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Psychological Correlates in Subjects with Hereditary Angioedema (HAE)

Marilisa Salemi[1], Francesca Di Bella[2], Antonino Miragliotta[2], Roberto Perricone[3], Maria Domenica Guarino[3], Marco Cicardi[4], Andrea Zanichelli[4], Valentina Selvaggio[5], Francesco Arcoleo[1] and Enrico Cillari[1*]

[1]*Department of Clinical Pathology V.Cervello Hospital, Azienda Ospedaliera Villa Sofia-Cervello, Palermo, Italy*
[2]*Faculty of Education, Master of Science in Psychology, University of Palermo, Palermo, Italy*
[3]*Unit of Rheumatology, Allergology, and Clinical Immunology, University of Rome Tor Vergata, Rome, Italy*
[4]*Department of Biological and Clinical Sciences Luigi Sacco, Luigi Sacco Hospital, University of Milan, Milano, Italy*
[5]*Tempor Agency, Genova, Italy*

Abstract

Objectives: Hereditary Angioedema (HAE) is a rare serious medical condition caused by a deficiency of C1-inhibitor, due to mutations in its structural gene. The disease appears clinically as cutaneous swelling of the extremities, face, genitals, and trunk, painful swelling of the gastrointestinal mucosa and life threatening laryngeal edema. In this study we evaluated in HAE patients and in the relative controls the psychological status and gender differences to verify if there is a link between disease and mental status.

Methods: We studied "psychological stress", using the Cognitive Behavioural Assessment 2.0 (CBA-2.0), in a total of 70 patients with confirmed HAE from different Italian Hospitals (41 women, 29 men; aged 17 to 78).

Results: The analysis of the majority factors of CBA-2.0 tests indicates a clear difference between male and female patients; in fact, women perceive more intensively than men the different signs of the disease (have more consciousness of the consequences that this illness provokes in their life).

Conclusion: Our data indicate that HAE is associated with emotional factors that can also complicate the clinical status of patients.

Keywords: Hereditary angioedema; Stress; Anxiety; Depression; Obsessions; Compulsions; Cognitive Behavioural Assessment 2.0 (CBA-2.0)

Introduction

Hereditary Angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare disease with an estimated prevalence of 1:50,000 in the general population. It is characterized by recurrent oedema of the subcutaneous and submucosal tissues. These symptoms are episodic with a high degree of variability, in frequency and severity, from patient to patient and within the same patient from time to time. Subcutaneous locations result in swelling of the extremities, face, and trunk. Mucosal edema develops in the gastrointestinal wall or in the mouth, pharynx and larynx. The first causes bowel sub occlusion, with severe pain vomiting and/or diarrhoea, the other dysphagia and respiratory distress up to asphyxia [1]. Laryngeal oedema can be lethal in 25-30% of HAE affected patients, in absence of correct diagnosis and/or treatment, and rare fatalities, less than 1%, (Cicardi's personal communication) are still registered also in patients properly diagnosed when the treatment is not promptly administered [2]. Non-fatal events affect the patients' quality of life at an extent that depends on the frequency and severity of recurrences. Thirty percent of HAE patients have more than one severe episode per month, which means nearly 100 days of illness per year. On the other side, 7% remain asymptomatic lifelong. The mechanisms governing these huge differences are unknown and C1-INH deficiency, the genetic defect characterizing HAE, does not per se explain the variable clinical phenotype of the disease. Angioedema attacks in HAE patients are characterized by activation of the systems controlled by C1-INH, i.e. contact, fibrinolytic, coagulation and complement that eventually leads to the release of bradykinin, the mediator of symptoms from High molecular weight Kininogen (HK) upon activation of the contact system, with the generation of activated factor XII (FXIIa) and plasma kallikrein from their precursor zymogens FXII and plasma prekallikrein [3-8]. Both histamine and bradykinin bound specific receptors on endothelial cells H1 and BK-R2 respectively, which activate the nitric oxide pathway and contract endothelial cell junctions eventually allowing plasma to flow from the intravascular to the extravascular compartment to form the interstitial edema.

