Original Article

Type I and Type II Hereditary Angioedema: Clinical and Laboratory Findings in Iranian Patients

Fatemeh Kargarsharif MD[1], Narges Mehranmehr MD[1], Sara Zahedi Fard MD[2], Mohammad Reza Fazlollahi MD[1], Maryam Ayazi MD[1], Iraj Mohammadzadeh MD[3], Mohammad Nabavi MD[4], Mohammad Hasan Bemanian MD[4], Abbas Fayezi MD[5], Masoud Movahedi MD[6], Marzieh Heidarzadeh MD[7], Najmodin Kalantari MD[7], Somaieh Arefimehr BSc[1], Shiva Saghafi PhD Student[1], Zahra Pourpak MD PhD•[1]

Abstract

Background: Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by C1-INH (C1 esterase inhibitor), low serum levels (type I), dysfunction (type II) or normal serum levels and function (type III), which lead to subcutaneous and submucosal edema attacks. The aim of this study was to investigate the demographic, clinical and laboratory findings of Iranian patients with HAE.

Methods: The patients with a history or symptoms of angioedema who were referred to Immunology, Asthma and Allergy Research Institute (IAARI) between Jan 2006 and Jan 2014, were assessed based on a specific questionnaire and laboratory evaluation. The patients with a definite diagnosis of HAE type I and type II were entered into this study.

Results: Among 51 patients, 63.3% were diagnosed with HAE type I and 36.7% with HAE type II. Fifteen patients were under 18 years and 36 were adults. The mean age of symptoms onset and diagnosis were 12.33 ± 10.20 years and 24.48 ± 14.64 years, respectively. The mean delay of diagnosis was 11.02 ± 11.60 years. The most commonly involved locations of edema were hands, face and genitalia. Moreover, laryngeal edema was observed in 61.2% of patients, which led to death in two patients during this study.

Conclusion: Hereditary angioedema is a life threatening disease with considerable morbidity and mortality. The outcomes of this study can be used to inform clinicians and health care providers about HAE, which can help earlier diagnosis and better management of the patients, specifically in life threatening attacks.

Keywords: C1 Esterase Inhibitor, hereditary angioedema, laryngeal edema, subcutaneous edema, submucosal edem

Cite this article as: Kargarsharif F, Mehranmehr N, Zahedi Fard S, Fazlollahi MR, Ayazi M, Mohammadzadeh I, Nabavi M, Bemanian MH, Fayezi A, Movahedi M, Heidarzadeh M, Kalantari N, Arefimehr S, Saghafi S, Pourpak Z. Type I and type II hereditary angioedema: Clinical and laboratory findings in Iranian patients. Arch Iran Med. 2015; 18(7): 425 – 429.

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disease with an estimated prevalence of between 1:10,000 and 1:50,000 in the world. HAE is described by recurrent non-pitting edema without urticaria and episodes of submucosal edema, particularly in gastrointestinal tract and upper airways.[1–3] HAE attacks are caused by deficiency of complement component 1 esterase inhibitor (C1) which induces overproduction of vasoactive peptide, bradykinin, and appearance of edema.[3] There are three types of hereditary angioedema, called types I, II, and III. Type I is characterized by decreased antigenic and functional levels of C1-INH (about 85%). Type II is characterized by normal or elevated antigenic level, but reduced functional activity of C1-INH (about 15%). Type III is a rare type characterized by normal C1-INH antigenic/functional levels, and is believed to be caused by a mutation in coagulation factor XII (HAE type III/estrogen-dependent).[1,4,5]

Acquired angioedema (AAE) and angiotensin-converting enzyme inhibitor-induced angioedema (ACE-induced angioedema) as differential diagnoses of HAE are characterized with an increased destruction or metabolism of C1-INH and elevated levels of bradykinin, respectively. AAE is different from HAE regarding Late-onset age (after 40 years) and accompanying with other diseases such as lymphoma or monoclonal gammopathy. Moreover, decreased levels of C1 q-r-s mostly occur in both AAE and ACE-induced angioedema.[6,7]

There are many different factors provoking the swelling attacks of HAE such as trauma, medical/dental procedures, emotional stress, menstruation, oral contraceptive use, infections and use of some medications such as ACE inhibitors. However, the swelling attacks of HAE can also occur spontaneously without any clear triggers.[8,9] There are two common and important symptoms in HAE: firstly, abdominal pain which might be confused with acute abdomen leading to unnecessary surgery;[8,10] secondly, laryngeal edema which can be life threatening and may be experienced by more than half of HAE patients at least once in their life.[8,11] According to the results of some reports, HAE is not usually well known and may remain misdiagnosed or undiagnosed for years in some patients.[1,12] The data on epidemiology, diagnostic features, and treatment protocols of HAE in Iran like other countries

