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Hereditary angioedema attack: what happens to vasoactive mediators?

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ABSTRACT

Hereditary angioedema is a disabling, life-threatening condition caused by deficiency (type I) or dysfunction (type II) of the C1 inhibitor protein (C1-INH-HAE) leading to bradykinin accumulation and recurrent episodes of edema attack. Vascular leakage is a complex process sustained by the coordinated production of several permeabilizing factors including vascular endothelial growth factors (VEGFs), angiopoietins (ANGPTs) and phospholipase A_2 enzymes (PLA_2). We previously reported that patients with C1-INH-HAE in remission have increased plasma levels of VEGFs, ANGPTs and secreted PLA_2. In this study, we sought to analyze plasma levels of these mediators in 15 patients with C1-INH-HAE during the acute attack compared to remission. Plasma concentrations of VEGF-A, VEGF-C and VEGF-D were not altered during attack compared to remission. Moreover, VEGF-D concentrations were not altered also in remission phase compared to controls. Concentrations of ANGPT1, a vascular stabilizer, were increased during attacks compared to symptoms-free periods, whereas ANGPT2 levels were not altered. The ANGPT2/ANGPT1 ratio was decreased during angioedema attacks. Platelet activating factor acetylhydrolase activity was increased in patients with C1-INH-HAE in remission compared to controls and was decreased during angioedema attacks. Our results emphasize the complexity by which several vasoactive mediators are involved not only in the pathophysiology of C1-INH-HAE, but also during angioedema attacks and its resolution.

1. Introduction

Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a dominant autosomal disorder characterized by recurrent episodes of tissue swelling (i.e., angioedema attack) involving the deeper layers of skin and/or submucosal tissue [1–28]. Two forms of C1-INH-HAE are currently recognized: type I is caused by low antigenic and functional C1-INH and type II is characterized by normal antigenic but low functional C1-INH [1]. C1-INH is a serine protease inhibitor involved in several systems such as complement, contact, fibrinolytic and coagulation and normally inhibits kallikrein which cleaves bradykinin (BK) from the high-molecular-weight kininogen (HMWK) [2]. Lack of C1-INH leads to an overshooting local production of BK which promotes vascular leakage and angioedema attack through the engagement of BK receptors type 2 on endothelial cells (ECs) [3]. Increased endothelial permeability is one of the signs of EC activation. Indeed, several EC

Abbreviations: ANGPT, Angiopoietin; BK, Bradykinin; C1-INH, C1 inhibitor; EC, Endothelial cell; HAE, Hereditary angioedema; C1-INH-HAE, Hereditary angioedema with C1 inhibitor deficiency; HMWK, High Molecular Weight Kininogen; PAF, Platelet activating factor; PAF-AH, Platelet activating factor acetylhydrolase; pKK, Plasma kallikrein; $sPLA_2$, Secreted Phospholipases A_2; PLA2G2A, Secreted Phospholipases A_2 Group IIA; VEGF, Vascular Endothelial Growth Factor; vWF, von Willebrand Factor

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activation markers such as von Willebrand Factor antigen (vWF), vWF collagen-binding activity, soluble E-selectin and endothelin-1 have been found increased in sera of C1-INH-HAE patients during edema attacks [4]. Accordingly, high concentrations of BK and cleaved-HMWK were found in C1-INH-HAE patients and further increased during angioedema attacks with a positive correlation between cleaved-HMWK and attack frequency [5].

