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The impact of puberty on the onset, frequency, location, and severity of attacks in hereditary angioedema due to C1-inhibitor deficiency: A survey from the Italian Network for Hereditary and Acquired Angioedema (ITACA)

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Introduction: Hereditary angioedema due to C1-inhibitor deficiency is influenced by hormonal factors, with a more severe course of disease in women. Our study aims to deepen the impact of puberty on onset, frequency, location and severity of attacks.

Methods: Retrospective data were collected through a semi-structured questionnaire and shared by 10 Italian reference centers of the Italian Network for Hereditary and Acquired Angioedema (ITACA).

Results: The proportion of symptomatic patients increased significantly after puberty (98.2% vs 83.9%, $p=0.002$ in males; 96.3% vs 68.4%, $p<0.001$ in females); the monthly mean of acute attacks was significantly higher after puberty, and this occurred both in females (median (IQR) = 0.41(2) in the three years before puberty vs 2(2.17) in the three years after, $p<0.001$) and in males (1 (1.92) vs 1.25(1.56) respectively, $p<0.001$). The increase was greater in females. No significant differences were detected in attack location before and after puberty.

Discussion: Overall, our study confirms previous reports on a more severe phenotype in the female gender. Puberty predisposes to increased numbers of angioedema attacks, in particular in female patients.

KEYWORDS

C1-inhibitor (C1INH), contact system, rare disease, hereditary angioedema (HAE), pediatric, puberty, ITACA

Introduction

The term angioedema (AE) comes from the union of the two ancient Greek words *αγγείον* (vessel) and *οίδημα* (edema) to emphasize how, unlike cardiovascular or renal edema that are driven by oncotic pressure and Starling's law, it is a disease that results from specific alterations in endothelial permeability (1). In most cases, especially in the pediatric population, AE is due to histamine release from mast cells and basophils, both when associated with urticaria and when it occurs in isolated manner (2, 3).

However, there are also some endotypes of AE mediated by bradykinin (BK), a vasoactive peptide produced in the circulation from high-molecular-weight kininogen (HMWK) upon activation of the contact system (4, 5). Angiotensin converting enzyme (ACE)-inhibitors (ACEI), which reduces BK catabolism by blocking ACE, the main proteases of BK, are the most frequent cause of bradykinergic AE (6, 7). Other drugs—among which gliptins, neprilysin inhibitors, and angiotensin-II-receptor antagonists—may also be involved in the pathogenesis of BK-mediated, iatrogenic angioedema that seldom affects pediatric population (8).

Infants, children and adolescents, on the other hand, represent an age cohort involved in hereditary angioedema due to C1-inhibitor (C1INH) deficiency (HAE-C1INH), which is also mediated by BK as the terminal effector (9, 10).

The history of HAE-C1INH is a long journey that started in 1882 with the first cases of angioedema in the modern era of medicine reported by Henrick Quincke, whose name later became the eponym for the disease (11). As thoroughly resumed by Reshef et al. (12), in the following decades Sir William Osler described the familiarity of the disease and Crowder the autosomal dominant transmission, but it took a century before the discovery of the pathogenetic roles of C1INH and bradykinin, respectively, by Virginia Donaldson in 1964 and Erich Nussberger in 1998. In the 2000s, six new hereditary variants of hereditary angioedema with normal C1INH have been identified to date since the mutation in the gene for factor XII described by Konrad Bork and Karen E. Binkley (13–15). Hereditary forms of angioedema of unknown origin also exist, but the most common one—although rare with an estimated prevalence of around 1:50,000—still by far remains HAE-C1INH (7, 16–21).

Although the first physiologic action of C1INH to be discovered consists in blocking the activation of the complement cascade, this protease inhibitor belonging to the serpin family exerts many actions on the contact system: in particular, it blocks the enzymatic activity of factor XII and kallikrein, thus reducing the generation of bradykinin from HMWK (22–24). Reduced or absent C1INH activity results, therefore, in increased BK production, predisposing to plasma leakage from the microcirculation (25, 26). When in HAE-C1INH, as well as in some hypertensive patients taking ACEI or in acquired forms of C1INH deficiency—even rarer than HAE (1:10) and not affecting the pediatric population as usually secondary to lymphoproliferative or autoimmune diseases (27, 28)—an additional stimulus of unknown nature locally adds, the plasma leaks from the capillary and elicits angioedema.

There is no itching or wheals, and many districts can be affected: subcutaneous tissue, with painful swelling and functional limitation that can persist several days if untreated; gastrointestinal and urogenital submucosa, with abdominal colic mimicking an acute abdomen and often leading to inappropriate surgery; upper airways, with life-threatening attacks when larynx is involved (29–32). The most common triggers of angioedema—which may be preceded by prodromes as erythema marginatum, irritability, sense of hunger, asthenia, or other signs and symptoms—are trauma, surgery, airway endoscopy, dental procedures, infections, and stressful conditions. In most cases, however, the onset of acute attacks occurs spontaneously and without any presaging sign (33–35).

