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Hereditary Angioedema
neurobiological factors and coping skills

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1. INTRODUCTION

Hereditary Angioedema (HAE) is a rare, chronic inherited diseases characterized by mild to severe episode of acute swelling, resulting from increased vascular permeability. It is estimated that the prevalence is about 1 in 10.000 and 1 in 50.000 and there are no know differences in gender, ethnic, or racial susceptibility[1-2].

The first full medical report of HAE of considerable medical entity in literature, is owed to the German physician Heinrich Ireanus Quincke (1882)[3], who reported a series of cases with swelling disorder but the term "angioneutotic edema" was first proposed in 1885 by Paul Strübing, who underscored a potential link between the nervous system and the process of edema formation, hypothesis sustained also by Bannister. About six years after Quincke's discovery, Sir William Osler enlightened the familiar nature of HAE[4], pointing out that there had to be a genetic common factor due to the syndrome was recorded in 28 members over five generations in a single family, which included even two members died of asphyxiation due to laryngeal edema. The autosomal-dominant mode of inheritance of HAE was outlined by Crowder and Crowder in 1971. Virginia Donaldson and Richard Evans in 1963 and 1964 discovered the biochemical abnormalities of the C1-INH and described HAE's path mechanisms[1], refuting the psychic origins of the symptoms caused by vasomotor nervous disturbance and naming it Hereditary Angioedema. HAE-1 and 2 were described by Rosen in 1965.

The C1 inhibitor is a protein of the complement system, a part the immune system, and the lack and/or reduced levels of it are causes of swelling that may affect any part of the body[5-6]. Steroids drugs are ineffective in treating a hereditary angioedema episode. The only possible treatment requires the intravenous administration of the C1 inhibitor or a subcutaneous administration of Icatibant (antagonist of bradykinin B2 receptor)[7]. An HAE attack can modify suddenly, deforming, the appearance of the patient who has the pathology, when oedema affects exposed parts such as the face and the limbs. In other case, it could be able to cause a serious and painful symptomatology, when it affects the internal organs such as the intestine whose transit is blocked, but also to put at risk, by asphyxiation the life of the patient, when it affects the mucous membranes of the upper respiratory tract such as the glottis[8]. However, the expression of clinical symptoms varies widely, even in the individual at different times, as well as among the different family members of a single family. Specific triggering events, as hormonal and estrogenic fluctuations,

oral surgery or dental procedure, mechanical stress, physical or minor trauma, infections, emotional stress or excitement, drugs (oestrogen, ACE inhibitors, some psycho-drugs), exposure to cold,

specific foods or beverages, insect bites, have been related to HAE attacks[9]. Even in the case of the same patient, a potential triggering factor can cause an attack on a single occasion and not on another. All this implies for the subject who is the carrier of this pathology, a quality of life dominated by uncertainty, anxiety for a sort of condition of "chronic fear" of the unknown and unpredictable because the attacks arise abruptly, in the absence of causes apparent.

The emotional stress, as trigger of the acute episodes, can explain the variety of expressions of the disease among the population and during the individual lifetime[10-11]. In my PhD Program in Neurosciences, I aimed to identify, first, the possible interrelations between anxiety, depression, intensity and frequency of angioedema attacks; second, to explore the connection between inflammation, stress, emotional status and variability of the attacks, in order to better rationalize the specific therapy.

My research project stems from the desire to understand if it is possible to use a holistic approach with HAE patients. So, try to reassert, once again, how soma and psyche should be considered mutually by the doctor who is facing any disease. This is because, as the masters teach, there is no illness but there is the sick, in his psycho-somatic uniqueness.

In summary, in the first part of my PhD program we enrolled 48 patients with a diagnosis of type 1 or 2 HAE, followed at the Regional Reference Centre for Hereditary Angioedema, Policlinic of Catania, for the psychological assessment, and we tried to identify possible correlations between anxiety, depression, severity and frequency of HAE attacks (article 1.). In the second part, we tried to identify possible joints between inflammation, stress, emotional status and variability of the attacks. This because we wanted to evaluate how and what change after a period of psychological support.

2. Article 1 *(IN PREPARATION)*

Hereditary Angioedema: From psychosomatic illness in hereditary condition.
Psychological assessment in individuals with symptomatic form of Angioedema

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ABSTRACT

Background: Hereditary angioedema is a rare, genetic disease due to C1 inhibitor deficiency. The C1 inhibitor is a protein of the complement system, a part the immune system. The lack a/or reduced levels of the C1 inhibitor are causes of swelling that may affect any part of the body. Steroids drugs are ineffective in treating a hereditary angioedema episode. The only possible treatment requires the intravenous administration of the C1 inhibitor or a subcutaneous administration of Icatibant (antagonist of bradykinin B2 receptor). Subjects with HAE are carriers of the genotype of the disease that is transmitted from parent to child because the transmission is of the autosomal dominant type.

However, the expression of clinical symptoms varies widely, even in the individual at different times, as well as among the different family members of a single family. Specific triggering events, as hormonal and estrogenic fluctuations,

oral surgery or dental procedure, mechanical stress, physical or minor trauma, infections, emotional stress or excitement, drugs (oestrogen, ACE inhibitors, some psycho-drugs), exposure to cold, specific foods or beverages, insect bites, have been related to HAE attacks. Even in the case of the same patient, a potential triggering factor can cause an attack on a single occasion and not on another.

Objective: to evaluate the psychological assessment in patients with symptomatic form of Hereditary Angioedema.

Methods: for all 48 patients (26 women and 22 men, mean age 40,25 ± 15,98) with a diagnosis of type 1 or 2 HAE were evaluated the collection of personal data, anamnestic and general lifestyle

data and the administration of psychological tests .We used the Hamilton Depression Rating Scale (HAM-D) to evaluate depressive symptoms and the Hamilton Anxiety Rating Scale to evaluate anxious symptoms. Coping strategies were evaluated using Coping Orientation to Problems Experienced (COPE) and the size of stress perception with the “Mesure du stress Psychologique” (MSP). We also evaluated the Attachment style using the Attachment Style Questionnaire (ASQ) and the personality with the Minnesota Multiphasic Personality Inventory-2 (MMPI2).

