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Hereditary angioedema: quality of life in Brazilian patients

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OBJECTIVE: Hereditary angioedema is a serious medical condition caused by a rare autosomal dominant genetic disorder and it is associated with deficient production or dysfunction of the C1 esterase inhibitor. In most cases, affected patients experience unexpected and recurrent crises of subcutaneous, gastrointestinal and laryngeal edema. The unpredictability, intensity and other factors associated with the disease impact the quality of life of hereditary angioedema patients. We evaluated the quality of life in Brazilian hereditary angioedema patients.

METHODS: Patients older than 15 years with any severity of hereditary angioedema and laboratory confirmation of C1 inhibitor deficiency were included. Two questionnaires were used: a clinical questionnaire and the SF-36 (a generic questionnaire). This protocol was approved by the Ethics Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

RESULTS: The SF-36 showed that 90.4% (mean) of all the patients had a score below 70 and 9.6% had scores equal to or higher than 70. The scores of the eight dimensions ranged from 51.03 to 75.95; vitality and social aspects were more affected than other arenas. The internal consistency of the evaluation was demonstrated by a Cronbach's alpha value above 0.7 in seven of the eight domains.

CONCLUSIONS: In this study, Brazilian patients demonstrated an impaired quality of life, as measured by the SF-36. The most affected domains were those related to vitality and social characteristics. The generic SF-36 questionnaire was relevant to the evaluation of quality of life; however, there is a need for more specific instruments for better evaluation.

KEYWORDS: Hereditary Angioedema; Quality of Life; Questionnaires; SF-36; Asphyxia.

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INTRODUCTION

Hereditary angioedema (HAE) is a serious medical condition caused by a rare autosomal dominant genetic disorder that is characterized by deficient production or dysfunction of the C1 esterase inhibitor. The C1 inhibitor acts as a regulatory protein in the complement, contact, coagulation and fibrinolytic systems (1). The prevalence of HAE is estimated to be between 1:10,000 and 1:50,000 (2).

Patients affected by HAE experience unexpected and recurrent ''attacks'' of bradykinin-mediated edema. Edema may occur in any part of the body but is most commonly observed in the face, extremities, genitals, gastrointestinal system and upper airways. Edema affecting the skin is typically painless but may cause disfigurement or difficulty driving or operating machinery. Gastrointestinal edema is very painful and can lead to unnecessary laparotomy, while upper airway edema can be life threatening due to swelling of the tongue and larynx (3).

Some patients are able to identify triggering factors, although in certain cases, no factors can be found. The most common triggering factors are emotional stress, local trauma, medical or dental procedures, infection, menses and oral contraceptives (4).

These attacks are unpredictable, intense and vary in terms of the site of edema. There is a potential risk of dying due to asphyxiation. The efficacy of long-term prophylactic treatment is inconsistent and it can cause side effects. All these factors decrease the quality of life of this patient population. However, few publications have described the quality of life in patients with hereditary angioedema and no specific questionnaire is currently available.

No potential conflict of interest was reported.

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The aim of the study was to evaluate the quality of life in Brazilian patients with angioedema.

METHODS

Ethical Aspects: The study protocol was approved by the Ethics Committee of the Clinics Hospital of the Faculty of Medicine of the University of São Paulo. All patients signed the informed consent form before any study procedures took place.

Patient Population: Patients older than 15 years with any severity of HAE and laboratory confirmation of C1 inhibitor deficiency were included.

Data Collection: Two questionnaires were used: a clinical questionnaire and the SF-36. The SF-36, a generic tool, was previously culturally adapted and validated in Brazil (5). The clinical questionnaire consisted of personal questions and information about the disease; patients were asked about their history of angioedema attacks in the previous six months, treatment, side effects of medication, influence on their social life, whether they had missed days of work or school due to attacks, visits to emergency rooms and psychological disturbances due to angioedema. A severity score was calculated according to the data considered by Agostoni et al. (3): adverse events from long-term therapy, the frequency of attacks, absence from school and/or work due to clinical symptoms, depression and anxiety, specific treatment and need for hospitalization and/or ICU. The SF-36 is a generic instrument that consists of 36 questions in eight domains, which are pooled into two domains: physical and mental.

The physical domain includes questions regarding the following items: physical function (10 questions related to routine activities), general health (five questions related to the patient's professional/educational life), pain (two questions) and physical aspects (four questions related to general well-being). The mental domain includes questions about mental health (five items), vitality (four items), social function (two items) and emotional well-being (three items). A question asking the patient to compare his/her current health to their health in the previous year is also included.