Physical and psychological stress act on the inflammatory reaction through the Hypothalamic-Pituitary-Adrenocortical (HPA) and Sympathetic-Adrenalmedullary (SAM) axes increasing secretion of the hormones cortisol, epinephrine and norepinephrine [9]. Some of HAE patients recognize physical and psychological stress associated to their angioedema attacks and complement activation depending on psychological stress has recently been reported [10]. Following a still undefined biochemical pathway, it is likely that in patients with C1-INH deficiency the stimulation of the nervous system could eventually favour the release of bradykinin. On the other hand, chronic diseases tend to influence the psychological pattern of a subject that may in turn affect the clinical expression of the disease [11]. Therefore, we investigated psychological symptoms using the Cognitive Behavioural Assessment 2.0 (CBA-2.0) which employs scales (primary, secondary and tertiary) and questionnaires capable of detecting psychological problems of the patients [12].

***Corresponding author:** Enrico Cillari, Department of Clinical Pathology V. Cervello Hospital, Azienda Ospedaliera Villa Sofia-Cervello, Palermo, Italy, Tel: 0039 091 6802882; Fax: 0039 091 6885343; E-mail: enrico.cillari@tiscali.it

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Methods

Patients and controls

We evaluated a total of 70 patients with confirmed HAE types I and II (41 women, 29 men; aged 17 to 78). Patient characteristics are summarized in Table 1A. The patient group enlisted in this study consisted of subjects from different Italian Hospitals (26 patients from Milan, 11 from Rome, 33 from Palermo) and all enrolled patients agreed to participate to the study. Qualifications, job, status of patient group are shown in Table 1A. The control group consisted of 70 apparently healthy subjects (35 women and 35 men; aged 17 to 78) were mainly from the city of Palermo, because in the experimental group were not highlighted particular differences concerning the place of birth. Control subjects were mainlyfamily members of HAE patients and were randomly selected with the sole prerogative of fall in the age group considered and none of the individuals approached declined participation. There were no significant differences between the two groups regarding qualifications, job and status. The study protocol was approved by the Local Ethic Committees and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh, 2000). All patients and control group participants included in the study gave written informed consent according to the Statement on Human Experimentation by the National Health and Medical Research Council (NHMRC). Diagnosis was confirmed by the medical history and a finding of antigenic (type I HAE) or functional (type II HAE) amount of C1 esterase inhibitor of less than half of normal levels. In our laboratory, normal C1-INH plasma values range between 70% and 130% (2.5 and 97.5 percentile) of normal pool. For those symptomatic patients without evidence of C1-INH deficiency within the family, the genetic origin of the disease was confirmed by the evidence of C1-INH gene (SERPING1) mutation. Functional C1-INH was measured using a chromogenic assay (Technochrom C1-inhibitor, Technoclone GmbH, Vienna, Austria ; C1-INH antigen was measured by rate nephelometry using the IMMAGE Immunochemistry System (Beckman Coulter, Fullerton, CA) [1,8].

A		N°	%
1) Sex	Males	29	41
	Females	41	59
2) City	Milan	26	37
	Rome	11	16
	Palermo	33	47
3) Title of study	Primary school	10	14
	Junior high school	17	24
	High school	30	43
	University diploma	5	7
	University degree	8	12
4) Job	Employees	39	56
	Unemployed persons	5	7
	Students	5	7
	Housewives	9	13
	Other conditions	12	17
5) Marital status	Singles	17	24
	Married	45	64
	Widower	2	3
	Separated	5	7
	Divorced	1	2
B			
1) Mild psychological problems		38	54
2) Moderate psychological problems		16	23
3) Middle psychological problems		11	16
4) Severe psychological problems		2	3
5) High severe psychological problems		3	4
C			
1) Anxiety status		15	51
2) Depression status		9	29
3) Fears		1	3
4) Psychosomatic disturbs		5	17

Table 1: Demographic data and principal characteristic (A) and psychological problems (B) and type of psychological problems (C) of the study sample, 70 patients with confirmed HAE.