In addition to BK, several vasoactive mediators can modulate vascular permeability and play a role in C1-INH-HAE pathophysiology [6]. For example, vascular endothelial growth factors (VEGFs), produced by endothelial cells and several circulating immune cells [7,8] modulate vascular permeability [9]. For instance, VEGF-A is a potent vasodilator through the release of nitric oxide [10]. A complementary endothelial pathway regulating vascular barrier function is the angiopoietin (ANGPT) system [11,12]. ANGPT2 promotes vascular permeability, whereas ANGPT1 favors endothelial stabilization [13–15]. Also the phospholipases A_2 (PLA_2) superfamily, including secreted PLA_2 ($sPLA_2$) and platelet activating factor acetylhydrolase (PAF-AH), can directly modulate vascular permeability [16,17]. The PAF-AH family comprises extracellular and intracellular enzymes. In particular, extracellular or plasma-type enzyme is found in association with lipoprotein and catalyzes the deacetylation and inactivation of PAF [17]. It also displays an anti-inflammatory function through marked reductions in PAF-induced vascular leakage [17]. We have recently described that plasma levels of VEGF-A, VEGF-C, ANGPT1, ANGPT2 and $sPLA_2$, in particular group 2A (PLA2G2A), are altered in C1-INH-HAE patients during symptom-free period [18,19]. Interestingly $sPLA_2$ activities are decreased during angioedema attacks [19]. To date, there are no data on the role of VEGFs, ANGPTs and PAF-AH during angioedema attacks.

Even if the pathogenesis of C1-INH-HAE is well denoted, mechanisms underlying the evolution and resolution of angioedema attacks are largely unknown. In this study we analyzed plasma concentrations of VEGFs and ANGPTs and plasma activity of PAF-AH in C1-INH-HAE patients during angioedema attacks in order to enlighten our knowledge on this phenomenon.

2. Materials and methods

2.1. Blood sampling

Blood was collected during routine diagnostic procedures and the remaining plasma sample was labeled with a code which was documented into a data sheet. Technicians who performed the assays were blinded to the patients' history. The samples were collected by means of a clean venipuncture and minimal stasis using sodium citrate 3.2% as anticoagulant. After centrifugation (2000 g for 20 min at 22°), the plasma was divided into aliquots and stored at −80 °C until used.

2.2. Study population

We studied 51 adult patients with C1-INH-HAE in remission and 31 healthy controls followed at the University of Naples Federico II (Naples, Italy) and the Semmelweis University (Budapest, Hungary). Clinical characteristics are reported in Supplementary Table 1. The Ethical Committee of the University of Naples Federico II (protocol number: 216/16) and Semmelweis University of Budapest (protocol number: BPR/021/09599-7/2014) approved that plasma obtained during routine diagnostics could be used for research investigating the physiopathology of hereditary angioedema and written informed consent was obtained from patients in according to the principles expressed in the Declaration of Helsinki. The diagnosis of C1-INH-HAE was based on presence of at least one clinical and laboratory criteria [1]. Fifteen patients out of 51 were followed also during acute angioedema attack and their specific clinical characteristics are reported in Supplementary Table 2. Regarding symptom-free samples, blood taking was performed at least two weeks since the date of the last angioedema attack. While regarding samples during attack, blood taking was performed within 6 hrs after the onset of the symptoms.

2.3. Complement system analysis

Plasma C1-INH was measured by radial immunodiffusion (NOR-Partigen, Siemens Healthcare Diagnostics, Munich, Germany). C4 antigen concentration in Italy was measured by radial immunodiffusion (NOR-Partigen) (the method is not specific for C4 fragments); in Hungary C4 was measured by turbidimetry (Roche Cobas Integra 800, Beckman Coulter Complement C4). The antibody employed in the Beckman Coulter C4 assay is directed against the common portion of the C4 molecule and it exhibits the same reactivity with C4 fragments as well as with the native molecule. C1-INH function was assessed as the capacity of plasma to inhibit the esterase activity of exogenous C1s as measured on a specific chromogenic substrate by means of a commercially available kit (Technoclone GmbH, Vienna, Austria). Reference ranges were 0.70–1.30 U C1-INH/ml (1 U C1-INH corresponds to the average C1-INH activity present in 1 ml of fresh citrated normal plasma). The functional activity of C1-INH was also expressed as a percentage of activity of C1-INH present in samples. Normal values of activity of C1-INH are greater than 0.7 U C1 INH/ml (> 70%). According to diagnostic criteria, all patients enrolled in this study had C1-INH functional activity lower than 50% of normal, positive family history, clinical symptoms of angioedema, low C4, normal C1q concentrations [1].