Authors' affiliations: [1]Immunology Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Pathology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Non-Communicable Pediatric Diseases Research Center, Babol University of Medical Sciences, Babol, Iran, [4]Department of Immunology and Allergy, Hazrat Rasoul Hospital, Iran University of Medical Sciences, Tehran, Iran, [5]Division of Allergy and Immunology, School of Medicine, Ahvaz University of Medical Sciences, Ahvaz, Iran, [6]Department of Immunology and Allergy, Children Medical Center, Tehran University of Medical Sciences, Tehran, Iran, [7]Department of Pediatrics, Kashan University of Medical Sciences, Kashan, Iran.
•Corresponding author and reprints: Zahra Pourpak, MD PhD, Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran. Postal Code: 1419733151, P. O. Box: 14185-863.
Tel: +98-21-66919587, Fax: +98-21-6642 89 95, E-mail: pourpakz@tums.ac.ir, pourpakz@sina.tums.ac.ir, zpourpak@yahoo.com.
Accepted for publication: 27 May 2015

seemed to be limited;[13] therefore, Iranian Hereditary Angioedema Registry (IHAER) was founded for data registration of HAE patients in Immunology, Asthma and Allergy Research Institute (IAARI) .The first case of HAE in Iran was reported more than 10 years ago by Farhoudi, et al.[13] In this study clinical and laboratory findings in Iranian patients with HAE were recorded in IHAER and the patients were assessed in order to expand knowledge about clinical features and laboratory findings of HAE.

Material and Methods

The patients suspected to hereditary angioedema with episodes of recurrent, non-pitting, non-pruritic, non-urticarial edema,[8] who had been referred to IAARI to establish a definite diagnosis from Jan 2006 to Jan 2014 were enrolled in this study.

A questionnaire was completed for each patient containing the following data: demographic data, family history of HAE, history of involved organs in HAE attacks, precipitating factors for edema attacks, as well as, their clinical findings.

After getting the permission by filling the informed consent, 3 milliliters of whole blood was taken in asymptomatic period of disease and divided in two tubes for the next evaluations. One milliliter of blood in a EDTA tube stored at -70 °C (our DNA bank) for future genetic analysis,[14] and the remaining blood was clotted at room temperature and used for serum preparation. Sera were stored at -70 °C for complement studies. Serum levels of C1-INH and C4 complement components were quantified by nephelometery method (MININEPH™ Human C1 inactivator Kit/ MININEPH™ Human C4 Kit, The Binding Site Ltd, Birmingham, U. K.). The C1-INH function was measured in serum by ELISA (Quidel Corporation, SanDiego, USA). Also, the level of C1q was measured for patients suspected to AAE (new onset of angioedema after 40 years of age), by radial immunodiffusion (human complement C1q NL BINDARID™ Kit).

Laboratory diagnosis of HAE type I and II was based on decreased levels and/or function of C1INH accompanying with low levels of C4 and normal C1q. A definite diagnosis of HAE (type I and II) was established by the presence of positive laboratory findings and aforementioned clinical symptoms.[10]

Patients with positive clinical findings of HAE who had meanwhile normal C1INH levels and function were excluded from this study to be assessed for HAE type III in further studies.

Results

In our study, HAE was confirmed in 51 patients based on the clinical symptoms and laboratory results. The patients were categorized in two groups; 63.3% of them with HAE type I based on C1INH deficiency (quantity) and 36.7% with HAE type II based on normal/increased levels of C1INH and a decrease in its function. The normal ranges of the quantitative C1 esterase inhibitor (C1INH Q), functional C1 esterase inhibitor (C1INH F) and C4 were 12-24 mg/dL, ≥ 68 % and 15 – 45 mg/dL, respectively according to the instructions of the relevant kits.