Methods

The instrument used in our study was the Cognitive Behavioural Assessment 2.0 (CBA-2.0) [12]. The CBA-2.0 Primary Scales is an automated assessment package investigating the cognitive-verbal response system. It consists of: (1) self-reports and questionnaires aimed at identifying and specifying the problems of the patients; (2) a group of programs and logical rules, implemented on personal computers, providing an editor with items, questionnaire scoring and an analysis of responses; (3) an intelligent program which analyses the responses emerging from the questionnaires and forms hypotheses for the selection of Secondary Scales and for further assessment. CBA-2.0 is a battery of tests over a wide spectrum, which is designed for multiple purposes as to provide a precise assessment of the problems that the subject complains, informing on the most appropriate for their in-depth understanding and collect evenly psychosocial history of the subject. Moreover CBA-2.0 gives a wide range of initial measurements, compared with which to evaluate the evolution of the case and the outcome of any treatment, providing measurements of some major psychological constructs such as state anxiety, depression, fears, obsessions, compulsions and the psycho-physiological disorders. Lastly, CBA 2.0 gives an assessment of some variables tract constituent's prognostic indices referring to the subject's risk of developing in the presence of certain environmental pressures, disorders and maladjustment, suggesting hypotheses concerning the functional relationships that can exist between problems, disorders and current events and any maladaptive present in the family and society and working life of the subject [13]. CBA-2.0 is part of a research project aimed at reducing part of the decision-making process to an operational language and simulating behavioural therapist's decisions in cases of clinical assessment [12].

Statistical analysis

Statistical analysis was performed using the chi-square test of independence and Students'- test to compare the means of two groups. P values less than 0.05 were considered significant. The correlation between item 4.41 and CBA 2.0 Primary Scales in the experimental group and between female and male subjects were calculated by Pearson and Spearman correlation coefficient [14].

Results

Demographic data and principal characteristics

In Table 1A are presented the demographic data and principal characteristics of our study sample (n=70). The study group was heterogeneous regarding sex, origin, title of study, job and status. All patients underwent clinical examination and biologic tests and completed CBA-2.0 self-reports and questionnaires aimed at identifying and specifying problems. Items regarding socio-demographic information are in form 1 of CBA-2.0 Primary Scales and consist of 25 items.

Psychological problems and type of psychological problems

Cognitive behavioural Assessment 2.0 includes an anamnestic schedule (Schedule 4) that consists of 59 items aimed to evaluate healthy conditions with specific emphasis on psychological problems that directly result from HAE [15]. These items bring to light the frequent presence of sleep disturbance, financial difficulties, dysfunctional eating behaviours, decrease in sexual activity and sexual dysfunction. Table 1B shows that the majority of patients with confirmed HAE present mild to moderate psychological problems. The 16% is affected by moderate psychological problems. Five subjects (7%) experience severe to highly severe psychological problems. The major psychological problems were depression and, especially, anxiety (51%). The 17% of patients showed psychosomatic disturbances. These data underline that HAE patients develop an anxious component resulting in daily social and psychological disadvantages.

