Review

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2017;174:1–6
DOI: 10.1159/000479839

Published online: September 27, 2017

An ABC of the Warning Signs of Hereditary Angioedema

Anete Sevciovic Grumach[a] Natasha Ferraroni[b] Maria Margarita Olivares[c]
Maria Concepción López-Serrano[d] Anette Bygum[e]

[a]Faculdade de Medicina ABC, Santo Andre and [b]Outpatient Clinic, Brasilia, Brazil; [c]Clinica Medellin Poblado, Medellín, Colombia; [d]Asociación Española de Pacientes con Angioedema Hereditario (AEDAF), Madrid, Spain; [e]HAE Centre Denmark, Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

Keywords
Warning signs · Hereditary angioedema · Diagnosis · Emergency care

Abstract
Hereditary angioedema (HAE) with C1 inhibitor deficiency is a genetic disorder that clinically manifests with attacks of angioedema in the subcutaneous and submucosal tissues, mainly in the extremities, abdomen, and upper airway. During attacks, vascular permeability is increased due to increased bradykinin (BK). This means that special therapies are needed for attacks that do not respond to traditional antiallergic therapies involving antihistamines, corticosteroids, and epinephrine. The recurring attacks may disable patients and lead to frequent visits to emergency rooms where misdiagnoses are common. HAE attacks may be fatal when upper-airway edema occurs, if proper treatment with a C1 inhibitor concentrate or BK receptor antagonist is not administered or an emergency tracheostomy is not performed. We propose a mnemonic method for the warning signs of HAE for the use as a diagnostic tool, i.e., the so-called "ABC" of the warning signs of HAE. The letters represent the following: A = Angioedema, B = Bradykinin, C = C1 inhibitor, D = Distress factors, E = Epinephrine nonresponsive, F = Family history, and G = Glottis/Gastrointestinal edema. To avoid fatalities, medical staff and patients, including family members, must be aware of HAE. An alphabetical mnemonic method has been developed and we hope it may benefit patients.
© 2017 S. Karger AG, Basel

Introduction

Hereditary angioedema (HAE) is an autosomal dominant condition involving antigenic and/or functional deficiency of the C1 inhibitor (C1-INH-HAE) [1]. A clinical condition with similar symptoms was identified in 2000 in which no C1-INH deficiency was detected (previously called HAE type III) and recognized as HAE with normal C1-INH [2].

The estimated prevalence of C1-INH-HAE is 1:50,000, and >500 mutations of the C1-INH gene, *SERPING1*, have been described [3]. HAE with normal C1-INH has been associated with mutations in exon 9 of factor XII (FXII-HAE), but there is still a high percentage of these patients in whom no mutations have been identified (U-HAE) [1, 4, 5].

The common denominator of HAE is bradykinin (BK), which is the final common biochemical mediator. BK is a linear nonapeptide that is produced endogenous-

KARGER

© 2017 S. Karger AG, Basel

E-Mail karger@karger.com
www.karger.com/iaa

Correspondence to: Dr. Anete Sevciovic Grumach
Department of Clinical Immunology, Faculty of Medicine ABC
Av Principe de Gales, 821
Santo Andre, SP 09060.650 (Brazil)
E-Mail asgrumach@gmail.com

Downloaded by: A. Mari - 31298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/14/2017 12:12:34 PM

ly in humans and other mammals as a result of the proteolytic activity of kallikrein on kininogens. During attacks of angioedema, vasodilation occurs, leading to increased capillary permeability and fluid extravasation through the interstitial space [6].

Clinical manifestations include subcutaneous or submucosal edema, without urticaria, that mainly affects the extremities, face, genitals, gastrointestinal tract, and upper airway. Unnecessary abdominal surgery and asphyxia can occur during the attacks if no specific therapy is implemented [7, 8].

Acquired angioedema with C1-INH deficiency (C1-INH-AAE) is an ultrarare disease with a clinical presentation and therapeutic response similar to that of HAE. C1-INH-AAE is characterized by low C1-INH concentrations, reduced C1q levels, and, often, measurable antibodies to C1-INH. AAE is associated with lymphoproliferative disorders and occasionally with autoimmune, neoplastic, or infectious diseases [9]. Finally, angioedema caused by the use of drugs, especially angiotensin-converting enzyme inhibitors (ACEI), can present as life-threatening angioedema episodes without associated urticaria or other signs of anaphylaxis [10].

