

Clinical profile and quality of life of Puerto Ricans with hereditary angioedema

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ABSTRACT

Background: There is limited data on clinical characteristics and quality of life (QoL) of Hereditary angioedema (HAE) patients in Puerto Rico.

Objective: Create an epidemiological and clinical profile of patients with HAE and assess the burden of this condition on the general health of Puerto Ricans suffering the disease.

Methods: A cross-sectional study was performed in 32 Puerto Rican patients with HAE. To obtain data on sociodemographic characteristics, clinical symptoms and treatment, a clinical survey based on a Spanish adaptation of the "HAEA Patient Summit Questionnaire 2015" was used. To measure QoL, the SF-36v2 questionnaire was used. IBM SPSS 22.0 (IBM, NY, USA) and QualityMetric Health Outcomes™ Scoring Software 4.5 was utilized for statistical analysis.

Results: The most common type of HAE was Type I (41.9%). In 1 year, 32.3% of patients present 2–3 attacks per month. The most common locations were: abdomen and face. Seventy-eight percent of patient developed laryngeal edema but only 6.5% needed tracheotomy. Fifty-eight percent of patients were using prophylaxis therapy; C1 esterase inhibitor (68.7%) being the most common. Eighty-one percent of patients were using rescue medication; Icatibant (80.8%) being the most common. Compared with US population norms of quality of life, patients with HAE in Puerto Rico reported significantly lower scores, both in the physical component (62%) and in the mental components (58%). The most affected parameters were emotional (38.52), physical (39.19) and social (39.79) components. Gender differences were observed in our sample; females scored below males in all components except for general health.

Conclusion: Puerto Rican Hispanics showed a similar epidemiologic and clinical profile to previous studies, however; higher frequency of attacks was prominent. Our study demonstrates a substantial and noteworthy decrease in quality of life in HAE patients and an increase risk for depression, particularly among woman.

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Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema without urticaria.¹ Most commonly affected areas include the extremities, face, genitalia, bowels, and larynx, beginning in childhood or adolescence and continuing throughout the patient's life. Laryngeal edema accounts for ~1% of all angioedema episodes; however, it occurs in ~50% of all patients over their life span. HAE affects men and women equally, with no racial preference. The most common forms of HAE are type I (HAE with deficient C1-inhibitor) (85%) and type II (HAE with dysfunctional

C1-inhibitor) (15%).^{2,3} HAE with normal C1-inhibitor is rare and is characterized by normal C1-inhibitor levels and function.

HAE attacks are unpredictable, frequently disabling, disfiguring, painful, and even potentially fatal.^{4–6} Factors found to affect patient's health-related quality of life (QoL) include the following: delay in diagnosis,^{1,7} pain, unnecessary medical procedures, treatment with ineffective drugs, decreased access to specific drug therapies, adverse effects of medication, and risk of death due to asphyxia.^{8,9} Puerto Ricans have an admixed population of white, indigenous, and African ancestral roots. HAE studies have focused mainly on white populations, and little has been published on Hispanic patients. The aim of this study was to configure an epidemiologic and clinical profile, assess the use of prophylactic and on-demand therapy, and evaluate the burden of disease and QoL among Puerto Rican patients with HAE.

METHODS

Study Population

A total of 32 patients were surveyed from 2015 to 2016 at two local association meetings of patients with

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HAE. The inclusion criteria were the following: self-reported HAE diagnosis, English or Spanish speaking, visual and auditory skills ample enough to complete assessment measures, and verbal consent to participate in the study. The exclusion criterion was patient or parental refusal to verbally consent to participate in the study. Subjects who met inclusion criteria were approached at two different local HAE meetings, and consent was obtained. For subjects ages < 21 years, parental verbal approval was required; after consent and approval, the parent completed the surveys. Eligible and consenting patients were asked to answer a clinical and QoL survey. The University of Puerto Rico Medical Science Campus Institutional Review Board approved this study.