Results: A total of 52,2% of patients were identified as experiencing mild depression (HAM-D >8 , 7,52±6,17) and the 17,4% severe anxiety (HAM-A > 17, 9,91±). The results of Coping Orientation to Problems Experienced (COPE >17, 21,83±5,35) showed pathological results in 82,6% of patients. Also, the test Mesure du Stress Psychologique underline that 17,4% of patients showed pathological results (MSP>56, 47,23±8,21). Finally, a total of 52% of patients present pathological attachment styles (ASQ).

Conclusion: our data and the literature support that anxiety and depression symptom are common in patients with HAE. Is this study we also found that a lot of patients have lower levels of resilience and high perception of stress and severity of illness. In view of the above, a psychological support can be very important for the best practice with HAE.

INTRODUCTION

The genetic error that prevents the development of a protein called inhibitor C1, essential for human life and which is placed at the base of the pathology known as "Hereditary Angioedema"[1], involves the onset of acute attacks consisting in circumscribed mucous membranes edema and subcutaneous that can suddenly change, deforming it, the appearance of the affected patient and risk his/her own life due to asphyxiation (when it affects the mucous membranes of the upper respiratory tract as the glottis)[2]. All this implies, for the person who is a carrier of this disease, a quality of life dominated by uncertainty and anxiety due to a sort of "chronic fear" of the unknown and of the unpredictable[3], which forces the affected people to depend on the specialized centers and/or the ER[4-5]. Despite the fact that the genetic error is the same for all the sick patients, only some of them show the most severe symptoms of the disease. Moreover, the same patient may have, during his/her own life, periods of repeated attacks and periods of symptomatic remission[6-7]. When you ask a patient (or if you participate to a HAE meeting, in order to have different opinions) any considerations, doubts or fears that he/she has experienced with the greatest suffering, the results are:

1 - The awareness of being a carrier of a disease so rare and little known even by many doctors[8];

2 - The awareness of being affected by a genetic disorder and therefore transmitted within his/her own family but also that it may be transmitted by joining in marriage;
3 - The peculiarity of acute attacks that cause impressive edema that are not only painful and disfiguring the appearance of the person during the minutes, hours or days of the attack, but that can also put the life of the patient in danger if the edema is located in the upper respiratory tract[9-10];
4 - Finally: the continuing bureaucratic difficulties due to the uneasy way of finding a specific medicine and to the fact that it may only be used in specialized centers or in the emergency department; the long hours spent waiting for their appearance to be normal again after the medicine has run its effect, and the quality of life very far from optimal, worsened by exigent circumstances linked to the uncertainty of short-term future, which frustrates the days spent to organize leisure or travels or just the wish to carry out his/her daily routine without knowing if he/she can really go on with it or if an attack could spoil everything.
In our work we are going to analyze the impact that such considerations may have on the psyche of HAE patients in order to hypothesize, in a next study, any possible measures to strengthen the resilience of the pathological organic event and to improve the quality of life of these patients[10].

METHODS

In the present study, we evaluated 48 patients (26 women and 22 men, mean age: 40,25 ± 15,98; mean age of first HAE attack: 14,61±12,46) with a diagnosis of type 1 or 2 HAE, followed at the Regional Reference Centre for Hereditary Angioedema, Policlinic of Catania. At the clinical evaluation, were carried out the collection of personal and general data on lifestyle and of anamnestic. The administration of psychological tests consisting of MSP (Mesure du Stress Psychologique)[11], COPE (Coping Orientation to Problems Experienced)[12-13-18], HAM-D (Hamilton Depression rating Scale)[14], HAM-A (Hamilton Anxiety rating Scale)[15], ASQ (Attachment Style Questionnaire)[16] questionnaires. Finally, we used the MMPI2 (Minnesota Multiphasic Personality Inventory-2)[17] to evaluate the personality traits.

RESULTS

The average number of HAE attacks in the year prior to patient evaluation date was 21,83±18,05; the number of HAE attacks during the previous month was 2,2±2,3 and the average attacks in the previous week were 0,62±0,740.
In this sample, 52,2% of patients had at least one anamnestic episode of laryngeal edema, which was reported as an event associated with increased subjective perception of death or increased risk of death; 56,5% of patients reported the presence of important prodromal symptoms belonging to

the psychic sphere and 78,3% reported the presence of "life events" prior to acute attack, considered by patients as prodromal syndromes; 65,2% of patients had a history of psychiatric disorders belonging to the anxious-depressive sphere. The results from HAM-D and HAM-A tests showed that a total of 52,2% of patients was identified as experiencing mild depression (HAM-D >8; 7,52±6,17) and the 17,4% severe anxiety (HAM-A > 17; 9,91±). The results of Coping Orientation to Problems Experienced test (COPE >17, 21,83±5,35) showed pathological results in 82,6% of patients. Also, the Mesure du Stress Psychologique test underline that 17,4% of patients showed pathological results (MSP>56, 47,23±8,21). Moreover 52% of patients present pathological attachment styles (ASQ). No significant results were found from the MMPI2 analysis.

Data	**Average ± Std. Deviation**
Number of patients	48
Age	40,25 ± 15,98
Age first HAE attack	14,61 ± 12,46
Number of attacks in the last 365 days	21,83 ± 18,05
Number of attacks in the last 30 days	2,2 ± 2,3
Number of attacks in the last 7 days	0,62 ± 0,740
HAM-D (Depression)	7,52± 6,17 >8
HAM-A (Anxiety)	9,91 ± 7,94 >17
COPE (Coping Orientation to problems Experiences)	21,83 ± 5,53 >18
MSP (Perception of severity of the disease)	47,23±8,21>56

