IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 24, Issue 1 Ser. 3 (January. 2025), PP 01-09
www.iosrjournals.org

The Epidemiological And Clinical Landscape Of Hereditary Angioedema (HAE) In Algerian Patients, With And Without C1 Inhibitor Deficiency

Hassen Messaoudi, Abdelbaset Ketfi, Azzedine Tahiat, Kamel Djenouhat
Department Of Internal Medicine, Rouiba Hospital, University Of Algiers 1, Algiers, Algeria,
Department Of Pneumology, Rouiba Hospital, University Of Algiers 1, Algiers, Algeria
Department Of Medical Biology, Rouiba Hospital, University Of Algiers 1, Algiers, Algeria,

Abstract
Introduction*: Hereditary angioedema (HAE) is a rare disease often diagnosed late due to a variable clinical presentation and a lack of understanding of the disease. Morbi-mortality is linked to upper airway edema and abdominal crises. HAE has an impact on the physical and psychological well-being of patients as well as their educational and professional activities. In this study we aimed to delineate the epidemiological and the clinical profile of Algerian patients with HAE, with or without C1 inhibitor (C1-INH) deficiency.*
Methods*: This prospective study enrolled 99 patients diagnosed with hereditary angioedema (HAE) between 2014 and 2017, including those with and without C1 inhibitor (C1-INH) deficiency. For each patient, detailed epidemiological data and clinical manifestations were systematically recorded and analyzed. All patients underwent an immunological assessment, including measurement of C4 and C1-INH levels. Additionally, a genetic analysis, specifically F12 sequencing, was performed in patients with normal C1-INH.*
Results*: Among the 99 patients, 74 were women (75.8%) and 25 were men (24.2%), with a sex ratio of 0.34. The average age was similar between sexes (37 ± 14.5 years vs. 38.3 ± 16.6 years). A family history of angioedema was present in 82.8% of cases, with 17% having sporadic HAE. C1-INH deficiency was more frequent than Type III HAE (76.7% vs. 17.17%). HAE Types 1 and 2 were predominant in women (70.3%), while Type III HAE was observed exclusively in women. The mean age of first attack was significantly earlier in men (13.4 vs. 17.8 years, P = 0.05). Laryngeal involvement was seen in 59.6% of patients, with other clinical manifestations occurring in approximately 80%.*
Conclusion*: HAE with or without C1-INH deficiency, has seen significant advances in both diagnosis and treatment in recent years. Our study is the first in our country to explore this condition, addressing a long-standing knowledge gap that has led to delayed diagnoses.*
Keywords: *Angioedema, Bradykinin, C1 inhibitor, abdominal pain, laryngeal edema*

Date of Submission: 03-01-2025 Date of Acceptance: 13-01-2025

I. Introduction:

Hereditary angioedema (HAE) is a rare and often underrecognized disorder, with literature typically reporting small patient cohorts. The estimated prevalence of HAE, both with and without C1 inhibitor (C1-INH) deficiency, varies significantly across geographical regions, generally not exceeding 1 case per 100,000 or 1 case per 50,000 individuals [1]. Despite its rarity, HAE warrants greater clinical attention due to its profound impact on quality of life, the risk of fatal complications from unrecognized attacks, and the emergence of effective therapeutic options that can dramatically improve patient outcomes [2].

Hereditary angioedema, previously referred to as angioneurotic edema [3], is an autosomal dominant condition characterized by sudden, localized swelling of subcutaneous or submucosal tissues [4]. The edema is typically non-pruritic, soft, well-circumscribed, and deforming, lasting 24 to 72 hours, and usually resolving without residual effects [5]. HAE is self-limiting and does not respond to antihistamines or corticosteroids, which differentiates it from histamine-induced angioedema [6]. The pathophysiology involves a sudden release of bradykinin, triggered by activation of the kallikrein-kinin system via Hageman factor, leading to increased vascular permeability [7].

Diagnosing HAE can be challenging, particularly when it presents as recurrent, familial, non-pruritic, or unexplained angioedema. Since 2006, a new form of HAE with normal C1-INH has been identified [8], which shares the same clinical manifestations and prognosis as C1-INH-deficient HAE, yet requires molecular genetic testing to identify mutations, such as those in factor VII and other related genes [9]. This study aims to evaluate the prevalence and clinical characteristics of the different forms of HAE in a public hospital setting, with the

objective of improving awareness of this rare condition. Given the potential for life-threatening laryngeal involvement, early identification and targeted management are critical for improving prognosis.

II. Patients And Methods

Study Design:

This multicenter prospective study was conducted across the Internal Medicine, Dermatology, and Allergology departments of both public and private healthcare facilities. A total of 99 patients with hereditary angioedema were enrolled over a three-year period, from February 2014 to June 2017. Each patient was monitored for one year, with or without treatment, to assess the clinical outcomes. The present study received ethical approval from the local committee in accordance with the declaration of Helsinki.