Trait-anxiety and state-anxiety

Trait-anxiety is a relatively stable element of the personality of everyone. Subjects that have a severe trait-anxiety react abnormally to normal stimuli with higher probability to develop an anxiety disorder [16]. We used Schedule 2, 3 and 10 of CBA-2.0 Primary Scales to evaluate trait-anxiety and disorder. Schedule 2 (X-1 form of the State Anxiety Inventory [STAI-X1]) consists of 20 items that provide 4 answers (nothing, little, sufficient, high) to evaluate state-anxiety [17]. Schedule 3 (X-2 form of the trait-anxiety inventory [STAI-X2]) is made of 20 items that provide 4 answers (never, sometimes, frequently, always) to investigate trait-anxiety [17]. Schedule 10, a reduced form of X-1 State-Anxiety Inventory (STAI-X1R), consists of 10 items. In Table 2 is reported the prevalence of trait-anxiety and state-anxiety in the study sample and control group according to gender. With regard to state-anxiety scores, no significant differences were observed in the patients with confirmed HAE and in the control subjects (mean values: 47.7 and 42.3, respectively). Our results reveal an interesting aspect regarding STAI-X2. Trait-anxiety scores were statistically significantly higher in patients compared to control subjects (62.2 vs. 40.5, respectively, t=4.43 with p<0.0001). These data highlight the fact that patients with HAE present a higher trait-anxiety than control subjects. The analysis shows that there is a gender difference in the trait-anxiety and in the state-anxiety, thus, scores were significantly higher in female patients than in males (mean state-anxiety 53.6 vs. 39.5 ; t=-2.024; p<0.046), and the mean of trait-anxiety was 71.6 in women and 48.8 in men (t=-3.300; p<0.0015). This result is particularly relevant because it is strictly related to the disease status, indeed in the control groups there are not gender differences. The very important data is the gender connection, since males affected by HAE do not present any alteration of psychological assessment as healthy control.

Stress and psychological disturbances

The term "psychological disturbances" indicates various troubles rising from the interactions between "psychological factors" and "physical factors". To evaluate the psycho-physiological reactivity of a subject we used the Psycho-Physiological Questionnaire (QPF) in Schedule 6 [18]. QPF is composed of 60 items; in this study we used the reduced form (QPF-R) consisting of 30 items that provide 4 answers (never, sometime, frequently, always). Table 3 A shows that patients with HAE obtained a higher score (mean 62.8; t=4.848; p<0.0001) than control group (mean 38.5). This result reveals how the HAE patients perceive, with excessive care, to be suffering from an uncommon disease. Again, female patients have more psychological disturbs than male ones (mean 69, 5 vs. 53, 2;p<0.0181); this observation was not detectable comparing male and female control subjects.

State-anxiety	Mean	SD	t	p
1) Study sample	47.7	29.3	1.13	0.25
2) Control group	42.3	27.2		
1) Study sample				
a) Males (n=29)	39.5	26.3	-2.024	0.046
b) Females (n=41)	53.6	30.2		
2) Control group				
a) Males (n=35)	41.94	25.3	-0.11	0.90
b) Females (n=35)	42.71	29.3		
a) Males (n=64)				
1) Study sample (n=29)	39.5	26.3	-0.374	0.71
2) Control group (n=35)	41.94	25.3		
b) Females (n=76)				
1) Study sample (n=41)	53.6	30.2	1.59	0.12
2) Control group (n=35)	42.71	29.3		
Trait-anxiety				
1) Study sample	62.2	30.4	4.43	0.0001
2) Control group	40.5	27.1		
1) Study sample				
a) Males (n=29)	48.8	30.2	-3.3	0.0015
b) Females (n=41)	71.6	27.1		
2) Control group				
a) Males (n=35)	39.88	25.3	-0.2	0.84
b) Females (n=35)	41.2	29.3		
a) Males (n=64)				
1) Study sample (n=29)	48.8	30.2	-0.374	0.71
2) Control group (n=35)	39.88	25.3		
b) Females (n=76)				
1) Study sample (n=41)	71.6	27.1	4,788	<0.0001
2) Control group (n=35)	41.2	29.3ù		

Table 2: Mean and standard deviation (SD) of the state-anxiety and trait-anxiety in the study sample (n=70 patients with confirmed HAE) and in the control group (n=70) according to the gender.

A	Mean	SD	*t*	p
Study sample	62.8	28.7	4.848	0.0001
Control group	38.5	30.2		
Study sample				
Males (n=29)	53.2	29.6	-2.422	0.0181
Females (n=41)	69.5	30.2		
Control group				
Males (n=35)	34.5	31	-1.128	0.2633
Females (n=35)	42.6	29.3		
B				
Study sample	55.6	29.5	3.62	0.004
Control group	38.7	25.7		
Study sample				
Males (n=29)	41.5	28.1	3.72	0.0004
Females (n=41)	66.1	26.3		
Control group				
Males (n=35)	36.5	28.1	-0.693	0.4909
Females (n=35)	40.8	23.4		

Table 3: Mean and standard deviation (SD) of the psychological disturbs (A) and depression (B) in the study sample (n=70 patients with confirmed HAE) and in the control group (n=70) according to the gender.