2.4. Assays of VEGFs and ANGPTs

Plasma levels of VEGF-A, VEGF-C, VEGF-D, ANGPT1 and ANGPT2 were measured using commercially available ELISA kits (R&D System, Minneapolis, USA) according to the manufacturer's instructions [18]. The ELISA sensitivity is 31.1–2000 pg/ml for VEGF-A, 62.5–4000 pg/ml for VEGF-C, 31.3–2000 pg/m for VEGF-D, 156.25–10,000 pg/ml for ANGPT1 and 31.1–4000 pg/ml for ANGPT2.

2.5. Assays of phospholipases

PLA_2 activity in plasma of C1-INH-HAE patients during remission and angioedema attacks was evaluated using commercially available kit (Life Technologies EnzChek® phospholipase A_2 assay) according to the manufacturer's instructions [19]. The activity of PAF-AH enzymes was determined in plasma of patients and healthy controls by using PAF-AH assay kits (Cayman Chemical) according to the manufacturer's instructions.

2.6. Statistical analysis

Data were analyzed with the GraphPad Prism 7 software package. Data were tested for normality using the D'Agostino-Pearson normality test. If normality was not rejected at 0.05 significance level, we used parametric tests. Otherwise, for not-normally distributed data we used nonparametric tests. Statistical analysis was performed by paired two-tailed *t*-test or two-tailed Mann-Whitney test as indicated in figure legends. Correlations between two variables were assessed by Spearman rank correlation analysis and reported as coefficient of correlation (r). Plasma concentrations of VEGFs and ANGPTs, the activity of PLA_2 and PAF-AH are shown as the median (horizontal black line), the 25th and 75th percentiles (boxes) and the 5th and 95th percentiles (whiskers) of C1-INH-HAE patients and controls. Statistically significant differences were accepted when the p value was ≤ 0.05.