C1INH deficiency may be due to impaired production of C1INH (HAE-C1INH type 1, 85% of cases) or to the synthesis of a dysfunctional protein (HAE-C1INH type 2) (1, 10). Both C1INH-HAE type 1 and type 2 have decreased C1INH activity. C1INH-HAE type 1 has a low amount of plasma C1INH caused by the lack of production from the mutated allele or production of a protein without function unrecognized in the antigen analysis. C1INH-HAE type 2 has low amount of functional C1INH in plasma and usually increased amounts of abnormal C1INH as this C1INH protein is unable to make complexes with target proteases. The phenotype and pattern of inheritance are the same, but the diagnostic approaches are different: while in HAE-C1INH type 1 it is sufficient to demonstrate an antigenic deficiency of the protein by turbidimetry, nephelometry, radial immunodiffusion, immunoblotting, or other immunologic methods, the diagnosis of HAE-C1INH type 2 requires assessment of functional C1INH activity by chromogenic or ELISAs, which need special attention even at the preanalytical stage (1, 10, 36–39). The C4 plasma concentration measurement, which is cheap, easy to perform, and worldwide available although nonspecific, can be very useful as a screening test because its level is reduced in around 95% of C1INH-deficient patients (19, 38–40). Finally, although HAE-C1INH is a genetic disease, mutational analysis of *Serpining1*, the gene on chromosome 11 that encodes for C1INH, is usually not necessary apart from, in rare cases of doubt, prenatal (chorionic villous sampling or amniocentesis) or preimplantation diagnosis of HAE and scientific purposes (1, 10, 39–43). Moreover, gene assessment may be helpful in the first year of life because too early testing in newborns may lead to a false diagnosis of HAE-C1INH (44, 45).

Despite diagnostic advances, including new tools that extend the possibility of diagnosis to reference centers and physicians who eventually lack the proper facilities (46, 47), the diagnostic delay in HAE-C1INH still remains significant as typical of rare diseases (48). In patients with type II HAE-C1INH and in the *de novo* mutations, which represents up to 20% of cases and have no parents affected, the interval between symptom onset and diagnosis has been reported to be even greater (19, 44, 49).

Although the majority of data and studies regarding hereditary angioedema are based on adults, HAE-C1INH is a disease of pediatric interest, as typical of most congenital diseases. The very early occurrence of potential life-threatening attacks, the unpredictable nature of acute episodes, and their negative consequences on normal daily, school and social activities

contribute to a significant disease burden and reduced quality of life (QoL) for both young patients and their parents, relatives, and caregivers (50–52). The onset of symptoms is reported to present in most cases in childhood, with median age of the first swelling ranging from 5 to 11 years and mean diagnostic age of diagnosis and diagnostic delay highly variable in different surveys (4, 53–60). However, these retrospective studies involve very limited populations and are so heterogeneous in their methods that they are difficult to compare with each other, and are not focused on the influence of puberty, which is expected to be relevant due to hormonal influences, psychological aspects, and the possible introduction of estroprogestin in the female population.

Our study aims to deepen our understanding of puberty on the onset, frequency, location, and severity of attacks in hereditary angioedema due to C1-inhibitor deficiency utilizing data shared by the Italian Network for Hereditary and Acquired Angioedema (ITACA, www.angioedemaitaca.org), which brings together Italian reference centers and uses an electronic disease registry where patients can directly enter data on their clinical course.

Patients and methods

This multicenter, retrospective observational study was performed on HAE patients from 10 ITACA centers throughout Italy, thus minimizing the potential bias caused by regional differences.

Inclusion criteria were age between 10 and 40 years, puberty already occurred, and enrollment in the ITACA Registry, approved by the ethics committee of the coordinating center (Comitato etico Milano area 1) on 5 May 2017. The patients were interviewed from 1 to 30 August 2022 by specialized personnel who administered a semistructured questionnaire (Supplementary Table S1) addressing patient characteristics and the effect of puberty on attack location, severity and frequency, related treatments, and overall burden of disease. Age of onset of puberty was defined as the age at menarche for females and the age at semenarche for males. In order to estimate attacks frequency, the patients were asked to report a monthly mean of attacks in the year and in the 3 years before and after puberty. All patients had previously provided written consent to be included in the registry and reiterated verbal consent at the time of the interview. For patients younger than 18 years, interviews were performed in the presence and with the consent of parents.

Statistical analysis

Continuous variables are shown as mean and SD or median and interquartile range (IQR) depending on their distribution. Shapiro–Wilk test was used to check if the variables followed a normal distribution. Categorical variables are shown as number and percentage. Student's *t*-test or Mann–Whitney test were used for comparisons between continuous variables, depending on their distribution; Chi-square test was used for comparisons between categorical variables (Fisher's exact test when the

number in any cell was smaller than 5). Binomial logistic regression was used to investigate the ability of a set of predictor variables to predict the outcome. All the analyses performed are detailed in Supplementary Table S2. Statistical analysis was performed with Jamovi [The jamovi project (2021). *jamovi* Version 1.6]. $p \leq 0.05$ was considered statistically significant.

Results

Population characteristics

Out of 147 eligible patients referring to the centers involved in the study, 118 (60 F, 58 M; HAE-C1INH type 1 = 113, type 2 = 5) were enrolled. As in Table 1, demographic and clinical characteristics were similar between males and females, but the age of puberty was lower in the female gender (median: 12 years in females vs. 13 years in males, $p < 0.001$); median age at the interview was 30 years (IQR = 13,75) in males and 29.5 years (IQR = 11,25) in females ($p = 0.779$); median age at first attack was 6 years (IQR = 6,5) in males and 8 years (IQR = 10) in females.