Depression, obsessions and compulsions

Depression is a condition characterised by grieved and disheartened

spirits and by motory and psychic inhibition. Considering the high prevalence of depression detectable in subjects affected by disease compared with healthy ones we added a "depression scale", (Schedule 8) of 24 items that provide 2 answers (yes, no), to the CBA-2.0 Primary Scales to evaluate even mild depression problems. High scores onthis tabindicate the existence ofa depressive conditionnot necessarily to be treated. Table 3B reports the mean and SD in the HAE patients and in the control group. The analysis shows that the study sample had a higher statistically significant score (55.6) than control subjects (38.7) (t=3.62; p<0.0004). The analysis shows that there is again a gender difference in the depression manifestations only in the HAE patients, but not in healthy control subjects. Scores were significantly higher in female than in male subjects (66.1 vs. 41.5; t=-3.720; p<0.0004). To investigate obsession and compulsion symptoms we used the Mania, Obsession, Compulsion Questionnaire Revisited (MOCQ-R) that is the Italian version of the questionnaire evaluating these disturbs [19]. MOCQ-R represents the Schedule 9 in CBA-2.0 Primary Scales and consists of 21 items providing two answers (true, false). With regard to obsession and compulsion scores, no significant difference were observed between patients and control subjects (mean values: 53.4 and 43.9, respectively) (Table 4). A relevant difference between women select for this study and male was detected in the Maudsley Obsessive-Compulsive Questionnaire; in fact values scores were significantly higher in the female patients than in men (mean values: 60.1 versus 43.9; t=-2.289, p<0.0252) [20]. This difference was also observed between female and male healthy control subjects (mean values: 54.3 versus 33.6; t=-3.009, p<0.0037), indicating that women in the experimental group, apart from HAE, show more cares, unpleasant troubles and obsessive disturbs than men.

Score frequencies angioedema crises

Next, we established a disease score to evaluate if the angioedema crises were associate directly to anxiety and depression. As shown in Table 5, patients were divided into four groups on the basis of the number of angioedema crises and their frequencies were compared with CBA 2.0 Primary Scales both in the total experimental group, comparing female and male patients using a Pearson test. Data indicate that female patients with a higher number of crises presented significant correlation with state-anxiety (p<0.02) and stress (QPF) (p<0.002) (Table 6). Hence, patients with more crises develop state-anxiety and susceptibility to stress. The Spearman correlation coefficient between item 4.41 and CBA 2.0 Primary scales indicates that female subjects have a significantly higher frequency of angioedema crises associated with stress (QPF) (p<0.01) compared with male patients (Table 7).

Discussion

This study assessed psychological correlates using validated scales (CBA-2.0 Primary and Secondary Scales) in subjects with confirmed HAE. Our results provide scientific support to the prevailing view that emotional profile of HAE patients differs from that of healthy controls [21]. No wonder that people react emotionally and negatively to modifications of the health's state, that provoke embarrassment and social separation. For the patients, the illness not only has a biological reality but, above all, it presents a psychological and social burden, which is integral part of the morbid course and from which can depend the degree of acceptance and adaptation to it [11]. Almost all rare illnesses are also chronic and invalidating and the patients must cohabit with the symptoms and the difficulties of the illness for the whole life, often since the birth [22]. Thus, the subjects with hereditary angioedema develop higher anxiety, depression and sensitivity to the stress. This study showed that patients have a very strong ability to control the illness, even if their psychological load is felt heavy from the majority of the subjects. Indeed, the acceptance of a chronic disease to progress uncertainly and unpredictably not only causes modifications in the relationship with themselves and with the environment, but also in the lifestyle [23]. Within the experimental group, the analysis

	Mean	SD	*t*	p
Study sample	53.4	29.9	1.85	0.066
Control group	43.9	30.4		
Study sample				
Males (n=29)	43.9	29.8	-2.289	0.0252
Females (n=41)	60.1	28.6		
Control group				
Males (n=35)	33.6	32.5	-3.009	0.0037
Females (n=35)	54.3	24.5		

Table 4: Mean and standard deviation (SD) of obsessions and compulsions in male and females patients (n=70 patients with confirmed HAE) and in the control healthy subjects (n=70) according to the gender.

