

Table II. Age of initial HAE manifestations and delay in diagnosis in the first and subsequent HAE patients in family.

Characteristics	Total (N = 126)	First in Family * (N = 52)	Not First in Family (N = 74)
Age of initial manifestations, years			
Mean \pm SD (minimum - maximum)	12.6 \pm 8.4 (0.0 - 47.0)	13.2 \pm 7.2 (0.0 - 30.0)	12.2 \pm 9.2 (0.0 - 47.0)
Median (Q1-Q3)	12.0 (6.0 - 18.0)	13.0 (8.0 - 18.0)	9.0 (5.5 - 17.0)
Age of initial manifestations, n (%)			
< 18y	85 (67.4)	34 (65.4)	51 (68.9)
\geq 18y	31 (24.6)	15 (28.8)	16 (21.6)
Unknown/Not reported	10 (7.9)	3 (5.8)	7 (9.5)
Age of diagnosis, years			
Mean \pm SD (minimum - maximum)	26.6 \pm 16.7 (0.0 - 70.0)	33.2 \pm 16.7 (4.0 - 70.0)	21.8 \pm 15.0 (0.0 - 55.0)
Median (Q1-Q3)	25.5 (13.8 - 37.5)	33.0 (20.0 - 40.0)	21.0 (9.5 - 30.0)
Age of diagnosis, n (%)			
< 18y	36 (28.6)	7 (13.5)	29 (39.2)
\geq 18y	80 (63.4)	42 (80.8)	38 (51.4)
Unknown/Not reported	10 (7.9)	3 (5.8)	7 (9.5)
Delay in diagnosis, years			
Mean \pm SD (minimum - maximum)	14.4 \pm 15.7 (0.0 - 66.0)	20.7 \pm 17.3 (0.0 - 66.0)	9.9 \pm 12.7 (0.0 - 43.0)
Median (Q1-Q3)	10.0 (1.0 - 24.0)	15.0 (8.0 - 30.0)	4.0 (0.0 - 15.8)
Delay in diagnosis (5-year groups), n (%)			
< 5	43 (34.1)	10 (19.2)	33 (44.6)
[5 - 10[13 (10.3)	5 (9.6)	8 (10.8)
[10 - 15[13 (10.3)	6 (11.5)	7 (9.5)
[15 - 20[7 (5.6)	4 (7.7)	3 (4.1)
\geq 20	37 (29.4)	22 (42.3)	15 (20.3)
Unknown/	13 (10.3)	5 (9.6)	8 (10.8)

Characteristics	Total (N = 126)	First in Family * (N = 52)	Not First in Family (N = 74)
Not reported			

HAE, hereditary angioedema; N, total number of patients; n, number of patients with available data; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation.

* First patients diagnosed in a family (if 2 or more patients are diagnosed in the same initial year, they are all considered as “First in Family”).

Table III. Cumulative symptoms present at disease onset, at the time of diagnosis and at the last clinical appointment (current).

Characteristics	At disease onset	At the time of diagnosis	Current
Asymptomatic patients, n (%)	14 (11.1)	14 (11.1)	7 (5.6)
Symptomatic patients, n (%)	112 (88.9)	112 (88.9)	119 (94.4)
Number of systems involved per patient			
Median (Q1-Q3)	1.0 (1.0 - 2.0)	2.0 (1.0 - 2.0)	2.0 (2.0 - 3.0)
Systems involved, n (%)			
Cutaneous only	48 (42.9)	29 (25.9)	14 (11.8)
Gastrointestinal only	21 (18.8)	7 (6.3)	6 (5.0)
Respiratory only	2 (1.8)	3 (2.7)	0 (0.0)
Cutaneous+Gastrointestinal only	27 (24.1)	41 (36.6)	39 (32.8)
Cutaneous+Respiratory only	3 (2.7)	9 (8.0)	9 (7.6)
Gastrointestinal+Respiratory only	1 (0.9)	2 (1.8)	0 (0.0)
Cutaneous+Gastrointestinal+Respiratory	10 (8.9)	19 (17.0)	51 (42.9)
Frequency of Cut, GI or Resp symptoms, n (%)			
Cutaneous	88 (78.6)	98 (87.5)	113 (95.0)
Gastrointestinal	59 (52.7)	69 (61.6)	96 (80.7)
Respiratory	16 (14.3)	33 (29.5)	60 (50.4)

HAE, hereditary angioedema; Cut, Cutaneous; GI, Gastrointestinal; Resp, Respiratory; n, number of patients with available data; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation.

Table IV. Long-term prophylaxis, short-term prophylaxis and on-demand treatment for the management of HAE, by age group.