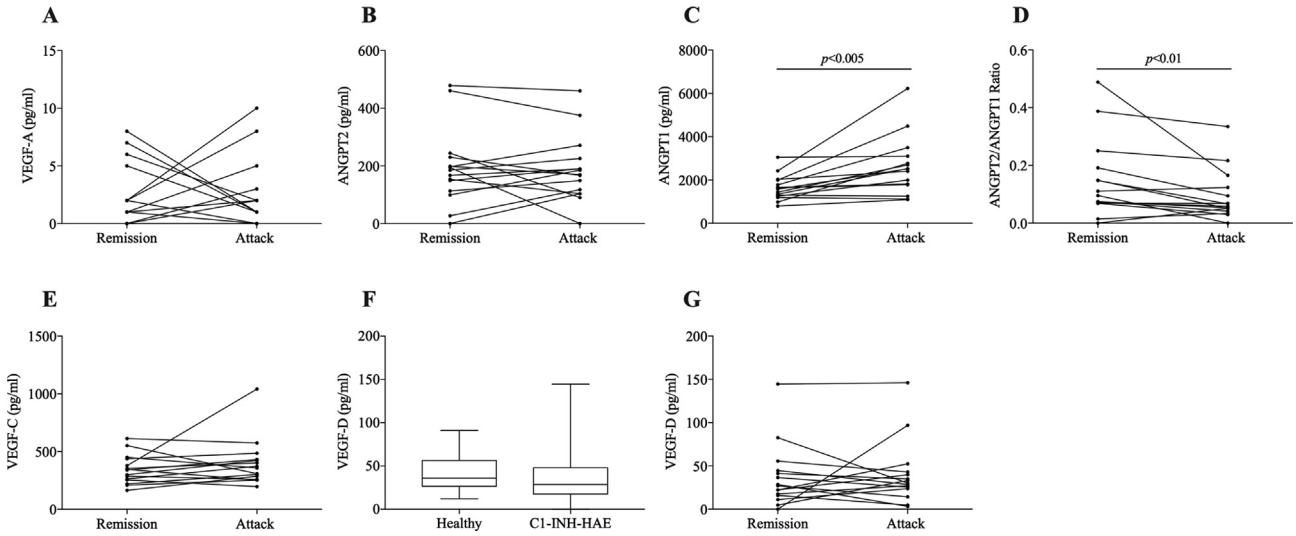

Fig. 1. Plasma concentrations of VEGFs and ANGPTs in patients with C1-INH-HAE in remission and during the angioedema attack. Plasma concentrations of VEGF-A (A), ANGPT2 (B), ANGPT1 (C), ANGPT2/ANGPT1 ratio (D), VEGF-C (E) and VEGF-D (G) in 15 patients with C1-INH-HAE during remission and angioedema attack. Plasma concentration of VEGF-D in 31 controls (Healthy) and 51 C1-INH-HAE during remission (F). Data are shown as the median (horizontal black line) of C1-INH-HAE patients or control, the 25th an 75th percentiles (whiskers). A p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. VEGF and ANGPT concentrations in patients with C1-INH-HAE during angioedema attack

Characteristics of patients with C1-INH-HAE and healthy controls are reported in Supplementary Table 1, whereas Supplementary Table 2 reports characteristics of C1-INH-HAE evaluated during angioedema attack. We have evaluated plasma concentrations of different permeability factors in patients with C1-INH-HAE during angioedema attack and in remission. VEGF-A concentrations (Figs. 1 and 2A) were not altered during acute attacks compared to symptom-free periods [attack-free 1 (0–8) *vs* angioedema attack 1 (0–10) pg/ml median values (interquartile ranges)]. Similarly we did not find modification in ANGPT2 levels during episodes of angioedema [185 (0–479) *vs* 170 (0–460) pg/ml] (Fig. 1B). By contrast, a significant increase of ANGPT1 concentrations was detected during the acute attack phase compared to remission phase [1578 (799–3052) *vs* 2518 (1096–6228) pg/ml] (Fig. 1C). In addition, the ANGPT2/ANGPT1 ratio was decreased in acute phases compared to symptom-free periods [0.09 (0–0.49) *vs* 0.06 (0–0.33)] (Fig. 1D). The concentrations of the lymphangiogenic factor VEGF-C during acute phase were similar to those during remission [341 (164–613) *vs* 358 (196–1042) pg/ml] (Fig. 1E). No previous data on the role of VEGF-D, another lymphangiogenic factor [20], have been reported in C1-INH-HAE patients. Differently from VEGF-C [18], VEGF-D concentrations were not increased in 51 patients with C1-INH-HAE compared to 31 healthy controls [healthy 36 (12–91) *vs* remission 29 (0–144) pg/ml] (Fig. 1F). Moreover, no differences in VEGF-D levels were found in C1-INH-HAE patients during angioedema attacks compared to symptom-free periods [symptom-free 27 (0–144) *vs* angioedema attack 30 (3–146) pg/ml] (Fig. 1G).

Interestingly, when we stratified our study group based on attack frequency (< 12 or ≥ 12 attacks/year) we observed, similarly to attack-free phase, an increasing trend in patients with high frequency (≥ 12/year) compared to patients with low frequency (< 12/year) for VEGF-A (Supp. Fig. 1A), VEGF-C (Supp. Fig. 1B), ANGPT2 and ANGPT2/ANGPT1 ratio (Supp. Fig. 1C and 1D).

3.2. PAF-AH activity in patients with C1-INH-HAE during angioedema attack

We have recently shown that plasma $sPLA_2$ activity and PLA2G2A levels are increased in symptom-free C1-INH-HAE patients compared to controls [19]. In this study we assessed the PAF-AH plasma activity of 51 C1-INH-HAE patients in remission and in 31 healthy controls. Interestingly, PAF-AH activity was increased in C1-INH-HAE patients in symptom-free period compared to controls [healthy 25 (0–46) *vs* attack-free 34 (0–54) nmol/min/ml median values (interquartile ranges)] (Fig. 2A). No correlation was found between $sPLA_2$ and PAF-AH activities ($r = 0.03$; NS). It has been shown that estrogens decrease PAF-AH plasma levels in adult male and female rats, while progestins have the opposite effect [21]. However, no differences in PAF-AH activity was found between males and females in both controls and patients. Moreover, there was no correlation between the age and PAF-AH activity in both patients and healthy controls (data not shown).