Patients' enrollment:

Subjects over 16 years of age, of both sexes, with recurrent angioedema episodes lasting 24 to 72 hours, with or without unexplained recurrent abdominal attacks (2 to 5 days), and with or without a family history, were systematically screened for HAE at the national reference laboratory (Laboratory of Medical Biology, Rouiba Hospital, Algiers, Algeria). Initial screening included measurement of serum C1-INH and C4 levels, followed by functional evaluation of C1-INH and, in some cases, serum C1q dosage.

Hereditary angioedema's known as types I and II are the consequence of a C1-inhibitor (C1-INH) deficiency. Type I (quantitative deficiency) is linked to a mutation in the SERPING1 gene (gene which codes for C1-INH). This mutation prevents the synthesis of the C1-INH protein. Biologically, there is therefore a low level of C1-INH. Type II (qualitative deficiency) is linked to a mutation in the same gene leading to the production of a non-functional C1-INH protein. Types I and II do not differ clinically. The only distinction is biological. There is a type III HAE (currently known as HAE A ci1 normal inhibitor) whose diagnosis must be considered if the concentration and functional activity of C1-INH are normal and if there is no mutation in the SERPING1 gene. This entity has been known since 2000. It is linked to an increase in the activity of kininogenases, the proteases which promote the appearance of bradykinin: Hageman factor, plasmin, kalllikrein. In 15% of patients with a type 3 form, a mutation responsible for a gain of function in the FXII coagulation gene is identified. Type III predominates in women. Hormonal factors play an important role in this type of HAE. Indeed, attacks are favored by taking estrogen-progestin pills and by pregnancies.

Immunological workup:

C1-INH and C4 levels were measured by laser nephelometry, using BN ProSpec System (Siemens, Germany). Functional evaluation of C1-INH activity was performed using a colorimetric method which measures the residual esterase activity of C1s, with inhibition expected after the addition of patient plasma . The functional activity of C1Inh is determined by referring to a standard curve established using 3 standards (120%, 60% and 30%). C1q concentration were determined by radial immunodiffusion (The Binding Site, UK).

Genetic study:

Patients with bradykinin angioedema and normal C1-INH were diagnosed with type III HAE when there was a positive family history. Where possible, patients with a diagnosis of type III HAE underwent coagulation factor XII (F12) gene sequencing (Sanger sequencing) to identify gain-of-function mutations.

Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables.

III. Results

Epidemiological characteristics:

Among the 99 patients, 74 were women (75.8%) and 25 were men (24.2%), with a sex ratio of 0.34 [Figure 1]. The mean age of our patients was 37 ± 14.5 years, with no significant difference between female [37.1 ± 13.8] and male [38.3 ± 16.6 years] patients [Table1].A majority of patients (72.8%) were under 45 years old, while only 11.1% were over 60 years old.

Figure 1: Distribution of patients by gender

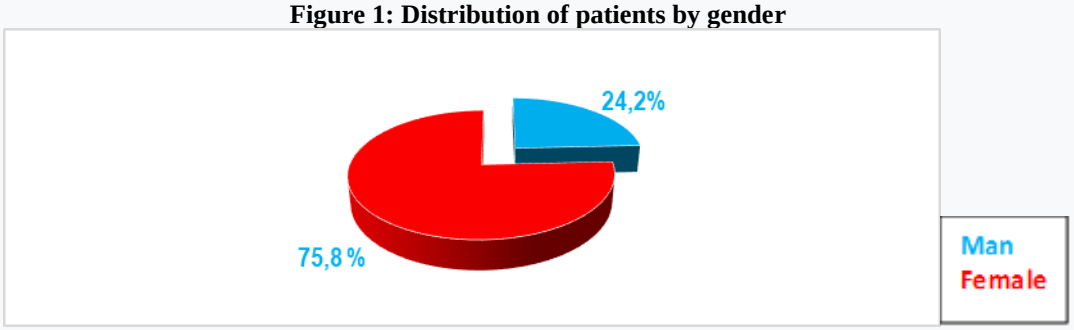
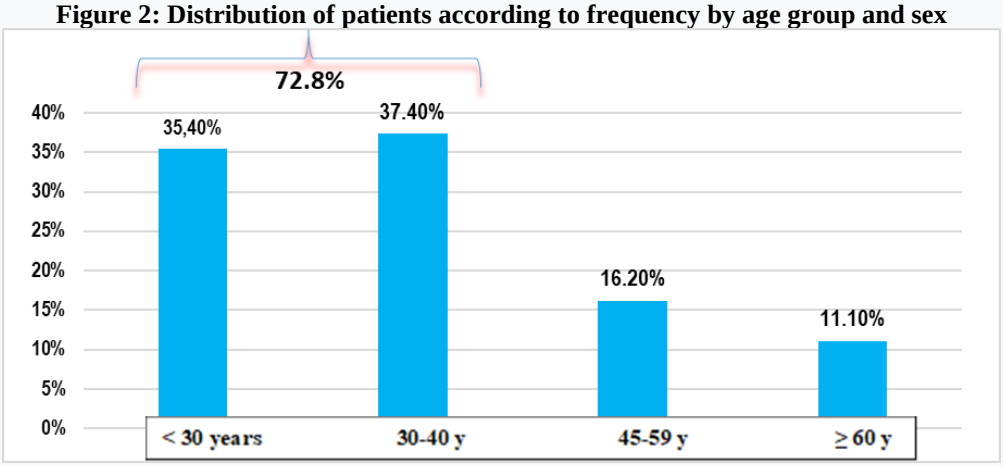