The impact of puberty on HAE: overall clinical picture

The proportion of symptomatic patients increased significantly after puberty in both males and females (97.3% vs. 76.1%, $p < 0.001$ in the whole cohort; 98.2% vs. 83.9%, $p = 0.002$ in males; 96.3% vs. 68.4% $p < 0.001$ in females) (Tables 2, 3). In the 24 patients who became symptomatic after puberty, the first attack occurred after a mean of 5.14 years and a median of 3.5 years.

The numbers of acute attacks were significantly higher after puberty when comparing both 1-year and 3-year periods pre/after menarche/semenarche ($p < 0.001$ and $p < 0.001$ in the whole cohort; $p = 0.035$ and $p < 0.001$ in males; $p = 0.004$ and $p < 0.001$ in females) (Figure 1).

Characteristics of HAE attacks and related treatments before puberty are reported in Table 2, and after puberty in Table 3. No significant differences were detected in the attack location before and after puberty (Figure 2).

The impact of puberty: gender differences

Although both the genders showed an increase in the number of HAE attacks after puberty, this occurred more in females than in males as detailed in Figure 3 (differences in monthly mean of acute episodes of angioedema pre/post puberty) and Figure 4 (percentage of males and females in which the number of attacks varies pre/post puberty). Specifically, the median increase of monthly mean of attacks between 3 years before and 3 years after puberty was 1 (IQR = 2) in females and 0 (IQR = 1) in males ($p = 0.02$); the increase was present, even if not significant, also considering 1 year before and after puberty. Moreover, significantly more females reported an increase of attacks in both

TABLE 1 Demographic and clinical characteristics of patients.

	Male	Female	All	<i>p</i> value
Subjects, number (%)	58 (49)	60 (51)	118 (100)	
Current age (years), median (IQR); <i>n</i> = 118	30 (13.75)	29.5 (11.25)	30 (13)	0.779
Type of angioedema, number (% within column); <i>n</i> = 118				0.677
HAE-C1INH type I	55 (94.8)	58 (96.7)	113 (95.8)	
HAE-C1INH type II	3 (5.2)	2 (3.3)	5 (4.2)	
Angioedema age of onset (years), median (IQR); <i>n</i> = 114	6 (6.5)	8 (10)	7 (8.75)	0.235
Asymptomatic, number (%)	2 (3.4)	2 (3.3)	4 (3.4)	0.976
Age at diagnosis (years), median (IQR); <i>n</i> = 118	9 (12.5)	8 (15)	8.5 (13)	0.676
Delay between first symptom and diagnosis (months), median (IQR); <i>n</i> = 94	18 (81)	24 (83)	24 (81)	0.832
Plasma C1-inhibitor antigen at diagnosis (mg/dL), median (IQR); <i>n</i> = 72 ^a	5.8 (4.07)	6.78 (4.27)	6.4 (4.34)	0.340
Plasma C1-inhibitor function at diagnosis (%), mean (SD); <i>n</i> = 77	22.85 (14.65)	28.52 (16.45)	25.50 (15.67)	0.101
Plasma C4 component at diagnosis (mg/dL), mean (SD); <i>n</i> = 77	7.08 (3.28)	6.116 (2.67)	6.61 (3.02)	0.219
Familiarity, number (% within column); <i>n</i> = 117				0.871
<i>De novo</i> mutations	12 (20.7)	10 (16.9)	22 (18.8)	
Father affected	24 (41.4)	(44.1)	50 (42.7)	
Mother affected	22 (37.9)	23 (39)	45 (38.5)	
Status of proband, number (% within column); <i>n</i> = 118	16 (27.6)	17 (28.3)	33 (28)	0.928
Number of siblings, median (IQR); <i>n</i> = 104	1 (1)	1 (1)	1 (1)	0.216
Number of affected siblings, median (IQR); <i>n</i> = 107	1 (1)	0 (1)	0 (1)	0.041
Puberty age of onset (years), median (IQR); <i>n</i> = 117	13 (2)	12 (1.5)	13 (1)	<0.001
First HAE-C1INH treatment used, number (% within column); <i>n</i> = 118				0.958
Plasma-derived C1INH	32 (55.2)	34 (56.7)	66 (55.9)	
Tranexamic acid	13 (22.4)	14 (23.3)	27 (22.9)	
Icatibant	6 (10.3)	3 (5)	9 (7.6)	
Plasma-derived C1INH + icatibant	2 (3.4)	2 (3.3)	4 (3.4)	
Plasma-derived C1INH + tranexamic acid	1 (1.7)	1 (1.7)	1 (1.7)	
Fresh frozen plasma	0	1 (1.7)	1 (0.8)	
None	4 (6.9)	5 (8.3)	9 (7.6)	
Beginning of HAE treatment before puberty, number (% within column); <i>n</i> = 107	27 (50)	25 (47.2)	52 (48.6)	0.770
Comorbidities (number)				
Breast cancer	0	1	1	
Autoimmune conditions ^b	1	5	6	
Congenital diseases ^c	3	1	4	
Hormonal disorders ^d	1	6	7	
Concomitant medications (number)				
Non-hormonal chemotherapy	0	1	1	
Levothyroxine	0	3	3	
DIMARDs ^e	1	2	3	
Hormones ^f	1	6	7	

IQR, interquartile range; HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency; INH, inhibitor; HAE, hereditary angioedema.