Table 1. Characteristics of patients registered in Iranian Herditary Angioedema Registry (IHAER)

Characteristics	Value
Number of patients	
Child (≤ 18years)	15
Adult (> 18 years)	36
Mean age (years)	
Child	10.66 ± 4.31
Adult	32.88 ± 11.87
Sex (F/M)	26/25
Type (I / II) (%)	63.3 / 36.7
The mean age of onset of disease (years)	
Child	6.56 ± 3.71
Adult	14.95 ± 11.14
The mean age at the time of diagnosis (years)	
Child	9.20 ± 4.30
Adult	31.02 ± 12.41
The duration of delay diagnosis(years)	
Child	2.63 ± 3.17
Adult	14.72 ± 12.05
Parental consanguinity (%)	29.2
Family history of HAE (%)	75
Number of families with history of death due to laryngeal edema	5
History of Laryngeal edema (%)	61.2
Number of patients with history of tracheotomy	2
History of abdominal pain (%)	73.5
History of abdominal surgery among of patients	
With a history of abdominal pain (%)	34.4
Duration of edema in most of patients(hours)	72–48
Mean & Range of C4 (mg/dL)	8.49 ± 5.77 mg/dL (3–30)
Mean & Range of C1INH Q (in type I HAE) (mg/d:)	9.15 ± 2.65 (2.10–14)
Mean & Range of C1INH F (in type I HAE) (%)	9.09 ± 15.92 (0–42)
Mean & Range of C1INH Q (in type II HAE) (mg/dL)	30.11 ± 13.02 (12–50)
Mean & Range of C1INH F (in type II HAE) (%)	19.22 ± 14.82 (0–42)

a: HAE: Hereditary angioedema; b: C1INH Q: Quantitative C1 esterase inhibitor; c: C1INH F: Functional C1 esterase inhibitor.

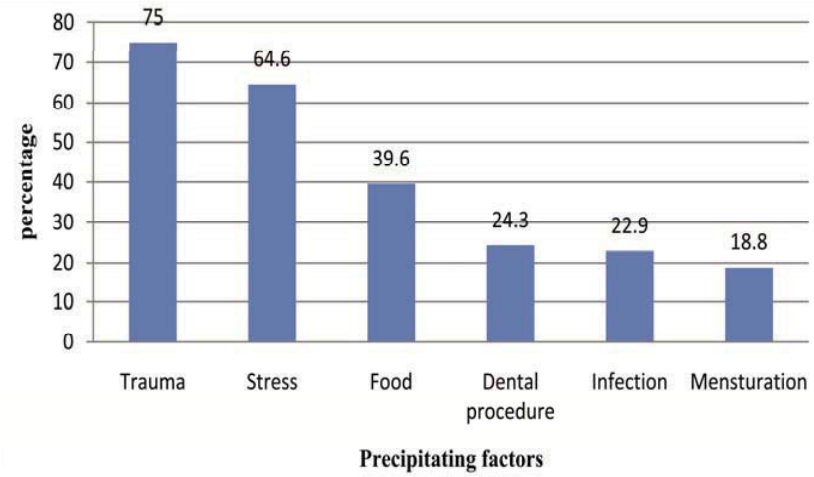

Figure 1. Frequency Percentage of precipitating factors of angioedema attacks in 51 Iranian patients.

The patients' mean serum levels of C1INH Q and C1INH F have been shown in Table 2. Although, a normal level of C4 complement component was detected in 7.8% of patients, but the mean level of C4 showed lower (8.49 ± 5.77 mg/dL) than the normal range (15 – 45 mg/dL) C4 (Table 1).

The study population included 26 females and 25 males from 32 unrelated families divided in two groups: 29.4% in child group (< 18 years of age) and 70.6% in adults. Most of our patients were from north of Iran (Mazandaran province), Tehran (capital of Iran) and Yazd province (in the central desert of Iran), respectively.

According to the data analysis, the average age of symptoms onset was 12.33 ± 10.20 years (range, 1 to 53 years). The mean age of patients at the time of diagnosis was 24.48 ± 14.64 years (range, 1.5 to 72 years) and the mean delayed diagnosis from the first symptoms was 11.02 ± 11.60 years (range 0 – 39). Mean age of onset of symptoms, as well as mean age of diagnosis and delayed diagnosis are shown in Table 1. Delayed diagnosis among children and adults were 2.63 and 14.72 years, respectively (Table 1). The family history of HAE was reported in 75% of patients and parental consanguinity was seen among 29.2% of them. Trauma (75%), stress (64/6%) and food (beef, fish, eggplant, spicy food, plum) (39.6%) were the most common precipitating factors for HAE attacks, however spontaneous attacks were also reported in 83.3% of the cases (Figure 1).