Data Collection

The clinical and QoL surveys were conducted in Puerto Rico between November 2015 and April 2016. The clinical survey was based on a Spanish adaptation of the "HAEA Patient Summit Questionnaire 2015." The HAE questionnaire content was translated and revised by three experts and by 50 health professionals who certified the survey to be well understood and correctly translated. Clinical characteristics of the subjects were assessed in an anonymous clinical survey that consisted of 16 items, which included demographic information, clinical aspects of their attacks, and use of medications. QoL was assessed with the Short Form (SF) 36v2, a general survey that consists of 36 questions in eight domains (physical functioning, role - physical, bodily pain, general health, vitality, social functioning, role - emotional, and mental health) as well as one item about perceived change in health status.¹⁰ A score of zero correlates with a lower QoL, and a score of ≥ 70 correlates with a superior QoL. Results of QoL in the HAE population were compared with those of a normative (healthy) U.S. population. Data were collected and stored without identifying information by using only serial numbers, from 02–33, with the key on a separate computer to protect confidentiality.

Statistical Analysis

The case descriptions of the demographic, clinical, and treatment characteristics were performed by using frequency distributions for categorical variables. The statistical program IBM SPSS 22.0 (IBM, NY) was used for statistical analysis. To measure the burden of disease on the QoL, we used QualityMetric Health Outcomes Scoring Software 4.5 (QualityMetric Inc., RI). The basic scoring algorithm for this software consists of rules that define the numerical coding of responses to survey items (questions) and the formulas for combining item scores to produce scale scores. For the

Table 1 Sociodemographic characteristics of the study population

	Frequency, no. (%)
Gender	
Female	25 (83.3)
Male	5 (16.7)
Total	30 (100)
Age	
1–15 y	3 (9.4)
16–25 y	6 (18.8)
26–35 y	4 (12.5)
36–45 y	2 (6.3)
46–55 y	8 (25.0)
56–65 y	5 (15.6)
>65 y	4 (12.5)
Total	32 (100)
Education	
<12 y	6 (18.8)
>12 y	26 (81.3)
Total	32 (100)
Employment status	
Employed	10 (31.3)
Unemployed	10 (31.3)
Retired	8 (25.0)
Student	4 (12.5)
Total	32 (100)

SF-36v2 health survey, eight profile scales and two component summary measures are produced. The T score for this instrument in the U.S. general population has a mean $\pm$ standard deviation (SD) of 50 ± 10 . The model output statistics uses 2009 T scores. By using the T-score method, data can be assessed in relation to U.S. general population T scores. All scores that are <50 can be interpreted as being lower than the U.S. general population T score and scores >50 can be interpreted as higher than the U.S. general population T score. The SD for each scale is 10 (10 points = 1 SD).

RESULTS

Patient Sociodemographic Characteristics

Demographic characteristics of the patient population are provided in Table 1. Data were collected from 32 patients with HAE; there was a male-to-female ratio of 5:25 (two participants did not answer the gender question). The age distribution was as follows: 1–15 years, 9.4%; 16–25 years, 18.8%; 26–35 years, 12.5%; 36–45 years, 6.3%; 46–55 years, 25%; 56–65 years, 15.6%; and >65 years, 12.5%. The majority of the participants (81.3%) had >12 years of education. Only 10 patients (31.3%) were currently employed.

Table 2 Clinical characteristics of the study population

	Frequency, no. (%)
Type of angioedema	
Type I	13 (41.9)
Type II	4 (12.9)
Type III	3 (9.7)
Unknown	11 (35.5)
Total	31 (100)
Physician	
Allergist/immunologist	29 (93.5)
Specialist/subspecialist not allergist/immunologist	2 (6.5)
Total	31 (100)
Age of first attack	
Never	1 (3.3)
1–5 y	6 (20.0)
6–10 y	4 (13.3)
11–17 y	6 (20.0)
18–25 y	6 (20.0)
>25 y	7 (23.3)
Total	30 (100)
Frequency of attacks in the past year	
2–3/wk	5 (16.1)
1/wk	3 (9.7)
2–3/mo	10 (32.3)
1/mo	1 (3.2)
1 every 2–3 mo	2 (6.5)
Approximately every 6 mo	7 (22.6)
Do not remember last attack	2 (6.5)
Never had an attack	1 (3.2)
Total	31 (100)
Last attack	
Today or yesterday	7 (22.6)
2–7 days ago	7 (22.6)
1–4 wk ago	5 (16.1)
1–3 mo ago	4 (12.9)
3–12 mo ago	3 (9.7)
>1 y ago	4 (12.9)
Never had an attack	1 (3.2)
Total	31 (100)
Most common localization of angioedema	
Never had an attack	1 (3.1)
Only face	3 (9.4)
Only hands	1 (3.1)
Only abdomen	11 (34.4)
Only genitals	1 (3.1)