Characteristics	Total (N = 126)	< 18y (N = 16)	≥ 18y (N = 110)
Long-term, n (%)			
Attenuated androgens	79 (62.7)	1 (6.3)	78 (70.9)
Antifibrinolytic	10 (7.9)	5 (31.2)	5 (4.5)
Plasma-derived C1-INH	1 (0.8)	0 (0.0)	1 (0.9)
Without LTP	36 (28.6)	10 (62.5)	26 (23.6)
Short-term, n (%)			
Plasma-derived C1-INH	26 (20.6)	2 (12.5)	24 (21.8)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.0]	1.5 [1.2 - 1.8]	1.0 [1.0 - 2.0]
On-demand, n (%)			
Attenuated androgens ¹	44 (34.9)	1 (6.2)	43 (39.1)
Median of administrations [Q1-Q3]	3.0 [2.0 - 6.2]	NA	3.0 [2.0 - 5.5]
Antifibrinolytic	40 (31.7)	7 (43.8)	33 (30.0)
Median of administrations [Q1-Q3]	3.0 [2.0 - 3.2]	3.0 [2.0 - 3.5]	3.0 [2.0 - 3.0]
Plasma-derived C1-INH	32 (25.4)	6 (37.5)	26 (23.6)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.2]	1.5 [1.0 - 2.8]	1.0 [1.0 - 2.0]
Icatibant	18 (14.3)	0 (0.0)	18 (16.4)
Median of administrations [Q1-Q3]	1.0 [1.0 - 2.0]	NA	1.0 [1.0 - 2.0]
Fresh frozen plasma	0 (0.0)	0 (0.0)	0 (0.0)
Median of administrations [Q1-Q3]	NA	NA	NA

HAE, hereditary angioedema; N, total number of patients; n, number of patients with available data; NA, not applicable; Q1, 1st quartile; Q3, 3rd quartile.

¹Attenuated androgens are not recommended as on-demand treatment, but the start of attenuated androgens and/or its increase of dosage were included as on-demand treatment.

Supplementary Table I. Criteria for evaluation of disease severity*.

Attack Severity	Score
Mild attacks (discomfort noticed, but no disruption of normal daily activity)	0.5 for each 24 hours
Moderate attacks (discomfort sufficient to reduce or affect normal daily activity)	1 for each 24 hours
Severe attacks (inability to work or perform daily activity)	2 for each 24 hours
Need for treatment:	
Emergency treatment: conservative, substitutive (C1-INH, FFP), bradykinin-receptor antagonist (icatibant)	5 each
Emergency treatment: invasive (intubation, tracheotomy)	25 each
Long-term prophylaxis for more than 6 months	25
Long-term prophylaxis for 3- 6 months	12.5

Score	Class	Degree
> 30	1	Severe
21-30	2	Moderate
11-20	3	Mild
1-10	4	Minimal
0	5	Asymptomatic

*These parameters are determined over the period of 1 year. The sum of the scores defines the severity of the disease for that year. Adapted from Agostoni A *et al.* (1).

Supplementary Table II. HAE classification in the cohort of HAE patients.

	Total (N = 126)
HAE classification n, (%)	
HAE-C1-INH type I	64 (50.8)
HAE-C1-INH type II	57 (45.2)
HAE-nC1-INH	5 (4.0)
HAE classification per family	
Number of families	45
HAE-C1-INH type I	28 (62.2)
HAE-C1-INH type II	13 (28.9)
HAE-nC1-INH	4 (8.9)

HAE, hereditary angioedema; N, total number of patients; n, number of patients

Supplementary Table III. Triggers of acute attacks.

Characteristics	Total (N = 126)
Patients with known trigger, n (%)	92 (73.0)
Number of triggers	
Mean ± SD (minimum - maximum)	1.5 ± 1.3 (0.0 - 6.0)
Median (Q1-Q3)	1.0 (0.0 - 2.0)
Triggers, n (%)	
Stress	60 (47.6)
Trauma	42 (33.3)
Infection	33 (26.2)
Contraception	15 (11.9)
Menstruation	7 (5.6)
Medication	6 (4.8)
Food	3 (2.4)
Burns	2 (1.6)
Other	18 (14.3)

HAE, hereditary angioedema; N, total number of patients; n, number of patients with available data; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation.

Supplementary Table IV. Severity of the disease in the total cohort, in first HAE patients in family and in subsequent HAE patients in family.

Characteristics	Total (N = 126)	First in Family * (N = 52)	Not First in Family (N = 74)
Severity Classification			
Mean ± SD (minimum - maximum)	2.6 ± 1.3 (1.0 - 5.0)	2.6 ± 1.4 (1.0 - 5.0)	2.6 ± 1.3 (1.0 - 5.0)
Median (Q1-Q3)	2.0 (2.0 - 3.0)	2.0 (2.0 - 3.2)	2.0 (2.0 - 3.0)

Characteristics	Total (N = 126)	First in Family * (N = 52)	Not First in Family (N = 74)
Severity Classification, n (%)			
1	20 (15.9)	10 (19.2)	10 (13.5)
2	63 (50.0)	26 (50.0)	37 (50.0)
3	13 (10.3)	3 (5.8)	10 (13.5)
4	6 (4.8)	2 (3.8)	4 (5.4)
5	24 (19.0)	11 (21.2)	13 (17.6)

HAE, hereditary angioedema; N, total number of patients; n, number of patients with available data; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation.

* First patients diagnosed in a family (if 2 or more patients are diagnosed in the same initial year, they are all considered as “First in Family”).

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