Table 1: Distribution of patients according to average age and sex

Sex	Workforce	Average age	Min	Max
Male	25	38.3±16.6 ans	16	78
female	74	37,1±13.8 ans	16	73
Total	99	37.4±14.5 ans	16	78

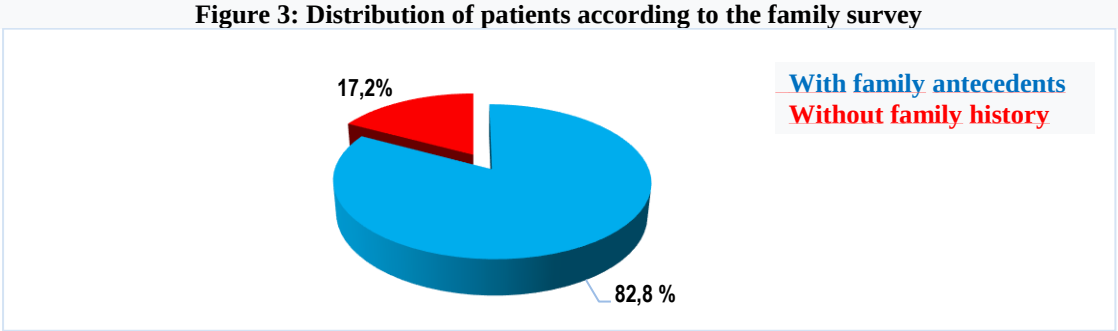
A clear female predominance was observed across all age groups [Figure 2]. 82.8% of patients have a family history of angioedema, as well as the presence of similar cases in siblings, this is explained by the high frequency of HAE with or without C1 INH deficiency, compared to angioedema. -hereditary edema without family history or a similar story in siblings [17.2%], found in our series **(**Figure3).

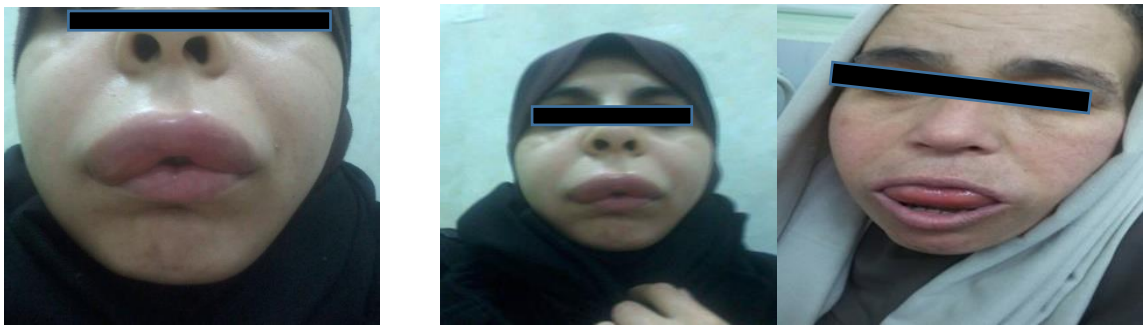
Figure 2: Distribution of patients according to frequency by age group and sex



In our series of 76 patients with HAE (type 1 and 2), between women and men were listed. We found 13 patients (17%) whose parents were not affected by the disease; this type of AO is called sporadic OAH due to "de novo" mutations [figure 4]

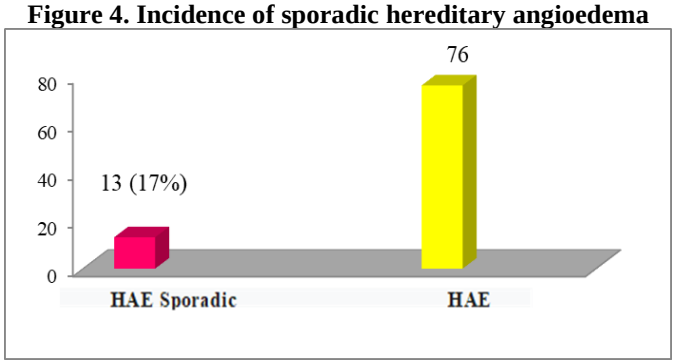
Figure 3: Distribution of patients according to the family survey