In C1-INH-HAE patients functional C1-INH levels are below 50% of normal value and C4 concentrations are usually reduced and can be used as a screening test [1]. We investigated whether differences in the complement component levels (C1-INH and C4) were associated with differences in PAF-AH activity. C1-INH activity did not correlate with PAF-AH activity ($r = 0.01$; NS) (Supp. Fig. 2A). Moreover, when we classified the C1-INH-HAE patients according to their concentrations of C1-INH and C4 (less than 25% or 25–50% of normal values), no differences in PAF-AH plasma activity between these groups were found (data not shown) (Supp. Fig. 2B and C).

When we assessed PAF-AH activity in patients with less (low frequency) or more (high frequency) than 12 attacks in the last 12 months we found that PAF-AH activity was increased in more severe patients (Fig. 2B). Then, we examined the relationship between PAF-AH activity and VEGFs and ANGPTs concentrations. PAF-AH activity did not correlate with VEGF-A (Supp. Fig. 3A), VEGF-C (Supp. Fig. 3B) and ANGPT1 (Supp. Fig. 3C) concentrations. By contrast, ANGPT2 concentrations and ANGPT2/ANGPT1 ratio inversely correlated with PAF-AH activity (Fig. 2C and D).

In a final series of experiments, we measured the PAF-AH activity in 15 patients with C1-INH-HAE during remission and during angioedema attacks. We found that the activity of PAF-AH was reduced in patients during attacks compared to basal conditions [symptom-free 32 (25–39) *vs* angioedema attack 19 (16–25) nmol/min/ml] (Fig. 2E).