Table 1*. Results.*

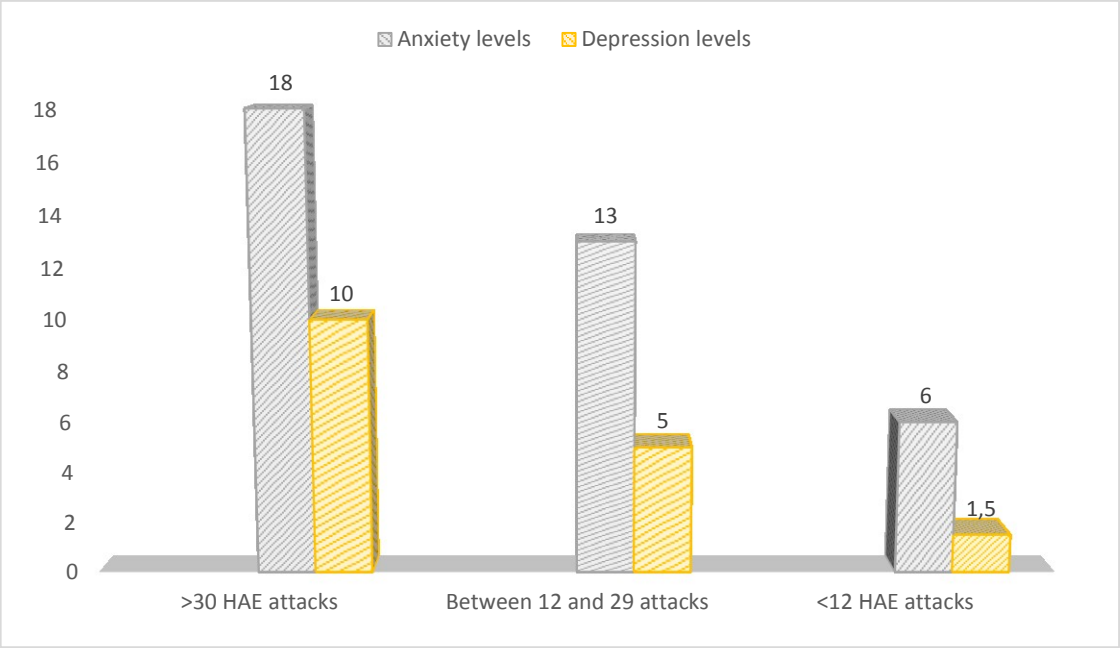

Table 2. *Division of patients by number of acute attacks in the last year and levels of anxiety and depression.*

CONCLUSION

HAE results in considerable humanistic burden to patients across physical and mental health domains; it negatively affects education, career, and work productivity and compounds the substantial economic burdens that are reported separately[10]. It is widely recognized that patients with HAE reported decreased physical and mental health compared to a normal population[20]. According to our data, the social effects of HAE had a larger impact on patient quality of life than their physical condition. In fact, in our work we found that a total of 52,2% of patients was experiencing mild depression and the 17,4% severe anxiety according to the highly comparable and valid Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale. The results of Coping Orientation to Problems Experienced showed pathological results in 82,6% of patients. Also, the test Mesure du Stress Psychologique underline that 17,4% of patients showed pathological results. In the other hand, a total of 52% of patients present pathological attachment styles (ASQ). Patients that experienced more HAE attacks during the last years showed high levels of anxiety and depressive symptoms. It could suggest that patients, which are less resilient to life stressor[3-19], are more exposed to HAE attacks during a week, month or year. This data was already observed during the first patients' interviews, at the enrollment phase. Patients often became anxious when they had to tell their medical history. Moreover, they also reported having a panic attack before or after an HAE attack at least once in their life. Obviously, this does not allow us to know, in a statistical way,

if the panic attack is a cause or a consequence of a HAE attack. In view of above, we can suppose that knowing how to recognize an anxiety or depressive disorder, in patients with HAE, could be very important for a more efficient therapeutic management.

In conclusion, this premise further reinforces the age-old concept that holistic approach of the patient's pathology combines "psyche and soma" in reciprocal influence.

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3. Article 2. *(IN PREPARATION)*

Hereditary Angioedema: neurobiological factors and coping skills

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Abstract

The genetic error that prevent the formation of a protein called C1 inhibitor, essential for the human's life, is the base of pathology known as "Hereditary Angioedema" (HAE). This pathology involves the onset of acute attacks consisting of circumscribed oedema of the mucous membranes and of the subcutaneous. An HAE attack can modify suddenly, deforming, the appearance of the patient who has the pathology, when oedema affects exposed parts such as the face and the limbs. In other case, it could be able to cause a serious and painful symptomatology, when it affects the internal organs such as the intestine whose transit is blocked, but also to put at risk, by asphyxiation the life of the patient, when it affects the mucous membranes of the upper respiratory tract such as the glottis. All this implies for the subject who is the carrier of this pathology, a quality of life dominated by uncertainty, anxiety for a sort of condition of "chronic fear" of the unknown and unpredictable because the attacks arise abruptly, in the absence of causes apparent. From this point of view, we wanted to evaluate how a psychological support could contribute to improving the quality of life. In a holistic approach to the patient, the aim of this work was the attempt to identify a correlation between psychological and neurobiological aspects (in detail with inflammatory cytokines such as TNF-α, IL-6 and cortisol) of the HAE.

Introduction

Hereditary Angioedema (HAE) is a rare disease characterized by a localized and self-limiting oedema of the subcutaneous and submucosal tissue, not associated with urticarial[1]. The best knows and common form of hereditary angioedema is due to a genetic deficiency of C1 inhibitor (C1-INH) with low functional plasma level (type1) or to a genetic dysfunction (type 2) of C1-INH[6-10]. However, other forms of familiar angioedema with normal concentrations of C1-INH have been

described in the past years, caused by a mutation of the XII coagulation factor (FXII-HAE)[11]. These mutations determinate the release of vasoactive mediators that increase vascular permeability, causing a tissue swelling that can deform the patient' face, cause episode of abdominal pain or also threaten their life. Some characteristics of C1-INH, such as low prevalence, inheritance, and delay in diagnosis, pain, unpredictable acute episodes that can be triggered by different stimuli, unnecessary medical procedures and treatment with ineffective drugs could significantly decrease patient's quality of live. The emotional stress, as trigger of the acute episodes, can explain the variety of expressions of the disease among the population and during the individual lifetime[14]. This work intends to explore the connection between inflammation, stress, emotional status and variability of the attacks[15]. We aim to identify possible etiopathogenetic joints and evaluate the possible interrelations between anxiety, depression, intensity and frequency of angioedema attacks in order to better rationalize the specific therapy.