The most frequent location of edema following the HAE attacks in our patients was hand (95.9%). Duration of edema was reported between 48 to 72 hours in most patients with the minimum and maximum duration of 3 hours and 7 days, respectively. The first symptom of HAE attack was reported as abdominal pain in 32.7%, the facial edema in 26.4% and the hand edema in 20.4% of the patients (Figure 2). We had reports of acute abdominal pain in 73.5% of the patients, which resulted in an urgent surgery in 34.4% of them. Our results showed that about 61.2% of HAE patients suffered from laryngeal edema at least once in their life. The mean lag time between the onset and maximum development of laryngeal edema attacks was about 7.14 ± 5.82 hours. Severe laryngeal edema in two affected patients led to tracheotomy, which was life-saving, but unfortunately two other patients died from laryngeal edema during this study (27-year-old female and 29-year-old male from different families). In addition, we had a history of death from laryngeal edema attack in families of three patients.

A schematic diagram of different medications prescribed by physicians for long prophylaxis in our patients has been shown in Figure 3. Most of our patients (44.7%) received Danazol and/or Tranexamic acid for long prophylaxis and 34% of them had no treatments.

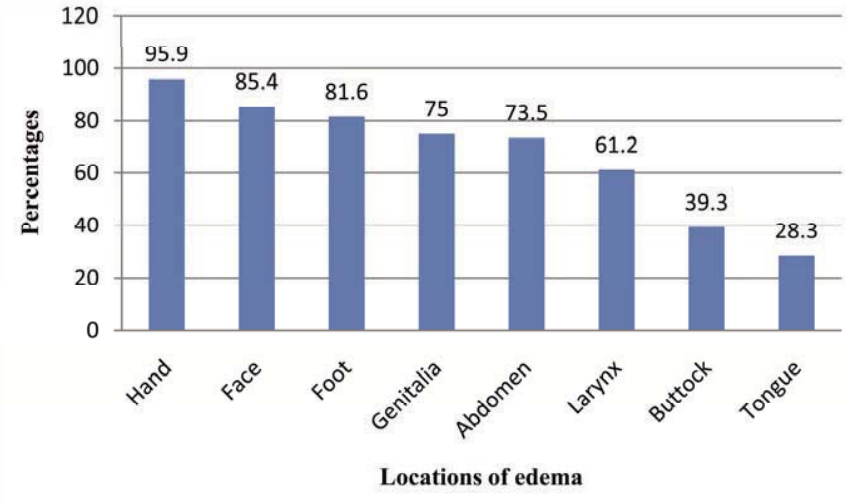

Figure 2. Frequency percentage of most commonly involved body sites in 51 Iranian patients with hereditary angioedema.

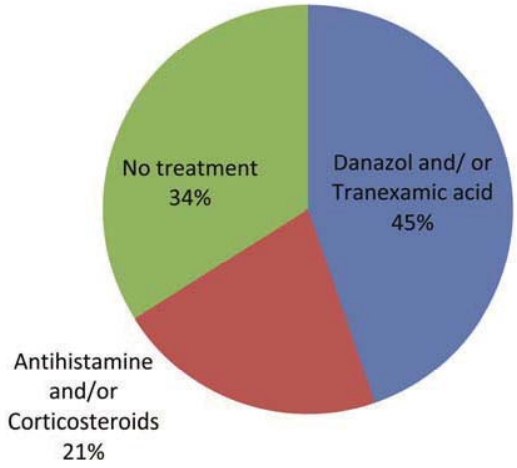

Figure 3. The frequency percentage of different treatments prescribed for long prophylaxis of hereditary angioedema in 51 Iranian patients.

Discussion

In this study, we investigated clinical features, demographic and laboratory data of Iranian patients with HAE to obtain more detailed findings about the presence of this disease.

According to other reports,[5,15] the frequency of HAE type I (about 85%) is about 4 times more than type II (about 15%). While in our study, HAE type I was diagnosed in 63.3% of Iranian patients that is about 2 times more than type II (36.7%). Thus, it seems HAE type II is more common in Iranian patients than those reported by other countries. This result may be associated with difference in race, genetic variations, higher consanguinity in Iran[16] and some other unknown environmental factors.[17] On the other hand, because IAARI is a referral centre for C1INH function evaluation, probably patients suspected of having HAE type II are more likely referred for diagnosis. However, more studies about the prevalence of HAE types including type III in Iranian patients seem to be helpful.

Although, decreased C4 serum levels is one of the main indicators of HAE diagnosis,[8] some reports have been published on the normal levels of C4 during the asymptomatic periods.[18,19] Similarly, normal levels of C4 in 7.8% (4 cases) of our patients during asymptomatic periods showed that C4 may not be a very specific test for HAE diagnosis and further studies with more cases seem to be required.