Some of patients with HAE in our cohort

Figure 4. Incidence of sporadic hereditary angioedema



A patients with HAE type 1 in our cohort

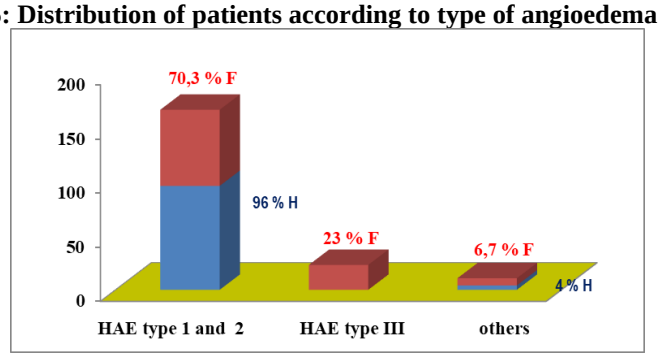
Clinical characteristics:

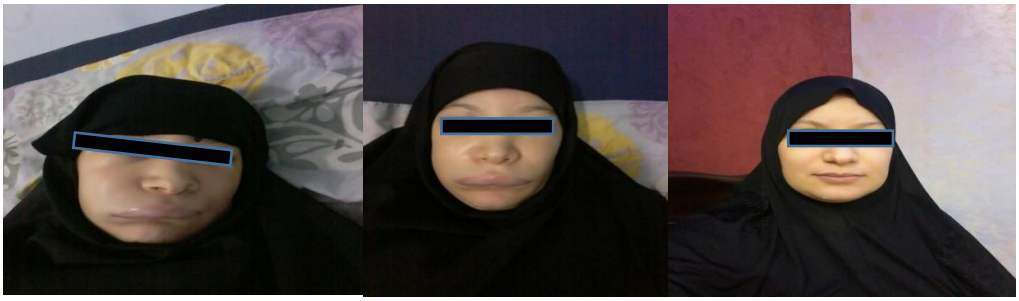
Distribution of patients according to the frequency of the type of hereditary angioedema: we adopted the classification of Cicardi et al [2014]. It is clear that the frequency of HAE due to C1 INH deficiency [HAE type 1 and 2] is higher than HAE due to factor XII mutation. [HAE Type III] [76.7% vs 17.17%]

Distribution of patients according to the type of angioedema and sex:

HAE types 1 and 2 are predominantly present in men [96%]. Despite the predominance of HAE types 1 and 2 [70.3%] in women, type 3 represents a significant proportion [23%]. Note that HAE type 3 is exclusively present in women in our series. [Figure 5]

Figure 5: Distribution of patients according to type of angioedema and sex



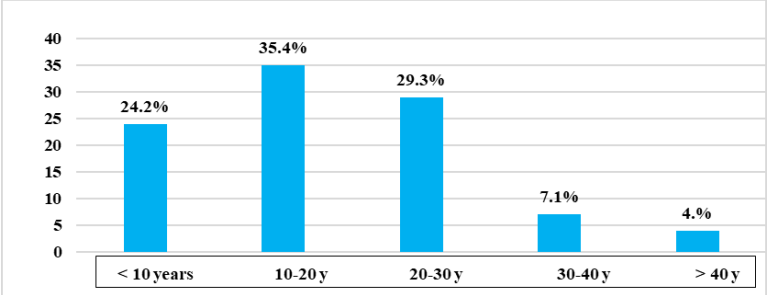


A patient of HAE with normal c1 inhibitor in our series

Distribution of patients according to the age of onset of the first attack:

Among our patients, almost 1/4 (24.20%) declare having had the first attacks during the first decade of their life, while only 4% among them, their first seizure appeared late after the age of 40. [Figure 6]

Figure 6: Distribution of patients according to age at onset of the first attack



Distribution of patients according to age at onset of the first attack and sex.

The average age of onset of first attacks is significantly lower in men [13.4±8.1 years] compared to women [17.8±10.5 years], [P=0.05]. [Table 2]

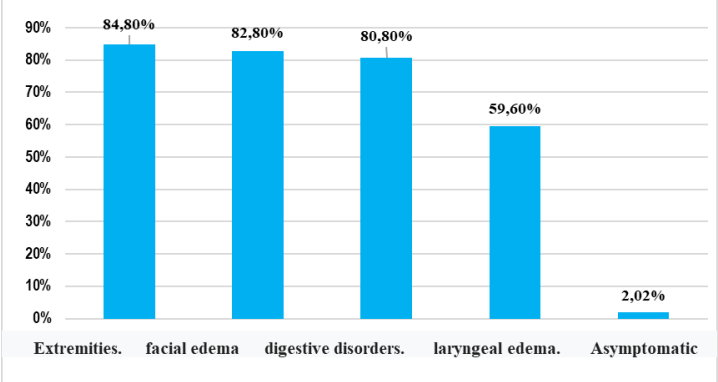
Table 2: Distribution of patients according to age at onset of the first attack and sex