Cytokines, Stress and HAE

Bradykinin (BK) is the main mediator of HAE's symptoms, predominantly dependent on stimulation of B2-receptor (B2R). Recent studies have shown that also B1-receptor (B1R) may intervene during the attacks. Considering that, the expression of B1R requires an inflammatory stimulus, we suppose that: patient with elevate proinflammatory cytokines plasma levels should have a more severe disease course and also B1R can be responsible of acute manifestations of HAE triggered by stress, when activation of the peripheral immune cells and the production of IL-1, IL-6 and TNFα[31]. The activation of the contact system ultimately leads to formation of the biologically active peptides BK and Lys-BK, which, on cleavage by kininase I and carboxypeptidase M (CPM), can yield desArg9-BK and Lys-desArg9-BK on BR2 and BR1, respectively, predicts that once generated, BK will first interact with B2R and then, with B1R. Furthermore, CPM augments B1R signalling in three ways. First, it generates the B1R agonist's desArg-BK. Second, CPM can serve as a co-receptor for B1R on the cell membrane and generate B1R agonists at a high concentration in close proximity of B1R. Third, CPM can directly activate B1R by means of conformational cross talk on binding of BK, decreasing the effective concentration of desArg9-BK necessary to stimulate B1R, despite its relatively low affinity. CPM is also induced by cytokines and endotoxins, which induce B1R too[36].

In addition, tissue and leukocyte enzymes with trypsin-like specificities can release either BK or Lys-BK from circulating kininogens in various forms of tissue injury.

The expression of B1R by endothelial cells, however, requires stimulation by cytokines such as IL-1 and TNFα, through the activation of NFkB. Cytokines and BK act in a synergistic fashion: Lys-desArg9-BK stimulates IL-1 production, and both Lys-desArg9-BK and IL-1 increase B1R expression. B1R is also less sensitive to desensitization than B2R, and confers biological activity to relatively abundant metabolites, because it is not phosphorylated nor internalized after agonist stimulation.

B1R expression in-patient with HAE likely is local and not generalized; this could yield local edema and explains also how swelling can develop at multiple locations, simultaneously during HAE attacks.

Specific triggering events have been related to HAE attacks, although these are variable from patient to patient. Even in the case of the same patient, a potential triggering factor can cause an attack on a single occasion and not on another. Some study suggests that some of HAE attacks may be triggered or affected by stress and emotional stress[43]. Furthermore, some researches underline the influence of the neurological correlatives of stress in the activation of the compliment cascade.

Patients with HAE show more frequently depressive symptoms such as insomnia, general somatic symptoms, anxious mood, difficulty in concentration, poor memory, loss of interest, reduced productivity, early waking and tension, as a potential consequence of pain, discomfort, disfigurement, potential life-threatening of acute attacks and the disease's unpredictability[33]. These feelings of depression and anxiety have probably also played a causative role in the initiation of an attack.

In view of the above, the literature on inflammation and depression suggests a possible link between HAE and mood disorders. Our intent is to demonstrate the link between HAE and stress, as trigger for acute attacks, measuring plasma levels of TNFα, IL-6, cortisol, adrenaline and noradrenaline, correlating them to number of attacks and anxiety and depression levels.

Materials and Methods

A prospective study was conducted since September 2016 at the Regional Reference Centre for Hereditary Angioedema, Policlinic of Catania. A team consisting of internists and a clinical psychologist (currently in charge of the International PhD research in neuroscience at University of Catania), followed a group of Sicilian patients with HAE. The protocol of study provided to evaluate for a:

1. Collection of personal data, anamnestic and general lifestyle data;
2. Evaluation of vital parameters and anthropometric measurements.

Administration for all patients:

3. Psychological tests: MSP[24], COPE[23], HAM-A[22], HAM-D[21].
4. From serum, the following was found:
   IL-6, TNF-alpha, and cortisol.

The sample of 48 patients consisted of 26 females and 22 males with mean age 40,25 ± 15,98, average of first HAE attacks 14,61±12.42.

All patients, on the day before the visit, were required to observe a standardized diet, to perform normal daily activities, to report any HAE attacks or prodromal symptoms, to avoid intense physical activity, alcohol consumption or medication intake.

Exclusion criteria included treatment with ACE inhibitors; hormone therapy, immunological therapy in the last 15 days, ongoing allergies, administration of anesthetics in the previous three months, night work in the last 15 days.

Subsequently, a new withdrawal was made in the two days following a possible attack and, whenever possible, in case of reports of prodromal symptoms. A psychological support course was then carried out through fifteen-day meetings aimed at containment of anxiety, understanding and management emotions, reduce the severity of perceived illness, and improve coping strategies.

Statistical analysis

Blood samples from all study subjects were taken between 8:00 a.m. and 9:00 a.m. By antecubital venipuncture into EDTA and 10 ml, dry biochemistry tubes. Serum was obtained by centrifugation in 15 min at 2000 rpm and then stored at -70 °C until the laboratory analysis was performed. Serum IL-6, TNFα and cortisol levels were measured with enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instruction.

Statistical analysis was performed using SPSS for Microsoft Windows (SPSS, Chicago, Illinois, USA). The variable levels were evaluated by means of Prism 4 software (Inc; San Diego CA, USA, 2003). $P<0.05$ was regarded as significant in all statistical analysis.

Psychological approach

The Psychologist used a Gestalt Therapy approach for all patients. It is a client-centered approach to psychotherapy that helps clients focus on the present and understand what is really happening in

their lives right now[46], rather than what they may perceive to be happening based on experience. Instead of simply talking about past situations, clients are encouraged to experience them, perhaps through re-enactment. Through the gestalt process, clients learn to become more aware of how their own negative thought patterns and behaviors are blocking true self-awareness and making them unhappy. A gestalt therapist focuses on what is happening in the moment and finding solutions in the present time. For examples, rather than discuss why something happened in the past, the therapist will encourage you to re-enact the moment and discuss how it feels right now. In other words, you will be asked to experience your feelings, rather than simply talk about them. The word "gestalt" means "whole" and in this kind of approach, humans are best viewed as a whole entity consisting of body, mind, and soul, and best understood when viewed through their own eyes, not by looking back into the past but by bringing the past into the present[47]. Gestalt therapy emphasizes that to alleviate unresolved anger, pain, anxiety, resentment, and other negative feelings; these emotions cannot just be discussed but must be actively expressed in the present time. If that does not happen, both psychological and physical symptoms can arise. By building self-awareness, gestalt therapy helps clients had better understand themselves and how the choices they make affect their health and their relationships. With this self-knowledge, clients begin to understand how their emotional and physical selves are connected and develop more self-confidence to start living a fuller life and more effectively deal with problems[48].

Results

The average number of attacks in the year prior to patient evaluation date was 21.83±18.5; the number of attacks during the previous month was 2.2±2.3 and the average of HAE attacks in the previous week were 0.62±0.74.