Regarding more referred patients from Mazandaran province (30% of total patients) and a history of two deaths of HAE attack in this province, it is recommended to provide more educational and medical facilities in the north of Iran.

The mean delay in diagnosis was 11.02 ± 11.60 years (range 0 – 39) in our study that is lower than the reports of Bygum et al, which was 16.3 years (between 0 to 63 years),[20] and Roch, et al. which was 13.1 years.[1] The shorter delayed diagnosis in our study may be due to the experience and awareness of physicians (specialist in Immunology and Allergy) who first noticed the patients with HAE and referred them to IAARI for confirming definite diagnosis. However, more studies could be suggested to focus on this issue. As shown in the results, delay in diagnosis significantly differs between children's group and adults (2.63 and 14.72 years, respectively). The shorter diagnostic delay in children can be related to improved awareness on clinical manifestations of HAE among clinicians in recent years. Moreover, latest improvement in laboratory techniques has helped the physicians with a better diagnosis of HAE.

Although, the exact causes of attacks were not found in many cases, it seems that trauma and emotional stress were the most common trigger factors among our patients (Figure 1). These results are in accordance with the previous and recent studies on HAE.[20–22]

Recurrent abdominal pain and laryngeal edema are known as two symptoms of HAE with high morbidity. In one study, most of Danish patients with HAE (96%) experienced abdominal pain, but abdominal complications like unnecessary surgery and/or laparoscopy was reported in 16.9% of them.[20] In our study, abdominal pain was reported in 73.5% of patients which led to unnecessary abdominal surgery in 34.4% of them. This shows more invasive procedures in Iranian HAE patients compared to Danish patients, which may be due to insufficient information of clinicians and health care providers about HAE clinical presentation.

Approximately 50% of patients with HAE may experience laryngeal edema that can result in asphyxiation with a mortality rate of 30%.[8] In a study conducted on 210 Brazilian HAE patients; laryngeal edema was observed in 21.4% of them.[12] This percentage was higher in the present study, as 61.2% of our patients experienced laryngeal edema. This discrepancy may be related to differences in the studied populations, the severity of the disease/attacks and delay in receiving medical care during attacks. Moreover, 34% of our patients were not under treatment due to poor compliance and 21% of them were not treated correctly (Figure 3).[23]

Unfortunately, death due to laryngeal edema was reported in five patients from five families (three patients out of our research period and two patients during the study). These two patients in our study developed laryngeal edema after quitting prophylactic treatment, which leads to death, although they underwent emergency care and treatment.

In addition to medications used during the attack; the most important approach would be prevention of the acute attacks using the prophylactic treatments.[1] According to the reports, effective treatments for preventing and/or controlling the life threatening features of HAE attacks include: intravenous plasma-derived C1inhibitor (Cinryze, Berinert, Cetor), recombinant C1inhibitor (Ruconest), Kallikrein inhibitors (Ecallantide) and bradykinin receptor antagonists (Icatibant).[11] Unfortunately none of the afore-

mentioned drugs are easily available for all patients around the world[3] as well as in Iran. Most of our patients (44.7%) instead received attenuated androgens (Danazol) and/or antifibrinolytics (Tranexamic acid) as long prophylaxis. Twenty-one percent of HAE patients were referred to us with the history of consuming medications such as antihistamine and/or corticosteroids, which are not effective in HAE treatment and are prescribed due to misdiagnosis of the disease (Figure 3).[1]

The subjects enrolled in this study were referred from many provinces of Iran to IAARI referral center. However, one of the limitations of this study is that our patients' population does not comprise subjects with HAE who were not referred to this center.

Our study population was comprised of patients referred to IAARI for definite diagnosis. Although these patients were from many different provinces of Iran, our study population may not include all Iranian patients with HAE, which is a limitation of this study.

In conclusion, we investigated demographic, laboratory and clinical features of HAE patients (registered in IHEAR afterwards) to draw more awareness and attention about HAE among clinicians and health care providers. We hope this information would decrease morbidity and mortality of HAE attacks through an earlier diagnosis and treatment.

The information could be more comprehensive, if non-referred patients with HAE were included. Thus, merging these results with the ones of further upcoming studies is suggested.

Acknowledgments

The authors wish to thank all the physicians who visited the patients and/or referred them to IAARI. We also would like to appreciate Dr. Maryam Nourizadeh from Immunology, Asthma and Allergy Research Institute/TUMS for editing the manuscript as well as Ms. Azadeh Talebzadeh for her collaborating in the laboratory.