^aFour subjects with functional deficit were not considered.

^bHashimoto thyroiditis, unspecified arthritis, diabetes insipidus, Sjogren syndrome, and lupus erythematosus.

^cArrhythmia, neurological, and hematological.

^dEndometriosis, hypogonadism, and polycystic ovary syndrome.

^eDisease modifying antirheumatic drugs: hydroxichlorquine and sulphasalazine.

^fEtinilestradiol/drospirenone, unspecified progestin, testosterone, and desmopressin.

periods: in the 3 years after puberty attacks were more frequent in 63.2% of the females and in 41.2% of the males ($p = 0.022$).

Nevertheless, no substantial differences were detected between males and females with regard to their subjective perception of illness before and after puberty (Table 4).

The impact of puberty: predictive factors

In regression analysis, female gender predicts the worsening of symptoms for both 1-year and 3-year periods after puberty (OR 2.2, Std Err 1.47–3.3, $p = 0.049$ and OR 2.44, Std Err 1.65–3.63,

$p = 0.024$, respectively). This is true for the 3-year period also when considering age of first menstruation as covariate [OR 2.43, Std Err 1.61–3.68, $p = 0.031$].

Discussion

Our retrospective survey in a large group of patients with HAE-C1INH from the ITACA cohort addresses the impact of puberty on the course of the disease.

Puberty is a dynamic, physical, and psychological growth process lasting several years and not a single event at a specific

TABLE 2 Angioedema attacks and treatments before puberty among male and female subjects.

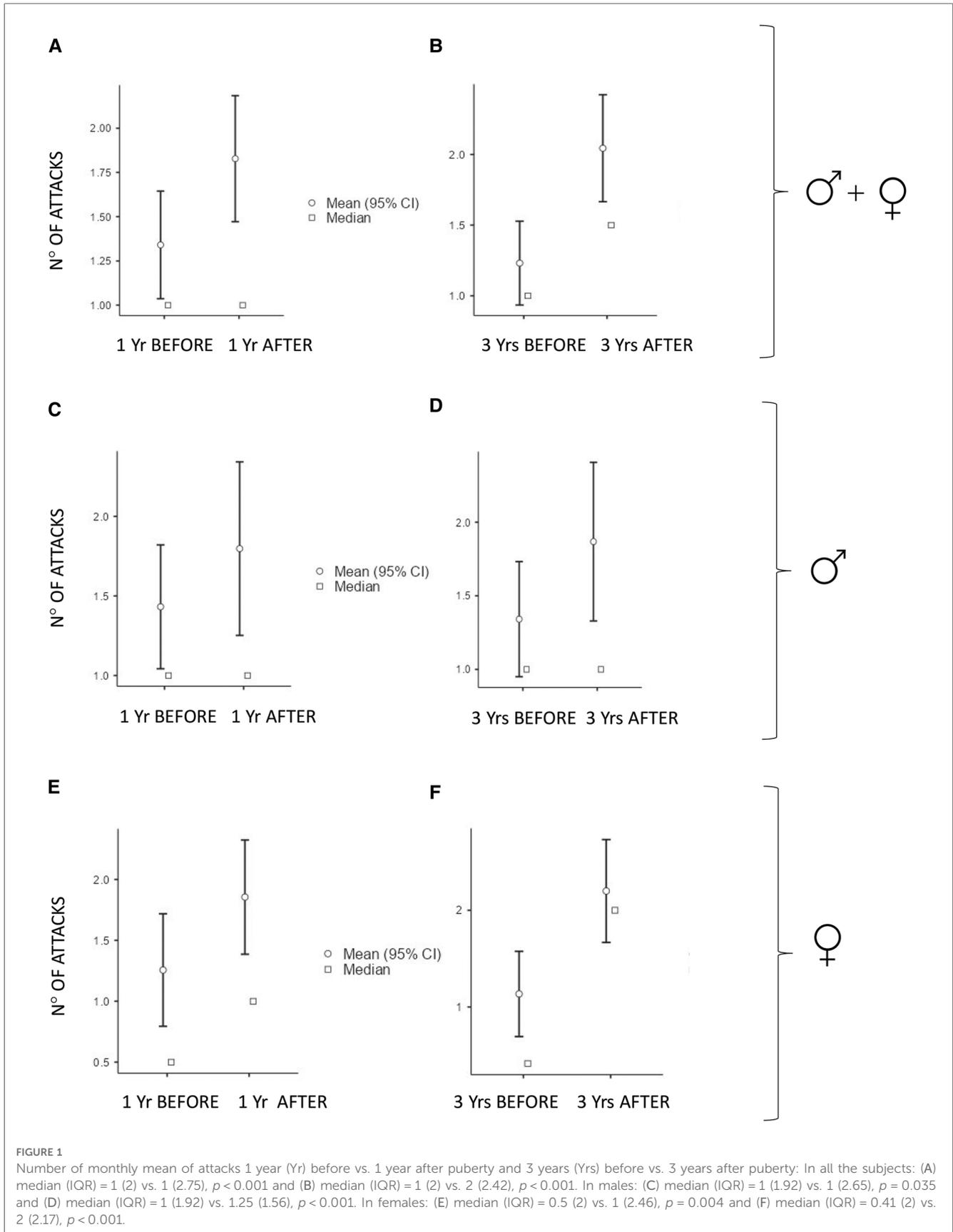
	Male	Female	All	<i>p</i> value
Monthly mean number of attacks in the year before puberty, median (IQR); <i>n</i> = 113	1 (1.92)	0.5 (2)	1 (2)	0.113
Monthly mean number of attacks in the 3 years before puberty, median (IQR); <i>n</i> = 113	1 (1.92)	0.41 (1)	1 (2)	0.048
Main site of attacks, number (% within column); <i>n</i> = 113				0.057
Cutaneous and abdominal	24 (42.9)	10 (17.5)	34 (30.1)	
Cutaneous	10 (17.9)	16 (28.1)	26 (23)	
Abdominal	9 (16.1)	8 (14)	17 (15)	
Upper airways	4 (7.2)	5 (8.9)	9 (8)	
No attacks	9 (16.1)	18 (31.6)	27 (23.9)	
Most common on-demand treatment, number (% within column); <i>n</i> = 102				0.349
Plasma-derived C1INH	18 (34)	10 (20.4)	28 (27.5)	
Tranexamic acid	8 (15.1)	7 (14.3)	15 (14.7)	
Plasma-derived C1INH and tranexamic acid	2 (3.8)	4 (8.2)	6 (5.9)	
Icatibant	1 (1.9)	0 (0)	1 (1)	
Plasma-derived C1INH and icatibant	1 (1.9)	0 (0)	1 (1)	
None	23 (43.4)	28 (57.1)	51 (50)	
Any long-term prophylaxis before puberty, number (% within column); <i>n</i> = 118	3 (5.2)	4 (6.7)	7 (5.9)	0.731
Long-term prophylaxis before puberty, number (% within column); <i>n</i> = 118				0.562
Tranexamic acid	2 (3.4)	2 (3.3)	4 (3.4)	
Plasma-derived C1INH and tranexamic acid	0 (0)	1 (1.7)	1 (0.8)	
Danazol	1 (1.7)	0 (0)	1 (0.8)	
Unspecified	0 (0)	1 (1.7)	1 (0.8)	
None	55 (94.8)	56 (93.3)	111 (94.1)	
Hospital accesses before puberty, median (IQR); <i>n</i> = 90	0 (1)	0 (0)	0 (1)	0.305
At least one hospital access before puberty, number (% within column); <i>n</i> = 118	25 (43.1)	18 (30)	43 (36.4)	0.139