Average cortisol value is 409.6±140.99 (250-550 nmol/l), 21% of subjects had higher levels than normal, 26.1% of subject showed values of IL-6 (1.83±3.9) greater than normal and 39.1% of subjects showed TNFα values (10.2±27.5) higher than normal.

In this sample, 52,2% of patients had at least one anamnestic episode of laryngeal edema, which was reported as an event associated with increased subjective perception of death or increased risk of death. The 56,5% of patients reported the presence of important prodromal symptoms belonging to the psychic sphere and 78,3% reported the presence of "life events" prior to acute attack, considered by patients as prodromal syndromes; 65,2% of patients had a history of psychiatric disorders belonging to the anxious-depressive sphere.

The results from HAM-D and HAM-A tests showed that a total of 52,2% of patients were identified as experiencing mild depression (HAM-D > , 7,52±6,17) and the 17,4% severe anxiety (HAM-A > 17, 9,91±). The results of Coping Orientation to Problems Experienced test (COPE >17, 21,83±5,35) showed pathological results in 82,6% of patients. Also, the Mesure du Stress Psychologique test underline that 17,4% of patients showed pathological results (MSP>56, 47,23±8,21).

Data	Average ± Std. Deviation
Number of patients	48
Age	40,25 ± 15,98
Age first HAE attack	14,61 ± 12,46
Number of attacks in the last 365 days	21,83 ± 18,05
Number of attacks in the last 30 days	2,2 ± 2,3
Number of attacks in the last 7 days	0,62 ± 0,74
IL-6	1,83 ± 3,9 >3,4
TNF-α	10,2 ± 27,5 >8,1
Heart rate	75,62 ± 14,998
BMI	25,276 ± 4,13
Cortisol	409,6 ±140,99 >550
HAM-D (Depression)	7,52± 6,17 >8
HAM-A (Anxiety)	9,91 ± 7,94 >17
COPE (Coping Orientation to problems Experiences)	21,83 ± 5,53 >18
MSP (Perception of severity of the disease (0= absent; 10 severe)	5,71 ± 2,610

Table 1. *Result.*

The number of attacks in the last year (variable chosen for the objective assessment of the clinical severity of the disease) is positively correlated with high levels of TNFα. Subjects who have had a recent acute attack show higher levels of TNFα and IL-6. Elevated levels of IL-6 positively correlate with elevated depression, anxiety and subjective perception of disease severity and negatively correlate to number of days the last attack. High levels of TNF-α correlate with greater number of acute attacks.

