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Delayed diagnosis of hereditary angioedema with C1-inhibitor deficiency in Iranian children and adolescents

To the editor,

Hereditary angioedema is an autosomal dominant deficiency of C1-inhibitor (C1-INH-HAE). This rare but potentially fatal disease gives rise to episodes of bradykinin-mediated edema in face, trunk, extremities, genitalia, gastrointestinal tract, and upper airway.¹ This leads to severe outcomes including asphyxiation, unnecessary emergency abdominal surgeries, and a considerably diminished quality of life in addition to high economic burden for the healthcare system. Rare nature, misleading symptoms, and a lack of awareness among healthcare providers have resulted in a worldwide delayed diagnosis of C1-INH-HAE.²

HAE symptoms have been reported to first manifest around the age of 10-12 years.^{3,4} In addition, there are growing evidence describing yet earlier onset of the disease (<10 years).^{5,6} This together with higher vulnerability in children highlights the importance of establishing a timely diagnosis in pediatric population. Considering the scarcity of studies focusing on this population, we investigated the delayed diagnosis and possible associated factors in Iranian children and adolescents with C1-INH-HAE.

Children and adolescents (1 < age ≤ 21)^{10,11} with clinical findings suggestive of HAE⁴ referred to Immunology, Asthma and Allergy

Research Institute (IAARI), Tehran, Iran, during 2006-2017 were thoroughly evaluated. The study was approved by IAARI ethics committee, and written informed consent was obtained from patients or legal guardian of minors. The data were analyzed using SPSS 16 (SPSS Inc, USA), and $P < 0.05$ was considered statistically significant.

A definite diagnosis of C1-INH-HAE was established in 30 children and adolescents (mean ± SD age: 13.43 ± 5.84 [1.5-21] years) based on suggestive history and clinical findings together with decreased serum C4 and C1-INH protein (type I) (MININEPH™ Human C1 Inactivator and C4 Kit, The Binding Site Ltd, UK) and/or low C1-INH functional level (type II) (Quidel Corporation, USA).³ The most commonly involved locations by the first attack were hand (30%), abdomen (30%), and face (26.7%). The median (Q1, Q3) delay in diagnosis was 3 (1.75, 7.25) [min-max: 0-20] years, which was in accordance with a similar study on symptomatic children in Hungary.⁷ Table 1 shows a comparison of diagnostic delay based on probable related variables.

Interestingly, we observed a longer diagnostic delay in the cases with a family history of C1INH-HAE. However, this was not

Variables	Groups	Median (Q1, Q3)	Mean ± SD	P value
Sex	Male (n = 14)	4 (0.37, 10.5)	5.78 ± 6.31	0.75
	Female (n = 16)	2.25 (2, 6)	4.25 ± 4.37	
HAE type	Type I (n = 17)	2 (1.5, 6)	4.73 ± 5.50	0.65
	Type II (n = 13)	3 (1.25, 9)	5.27 ± 5.25	
Family history of HAE	Positive (n = 20)	3 (2, 9.5)	5.85 ± 5.99	0.27
	Negative (n = 9)	1.5 (0.12, 5)	3.27 ± 3.27	
Attack triggers				
Food	Yes (n = 11)	8 (2, 15)	8.86 ± 6.71	0.01
	No (n = 19)	2 (0.5, 5)	2.47 ± 2.78	
Trauma	Yes (n = 18)	4 (2, 9)	6.5 ± 5.81	0.01
	No (n = 12)	1.25 (0, 4.5)	2.66 ± 3.54	
Stress	Yes (n = 15)	3 (2, 9)	4 ± 4.5	0.68
	No (n = 14)	2.75 (0, 4.5)	4.92 ± 4.75	
Infection	Yes (n = 7)	1 (2, 9)	4.57 ± 7.52	0.17
	No (n = 23)	3 (0, 4.5)	5 ± 4.66	
Location of symptoms				
Periorbital	Yes (n = 23)	3 (2, 8)	5.84 ± 5.55	0.03
	No (n = 7)	0.5 (0, 3)	2.07 ± 3.27	
Lip	Yes (n = 23)	3 (2, 8)	5.54 ± 5.65	0.26
	No (n = 7)	2 (0, 6)	3.07 ± 3.72	
Cheek	Yes (n = 22)	3 (2, 7.25)	5.38 ± 5.73	0.53
	No (n = 8)	2.5 (0.12, 8.25)	3.81 ± 4.03	
Upper extremities	Yes (n = 28)	2.25	4.5 ± 5.54	0.71
	No (n = 2)	6	6 ± 1.41	
Lower extremities	Yes (n = 22)	2.25	4.72 ± 5.61	0.90
	No (n = 8)	4	4.43 ± 5.01	
Genitalia	Yes (n = 17)	2.5	5.76 ± 6.39	0.17
	No (n = 13)	3	2.90 ± 2.54	
Upper airway	Yes (n = 14)	6.5 (2.75, 12.75)	8.14 ± 6.03	0.001
	No (n = 16)	2 (0.12, 3)	2.18 ± 2.30	
Abdominal Pain	Yes (n = 18)	6 (2.87, 10.5)	7.03 ± 5.67	<0.001
	No (n = 11)	1 (0, 2)	1.40 ± 1.59	

Mann-Whitney test was used to compare the difference between delays in two different independent groups.