Sex	Effective	Average age of onset of first seizures	Minimum	Maximum	
Male	25	**13.4±8.1 ans**	02	30	**P=0.05**
Female	74	**17.8±10.5 ans**	02	46	
Total	99	17± 9.9	02	46	

Distribution of patients according to the frequency of different clinical manifestations

The frequency of damage to the upper and lower extremities [84.8%] was not significantly higher than facial damage [82.8%] as well as digestive damage [80.8%]. More than half of our patients had laryngeal involvement [59.6%], while only 2.02% had no clinical manifestations [asymptomatic]. [Figure]

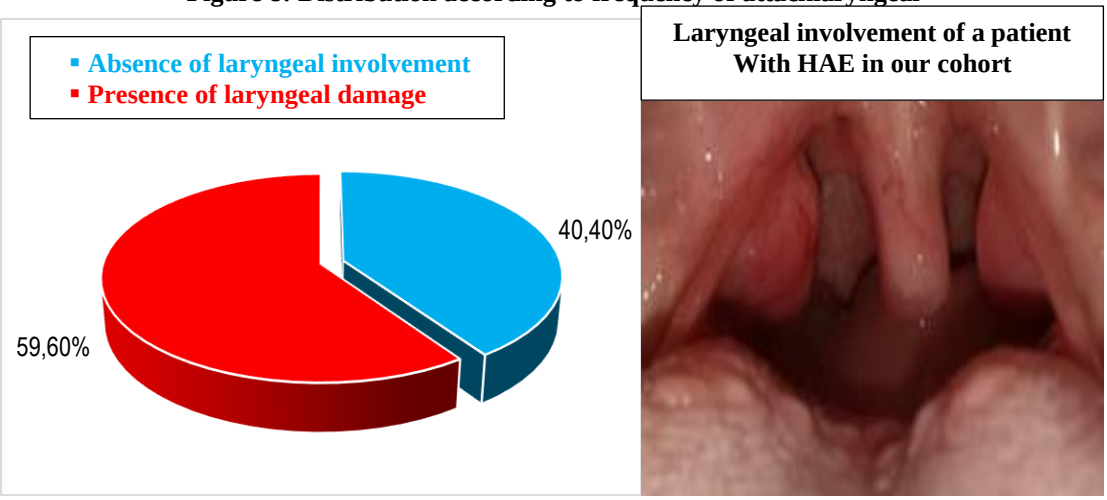
Figure 7: Distribution of patients according to the frequency of different clinicalManifestations



Distribution of patients according to the frequency of laryngeal damage

More than half of the patients [59.6%] of patients had at least one serious laryngeal damage, thus demonstrating the high frequency of this damage during HAE. in our [figure 8]

Figure 8: Distribution according to frequency of attacklaryngeal



IV. Discussion

A total of 99 patients with bradykinin angioedema [AOB] were recruited. We will describe the epidemiological and clinical characteristics of our patients.

Distribution of patients by sex

We noted a clear female predominance [75.8% vs 24.2%] which is consistent with most of the results of the data in the literature and in particular those of the following studies:

1- Ciccardi's team in Italy [10] carried out a national survey including 17 centers on 983 C1-INH-HAE patients, where he found a slight predominance of the female sex [53%] vs 47%], which has also been reported in other studies in Denmark [11].

2- A study in Brazil (12) involved 120 patients, 2/3 of the patients were female

3- A Spanish series [13], of 639 patients, noted a female predominance [59.9% vs 41.1%],

4- The French series by L Bouillet [14], which involved 193 patients, 69.4% of whom were women

This female predominance, whatever its frequency, as reported by these different studies, would probably be explained by the fact that women are more receptive to triggering factors such as taking estrogen-progestin pills, emotional stress, menstruation and pregnancy.

Distribution of patients according to average age and sex

The average age of our patients was 37 ± 14.5 years, it does not differ significantly between women [37.1 ± 13.8] and men [38.3 ± 16.6 years]. Our results are compatible with those found by the French teams (average 45 years) [14], Spanish (48.6 years) [15], and Italian (45 years) [16] except in the Brazilian series [17] or the average of the age is higher in females, this can be explained by the sick population in Brazil which includes more women than men and this has an impact on the average age of subjects suffering from HAE, composed mainly of women

Distribution of patients according to age group and sex

[72.8%] of our patients were under 45 years old and only [11.1%] were over 60 years old. The female predominance was clear for all age groups. The results of an American retrospective study [18] published in 2018 and focusing on age groups had identified [51.7%] of patients under 46 years of age suffering from HAE type 1 without taking into account their gender. This difference could be due to: a better knowledge of this condition, knowing that the molecular anomaly was discovered in this region in 1963 (Massachusetts).