Episode frequency/year	N°	%
< 1	6	8.5
< 12	24	34.3
Dec-52	27	28.6
>52	13	18.6

Table 5: Episode frequencies of angioedema crises in the study sample (n=70 patients with confirmed HAE).

	Correlation	*P-Value*
State-anxiety	-0.267	0.0249
Trait-anxiety	-0.2	0.0975
E	-0.125	0.3033
N	-0.17	0.1598
P	0.024	0.8438
L	0.005	0.9694
QPF	-0.358	0.0022
IP/R	-0.13	0.2849
QD	-0.157	0.1936
MOCQ/R	-0.093	0.4431

E: Extroversion; N: Neuroticism; P: Psychotic; L: Lie; QPF: Psycho-Physiological Questionnaire; IP/R: Internet Pain/Revisited ; QD: Questionnaire Depression; MOCQ/R: Mania, Obsession, Compulsion Questionnaire/Revisited

Table 6: Correlation coefficient between item 4.41 (attack frequency of angioedema crises) and CBA-2.0 Primary Scales in the study group, 70 patients with confirmed HAE.

	Rho	*Z-Value*	*P-Value*
State-anxiety	-0.17	-1.412	0.158
Trait-anxiety	-0.157	-1.3	0.1935
E	-0.053	-0.444	0.6571
N	-0.115	-0.954	0.34
P	0.029	0.244	0.8076
L	0.116	0.967	0.3334
QPF	-0.307	-2.552	0.0107
IP/R	-0.037	-0.309	0.7572
QD	-0.118	-0.963	0.3356
MOCQ/R	-0.121	-1.005	0.3151

E: Extroversion; N: Neuroticism; P: Psychotic; L: Lie; QPF: Psycho-Physiological Questionnaire; IP/R: Internet Pain/Revisited ; QD: Questionnaire Depression ; MOCQ/R: Mania, Obsession, Compulsion Questionnaire/Revisited

Table 7: Spearman correlation coefficients between item 4.41 (attack frequency of angioedema crises) and CBA-2.0 Primary Scales in female compared with male patients (study sample n=70).

of the majority factors of CBA-2.0 tests indicates that female patients present more state-anxiety, trait-anxiety, depression and psychological disturbs (Tables 1-3) than male ones. These psychological problems appear strictly related to the disease carrying status, since these gender differences were not detectable in the control group. Gender differences were detectable also for obsessions and compulsions (Table 4). However, this psychological alterations were also seen in control group, indicating that the women selected for this study have more obsessive disturbs than men. The female susceptibility, in case of HAE, could be explained by the fact that women perceive more intensively than men the different signs of the disease. Therapy of hereditary angioedema not differ between male and female, but it is likely that women are more worried than men by side effects induced by prophylaxis with attenuated androgens (alterations of the menstrual cycle and irsutism) [24,25]. Furthermore, female patients have a lot of worries for their pregnancy, both for the fear that the disease and the possible crisis may be a risk factor for pregnancy. Besides, they are concerned about transmitting of this diseaseto their child, with consequent demonstration of a strong sense of guilt. Accordingly, it is interesting to highlight that we have detected during interviews that a relevant number of women in study have fear and unwillingness to procreate (data not shown). It is important to note that all subjects expressed great interest towards this study, because they are convinced that the psychological intervention is an important aspect in the disease treatment. The analysis of frequency score of angioedema crises indicates that the enhancing of the number of the crises, especially in the female group, causes an increase of the depression level. In conclusion, this study supports the idea that there is a reciprocal influence between HAE disease and psychological correlates providing evidence that HAE can modify the psychological status and the mental health of female patients.

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