Table 2 Continued

	Frequency, no. (%)
Only larynx	2 (6.3)
Larynx and tongue	1 (3.1)
Abdomen and larynx	1 (3.1)
Face and feet	1 (3.1)
Hands and feet	1 (3.1)
Abdomen and feet	1 (3.1)
Face and larynx	1 (3.1)
Hands, feet, and abdomen	1 (3.1)
Hands, feet, abdomen, and larynx	1 (3.1)
Face, hands, feet, and abdomen	1 (3.1)
Face, hands, feet, abdomen, and genitals	1 (3.1)
Face, hands, feet, larynx, tongue, and genitals	1 (3.1)
Face, hands, feet, abdomen, larynx, and tongue	1 (3.1)
Face, hands, feet, abdomen, larynx, tongue, and genitals	1 (3.1)
Total	32 (100)
Laryngeal edema	
Yes	25 (78.1)
No	7 (21.9)
Total	32 (100)
Tracheotomy	
Yes	2 (6.5)
No	29 (93.5)
Total	31 (100)

Patient Clinical Characteristics

Clinical characteristics of the study population are presented in Table 2. The diagnosis of HAE was previously confirmed by a physician. HAE type I was reported in 13 patients (41.9%), type II in 4 patients (12.9%), and Hereditary angioedema with normal C1 inhibitor (nC1-INH-HAE) in 3 patients (9.7%). Eleven patients (35.5%) were not aware of their type of angioedema. Twenty-nine patients (93.5%) were being followed up by an allergist and immunologist. The mean frequency of attacks in the last year reported was 2.5 attacks per month (32.3%). When asked about their most recent attack, 14 patients (45.2%) reported their last attack to have occurred in the past 7 days. The most common locations of attacks were the face and abdomen. Most patients (78%) reported having at least one laryngeal attack; 6.5% required tracheostomy.

Table 3 Treatment use of the study population

	Frequency, no. (%)
Use of prophylaxis	
Yes	18 (58.1)
No	13 (41.9)
Total	31 (100)
Prophylaxis medication	
Cinryze	11 (68.7)
Danazol	3 (18.7)
Cinryze and danazol	1 (6.3)
Cinryze, berinert, and danazol	1 (6.3)
Total	16 (100)
Use of rescue treatment	
Yes	26 (81.3)
No	6 (18.8)
Total	32 (100)
Rescue medication	
Cinryze	1 (3.8)
Kalbitor	2 (7.7)
Firazyr	21 (80.8)
Kalbitor and Firazyr	1 (3.8)
Cinryze, Recunest, and Firazyr	1 (3.8)
Total	26 (100)

Treatment

The distribution of prophylactic and on-demand drugs, and the percentages calculated for the 32 patients are shown in Table 3. A total of 18 patients (58.1%) received prophylactic treatment. Intravenous infusion of C1-inhibitor was the most commonly used prophylactic treatment (11 patients [68.8%]). In the evaluation of on-demand therapy, 26 patients (81.3%) were treated with on-demand therapy. The most commonly used treatment was icatibant injection (21 [80.8%]).

QoL

The QoL survey was answered by 30 subjects. Compared with U.S. population norms of QoL, in Puerto Rico, patients with HAE reported significantly lower scores, both in the physical component and in the mental components. More than half of the patients scored lower than the general normative U.S. population in all elements of physical and mental components (Table 4). In Puerto Rico, the most affected parameters among patients with HAE were emotional (38.52), physical (39.19) and social (39.79) components (Fig. 1). Fifty-four percent of the subjects were at risk for depression compared with 18% in the general U.S. population (Table 5). Gender differences were observed in our sample; female subjects scored lower than the male subjects in all

components except for general health (Figs. 2 and 3; Tables 6 and 7). Significantly, depression scores were higher in the female subjects than in the male subjects (61% versus 20%) (Tables 8 and 9).