Neither of the abovementioned subtypes of BK-mediated angioedema is responsive to treatment with traditional antiallergic therapies such as antihistamines, corticosteroids, or epinephrine [11]. In recent years, new drugs and approaches for treating C1-INH-HAE have emerged, but access to diagnosis and therapy is still restricted in developing countries [7]. Additionally, it is a common complaint that, even in developed countries, the staff of the emergency room is not fully aware of these diseases and their treatment options [12].

The Warning Signs

Taking into consideration the need to improve diagnosis and emergency assistance, we organized a simple mnemonic rule with selected signs and symptoms to be applied especially for emergency room physicians.

Warning signs were selected after listing the main relevant issues of the pathophysiology, symptoms and signs, laboratory diagnosis, and specific therapies associated with HAE. To make the pneumonic easier to memorize, the chosen points appear in alphabetical order. This approach was applied according to previously reported experiences with establishing warning signs for primary immunodeficiencies [13, 14] and other diseases [15, 16].

Symptoms, signs, diagnosis, and responses to therapy were condensed as warning signs listed in alphabetical order (Fig. 1).

Comments

HAE is a rare disease that occurs worldwide without ethnic or geographical preferences. In Denmark, Spain, and Italy, prevalences of 1.41, 1.09, and 1.65 per 100,000 inhabitants have been reported, respectively [17–19]. US estimates of annual emergency department visits for angioedema of all types have reached >108,000 [20]. Misdiagnosis and delayed diagnosis due to the lack of recognition of the disease may suggest that the prevalence could even be underestimated. One point to be discussed is that patients experience distress and feel rejected when physicians do not believe in their diagnosis, especially in emergency departments. In cases of life-threatening laryngeal attacks, the patients would not be able to argue with the physicians about the nature of and treatment responses to their disease [21]. The consequence is the occurrence of deaths due to inappropriately treated HAE attacks, even though drug therapy is available [8, 22, 23]. Before the introduction of effective therapies for HAE, one-third of patients died of asphyxiation [23]. Mortality was reported to occur from asphyxiation during a laryngeal attack in 70 of 728 patients diagnosed with HAE owing to a C1-INH deficiency in Germany [8]. Emergency treatment, such as immediate endotracheal intubation or percutaneous tracheotomy, may be necessary if the airway is threatened. Specific therapy for HAE attacks is needed.