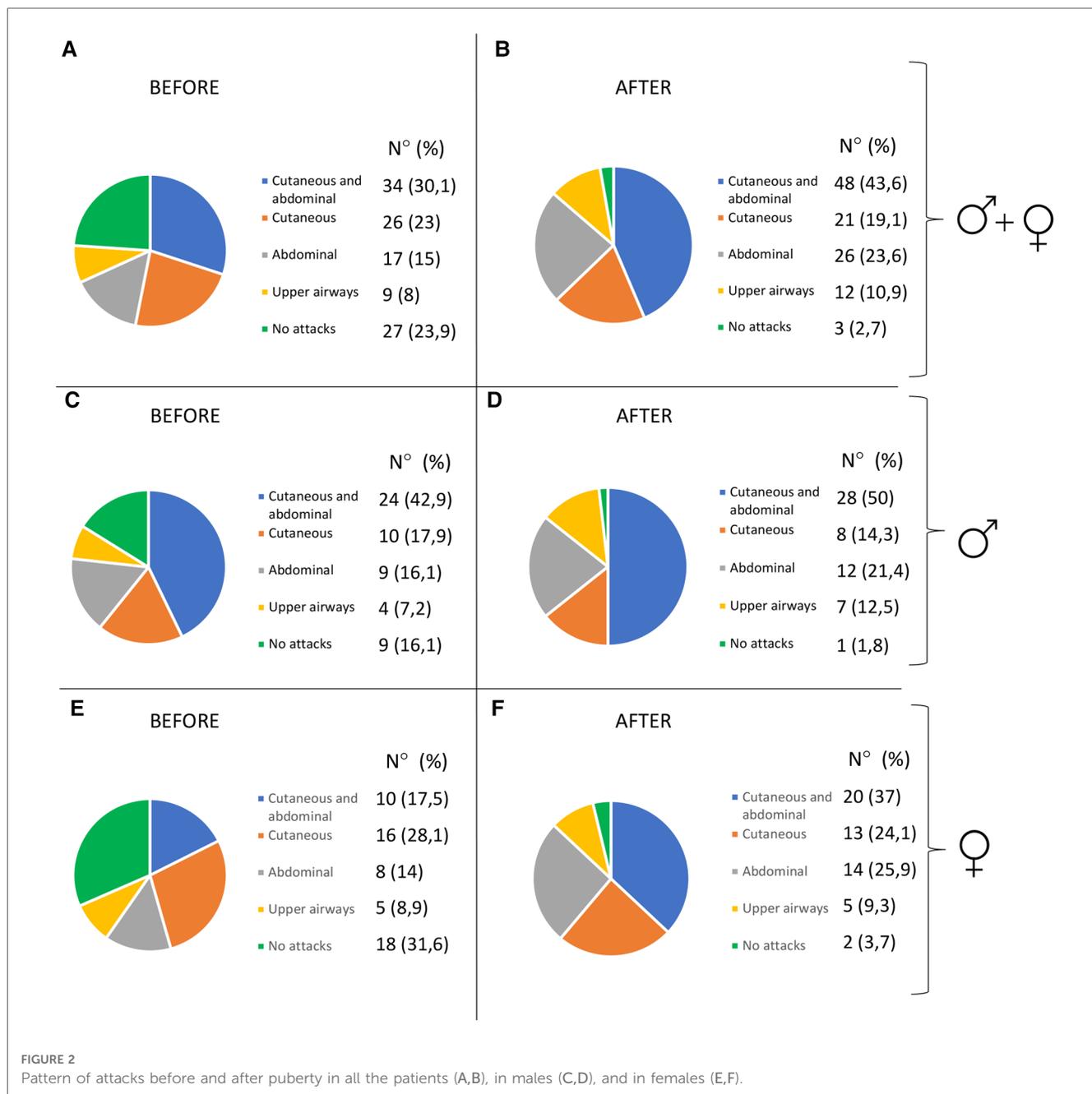
IQR, interquartile range; C1INH, C1-inhibitor.