References

1. 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. Annals of Allergy, Asthma & Immunology : Official Publication of The American College of Allergy, Asthma, & Immunology. 2005; 94(4): 498 – 503.
2. Levy JH, Freiberger DJ, Roback J. Hereditary angioedema: current and emerging treatment options. Anesthesia and Analgesia. 2010; 110(5): 1271 – 80.
3. Cicardi M, Johnston DT. Hereditary and acquired complement component 1 esterase inhibitor deficiency: a review for the hematologist. Acta Haematologica. 2012; 127(4): 208 – 210.
4. Temino VM, Peebles RS, Jr. The spectrum and treatment of angioedema. The American Journal of Medicine. 2008; 121(4): 282 – 286.
5. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2010; 6(1): 24.
6. Craig T, Aygoren–Pursun E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO Guideline for the Management of Hereditary Angioedema. The World Allergy Organization Journal. 2012; 5(12): 182 – 199.
7. Cicardi M, Zanichelli A. Acquired angioedema. Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2010; 6(1): 14.
8. Parish LC. Hereditary angioedema: diagnosis and management – a perspective for the dermatologist. Journal of the American Academy of Dermatology. 2011; 65(4): 843 – 850.
9. Wahn V, Aberer W, Eberl W, Fasshauer M, Kuhne T, Kurnik K, et al. Hereditary angioedema (HAE) in children and adolescents – – a consensus on therapeutic strategies. European Journal of Pediatrics. 2012; 171(9): 1339 – 1348.
10. Longhurst H, Cicardi M. Hereditary angio–oedema. Lancet. 2012; 379(9814): 474 – 481.
11. Bork K. Current management options for hereditary angioedema. Current Allergy and Asthma Reports. 2012; 12(4): 273 – 280.
12. Grumach AS, Valle SO, Toledo E, de Moraes Vasconcelos D, Villela MM, Mansour E, et al. Hereditary angioedema: first report of the Brazilian registry and challenges. JEADV. 2013; 27(3): e338 – e344.
13. Farhoudi A, Bazargan N, Pourpak Z, Mahmoudi M. Two related cases of primary complement deficiency. Immunol Invest. 2003; 32(4): 313 – 321.
14. Esmaeili B, Fazlollahi MR, Dashti P, Farzaneh P, Pourpak Z, Moin M. Organization and establishment of DNA banks in biomedical research centers: a report from immunology, asthma and allergy research institute. Iranian Journal of Allergy, Asthma, and Immunology. 2013; 12(1): 96 – 98.
15. Lang DM, Aberer W, Bernstein JA, Chng HH, Grumach AS, Hide M, et al. International consensus on hereditary and acquired angioedema. Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology. 2012; 109(6): 395 – 402.
16. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, et al. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. American Journal of Reproductive Immunology. 2006; 56(2): 145 – 151.
17. Fattahi F, Badalzadeh M, Sedighipour L, Movahedi M, Fazlollahi MR, Mansouri SD, et al. Inheritance pattern and clinical aspects of 93 Iranian patients with chronic granulomatous disease. Journal of Clinical Immunology. 2011; 31(5): 792 – 801.
18. Karim Y, Griffiths H, Deacock S. Normal complement C4 values do not exclude hereditary angioedema. Journal of Clinical Pathology. 2004; 57(2): 213 – 214.
19. Tarzi M, Hickey A, Förster T, Mohammadi M, Longhurst H. An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: Normal serum C4 does not exclude hereditary angio-oedema. Clinical & Experimental Immunology. 2007; 149(3): 513 – 516.
20. Bygum A. Hereditary angio–oedema in Denmark: A nationwide survey. The British Journal of Dermatology. 2009; 161(5): 1153 – 1158.
21. Cicardi M, Bergamaschini L, Marasini B, Boccassini G, Tucci A, Agostoni A. Hereditary angioedema: an appraisal of 104 cases. The American Journal of The Medical Sciences. 1982; 284(1): 2 – 9.
22. Agostoni A, Cicardi M. Hereditary and acquired C1–inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine. 1992; 71(4): 206 – 15.23.
23. Giavina–Bianchi P, Franca AT, Grumach AS, Motta AA, Fernandes FR, Campos RA, et al. Brazilian guidelines for the diagnosis and treatment of hereditary angioedema. Clinics. 2011; 66(9): 1627 – 1636.