DISCUSSION

There are limited data on the HAE population in Puerto Rico. Our study was the first to evaluate QoL in Puerto Rican patients with HAE. A previous study, conducted by Santaella and Martino,¹¹ in 2004, evaluated 30 Puerto Rican patients with HAE, but QoL was not assessed. Our findings were in accordance with Santaella and Martino,¹¹ and with worldwide literature. Type I HAE was the most frequent type in the Puerto Rican population. Of note, a high percentage of patients (35.5%) did not know their type of HAE, despite the majority being treated by an allergist and immunologist. High female sampling was observed in our study, with a male-to-female ratio of 5:25, which was higher than the study by Santaella and Martino.¹¹ Female predominance could be due to gender differences in participation of health-related events or a reflection of disease severity. For age of onset, we demonstrated that a larger-than-anticipated number of patients reported their first symptoms after age 25 years, which differed from published data.⁵ Employment in our HAE population (31.3%) was significantly less than that in general. The employment rate in Puerto Rico averaged 39.02% from 1990 until 2018 and reached 44.70% in March of 2006, and a record low, of 33.50%, in September of 2014. Analysis of these data demonstrated reduced working opportunities for patients with HAE due to symptoms of the disease.

Several published studies reported similar locations of the attacks. Bork *et al.*,⁵ Iwamoto *et al.*,¹² and Bouillet *et al.*¹³ evaluated patients with HAE and describe common locations of attacks to include the abdomen, peripheral limbs, and the face. Comparable results were found in our study, in which the most common locations were the face and abdomen, followed by hands and the larynx. There are published data that approximately one half of the patients with HAE experienced a laryngeal attack; however, in our study, laryngeal edema was reported far more frequently. Twenty-five patients, 78.1% of our cohort, experienced upper-airway swelling, significantly higher compared with laryngeal episodes reported by Bork *et al.*,⁵ of 54%. Fortunately, tracheotomy was required in only two patients (6.25%).

A mean of two to three attacks per month was observed in our survey, which was higher than other studied populations. In a study performed in France, in a 12-month period, the mean number of HAE attacks was 7.6.¹³ In addition, the study performed in

Table 4 Scores for the general population in all components*

	Scores Lower Than the Normative U.S. Population, %	Scores at the Normative U.S. Population, %	Scores Higher Than the Normative U.S. Population, %
Physical functioning	61	21	18
Role - physical	70	22	7
Body pain	62	17	21
General health	52	26	22
Vitality	50	21	29
Social functioning	73	10	17
Role - emotional	62	17	21
Mental health	50	36	14
Physical component summary	62	29	8
Mental component summary	58	29	12

*The mean score of the normative U.S. population was 50.

Scores for Total Sample

Figure 1. The scores of the physical (light color) and mental (dark color) components for the total sample. PCS = Physical component summary; MCS = mental component summary; PF = physical functioning; RP = role - physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role - emotional; MH = mental health.