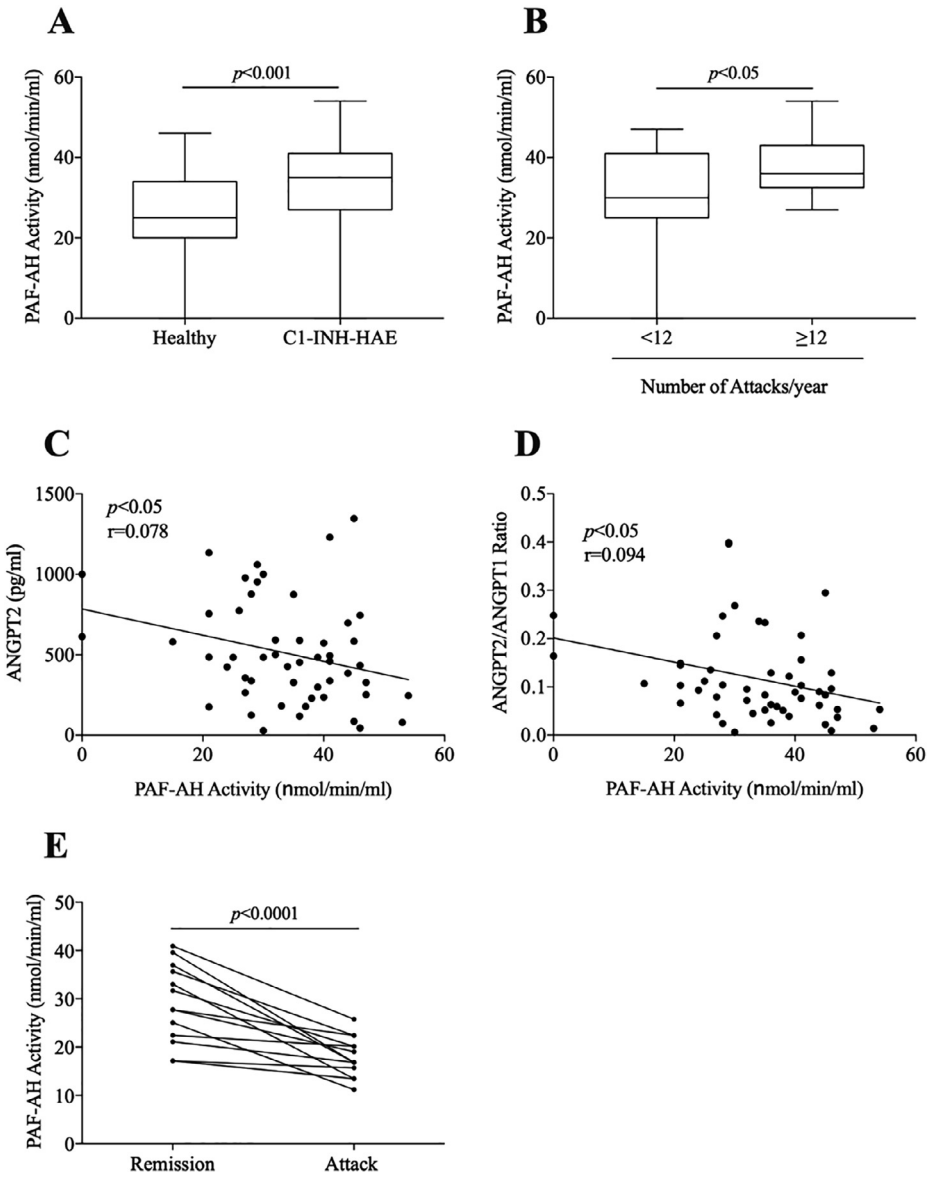

Fig. 2. PAF-AH activity in patients with C1-INH-HAE compared to healthy controls and during angioedema attacks. Plasmatic PAF-AH activity was evaluated in 31 healthy controls and 51 C1-INH-HAE patients in remission (A) and in patients stratified based on attack frequency (< 12 or ≥12 attacks/year) (B). Data are shown as the median (horizontal black line), the 25th an 75th percentiles (whiskers). Correlation between two variables: PAH-AH activity and ANGPT2 (C) and PAF-AH activity and ANGPT2/ANGPT1 ratio (D) were assessed by Spearman rank correlation analysis and reported as coefficient of correlation (r). PAF-AH activity was evaluated in 15 C1-INH-HAE patients during remission and angioedema attack (E). A *p*-value ≤ 0.05 was considered statistically significant.

4. Discussion

C1-INH-HAE is an autosomal disease characterized by recurrent nonpitting edema attacks associated with morbidity and mortality [22,23]. Edema attack is an unpredictable event characterized by increase in vascular permeability and subsequent swelling of the skin, gastrointestinal tract and upper airways that resolve within 48–96 hrs. Angioedema attacks are associated with reduced plasma levels of C1-INH leading to activation of the contact activation which triggers high levels of BK [3]. Frequency and severity of symptoms occur with intra- and inter- patient variability and the mechanism governing this variability is not completely understood. It is becoming clear that several factors are involved during the acute attack such as cleaved-HMWK [5], EC activation markers [4] and PLA2G2A [19], in addition to BK [24]. We previously reported that VEGF-A, VEGF-C, ANGPT1 and ANGPT2 plasma levels are increased in C1-INH-HAE patients during remission compared to healthy controls [18] contributing to create a sort of "vascular preconditioning" that may predispose to the angioedema attack. Instead the scenario during the angioedema attack seems to be completely different. In this study, we found no differences in VEGF-A and ANGPT2 levels during acute attack compared to remission. Interestingly, a significant increase of ANGPT1 was detected during angioedema attack. ANGPT1 is an agonist of Tie2 receptor and plays an important role in vascular stabilization [15]. It has been recently reported that missense mutation of *ANGPT1* gene is associated to a novel endotype of angioedema [25]. The mutation leads to a reduced binding of ANGPT1 to its Tie2 receptor caused by a lacking of ANGPT1 multimers formation [25] which results in vascular destabilization. Our data suggest that ANGPT1, a unique vascular stabilizer, may play an important role in restoring physiological vascular homeostasis during angioedema attack. This hypothesis is indirectly supported by decreased ANGPT2/ANGPT1 ratio, which is an index of vascular permeability.