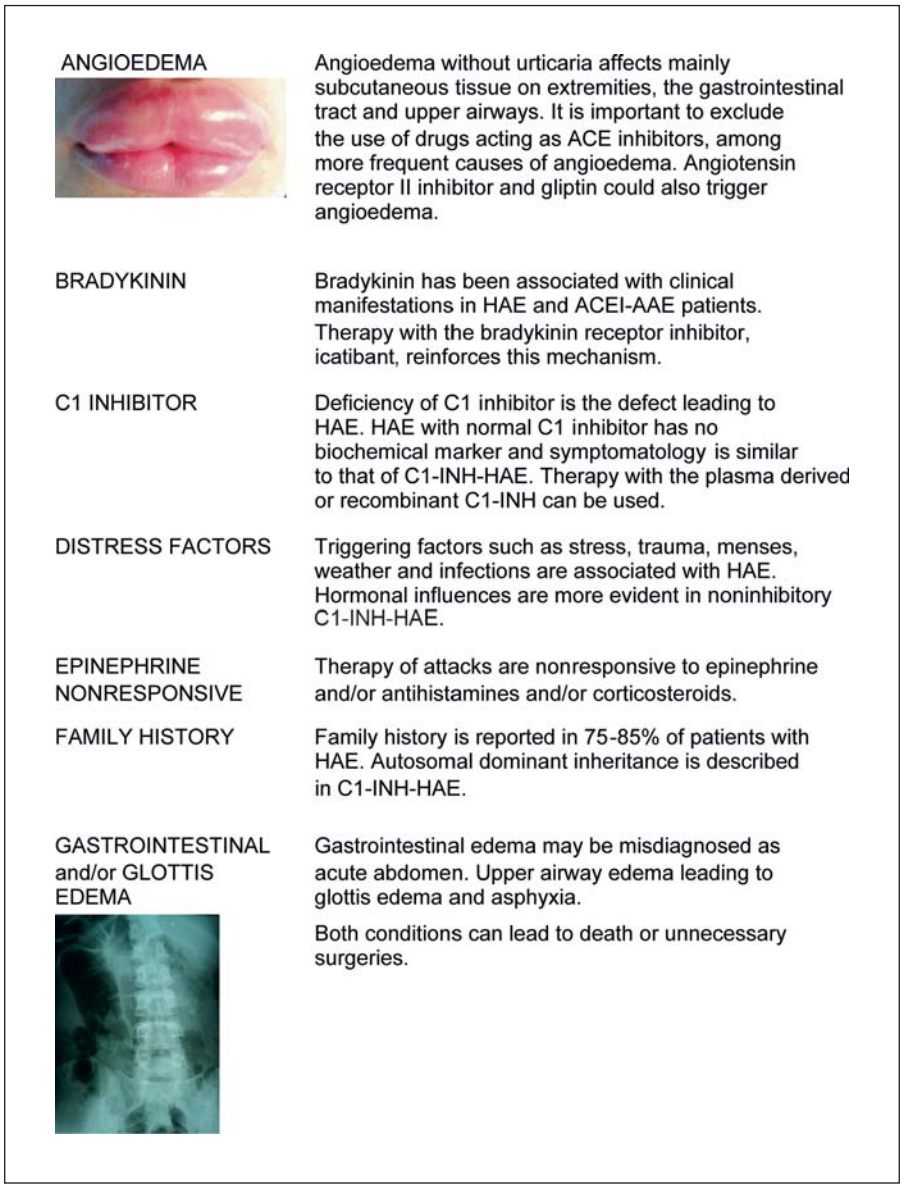
A descriptive epidemiology of visits to emergency departments in the USA documented >5,000 patients with confirmed HAE diagnoses in 2006–2007. Among all the HAE patients evaluated, >50% had symptoms directly related to HAE, 10% had abdominal pain, and approximately 40% of the cases were hospitalized [24].

We propose an alphabetical mnemonic to remind physicians and other health care personnel about the diagnosis of HAE. When using this "ABC", HAE may be easily recognized in the emergency room. Moreover, patients without a confirmed diagnosis could access this ABC and identify themselves as affected.

Angioedema

The first meaningful symptom is angioedema without urticaria. The emphasis on the absence of urticaria could aid the faster identification of the disease. Differential di-

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/14/2017 12:12:34 PM



Color version available online

Fig. 1. ABC of angioedema: symptoms, signs, diagnosis, and responses to therapy.

agnosis would be accessed with a few questions, such as about the use of ACEI or the late onset of the disease [1, 25]. The incidence of ACEI-acquired angioedema (ACEI-AAE) arising during treatment ranges from 0.2 to 0.7%, and corresponds to a potentially substantial number of cases [10, 26].

Angioedema preferentially affects the face, extremities, and genitals. Furthermore, gastrointestinal involvement is quite common and it can lead to unnecessary surgery. Laryngeal edema and airway obstruction are more rare [1, 27, 28]. Unlike HAE, the main site of the swelling in ACEI-AAE tends to be the face and not the abdomen [8, 9, 29, 30]. The treatment of the underlying condition, i.e., hypertension, should instantly be continued with a drug of a different class. Angioedema due to angiotensin II receptor blockers in patients who have previously experienced angioedema due to ACEI treatment has already been reported [31].

Bradykinin

BK is a nonapeptide that is cleaved from high-molecular-weight kininogen by kallikrein, and it is the main vasoactive peptide generated during HAE attacks. Drugs that inhibit kallikrein or block the interaction of BK with

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/14/2017 12:12:34 PM

bradykinin receptor 2 (B2R) diminish the increased vasopermeability and reduce the intensity and duration of angioedema attacks in patients with HAE [27]. This is also the case for ACEI-AAE, and such treatments lead to an increased concentration of BK [10, 29, 30].