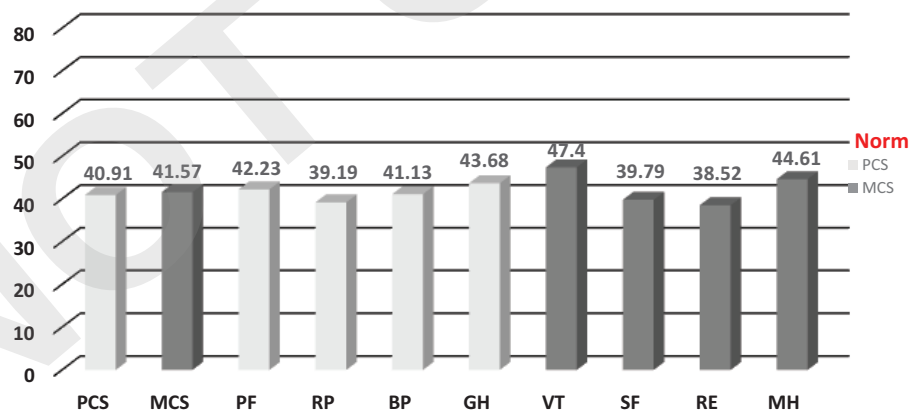


Table 5 Depression screening among the subjects

	Risk of Depression, %
Normative U.S. population	18
Report sample	54

Puerto Rico by Santaella and Martino,¹¹ the number of attacks during the time of maximum symptoms was reported as one per month in most of the participants. Zuraw and Christiansen¹⁴ affirmed that, in patients not on long-term prophylaxis, the average attack frequency is 7–14 days but can range from never to every 3 days.

In our surveyed population, more than half of our patients were currently using prophylaxis (58.1%). Despite the use of prophylaxis therapy, the patients still reported an excessive number of attacks. The high prevalence of laryngeal attacks (78% of pa-

tients) may be a reason for our high use of prophylaxis therapy. Intravenous C inhibitor (68.6%) was the most commonly used prophylactic treatment, followed by danazol (18.8%). Danazol has multiple adverse effects: hirsutism, menstrual irregularities, acne, hypertension, thromboembolism, among others. The high number of patients on androgens reflects the need to increase education and awareness of newer treatments with fewer adverse effects and better efficacy.

In terms of on-demand therapy, it was reassuring that most patients have on-demand therapy (81.3%). Our study demonstrated that icatibant was the most frequently used medication for on-demand therapy. Poor access to nursing services, subcutaneous administration, prefilled syringes, and temperature stability may account for the preference of icatibant. Another available on-demand therapy, ecallantide, requires administration by a health-care professional and may limit its utilization. At the time of the questionnaire, neither

Scores by Gender: Female

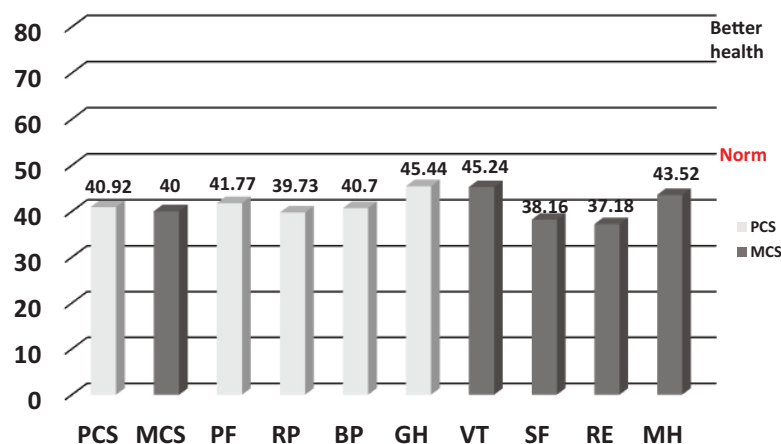


Figure 2. The scores of the physical (light color) and mental (dark color) components among the female subjects. PCS = Physical component summary; MCS = mental component summary; PF = physical functioning; RP = role - physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role - emotional; MH = mental health.

Scores by Gender: Male

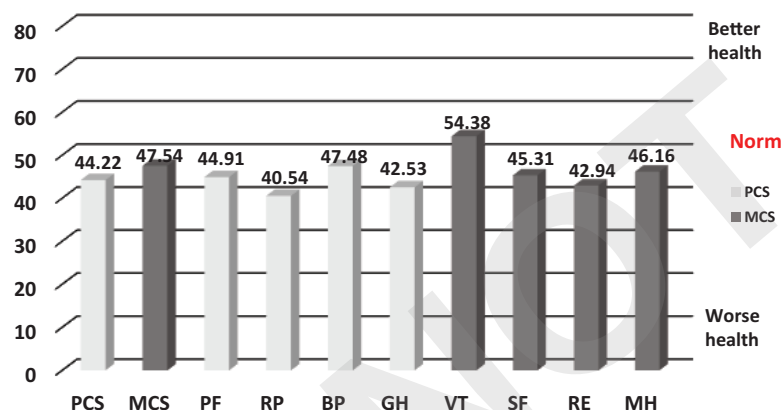


Figure 3. The scores of the physical (light color) and mental (dark color) components among the male subjects. PCS = Physical component summary; MCS = mental component summary; PF = physical functioning; RP = role - physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role - emotional; MH = mental health.