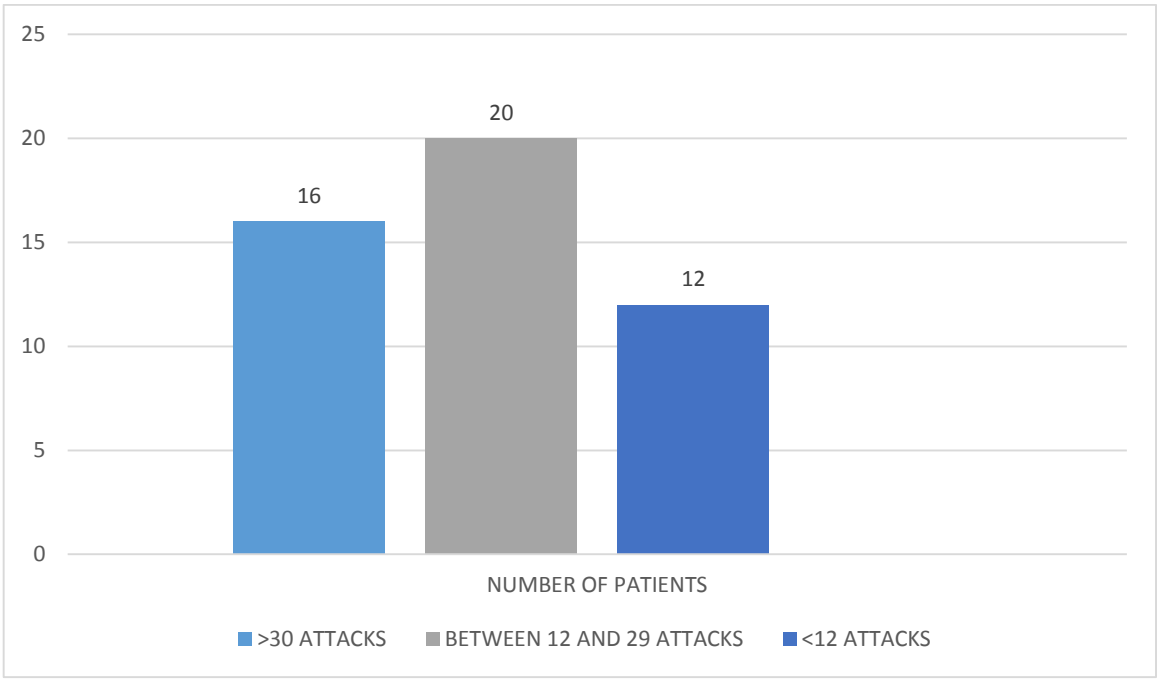

Table 2. *Division of patients by number of acute attacks in the last year*

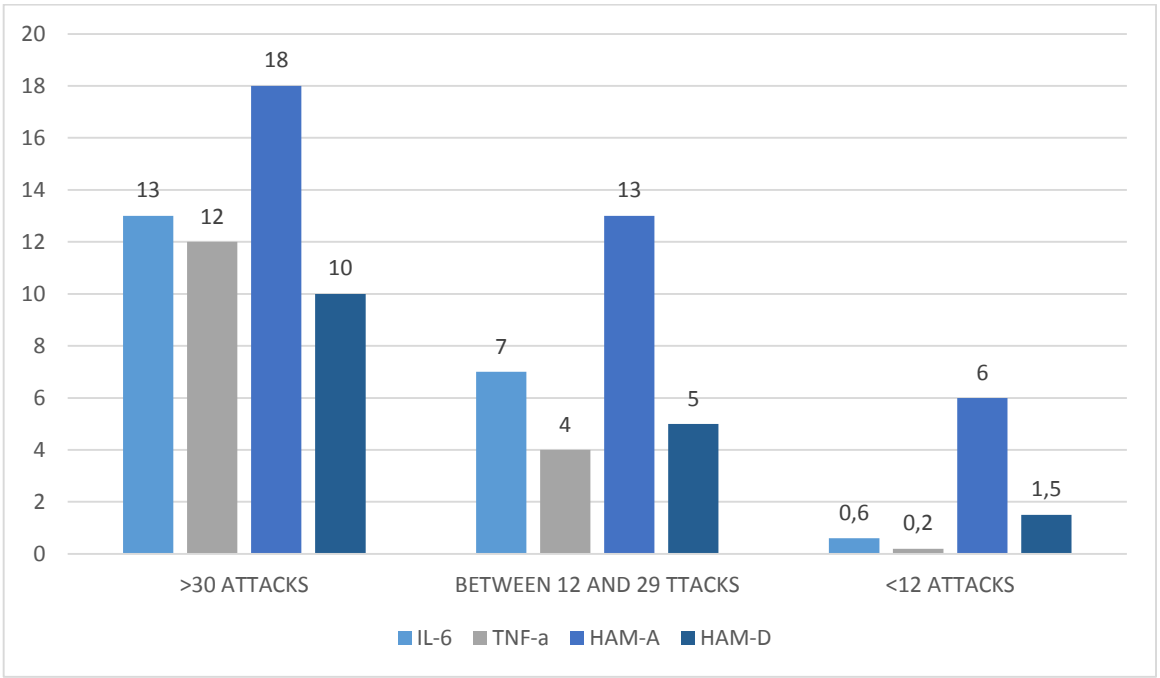

Table 3. *Correlation between number of acute attacks in the last year and levels of proinflammatory cytokines, anxiety and depression.*

A first follow-up after six months of psychological support, showed an improvement on the emotional and relational side with reintegration into social activities by patients (COPE 17,464 ± 4,24; HAM-A 6,937 ± 5,598; HAM-D 17,464 ± 4,24 and MSP 4,99 ± 2,088). HAE Attacks decreased by about 30% (7,637 ± 6,317), IL-6 (1,28 ± 2,73), TNF-α (8,16 ± 2,01) and Cortisol (327,2 ±112,79) decreased to between 20%-30%.

Data	Average ± Std. Deviation	1° follow-up after 6 month (Jun 2017)
Number of patients	48	48
Age	40,25 ± 15,98	40,25 ± 15,98
Age first HAE attack	14,61 ± 12,46	14,61 ± 12,46
Number of attacks in the last 365 days	21,83 ± 18,05	7,637 ± 6,317 ↓
Number of attacks in the last 30 days	2,2 ± 2,3	1,54 ± 1,61 ↓
Number of attacks in the last 7 days	0,62 ± 0,740	-
IL-6	1,83 ± 3,9 >3,4	1,28 ± 2,73 ↓
TNF-α	10,2 ± 2,75 >8,1	8,16 ± 2,01 ↓
Heart rate	75,62 ± 14,998	-
BMI	25,276 ± 4,13	-
Cortisol	409,6 ±140,99 >550	327,2 ±112,79 ↓
HAM-D (Depression)	7,52± 6,17 >8	5,264± 4,13 ↓
HAM-A (Anxiety)	9,91 ± 7,94 >18	6,937 ± 5,598 ↓
COPE (Coping Orientation to problems Experiences)	21,83 ± 5,53 >17	17,464 ± 4,24 ↓

Table 4. *First follow-up after six months of psychological support.*

Since September 2017 (T0), we also wanted to check the improvement on the emotional and relational side with reintegration into social activities of the patients by the SF-36 questionnaire after psychological support. Subsequently we established a second follow-up in March 2018 (T1) and a third in September 2018 (T2).

The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile including, for the physical status, physical functioning (PF), role physical (RP), bodily pain (BP), and general health (GH) while for the mental status it value vitality (VT), social functioning (SF), role emotional (RE), mental health (MH).

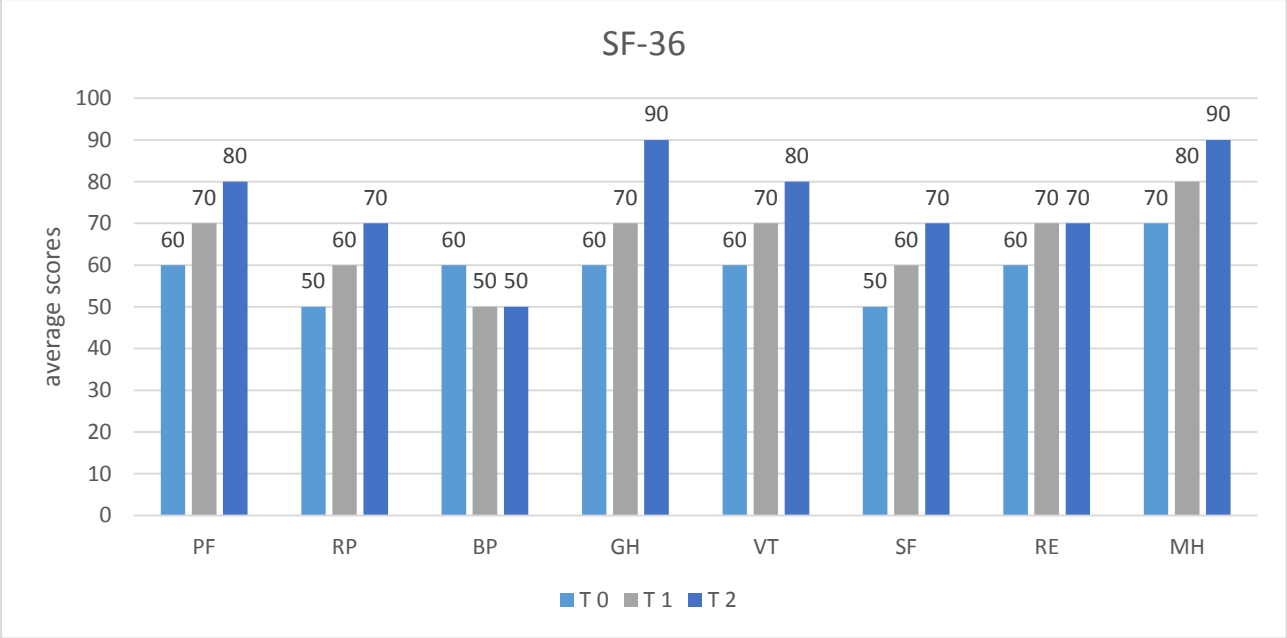

Table 5. Results from the SF-36 after 1 year of psychological support. T0 Sept 2017, T1 March 2018, T2 Sept 2018.