Statistical Analysis: The data were evaluated with Microsoft Excel 2007, SPSS 17 and Statistica 7.0. Endpoints were considered statistically significant at $p<0.05$. The SF-36 internal reliability was tested using Cronbach's alpha with a range of zero to one, with zero indicating the absence of correlation between items and one indicating perfect correlation. A Cronbach's alpha value equal to or greater than 0.7 was considered acceptable.

RESULTS

Thirty-five patients were included in the study. The majority of patients were female (25 = 71.4%), from an urban area (85.7%) and had an average level of education (42.9%) and a medium-low socio-economic level (57.1%). The mean age was 40.7 years (DP $\pm$ 16.6 years).

In 54% of the patients, the disease was well controlled, while 32% had mild symptoms and 14% had a moderate degree of symptoms.

The SF-36 showed that 90.4% (mean) of patients had a score below 70 and 9.6% had scores equal to or higher than 70. The scores of the eight dimensions applied in all patients varied from 51.03 to 75.95; vitality and social aspects were more affected. The internal consistency of the evaluation was demonstrated by a Cronbach's alpha above 0.7 in seven of the eight domains (Table 1).

There were no differences between the mean scores of the SF-36 in relation to gender, age, education level, or disease severity.

DISCUSSION

Although HAE is a rare disease, the patient burden is similar to other more common chronic diseases (6); the decrease in work productivity experienced by HAE patients is comparable with that experienced by patients with Crohn's disease or severe asthma. In addition, HAE patients must contend with the uncertainties of their disease. In our case, it should be considered that Brazil has yet to invest in the identification of these patients or access to therapy for the attacks.

Danazol, the only medication supported by the Brazilian government, is classified as a high-cost drug. Patients taking androgens have reported more depressive symptoms and reduced productivity levels compared to patients not taking androgens (6). Androgens are often prescribed to patients with higher attack frequencies and more severe disease profiles (2).

Only a few studies have evaluated quality of life (QOL) in HAE patients (6-8). In this study, Brazilian patients exhibited an impaired QOL, as measured by the SF-36, which is a generic questionnaire. The areas of their lives that were most affected were those related to vitality and social arenas. The patients felt tired, and their physical and emotional conditions impacted their social and professional

Table 1 - Descriptive analysis of the SF-36 domains in 35 hereditary angioedema patients and Cronbach's alpha values.

	N	Minimum	Maximum	Mean	Median	Standard deviation	Cronbach's alpha
Physical functioning	35	15.00	100.00	75.57	85.00	22.61	0.90
Lim. physical health	35	0.00	80.00	60.57	70.00	22.02	0.94
Body pain	35	0.00	100.00	58.10	52.00	30.15	0.90
General health perception	34	20.00	90.00	59.26	40.00	18.71	0.84
Vitality	34	15.00	65.00	51.03	60.00	12.42	0.78
Social functioning	35	25.00	87.50	54.29	50.00	13.87	0.66
Lim. emotional problems	35	0.00	100.00	75.95	83.30	25.14	0.90
Mental health	34	25.00	91.67	65.20	64.58	16.85	0.86

activities. Poon et al. measured and compared Dermatology Life Quality Index (DLQI) scores in different dermatological conditions and included five patients with HAE (7). Bygum et al. addressed the improvement in the QOL of seven HAE patients related to medication used to ameliorate the edema (8). Most recently, Lumry et al. (6) evaluated the impact of HAE on QOL, applying one disease-specific survey and three standardized instruments; approximately 19% of the patients invited by the US HAE Association (n = 457) responded to the questionnaires. Patients with HAE reported decreased physical and mental health compared to a normal population ($p<0.001$) for all subscales and overall summary components. According to our data, the social effects of HAE had a larger impact on patient QOL than their physical condition.

Several questionnaires have been developed to evaluate health-related quality of life. They provide information while evaluating or comparing the effects of clinical interventions or treatments, comparing differences between groups and evaluating the impact of side effects and potential problems demanding medical intervention. These questionnaires also help to decide resource allocation (9). The generic SF-36 questionnaire is important in the evaluation of quality of life in HAE patients; however, there is a need for studies using disease-specific surveys with specific instruments to serve as a point of comparison with generic questionnaires and evaluate the correlation with clinical severity (10). A specific HAE QOL questionnaire is currently being developed in Spain and will soon be translated and validated in other countries, including Brazil (11).

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AUTHOR CONTRIBUTIONS

Gomide MA and Grumach AS participated in the conception and design of the study, data acquisition, analysis and interpretation, and manuscript draft, revision and approval. Toledo E, Valle SO, Campos RA and França AT participated in the study design, data acquisition, analysis, and interpretation and manuscript draft, revision and final approval. Gomez NP and Caballero T participated in the conception of the study, data analysis and interpretation, and manuscript draft, revision and final approval. Andrade Jr HF participated in data analysis and interpretation, and manuscript draft, revision and final approval.

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