TABLE 1 Comparison of delay in diagnosis (year) based on subject's demographics and clinical characteristics in the Iranian pediatric patients with hereditary angioedema

statistically significant, which might be due to small study population. It is expected that existence of C1-INH-HAE or angioedematous symptoms in the family guarantees a timely diagnosis brought by earlier evaluations and screening of other family members.^{3,4,10} Although this idea is supported by several studies reporting a zero diagnostic delay in patients with a family history,^{3,5,9} some other studies including ours provided evidence against it. A survey across 8 European countries and a nationwide survey of HAE in Denmark demonstrated that diagnostic delay was not lower in patients with an HAE family history.^{2,6}

Based on our experience from Iran HAE national registry (IHAER) with a network of 42 immunology/allergy sub-specialists from all over the country,¹ this intriguing finding could be attributed to

several reasons. Firstly, there is a social stigma attached to having a disease, especially a hereditary one in some cultural backgrounds such as Iran. Therefore, physician consult for patients' family members or screening for their children is deliberately avoided due to fear and denial. Moreover, the patient may hide diagnosis from other family members (eg, siblings or cousins) suffering from the same disease.

The on-demand and prophylactic treatment in Iran are limited to FFP and danazol/tranexamic acid, respectively. Therefore, it could be argued that unsatisfactory condition of the index patient after diagnosis including limited access to effective and safe treatment may discourage patients' family members with the same symptoms from seeking medical consultation. On the other hand, long years of living

with C1-INH-HAE desensitize family members to HAE symptoms, especially milder ones such as hand edema. Hence, they consider it as rather known or normal, which might procrastinate their referral to the physician. Finally, inefficient screening strategies might also play a role in this issue.

Our findings showed for the first time a significant higher diagnostic delay in patients reporting trauma and food as a trigger of their attacks. These might have been mistaken for the main etiology of the attacks. For instance, parents simply associate the edema with traumas, which often happen in pediatric age due to high physical activity. Hence, they do not visit a physician until attacks are more severe. Likewise, parents and physicians might connect attacks precipitated by food consumption with food intolerance/allergy.¹²

In line with expectations, diagnostic delay was significantly higher in abdomen, upper airway, and face involvement, as these are often misdiagnosed for acute abdomen (unnecessary surgery in six patients) and allergic reactions.^{6,12}

We observed no association between delayed diagnosis and C1INH-HAE type. In contrast, a study by Zanichelli et al on HAE patients [median age: 0-62.0 years] showed a higher diagnostic delay in those with C1INH-HAE II.² It may be that all our patients in IAARI were simultaneously evaluated for C1INH-HAE I and II.¹ Therefore, there was no time lag between a normal C1-INH quantity and performing a function test, which mirrors the findings reported from Czech.¹³

The negative correlation found between age of symptom onset and delayed diagnosis (Figure 1) is in accordance with the findings of a large cohort by Christiansen et al.¹⁰ As mentioned, it is probable to misinterpret HAE manifestations such as abdominal pain as

symptoms of common diseases at early childhood. This finding is crucially important considering that earlier onset of symptoms is associated with a more severe course of the disease.⁴ Thus, this higher delayed diagnosis is likely to endanger pediatrics more severely.

In conclusion, despite developments in our knowledge about HAE besides significant clues to diagnosis like family history there is still an unacceptable diagnostic delay among pediatric population. Therefore, raising awareness of healthcare providers and establishing a screening program are necessary to optimize diagnosis, which in turn reduces mortality/morbidity. Furthermore, public awareness is a key to promoting culture and removing the social stigma attached to this disease, which impedes timely referral. Considering small population and retrospective nature of this study, further research on C1-INH-HAE in pediatric population is recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this study.

AUTHOR CONTRIBUTION

Maryam Ayazi substantially contributed to the conception and design, acquisition, analysis, and interpretation of data; drafted the article or revised it critically for important intellectual content; and contributed to final approval of the version to be published. Mohammad Reza Fazlollahi, Iraj Mohammadzadeh, Abbas Fayezi, Mohammad Nabavi, Seyed Alireza Mahdavian, Masoud Movahedi, and Marzieh Heidarzadeh substantially contributed to acquisition of data; drafted the article or revised it critically for important intellectual content; and contributed to final approval of the version to be published. Shiva Saghafi, Raheleh Shokouhi Shoormasti, Sajedeh Mohammadian, and Henriette Farkas substantially contributed to analysis and interpretation of data; drafted the article or revised it critically for important intellectual content; and contributed to final approval of the version to be published. Zahra Pourpak substantially contributed to conception and design, analysis, and interpretation of data; drafted the article or revised it critically for important intellectual content, and contributed to final approval of the version to be published.

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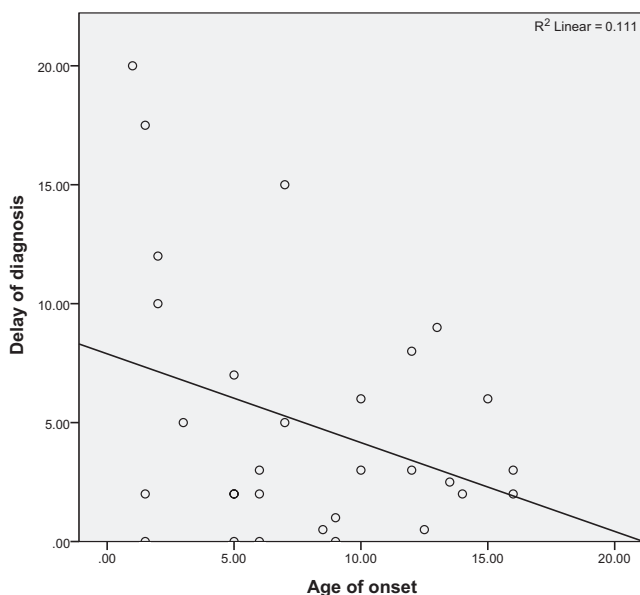


FIGURE 1 Negative correlation between age of onset (years) of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) and delay in diagnosis (years). * (mean $\pm$ SD) of symptom onset: 7.83 ± 4.74 [1-16] years. **Spearman's test was used to determine the correlation of two quantitative variables

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