Data obtained by SF-36, after 1 year, seems to demonstrate a better general and mental health, vitality, social functioning and emotional status. In the other hand, we can find a less bodily pain perception that helps patient in physical functioning.

As a final point, in June 2019, we used for all patients a battery of psychological tests, the same as those we used at the beginning of the study (MSP, COPE, HAM-A, HAM-D), and we evaluated at the same time, the results from the serum of IL-6, TNF-alpha, cortisol.

Data	Average ± Std. Deviation	1° follow-up after 6 month (Jun 2017)	Endpoint Jun 2019
Number of patients	48	48	48
Age	40,25 ± 15,98	40,25 ± 15,98	40,25 ± 15,98
Age first HAE attack	14,61 ± 12,46	14,61 ± 12,46	14,61 ± 12,46
Number of attacks in the last 365 days	21,83 ± 18,05	7,637 ± 6,317 ↓	15,71 ± 12,99 ↓↓
Number of attacks in the last 30 days	2,2 ± 2,3	1,54 ± 1,61 ↓	1,48 ± 1,55 ↓
Number of attacks in the last 7 days	0,62 ± 0,74	-	0,43 ± 0.51 ↓
IL-6	1,83 ± 3,9 >3,4	1,28 ± 2,73 ↓	1,30 ± 2,65 ↓
TNF-α	10,2 ± 2,75 >8,1	8,16 ± 2,01 ↓	8,21 ± 1,99 ↓
Heart rate	75,62 ± 14,998	-	-
BMI	25,276 ± 4,13	-	-
Cortisol	409,6 ±140,99 >550	327,2 ±112,79 ↓	325,7 ± 111,80 ↓
HAM-D (Depression)	7,52± 6,17 >8	5,264± 4,13 ↓	5,04 ± 2,89 ↓
HAM-A (Anxiety)	9,91 ± 7,94 >18	6,937 ± 5,598 ↓	6,41 ± 4,76 ↓
COPE (Coping Orientation to problems Experiences)	21,83 ± 5,53 >17	17,464± 4,24 ↓	16,56 ± 3,57 ↓
MSP (Perception of severity of the disease (0= absent; 10 severe)	5,71 ± 2,610	4,99 ± 2,088 ↓	4,36 ± 2,001 ↓

Table 6. *Results of the study.*

Results of the study showed that after more than 1 year of psychological support, patients maintained an improvement on the emotional and relational side, the complete reintegration into social activities and an improvement on the emotional and relational (COPE 16,56 ± 3,57; HAM-A 6,41 ± 4,76; HAM-D 5,04 ± 2,89). Also, the perception of severity of the disease is less than the beginning of the study (MSP 4,36 ± 2,001). Results from the serum suggest that also cytokines

levels are better than the first evaluation (IL-6 1,30 ± 2,65; TNF-α 8,21 ± 1,99; Cortisol 5,04 ± 2,89).

Conclusion

Confirming our hypothesis, the study data show that high levels of anxiety and depression are conditions who can predispose to acute attack[44]. In fact, about possible link between stress and cytokines cascade[37-40-41], subject with higher disease severity (described by the number of attacks per year) show higher levels of TNFα and IL-6. Subjects with high level of anxiety, depression and subjective perception of disease severity also show elevated IL-6 and TNF-α plasma levels.

Certainly, our sample is very small because HAE is a rare disease, but the number of patients observed in our study could be significant. In our opinion, it is possible to establish two important points. First, reducing anxiety and depression levels, maybe it is possible to reduce the number of acute attacks, when patients can manage the stress and their emotions. Second, it is possible to help patient manage and control better the attacks of lesser severity, thus, to improve their quality of life.

Although our study seems to demonstrate fewer HAE attacks after psychological support, to confirm that, we need more time to observe behavioral aspect and a larger sample. Against this, we believe that our study shows how psychological support improved the quality of life of our patients and reinforced the resilience in order to manage an HAE attack. From this point of view, fewer attacks could coincide with a better evaluation of HAE's symptoms, in such way that mild edema goes unnoticed.

This study supports the idea that there is a reciprocal influence between HAE and psychological status, probably caused by higher expression of B1R induced by cytokines, such as TNF-α, induced by stress disorders themselves.

This premise further reinforces the age-old concept that holistic approach of the patients' pathology combines "psyche and soma" in reciprocal influence. Future studies may enroll a larger number of subjects, consider blood levels of other proinflammatory cytokines, how they change during the acute attacks on the base of psychological status and levels of anxiety and depression, and how their reduction improve patients' quality of life.

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4. GENERAL DISCUSSION.

In the first part of the study, our data showed that the social effects of HAE had a larger impact on patient quality of life than their physical condition[30]. In fact, in our work we found that a total of 52,2% of patients was experiencing mild depression and the 17,4% severe anxiety according to the highly comparable and valid Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale. The results of Coping Orientation to Problems Experienced showed pathological results in 82,6% of patients. Also, the test Mesure du Stress Psychologique underline that 17,4% of patients showed pathological results. In the other hand, a total of 52% of patients present pathological attachment styles (ASQ). Patients that experienced more HAE attacks during the last years, before the evaluation, showed high levels of anxiety and depressive symptoms. It could suggest that patients, which are less resilient to life stressor, are more exposed to HAE attacks during a week, month or year. This data was already observed during the first patient's interviews, at the enrollment phase. Patients often became anxious when they had to tell their medical history. Moreover, they also reported having a panic attack before or after an HAE attack at least once in their life. Obviously, this does not allow us to know, in a statistical way, if the panic attack is a cause or a consequence of a HAE attack.

In the second part of the study, the intend was to explore the connection between inflammation, stress, emotional status[20] and variability of the attacks, and to identify possible etiopathogenetic joints to evaluate the possible interrelations between anxiety, depression, intensity and frequency of angioedema attacks in order to better rationalize the specific therapy. This because the emotional stress, as trigger of the acute episodes, can explain the variety of expressions of the disease among the population and during the individual lifetime[16-19-29].

At the same time, a psychological support course was carried out through fifteen-day meetings aimed at containment of anxiety, understanding and management emotions, reduce the severity of perceived illness, and improve coping strategies.