TABLE 3 Angioedema attacks and treatments after puberty among male and female subjects.

	Male	Female	All	<i>p</i> value
Monthly mean number of attacks in the year after puberty, median (IQR); <i>n</i> = 113	1 (2.65)	1 (2.46)	1 (2.75)	0.764
Monthly mean number of attacks in the 3 years after puberty, median (IQR); <i>n</i> = 111	1.25 (1.56)	2 (2.17)	2 (2.42)	0.327
Main site of attacks, number (% within column); <i>n</i> = 110				0.496
Cutaneous and abdominal	28 (50)	20 (37)	48 (43.6)	
Cutaneous	8 (14.3)	13 (24.1)	21 (19.1)	
Abdominal	12 (21.4)	14 (25.9)	26 (23.6)	
Upper airways	7 (12.5)	5 (9.3)	12 (10.9)	
No attacks	1 (1.8)	2 (3.7)	3 (2.7)	
Most common on-demand treatment after puberty, number (% within column); <i>n</i> = 106				0.947
Plasma-derived C1INH	29 (53.7)	28 (53.8)	57 (53.8)	
Tranexamic acid	1 (1.9)	2 (3.8)	3 (2.8)	
Plasma-derived C1INH and tranexamic acid	2 (3.7)	2 (3.8)	4 (3.8)	
Icatibant	11 (20.4)	8 (15.4)	19 (17.9)	
Plasma-derived C1INH and icatibant	6 (11.1)	7 (13.5)	13 (12.3)	
Plasma-derived C1INH, icatibant, and tranexamic acid	1 (1.9)	0 (0)	1 (0.9)	
None	4 (7.4)	5 (9.6)	9 (8.5)	
Long-term prophylaxis in the 3 years after puberty, number (% within column); <i>n</i> = 118	5 (8.6)	11 (18.3)	16 (13.6)	0.123
Long-term prophylaxis in the 3 years after puberty, number (% within column); <i>n</i> = 118				0.099
Tranexamic acid	0 (0)	5 (8.3)	5 (4.2)	
Danazol	4 (6.9)	3 (5)	7 (5.9)	
Lanadelumab	1 (1.7)	0 (0)	1 (0.8)	
Unspecified	0 (0)	1 (1.7)	1 (0.8)	
None	53 (91.4)	49 (81.7)	102 (86.4)	
Hospital accesses in the year after puberty, median (IQR); <i>n</i> = 102	0 (0.50)	0 (0)	0 (0)	0.718
Hospital accesses in the 3 years after puberty, median (IQR); <i>n</i> = 95	0 (0)	0 (0)	0 (1)	0.560

IQR, interquartile range; C1INH, C1-inhibitor.