The lymphatic system is constituted by lymphatic vessels and lymph nodes and form an elaborate vascular system that drain fluids from your body's tissues [26]. Lymphatic vessels maintain fluid balance in tissues by returning filtered lymph fluid back to the bloodstream. They interact with blood vessels and play important functions in interstitial fluid drainage, lipid absorption, and immune responses [26]. Lymphangiogenesis, the growth of lymphatic vessels from preexisting vessels, is supported by lymphangiogenic factors such as VEGF-C and VEGF-D [7,26]. We have previously demonstrated that VEGF-C concentrations were increased in asymptomatic patients with C1-INH-HAE and were further increased in more severe C1-INH-HAE patients [18]. In this

study we found that VEGF-D concentrations, differently from VEGF-C [18] were not altered in asymptomatic C1-INH-HAE patients compared to healthy controls. Neither VEGF-C nor VEGF-D were altered in angioedema attack compared to remission phase. These results indicate that two lymphangiogenic factors (i.e., VEGF-C and VEGF-D) behave differently between them in remission and during angioedema attack.

Plasma concentrations of VEGFs and ANGPT2 in remission are even higher in C1-INH-HAE patients experiencing more than 12 attacks per year than in those who had less than 12 attacks [18]. Interestingly, despite VEGF-A, VEGF-C and ANGPT2 levels seem not to be altered during the angioedema attack compared to remission, the division of our study population during angioedema attack based on attack frequency seem to markedly maintain a strong trending differences between patients experiencing less than 12 attacks/years and more than 12 attack/years. These findings support the correlation of VEGFs and ANGPTs with disease phenotype in different phases of disease.

Local generation of BK is considered the central mediator of vascular leakage in C1-INH-HAE-related swelling attacks [24]. It is yet unclear whether BK generation is sufficient to cause an angioedema attack or other mechanisms are required. BK induces the production of several vascular permeability factors and enzymes, including PLA_2 and PAF by endothelial cells [27]. The superfamily of PLA_2 directly modulates endothelial cell migration and vascular permeability *in vitro* [16] and comprises different proteins including PAF-AH. PAF-AH degrades not only PAF but also oxidatively fragmented phospholipids with potent biological activities and has been the target of many clinical studies in inflammatory diseases, such as asthma, sepsis, and vascular diseases [27]. In this study, we found that C1-INH-HAE patients in remission have increased PAF-AH activity compared to healthy controls. Interestingly, plasma PAF-AH activity is even higher in C1-INH-HAE patients experiencing more than 12 attacks per year than in those who had less than 12 attacks. Similarly to $sPLA_2$, we observed decreased PAF-AH activity during angioedema attack. The explanation of this observation is still unclear. It is conceivable that decreased activity of PAF-AH could be due to its exhaustion in order to degrade PAF and other metabolites released during the angioedema attack or to its sequestration (binding to the surface and/or internalization), similarly to other $sPLA_2$ [28] by activated endothelial cells during the acute phase. Whatever the mechanisms, the alterations of PAF-AH during both remission and clinical attack suggest a possible involvement of this mediator in C1-INH-HAE.

Collectively, our results add important information to our knowledge on the role of vasoactive mediators possibly involved in acute phase of C1-INH-HAE. It seems that several permeabilizing factors, such as VEGF-A, VEGF-C, ANGPT2, PLA2G2A and PAF-AH, together with BK can act on endothelium and enhance a vascular preconditioning to leakage. A different scenario can be observed during the angioedema attack, when several permeability factors (i.e., VEGF-A, ANGPT2) remain unchanged. By contrast, ANGPT1, a vascular stabilizer, is increased and an inhibitor of vasodilating factors (i.e., PAF-AH) is decreased during the attack.

In conclusion, our results highlight the complexity by which several vasoactive mediators are implicated not only in the pathophysiology of C1-INH-HAE, but also in the resolution of increased vascular permeability during angioedema attack.

CRediT authorship contribution statement

Anne Lise Ferrara: Conceptualization, Data curation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Maria Bova:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Angelica Petraroli:** Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Nóra Veszeli:** Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Maria Rosaria Galdiero:** Funding, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Mariantonia Braile:** Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Giancarlo Marone:** Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Leonardo Cristinziano:** Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing. **Simone Marcella:** Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Luca Modestino:** Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing. **Henriette Farkas:** Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Stefania Loffredo:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have no relevant affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony or patents received or pending, or royalties.

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Appendix A. Supplementary material

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