The Psychologist used a Gestalt Therapy approach[45] for all patients. It is a client-centered approach to psychotherapy that helps clients focus on the present and understand what is really happening in their lives right now, rather than what they may perceive to be happening based on experience. Instead of simply talking about past situations (in this case the therapist focused on traumatic HAE history), clients are encouraged to experience them, perhaps through re-enactment[46]. Through the gestalt process, clients learn to become more aware of how their own negative thought patterns and behaviors are blocking true self-awareness and making them unhappy. In simple terms, a gestalt therapist focuses on what is happening in the moment and finding solutions in the present time[47].

Results from this second part of the study showed that the average number of attacks in the year prior to patient evaluation date was 21.83±18.5; the number of attacks during the previous month was 2.2±2.3 and the average of HAE attacks in the previous week were 0.62±0.74.

Average cortisol value is 409.6±140.99 (250-550 nmol/l), 21% of subjects had higher levels than normal, 26.1% of subject showed values of IL-6 (1.83±3.9) greater than normal and 39.1% of subjects showed TNFα values (10.2±27.5) higher than normal.

In our sample, 52,2% of patients had at least one anamnestic episode of laryngeal edema, which was reported as an event associated with increased subjective perception of death or increased risk of death. The 56,5% of patients reported the presence of important prodromal symptoms belonging to the psychic sphere and 78,3% reported the presence of "life events" prior to acute attack, considered by patients as prodromal syndromes; 65,2% of patients had a history of psychiatric disorders belonging to the anxious-depressive sphere. The number of attacks in the last year (variable chosen for the objective assessment of the clinical severity of the disease) was positively correlated with high levels of TNFα. Subjects who have had a recent acute attack show higher levels of TNFα and IL-6. Elevated levels of IL-6 positively correlate with elevated depression, anxiety and subjective perception of disease severity and negatively correlate to number of days the last attack. High levels of TNF-α correlate with greater number of acute attacks.

A first follow-up after six months of psychological support, showed an improvement on the emotional and relational side with reintegration into social activities by patients (COPE 17,464 ± 4,24; HAM-A 6,937 ± 5,598; HAM-D 17,464 ± 4,24 and MSP 4,99 ± 2,088). HAE Attacks decreased by about 30% (7,637 ± 6,317), IL-6 (1,28 ± 2,73), TNF-α (8,16 ± 2,01) and Cortisol (327,2 ±112,79) decreased to between 20%-30%. Also quality of life results, obtained by SF-36, after 1 year, seems to demonstrate a better general and mental health, vitality, social functioning and

emotional status. In the other hand, we can find a less bodily pain perception that helps patient in physical functioning.

As a final point, in June 2019, we used for all patients a battery of psychological tests, the same as those we used at the beginning of the study (MSP, COPE, HAM-A, HAM-D), and we evaluated at the same time, the results from the serum of IL-6, TNF-alpha, cortisol.

The latest results of the study showed that after more than 1 year of psychological support, patients maintained an improvement on the emotional and relational side, the complete reintegration into social activities and an improvement on the emotional and relational (COPE 16,56 ± 3,57; HAM-A 6,41 ± 4,76; HAM-D 5,04 ± 2,89). Also, the perception of severity of the disease is less than the beginning of the study (MSP 4,36 ± 2,001). Results from the serum suggest that also cytokines levels are better than the first evaluation (IL-6 1,30 ± 2,65; TNF-α 8,21 ± 1,99; Cortisol 5,04 ± 2,89).

Confirming our hypothesis, the study data show that high levels of anxiety and depression are conditions who can predispose to acute attack.

Certainly, our sample is very small because HAE is a rare disease, but the number of patients observed in our study could be significant. In our opinion, it is possible to establish two important points. First, reducing anxiety and depression levels, maybe it is possible to reduce the number of acute attacks, when patients can manage the stress and their emotions. Second, it is possible to help patient manage and control better the attacks of lesser severity, thus, to improve their quality of life. Although our study seems to demonstrate fewer HAE attacks after psychological support, to confirm that, we need more time to observe behavioral aspect and a larger sample. Against this, we believe that our study shows how psychological support improved the quality of life of our patients and reinforced the resilience in order to manage an HAE attack. From this point of view, fewer attacks could coincide with a better evaluation of HAE's symptoms, in such way that mild edema goes unnoticed. This study supports the idea that there is a reciprocal influence between HAE and psychological status, probably caused by higher expression of B1R induced by cytokines, such as TNF-α, induced by stress disorders themselves.

This premise further reinforces the age-old concept that holistic approach of the patients' pathology combines "psyche and soma" in reciprocal influence.

5. CONCLUSIONS

"*Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no to individuals react alike and behave alike under the abnormal conditions which we know as disease."*

William Osler, On the Educational Value of the Medical Society (1903).

Sir William Osler concluded his article in 1888[4] urging the scientific community to investigate and understand the causes of hereditary angioedema, hoping that someday, better treatments would be discovered than those he himself could offer at the time. Perhaps he would be stunned by the numerous data, models, hypotheses and therapies we have available today; for sure he would be pleased. However, our understanding of HAE is still undermined by several unknowns, including the disconnect between genotype-phenotype that puzzles the researchers of the SERPING1 gene. It is from this perplexity that this thesis starts, and it is the clinical experience that informs the content. What may be missed by biochemical, genetic analyzes, becomes evident for the doctor who follows HAE subjects for a long time: the psyche has an important role on the disease. The present work is not able to confirm if this thought is true for all patients, or only quantify the effective importance of this consideration; rather the real purpose is to offer new insights on aspects of the pathogenesis that are still unknown.

Psychological factors such as stress, or depressive symptoms, have important effects on inflammation, coagulation, and on numerous other organism system[12-15-20], and it is not absurd to believe that any of these effects could significantly influence the clinical expression of HAE. In my PhD program in Neurosciences, I wanted to investigate a known biological correlation of stress: the inflammation. Our data, significant though presenting the limits due to the size of the sample, support the hypothesis that there is a reciprocal influence between HAE and psychological status. Future studies may enroll a larger number of subjects, consider blood levels of other proinflammatory cytokines, how they change during the acute attacks on the base of psychological status and levels of anxiety and depression, and how their reduction improve patients' quality of life.

6. GENERAL LIST OF REFERENCES

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