Distribution of patients according to the family survey

In our study we found that 82.8% of patients have a family history of angioedema, as well as the presence of similar cases in siblings, this is explained by the high frequency of HAE with or without C1 INH deficiency. Compared to other types of angioedema [17.2%], found in our series. [Table 34]. In the Brazilian study developed

by A.S. Grumacha et al [19], reported a series of 120 cases, of which, 91.7% of patients had a family history, these results are close to ours [82.8%] thus agreeing with the data from the literature [20].

Distribution of sporadic hereditary angioedema

In our series of 76 patients with HAE; 13 patients (17%) are de novo, without family history referred to as sporadic or de novo OAH. The causal mutation is inherited from a parent or appears de novo in the patient, which means that the absence of family context should not

Cannot exclude a hereditary C1Inh deficiency. The same results were found in the Spanish study [15], as well as the French team [21] which found between 20 and 25% sporadic HAE. According to the study conducted by Bork et al [22], out of 283 patients suffering from HAE, 11 patients had no family history (de novo HAE). Nzeako et al [23] at Mayo Clinic (USA) estimated that sporadic HAE affects more than 10% of their study population. The values ranging from 10 to 25% objectified in the various works are comparable with what we found in our work which are of the order of 17%

Distribution of patients according to the frequency of the type of hereditary angioedema

Our results showed that the frequency of HAE due to C1 INH deficiency is higher than HAE Type III [76.7% vs 17.17%]. If we have to compare them, the frequency of HAE type 1 is usually around 85% vs. 74.7% found in our study, while type 2 is 15% in the literature compared to the 2% described in our series. This type of angioedema is very rare in the literature as reported by Mohamed Abuzakouk [24]. As for the frequency of HAE type III [hereditary angioedema with normal C1 inh,] which is around 17.17%.

Distribution of patients according to type of angioedema and sex

HAE types 1 and 2 are predominantly present in men [96%]. Despite the predominance of AOB types 1 and 2 [70.3%] in women, type 3 represents a significant proportion [23%]. Note that HAE type 3 is present exclusively in women in our series. Bork et al [23], and Binkley and Davis [25] described this variant [C1-INH-HAE], which mainly affects women. In the study by A Deroux et al [26] on 57 patients with HAE at C1 Normal Inhibitor are exclusively women. In our series of 74 women affected by bradykinin angioedema, 17 affected patients [23%] were exclusively female, as described in a large German family. F12 transcription is upregulated by estrogen, which may explain why only females are affected. Type III was observed exclusively in women in our series, where there seems to be a correlation with hyperestrogenism (pregnancy and oral contraceptives). Recently, cases of HAE type III in males have been reported in the literature without being able to explain the mechanism of action [27].

Distribution of patients according to age of onset of the first attack

In our series, a quarter of our patients (24.20%) declared having had the first attacks during the first decade of their life, while only 4% of them saw their first attack appear late after the age of 40 years. The majority of our patients (35.40%) had the first attacks during the second decade as reported by the American serine of Banerji [18] or more than half of the patients had their first attack between 06 and 16 years old, whereas in the majority of cases, the first attacks appear around the second decade of life, coinciding with the hormonal changes caused by puberty as reported in the literature [28] where the age of onset of the first symptoms is 15 years.

Distribution of patients according to age of onset of the first attack and sex

The first attacks appear earlier in men [13.4±8.1 years] compared to women [17.8±10.5 years], [P=0.05] in our work, and as shown in certain series [29]. This suggests that infections and microtraumas which affect more male patients [efforts, physical contact, the nature of the profession and male spots] represent the main factors triggering HAE attacks in male patients. male of our series.

Distribution of patients according to the frequency of different clinical manifestations

Clinical Manifestations	ALGERIA (Our Work)	FRANCE (Deroux et al) [26]	BRAZIL (Grumacha et al)[30]	FRANCE L Bouillet[31]
Edema of the extremities	84,8 %	87%	97% d	42,5%
Facial edema	82.8%	91%		6,9**%**
Abdominal pain	80.8%	80%	43,1%	57,1%
Laryngeal involvement	59.6%,		25%	7,9%

In the USA, more than 80% of patients with HAE have digestive symptoms as we have highlighted in our work, which is enormous. In the light of these different studies, more than half of our patients have had a laryngeal involvement [59.6%], and more abdominal involvement [80.8%] testifying to the fairly high frequency

of this serious localization in our population due to the lack of knowledge of the disease and especially the absence of medication as a basic treatment can reduce its frequency

Distribution of patients according to the frequency of laryngeal involvement

Studies	Algerian Cohort	Deroux [26] France	Zuraw [32] USA	Farcas [33] Hongris	Bork [34] (2006) Allemagne	Bork [35] 2012 Allemagne	Gombel [36] France
Laryngeal involvement	**59 %**	74%	>50%	30-50%	[40%]	[32%]	50%

In view of all these studies illustrated in the table above, an original and somewhat specific result of the Algerian series is this high frequency of this attack, [59.6%] which is enormous in our study population. Which could be explained by the following causes: by not taking long-term preventive treatment and/or just treatment during crises, but above all by the absence of specific innovative treatments in our country.

