergic disorder, reported, was asthma. In patients with HAE, family history was present in 2.9 % of the patients.

According to the findings in our research, half of the patients were diagnosed at the specialised Clinics of Allergic Disorders, in 20% of the cases, the primary care physician established the diagnosis, the remaining-were diagnosed at the Emergency Centers-15.9%. Most patients were diagnosed after having recurrent attacks-43.2%, only 5% were diagnosed after the first attack. The diagnosis of AE was based on the internationally established criteria – history, clinical symptoms and allergic status; laboratory tests were performed in 54% of the patients. Clinically, AE most frequently affected the face, including the lips and eyelids (43.2%). The oedema was located on the lips only in ¼ of the patients, the involvement of the eyelids was even less frequent-13.6%. Facial oedema, progressing to involve the upper respiratory

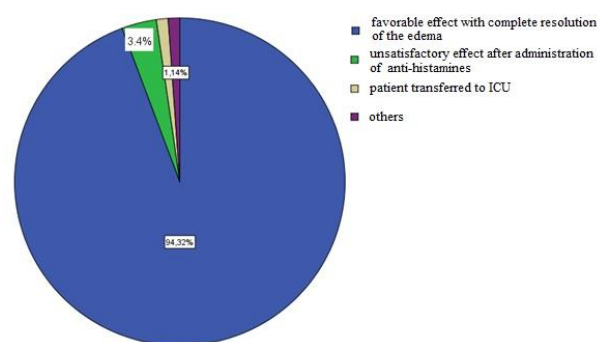
tract was seen only in 9.1%. It is worth noting that prodromal symptoms were seen in the majority of cases – 84.1% of our cases. Prodromal symptoms are presented in Table 3.

**Table 3: Signs and symptoms associated with AE**

| Symptoms         | Based on the patient's history |      |      |        |      |      | Total  |     |
|------------------|--------------------------------|------|------|--------|------|------|--------|-----|
|                  | No                             |      |      | Yes    |      |      | Number | %   |
|                  | Number                         | %    | Sp   | Number | %    | Sp   |        |     |
| Itching          | 29                             | 33.0 | 5.01 | 59     | 67.0 | 5.01 | 88     | 100 |
| Redness          | 66                             | 75.0 | 4.62 | 22     | 25.0 | 4.62 | 88     | 100 |
| Pain             | 86                             | 97.7 | 1.59 | 2      | 2.3  | 1.59 | 88     | 100 |
| Rash             | 42                             | 47.7 | 5.32 | 46     | 52.3 | 5.32 | 88     | 100 |
| Breathlessness   | 81                             | 92.0 | 2.88 | 7      | 8.0  | 2.88 | 88     | 100 |
| Hoarseness       | 78                             | 88.6 | 3.38 | 10     | 11.4 | 3.38 | 88     | 100 |
| Nasal congestion | 85                             | 96.6 | 1.93 | 3      | 3.4  | 1.93 | 88     | 100 |
| Running nose     | 85                             | 96.6 | 1.93 | 3      | 3.4  | 1.93 | 88     | 100 |
| Wheezing         | 86                             | 97.7 | 1.59 | 2      | 2.3  | 1.59 | 88     | 100 |
| Other            | 69                             | 78.4 | 4.39 | 19     | 21.6 | 4.39 | 88     | 100 |

In most cases, AE is accompanied by other symptoms as follows: 30.7 % of the patients present with at least two accompanying symptoms, 23.9%-report three symptoms and 20.5% had only one accompanying symptom. Another important issue, regarding AE is the evolution and course of oedema as it influences the choice of treatment approaches. Based on our research, in 71.6% of the cases, the oedema is self-limiting and does not progress to involve other body parts; oedema expands in 15.9% of the cases; in 12.5% of the patients, its duration was more than 24 hours regardless of the administered therapy. In 35.2% of the patients, AE is the only presentation and is rarely associated with other allergic and auto-immune disorders.

In our study patients, the diagnosis was based on the established diagnostic criteria. Laboratory tests were performed in 54%. All patients received anti-histamines and steroids with a very good therapeutic effect. The results are presented in Figure 2.



**Figure 2: Treatment outcome in angioedema**

All patients in our study received treatment. In 95.4% of them, it resulted in complete resolution of AE after the application of anti-histamines and steroids. In 73.3% of the patients, favourable therapeutic results were seen after the third hour.

Laboratory tests were performed in 23.9 % of the patients to exclude HAE. Diagnostic laboratory tests were: the level of C1 esterase inhibitor, the level of functional C1INH and the level of C4. In all cases, the tests were within the reference levels. Skin allergy prick tests were performed in 52 patients, and IgE levels were tested in 86 patients. Allergy to pollens was noted in 13.6% of the patients, to occupational allergens in 8.0%; the remaining 4.5% had documented allergy to domestic dust, mites and pets. Specific IgE was detected in only one patient.