Icatibant is an inhibitor of B2R which, given subcutaneously, has proven its efficacy and safety in the treatment of HAE attacks; this reinforces the role of BK in the physiopathology of the disease. The response to this therapy is good, with <8% of patients requiring additional doses [32].

C1 Inhibitor

C1-INH deficiency is the biomarker for C1-INH-HAE. A quantitative deficiency affects approximately 90% of patients and impaired functional C1-INH activity has been described in 10%. C4 concentrations could be measured as a screening test because they will be low during C1-INH-HAE attacks but also out of them [19, 27, 28]. No biomarker has been established for HAE with normal C1-INH.

In addition to mentioning this protein evaluation for diagnosis, plasma-derived C1-INH has been used for >30 years to treat attacks. It is not necessary to hospitalize the patient or go to an emergency department to receive this therapy. Self-administration has been established in several centers and has led to significantly lower numbers of missed work and school days as well as the tendency to initiate the infusion earlier, which results in an earlier improvement of symptoms. In summary, plasma-derived C1-INH influences the burden of the disease [33, 34]. A recombinant C1-INH is also available to treat attacks with the same efficacy as the plasma-derived product, although due to its faster metabolism, recombinant C1-INH should be given at a higher dosage [35].

Distress Factors

Distress or other possible triggering factors have been associated with the attacks and include the following: stress, physical trauma, more estrogen (due to menses, pregnancy, or contraceptives), infections, and cold weather. Dental extraction is a dangerous procedure for HAE patients, and plasma-derived C1-INH should be used for short-term prophylaxis [8].

Epinephrine (Nonresponsive)

When a patient does not respond to the drug epinephrine, this should trigger a suspicion that a different mechanism is involved. The α-adrenergic, vasoconstrictive effect of epinephrine reverses peripheral vasodilation, which reduces angioedema and urticaria. A temporary improvement can also be reported due to the placebo effect. Nevertheless, this approach will not result in edema resolution [36, 37]. As previously mentioned, a response to icatibant could be interpreted as BK-mediated edema [32].

The lack of a response to conventional antiallergic therapies, corticosteroids, and antihistamines, and often also the seriousness of the swelling attacks in BK-mediated angioedema can provide clues. This sign is not exclusive to HAE attacks. Patients with ACEI-AAE do not respond to conventional therapy; therapy with plasma-derived C1-INH or an inhibitor of the B2R (icatibant) have proven effective in such situations [10]. Additionally, the use of ACEI in HAE patients is contraindicated as it increases the risk of angioedema [30, 35].

Family History

A family history in association with clinical criteria is crucial for HAE because this condition is an autosomal-dominant disease. Approximately 75–85% of patients have a positive family history of angioedema [28]. The child of a patient with C1-INH-HAE has a 50% chance of carrying the abnormal gene [38, 39].

Gastrointestinal/Glottis Edema

Gastrointestinal edema is very common and causes abdominal HAE attacks in up to 85% of patients [7, 38]. These attacks are severely painful and often mimic other diseases, such as appendicitis, diverticulitis, small-bowel obstruction, cholecystitis, and inflammatory bowel diseases. It is not unusual for patients to undergo unnecessary abdominal surgery including exploratory laparotomy and even hysterectomy [7, 27, 40].

Although laryngeal attacks with glottis edema are rare (occurring in approx. 5% of HAE attacks), at least 50% of patients with HAE experience a laryngeal attack at least once in their lifetime [27, 28]. In the past, before therapy, up to 30% of such patients died due to asphyxiation [22]. HAE attacks are often painful and unpredictable, and they can vary in severity, frequency, and anatomical location in different patients. Consequently, attacks can be debilitating and result in a significant and multifaceted disease burden. Newly approved and emerging therapies provide safe and effective relief for a significant proportion of patients with HAE [12, 19].

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/14/2017 12:12:34 PM

Conclusion

HAE is a rare condition, but it remains a disabling lifelong disease that should be diagnosed and treated correctly to avoid fatalities. Indeed, in order for this to happen, medical staff, patients, and family members must be aware of this disease. An alphabetical mnemonic method has been developed, and we hope it may benefit patients.