Strengths and Limitations

Strengths:

This study is the first to provide an epidemiological and clinical analysis of HAE among Algerian patients, a population with limited prior data. The multicenter approach and substantial sample size improves the study's reliability, while prospective tracking allows for comprehensive symptom documentation.

Limitations:

The limited access to genetic testing, particularly for factor XII mutations, restricts the studies ability to capture the prevalence of Type III HAE, potentially underrepresenting this subtype.

The lack of male representation for Type III HAE also limits the generalizability of findings across all demographic groups. Furthermore, the unavailability of advanced treatment options in Algeria likely affected the observed frequency and severity of symptoms.

V. Conclusion

Hereditary angioedema (HAE), whether or not associated with C1Inh deficiency, has undergone a therapeutic revolution in recent years. This first estimate of the prevalence of HAE for an Algerian population shows a frequency slightly lower than those reported by studies carried out in other countries. This is explained by the long diagnostic delay reflecting a lack of awareness of HAE, particularly when there is no known family history due to the fact that it is a rare disease. Our work stands out for its innovative theme which has never been treated before in our country on the epidemiological and clinical level in an Algerian cohort compared to neighboring countries.

References

[1] Laurence Bouillet. Diagnostic Des Angiocœdèmes Héréditaires. Presse Med. 2015 ; 44 : 52–56

[2] Sara Barmettler, Yu Li, Aleena Banerji . New And Evolving Therapies For Hereditary Angioedema. Allergy Asthma Proc. 2019 Jan 1; 40(1):7-13.

[3] O. Bonhomme, M. Moutschen. Diagnostic Et Traitement Des Œdèmes Angioneurotiques Héréditaires : Illustration Clinique Et Brève Revue De La Littérature. Rev Med Liège 2014 ; 69 : 10 : 541-548 541

[4] L. Bouillet. Les Angiocœdèmes Héréditaires. La Revue De Médecine Interne 31s [2010] S29–S31

[5] A. Du-Thanh, N. Raison-Peyron, B.Guillot. Les Angiodémes A Bradykinines. Annales DeDermatologie Et De Vénéréologie, Volume138, N°4 Pages 328-335 [2011]

[6] Loverde D, Files Dc, Krishnaswamy G.Angioedema. Crit Care Med 2017; 45[4]:725-35.

[7] Krystyna Obtułowicz. Bradykinin-Mediated Angioedema.Polskie Archiwum MedycynyWewnętrznej 2016; 126 [1-2]

[8] Loverde D, Files Dc, Krishnaswamy Angioedema. Crit Care Med 2017; 45[4]:725-35.

[9] L. Bouillet. Les Angiocœdèmes Héréditaires De Type Iii : Nouvelle Maladie Ou Nouveau Diagnostic? Revue Française D'allergologie Et D'immunologie Clinique 48 [2008] 155–158

[10] Y. O. Xu-Cai Et Al. Factor Xii Gene Mutation In The Hageman Family Thromb Haemost.2011 November; 9[11]: 2329–2331

[11] Cicardi M., Zingale L.C., Bergamaschini L., Agostoni A. Angioedema Associated With Angiotensin - Converting Enzyme Inhibitor Use: Outcome After Switching To A Different Treatment. Arch. Intern. Med., 164: 910-3.2004

[12] Bygum A. Hereditary Angio-Oedema In Denmark: A Nationwide Study. Br J Dermatol 2009;61:1153–1158.

[13] Grumach Et Al. Hereditary Angioedema: First Report Of The Brazilian Registry And Challenges Journal Of The European Academy Of Dermatology And Venereology .1468-3083.2012.

[14] Takejima, P And Al.Gender Influence On Hereditary Angioedema With C1-InhibitorDeficiency. Journal Of Allergy And Clinical Immunology, 139[2], 2016.12.762

[15] L. Bouillet Et Al. Hereditary Angioedema With C1 Inhibitor Deficiency: Clinical Presentation And Quality Of Life Of 193 French Patients. Ann Allergy Asthma Immunol 111 [2013] 290e294

[16] Roche O, Blanch A Caballero T, Sastre N, Callejo D, Lopez-Trascasa M.Hereditary Angioedema Due To C1 Inhibitor Deficiency: Patient Registry And Approach To The Prevalence In Spain. Ann Allergy Asthma Imunol. 2005; 94 [4]: 498-503.