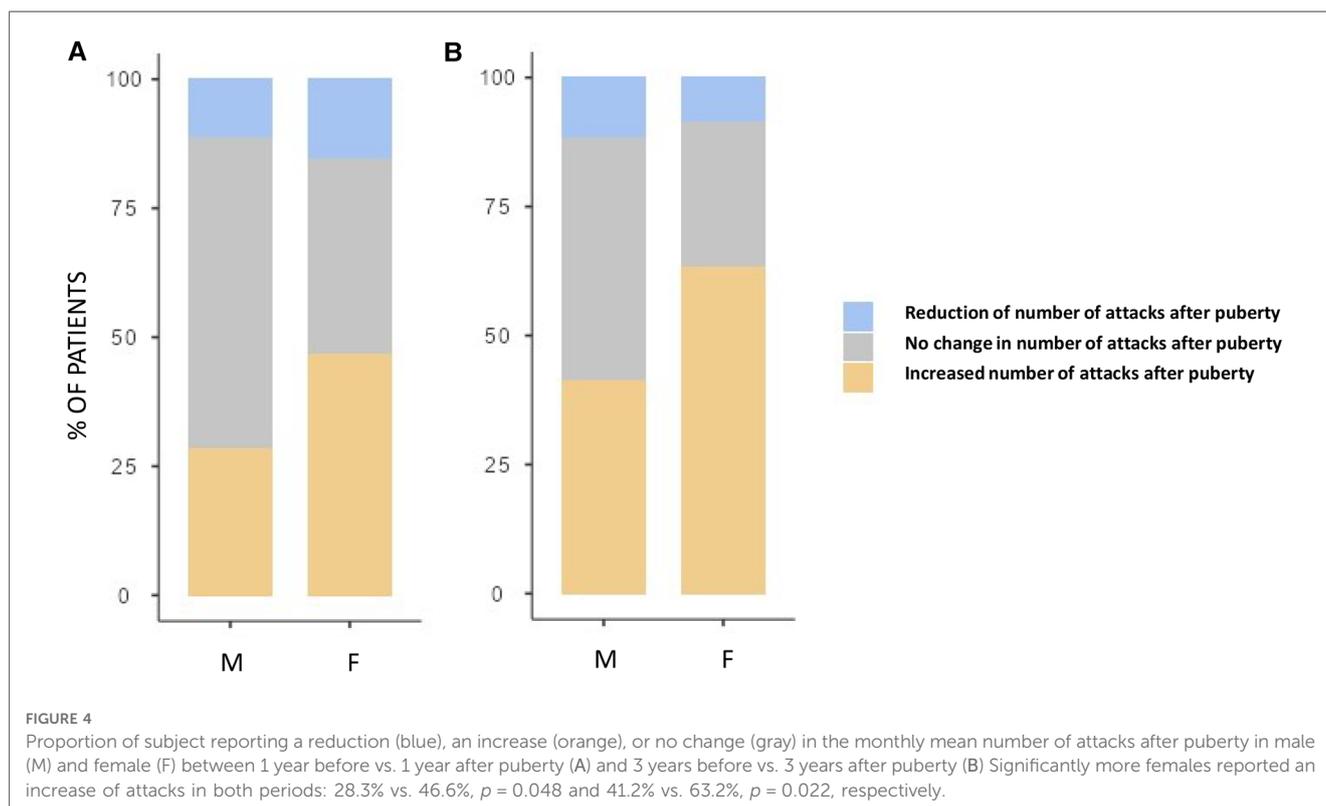
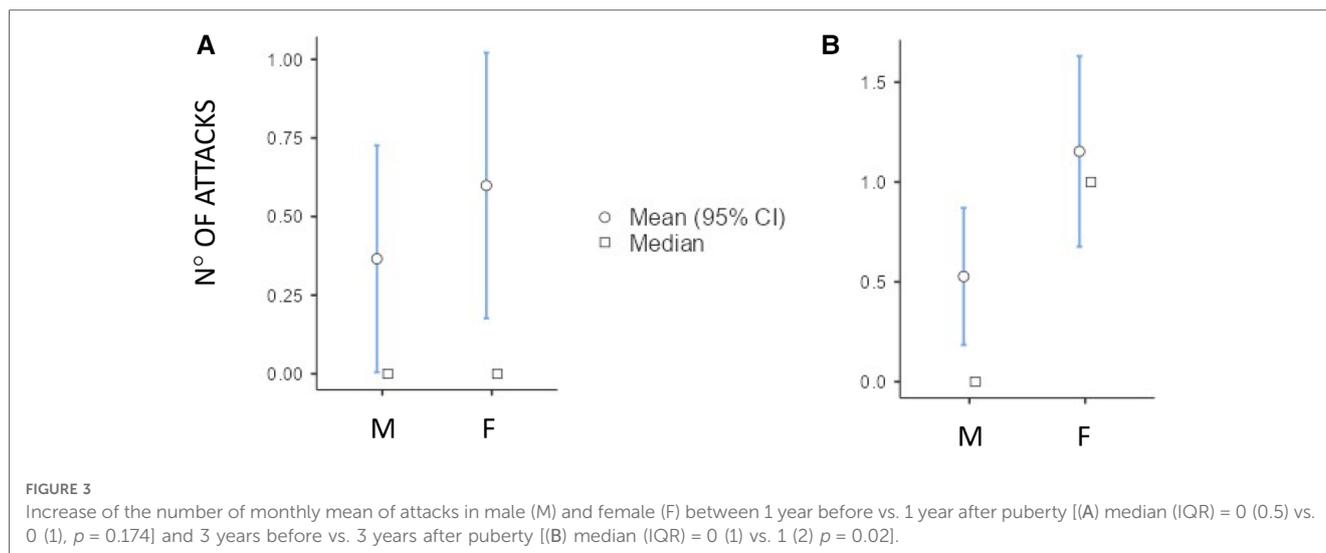
age (59). However, we decided to identify a significant feature of puberty easy to be recognized and remembered in order to assess the impact of puberty on patient symptoms in our survey. Thus, we chose the onset of menstruation and semenarche as the key indicator in pubertal development for their biological, psychological, and relational relevance.

The mean age indicated for these two events by our study population, 12 and 13 years for males and females (Table 1), was not different from data reported in the overall population (61–63). This finding is consistent with the empirical evidence from clinical practice of normal sexual development of children affected by HAE-C1INH.

The frequency of HAE attacks before puberty was similar between males and females, with numbers of acute episodes

slightly higher in males in the prepubertal 3-year period (median of monthly mean: M = 1.0; F = 0.41; $p = 0.048$; Table 2). However, female gender predicts a worsening of symptoms in the 1-year and 3-year period after puberty compared to the same pre-puberty time intervals ($p = 0.049$ and 0.024 , respectively). Symptom worsening after puberty occurred to a greater extent in female subjects than in males (Figures 3, 4). On the contrary, there was no significant variation in the location of the attacks, which were reported mostly as abdominal and subcutaneous both before and after puberty by both the genders, similar to what is described for HAE-C1INH patients of any age and sex (10) (Figure 2).