Table 6 Summary of physical and mental components among the male subjects

Component Summary	Scores Lower Than the Normative U.S. Population, %	Scores at the Normative U.S. Population, %	Scores Higher Than the Normative U.S. Population, %
Physical	40	0	60
Mental	40	40	20

recombinant C1-inhibitor nor human-derived plasma C1-inhibitor (CSL Behring; Marburg, Germany) were available in Puerto Rico. Patients who reported its use may have received the medications from the continental United States.

It is not unfamiliar nor surprising that HAE affects QoL in patients with HAE. In our study, we found significantly lower QoL scores, both in physical and mental health, in comparison with those of a normative U.S. healthy population for all elements. The scores in our population for all eight components ranged from 38.5 to 47.4; T-score-based scores in the U.S. general population were a mean of 50. Emotional, physical, and social components were the most frequently af-

fected, consistent with cited studies.^{15,16} The impact of HAE on QoL has also been demonstrated in other populations; however, our QoL scores were significantly lower. Gomide *et al.*¹⁵ showed a score of <70 in 90.4% of patients by using the SF-36. In Colombia, Sanchez *et al.*¹⁶ showed a high impact on psychological well-being of children and on the physical and emotional role of adult patients with HAE.

The risk for depression has also been found to be significantly increased in patients with HAE in concordance with our findings. We also found the risk for depression to be higher in female subjects. Fouché *et al.*¹⁷ support that depression and anxiety symptoms are common features in patients with

Table 7 Summary of physical and mental components among the female subjects

Component Summary	Scores Lower Than the Normative U.S. Population, %	Scores at the Normative U.S. Population, %	Scores Higher Than the Normative U.S. Population, %
Physical	67	22	11
Mental	61	28	11

Table 8 Depression screening among the male subjects

	Risk of Depression, %
Normative U.S. population	15
Report sample	20

Table 9 Depression screening among the female subjects

	Risk of Depression, %
Normative U.S. population	19
Report sample	61

HAE, reporting 39% of depression and 15% of significant anxiety. Similarly, Caballero *et al.*¹⁸ also found 38% and 14% of anxiety and depression, respectively, in their study.

One of the limitations of our study was the small number of patients, which may have limited the statistical analysis. The diagnosis and the type of HAE was self-reported, which could have led to errors in disease classification. As noted earlier, our large number of patients with nC1-INH-HAE was unexpected due to the rarity and the uncertainty surrounding this diagnosis. This limitation may have influenced our findings. In addition, we used the general survey SF-36v2 because, at the time of the study, a QoL survey specific for patients with HAE was not available. Currently, there is an HAE QoL survey for adult patients with C1-INH-HAE. Future studies in HAE QoL could be more precise by using this survey especially for the specific needs of the HAE population. Also, we compared QoL with a general population in United States because no standards are available for Puerto Rico. Cultural, economic, and health-related access issues may affect the subject's perception of well-being.

CONCLUSION

Limited information is available for the Puerto Rican population of patients with HAE. In recent years, new therapeutic alternatives have been introduced for patients with HAE, but, to our knowledge, there were no

published studies on medication use and attack frequency for patients in Puerto Rico until this study. One distinction was the high frequency of attacks despite a significant percentage of patients with prophylaxis therapy and the high percentage of patients who experience upper-airway symptoms. We also found that our patients had a significant burden of disease, with a reduction on the QoL. A positive finding was that most patients had on-demand therapy and were managed by a subspecialist in allergy and immunology. Efforts are needed to continue to assess the Puerto Rican population, increase disease awareness, decrease burden of disease for patients with HAE, and improve QoL of Puerto Rican patients with HAE. We are excited about new innovations in the disease and hope that the utilization of these therapies may improve the QoL of patients in Puerto Rico and return them to a state equal to the average American.

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