[17] M. Mansi, A. Zanichelli, A. Coerezza, And Al. Presentation, Diagnosis And Treatment Of Angioedema Without Wheals: A Retrospective Analysis Of A Cohort Of 1058 Patients - Journal Of Internal Medicine, 2015, 277; 585–593

[18] Grumach Et Al.Hereditary Angioedema: First Report Of The Brazilian Registry And Challenges Journal Of The European Academy Of Dermatology And Venereology .1468-3083.2012.
[19] Aleena Banejri, Yu Li, Paula Busse Et Al. Hereditary Angioedema From The Patient's Perspective: A Follow -Up Patient Survey. Allergy Asthma Proc 39: 212-223, 2018
[20] Grumach Et Al. Hereditary Angioedema: First Report Of The Brazilian Registry And Challenges Journal Of The European Academy Of Dermatology And Venereology .1468-3083.2012.
[21] Ugochukwu C. Nzeako, And Al .Hereditary Angioedema A Broad Review For Clinicians.Arch Intern Med. 2001 ; 161[20]:2417-2429
[22] Boccon-Gibod, A. Gompel, O. Fain,D. Launay, Y. And Al [Creak].Angioœdèmes Héréditaires A C1-Inhibiteur Normal Avec Mutation Du Facteur Xii :Etude D'une Cohorte Française. La Revue De Médecine Interne 34s [2013] A22–A
[23] Bork K., Barnstedt S., Koch P., Traupe H. Hereditary Angioedema With Normal C1 Inhibitor Activity In Women. Lancet, 356: 213-7.2000
[24] Ugochukwu.C. Nzeako And Al. Hereditary Angioedema: A Broad Review For Clinicians Arch Intern Med: 2001; 161:2417.2429
[25] Mohamed Abuzakouk, Nada Al Mahmeed And Al. Hereditary Angioedema Type Ii: First Presentation In Adulthood With Recurrent Severe Abdominal Pain. Hindawi Case Reports In Immunology; Volume 2018, Article Id 7435870, 5 Pages
[26] Karen E. Binkley, Alvin E. Davis Iii. Estrogen-Dependent Inherited Angioedema. Transfusion And Apheresis Science 29 [2003] 215–219
[27] A. Deroux Et Al. Hereditary Angioedema With Normal C1 Inhibitor And Factor Xii Mutation: A Series Of 57 Patients From The French National Center Of Reference For Angioedema. Clinical And Experimental Immunology. 2016; 185: 332–337
[28] Konrad Bork . Diagnosis And Treatment Of Hereditary Angioedema With Normal C1 Inhibitor Allergy, Asthma & Clinical Immunology 6, 15 (2010) 18. Aleena Banejri, Yu Li, Paula Busse Et Al. Hereditary Angioedema From The Patient's Perspective: A Follow -Up Patient Survey. Allergy Asthma Proc 39: 212-223, 2018
[29] C. Serrano, M. Guilarte, R. Tella,G. Dalmau, J. Bartra, P. Gaig,M And Al.Oestrogen-Dependent Hereditary Angio-Oedema With Normal C1inhibitor: Description Of Six New Cases And Review Of Pathogenic Mechanisms And Treatment .Allergy 2008: 63: 735–741
[30] Martin L, Degenne D, Toutain A, Ponard D, Watier H: Hereditary Angioedema Type Iii: An Additional French Pedigree With Autosomal Dominant Transmission. J Allergy Clin Immunol. 2001, 107: 747-748. 10.1067/Mai.2001.114242.
[31] Grumach A.S., Pires Correie A., Valle S., Franca A.T., Pinto J.A., Duarte A.J.S.
Heriditary Angioedema In Brazil: Registry Of 1 20 Cases. Mol. Immunol., 44[16]: 3963. 2007
[32] L. Bouillet Et Al. Hereditary Angioedema With C1 Inhibitor Deficiency: Clinical Presentation And Quality Of Life Of 193 French Patients. Ann Allergy Asthma Immunol 111 [2013] 290e294
[33] Sandra C. Christiansen, And Bruce L. Zuraw, Hereditary Angioedema: Management Of Laryngeal Attack. American Journal Of Rhinology & Allergy; 2016 05:16:40
[34] Henriette Farkas. Management Of Upper Airway Edema Caused By Hereditary Angioedema Allergy, Asthma & Clinical Immunology 2010, And 6:19
[35] Konrad Bork, Md; Katharina Siedlecki And Al. Asphyxiation By Laryngeal Edema In Patients With Hereditary Angioedema. Mayo Clin Proc. 2000; 75:349-354
[36] Bork K, Hardt J, Witzke G. Fatal Laryngeal Attacks And Mortality In Hereditary Angioedema Due To C1-Inh Deficiency. J Allergy Clin Immunol 2012 ; 130 : 692–7.
[37] A. Gompel. Pilule Et Angioœdèmes A Bradykinines. La Lettre Du Gynécologue N° 357-Janvier 2011