## Discussion

Regarding the social and demographic characteristics, our research showed that most admitted patients were over 50 years of age. This fact seems related to the finding that medication was the most common triggering factor for AE with NSAID being predominant. No significant differences based on sex were reported unlike other studies (Cohen et al.) that found female predominance [15]. However, male predominance has also been reported [16], [17]. The likely explanation for female predominance is that estrogens have been found to exacerbate type III HAE. In our study, no sex differences were established. However, hormones were the third most common triggering factor for AE. A total of 88 patients were diagnosed and treated for AE at the Clinics in the studied period. Among them, urban residents were 53.3%, of them working women were predominant. More cases were registered in the early spring and autumn. It is known from the literature that AE has been frequently associated with other allergic and autoimmune disorders. Our study provides further evidence of this finding – the most common accompanying allergic disorder in our patients was atopic asthma followed by allergic rhinitis.

Regarding autoimmune disorders, thyroiditis was the second most common co-morbidity. Based on the European guidelines, an attempt was made to establish the triggers, however, even at discharge the aetiology remained unclear in 81.61% of the cases, and 13.79 % of the patients had accompanying urticaria. The detailed analysis of the triggering factors found out that our data was similar to data from the literature [18], 42.05% of our patients have a history of medication intake-aspirin, (15.9%), other NSAIDs (8%), antibiotics (11%), analgesics (8%), hormones(4.5%). Rarely there is a history of intake of more than 3 different medications. Most patients do not associate the AE with food, however, some (9.09%) report that certain foods could trigger AE – most frequently nuts (5.7%) eggs (4.5%) and fish and seafood – 1.1%. This incidence is lower compared to literature data [19]. Allergic reaction to food can cause IgE mediated hypersensitivity and release of

mediators from mast cells, followed by accumulation of mononuclear cells and neutrophils as part of systemic anaphylaxis. However, food allergy can occur in cases of direct mast cell mediator release.

Interestingly, available literature data show a relationship between sustained trauma and AE in 54% of the cases [20]. In our research, there is a relation between trauma and AE but only 30% of the cases. Another finding is the association of AE and urticaria with other co – morbidities as those with immune etiology [20], [21], [22], [23], [24] – a history of atopic asthma – in 26 patients (33.3%), allergic rhinitis – in 4 patients and other allergic conditions in 17 patients (eczema atopic dermatitis etc.). In our study, cardiac conditions were the most common comorbidities (33.3%), followed by auto-immune thyroiditis (14.8%) and musculoskeletal disorders (10.2%). In these patients, AE seems related to the use of ACEI and NSAIDs. The percentage of accompanying auto-immune disorders is similar to that established by other authors [25]. A family history of HAE was established in only 0.9% of the cases, which is less than the established incidence at the population level. There was a family history of allergic disorders (8.4%), most commonly asthma – 56%.

Many authors working in the field of AE, report that the diagnosis of the disease usually takes time. According to a large study in Spain [25], the median time between the first attack and the diagnosis of AE is 13 years. In our study, we document that in most cases, the diagnosis requires evaluation by a specialist. More rarely it is diagnosed by the GP and at the Emergency Centers. Regarding the clinical features of AE, our findings were similar to those reported by other authors [26]- oedema involved most frequently the face, the lips and the eyelids. The course was self-limiting in 71.6% of the cases, rarely progressed to involve other body parts – 15% and the duration of the symptoms was more than 24 hours in 12.4%. The international group on AE has reported similar findings. Most patients present with accompanying symptoms (84.1%). This fact has been documented by other authors [26]. Based on the results from our study, these symptoms are – itching (67%), rash (52.3%) and erythema in the oedema zone (25%). Compared to other authors, the percentage of redness is slightly higher – 48 %. Most patients were admitted and treated at the Clinics after they had had more than three attacks (43.2%). This finding confirms that the diagnosis of AE is often delayed, similarly to other reports in the literature.

In our study, the diagnosis was based on history, clinical features and allergy status. Laboratory tests were performed in 54% of the patients. The C1, C1INH and C4 levels were tested as well as skin prick tests and specific IgE. At least two diagnostic procedures were used. All our patients received treatment – steroids and anti-histamines, which resulted in resolution of symptoms. Specific HAE therapy was not applied. No invasive procedures

(intubation) were necessary.

In conclusion, this study presents an overview of AE. We attempt to analyse the socio-demographic characteristics of AE as well as its most important etiological and clinical features. Based on our result, this is not an uncommon medical condition. The diagnosis is often difficult and delayed and requires specialist evaluation. If recognised on time and adequately treated, the outcomes are favourable.

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