Previous data suggested that adults present a higher frequency of acute episodes of angioedema than the pediatric population (64–



66), although a thorough comparison between pediatric and adult patients is still lacking. Among the several biological factors involved in the process of growth that could theoretically contribute to this increase, hormonal factors certainly play a role (67–70). In fact, estrogen hormones promote a pattern of protein expression, which ultimately increases the activity of the contact system (71, 72) and female patients tend to present a more severe disease (1). In the present manuscript, we show that puberty is a watershed moment of life when the disease starts to get worse for women. Moreover, in

our cohort, puberty seemed to represent a turning point also for male subjects: although on semenarche an androgen-dominated pattern of hormones is secreted (73), we might speculate that the bioactive metabolite of testosterone estradiol can act on the contact system and worsen symptoms in the male gender.

Finally, we were not able to demonstrate a parallel worsening of QoL in the period after menarche and semenarche compared to the prepubertal situation. This is because it is well recognized that the frequency of attacks is not the only factor affecting patient QoL, as

TABLE 4 Overall impact of puberty among male and female subjects.

	Male	Female	All	p value
Difference in the number of monthly mean of attacks between 1 year before vs. 1 year after puberty, median (IQR) <i>n</i> = 109	0 (0.5)	0 (1)	0 (1)	0.174
Difference in the number of monthly mean of attacks between 3 years before vs. 3 years after puberty, median (IQR) <i>n</i> = 106	0 (1)	1 (2)	0.125 (1)	0.020
Patients in which the number of attacks varies after 1 year from puberty, number (% within column); <i>n</i> = 111				0.059 (0.048 when considering increase vs. no change + reduction)
Reduction	6 (11.3)	9 (15.5)	15 (13.5)	
No change	32 (60.4)	22 (37.9)	54 (48.6)	
Increase	15 (28.3)	27 (46.6)	42 (37.8)	
Patients in which the number of attacks varies after 3 years from puberty, number (% within column); <i>n</i> = 108				0.070 (0.022 when considering increase vs. no change + reduction)
Reduction	6 (11.8)	5 (8.8)	11 (10.2)	
No change	24 (47.1)	16 (28.1)	40 (37)	
Increase	21 (41.2)	36 (63.2)	57 (52.8)	
Subjective feelings of symptoms worsening after puberty, number (% within column); <i>n</i> = 114	23 (41.1)	32 (55.2)	55 (48.2)	0.132
Symptoms worsening permanently, number (% within column); <i>n</i> = 114	18 (32.1)	23 (39.7)	41 (36)	0.403
Type of Symptoms worsening, number (% within column); <i>n</i> = 55				
Frequency of attacks	8 (34.8)	10 (31.3)	18 (32.7)	0.456
Increased duration/intensity of attacks	1 (4.3)	0 (0)	1 (1.8)	
Both	14 (60.9)	22 (68.8)	36 (65.5)	

the severity of single HAE episodes and the unpredictability of their onset play a crucial role in the global burden of disease (52). Moreover, the study design did not allow us to use specific tools to assess QoL variations.

Further limitations of the study derive from the retrospective approach and the approximate quantification of the number of attacks not included in the register, active since 2017, especially in patients who had been through puberty for over a decade. Several biases could influence the accuracy of attack frequency, when retrospectively reported. Among others, subjects may have been influenced by the interviewers, and attacks occurred in young age might be more easily forgotten.

Moreover, treatment strategies were highly variable, also because of the many new drugs developed in recent years. Thus, although we tried to limit these biases by including in the study only subjects under 40 years of age, we were well aware that a comparison of on-demand treatment before and after puberty was unreliable and reported only the descriptive statistics. Nevertheless, the prevalence of patients on long-term prophylaxis for HAE-C1INH had raised from 5.9% before puberty to 13.6% in the 3 years after menarche or semenarche (Tables 2, 3), thus strengthening the evidence of symptom worsening after puberty.

Overall, our study confirms previous reports on a more severe phenotype in the female gender and provides new insights on the impact of puberty on a large cohort of HAE patients from the ITACA network. Results show that puberty predisposes to increased

numbers of angioedema attacks, in particular in female patients. Retrospective data collection should be confirmed in prospective assessments, which are challenging in the field of rare diseases but may be favored by patient adherence to disease registries.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comitato etico Milano area 1. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MC promoted the study on behalf of ITACA. MC, PT, and RS contributed to the conceptualization and scope, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

MC received speaker/consultancy fees from BioCryst, CSL Behring, Kalvista, Pharming, SOBI, and Takeda. PT received speaker/consultancy fees from CSL Behring and Takeda. FA received consultancy fees or research grants from CSL Behring and Takeda. DF received speaking fees or research grants from CSL-Behring and Takeda. MDG received speaker fees from CSL Behring. VM received speaker/consultancy fees from BioCryst, CSL Behring, GSK, Kyowa Kirin, Takeda, and Vifor. MG received speaker fees from Takeda, Sanofi, and Astrazeneca. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The reviewer AZ declared a past co-authorship with the authors MC, FA, VM, and RS to the handling editor.

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Supplementary material

The Supplementary Material for this article can be found online at <https://www.frontiersin.org/articles/10.3389/fped.2023.1141073/full#supplementary-material>.

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