Disclosure Statement

A.S.G. has been a speaker/consultant for Baxalta/Shire, BioCryst and CSL Behring, and has a grant from Shire Investigators Initiative for Research. A.B has received research grant support and/or speaker/consulting fees from CSL Behring, Shire/Jerini AG and ViroPharma, and participated in a clinical trial for BioCryst and Jerini AG. She is an advisor for the HAE Scandinavian Patient Organization. None of the other authors have any conflicts regarding this publication.

References

1 Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, Caballero T, Farkas H, Grumach A, Kaplan AP, Riedl MA, Triggiani M, Zanichelli A, Zuraw B: Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy 2014;69:602–616.

2 Bork K, Barnstedt SE, Koch P, Traupe H: Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 2000;356:213–217.

3 Cagini N, Veronez CL, Constantino-Silva RN, Buzolin M, Martin RP, Grumach AS, Velloso LA, Mansour E, Pesquero JB: New mutations in *SERPING1* gene of Brazilian patients with hereditary angioedema. Biol Chem 2016;397:337–344.

4 Dewald G, Bork K: Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Commun 2006;343:1286–1289.

5 Cichon S, Martin L, Hennies HC, Müller F, Van Driessche K, Karpushova A, Stevens W, Colombo R, Renné T, Drouet C, Bork K, Nöthen MM: Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. Am J Hum Genet 2006;79:1098–1104.

6 Bossi F, Fischetti F, Regoli D, Durigutto P, Frossi B, Gobeil F Jr, Ghebrehiwet B, Peerschke EI, Cicardi M, Tedesco F: Novel pathogenic mechanism and therapeutic approaches to angioedema associated with C1 inhibitor deficiency. J Allergy Clin Immunol 2009;124:1303–1310.

7 Grumach AS, Valle SOR, Toledo E, de Moraes Vasconcelos D, Villela MMS, Mansour E, Pinto JA, Campos RA, França AT; Group interested in HAE (GINHA): Hereditary angioedema: first report of the Brazilian registry and challenges. J Eur Acad Dermatol Venereol 2013;27:e338–e344.

8 Bork K, Hardt J, Witzke G: Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 2012;130:692–697.

9 Cugno M, Castelli R, Cicardi M: Angioedema due to acquired C1-inhibitor deficiency: a bridging condition between autoimmunity and lymphoproliferation. Autoimmun Rev 2008;8:156–159.

10 Javaud N, Achamlal J, Reuter PG, Lapostolle F, Lekouara A, Youssef M, Hamza L, Karami A, Adnet F, Fain O: Angioedema related to angiotensin-converting enzyme inhibitors: attack severity, treatment, and hospital admission in a prospective multicenter study. Medicine 2015;94:e1939.

11 Ismail S, Cheng L, Grigoriadou S, Laffan J, Menon M: Lesson of the month 2: the limitations of steroid therapy in bradykinin-mediated angioedema attacks. Clin Med 2015;15:101–103.

12 Otani IM, Christiansen SC, Busse P, Camargo CA Jr, Zuraw BL, Riedl MA, Banerji A: Emergency department management of hereditary angioedema attacks: patient perspectives. J Allergy Clin Immunol Pract 2017;5:128–134.e124.

13 Subbarayan A, Colarusso G, Hughes SM, Gennery AR, Slatter M, Cant AJ, Arkwright PD: Clinical features that identify children with primary immunodeficiency diseases. Pediatrics 2011;127:810–816.

14 Costa-Carvalho BT, Grumach AS, Franco JL, Espinosa-Rosales FJ, Leiva LE, King A, Porras O, Bezrodnik L, Oleastro M, Sorensen RU, Condino-Neto A: Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014;34:10–22.

15 Neiberger RE: The ABC's of evaluating children with hematuria. Am Fam Physician 1994;49:623–628.

16 Sicuro Correa L, Hökerberg YH, Oliveira RV, Barros DM, Alexandria HA, Daumas RP, Andrade CA, Passos SR, Brasil P: Use of warning signs for dengue by pediatric health care staff in Brazil. PLoS One 2016;11:e0163946.

17 Bygum A: Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol 2009;161:1153–1158.

18 Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López -Trascasa M: Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol 2005;94:498–503.

19 Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, et al: A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. Orphanet J Rare Dis 2015;10:11.

20 Kelly M, Donnelly JP, McAnnally JR, Wang HE: National estimates of emergency department visits for angioedema and allergic reactions in the United States. Allergy Asthma Proc 2013;34:150–154.

21 Fouche AS, Saunders EF, Craig T: Depression and anxiety in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2014;112:371–375.

22 Kim SJ, Brooks JC, Sheikh J, Kaplan MS, Goldberg BJ: Angioedema deaths in the United States, 1979–2010. Ann Allergy Asthma Immunol 2014;113:630–634.

23 Frank MM: Hereditary angioedema: the clinical syndrome and its management in the United States. Immunol Allergy Clin North Am 2006;26:653–668.

24 Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G: Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006–2007. Allergy Asthma Proc 2011;32:390–394.

25 Jaiganesh T, Wiese M, Hollingsworth J, Hughan C, Kamara M, Wood P, Bethune C: Acute angioedema: recognition and management in the emergency department. Eur J Emerg Med 2013;20:10–17.

26 Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE: Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension 2008;51:1624–1630.

27 Bork K, Meng G, Staubach P, Hardt J: Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 2006;119:267–274.

28 Henao MP, Kraschnewski JL, Kelbel T, Craig TJ: Diagnosis and screening of patients with hereditary angioedema in primary care. Ther Clin Risk Manag 2016;12:701–711.

Downloaded by: A. Mari - 31.298 Universita degli Studi, Bibl. Area Biomed. Tor Vergata 160.80.2.38 - 10/14/2017 12:12:34 PM

29 Bluestein HM, Hoover TA, Banerji AS, Camargo CA, Reshef A, Herscu P: Angiotensin-converting enzyme inhibitor–induced angioedema in a community hospital emergency department. Ann Allergy Asthma Immunol 2009;103:502–507.
30 Rasmussen ER, Mey K, Bygum A: Angiotensin-converting enzyme inhibitor-induced angioedema – a dangerous new epidemic. Acta Derm Venereol 2014;94:260–264.
31 Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ: Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Asthma Immunol 2008;101:495–499.
32 Lumry WR, Farkas H, Moldovan D, Toubi E, Baptista J, Craig T, Riedl M: Icatibant for multiple hereditary angioedema attacks across the controlled and open-label extension phases of FAST-3. Int Arch Allergy Immunol 2015;168:44–55.
33 Petraroli A, Squeglia V, Di Paola N, Barbarino A, Bova M, Spano R, Marone G, Triggiani M: Home therapy with plasma-derived C1 inhibitor: a strategy to improve clinical outcomes and costs in hereditary angioedema. Int Arch Allergy Immunol 2015;166:259–266.
34 Bernstein JA, Riedl M, Zacek L, Shapiro RS: Facilitating home-based treatment of hereditary angioedema. Allergy Asthma Proc 2015;36:92–99.
35 Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, Reshef A, Zuraw B: Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an international Working Group. Allergy 2012;67:147–157.
36 Bernstein JA, Moellman J: Emerging concepts in the diagnosis and treatment of patients with undifferentiated angioedema. Int J Emerg Med 2012;5:39.
37 Oswalt ML, Kemp SF: Anaphylaxis: office management and prevention. Immunol Allergy Clin North Am 2007;27:177–191.
38 Zuraw BL, Christiansen SC: HAE pathophysiology and underlying mechanisms. Clin Rev Allergy Immunol 2016;51:216–229.
39 Pappalardo E, Cicardi M, Duponchel C, Carugati A, Choquet S, Agostoni A, Tosi M: Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. J Allergy Clin Immunol 2000;106:1147–1154.
40 Rubinstein E, Stolz LE, Sheffer AL, Stevens C, Bousvaros A: Abdominal attacks and treatment in hereditary angioedema with C1-inhibitor deficiency. BMC Gastroenterol 2014;14:71.

Downloaded by: A. Mari - 31.298
Universita degli Studi, Bibl. Area Biomed. Tor Vergata
160.80.2.38 - 10/14/2017 12:12:34 PM