Hereditary Angioedema: An Updated Experience with Patients with Angioedema in Puerto Rico

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Objective: This was a study of patients with hereditary angioedema (HAE) and their responses to new therapies, measured in terms of HAE attack rates, the number of hospitalizations and emergency room (ER) visits, and the impact of HAE on their quality of life (QOL).

Methods: Patients that came at a private practice with recurrent angioedema without urticaria from 2013 through 2016. All HAE (types I & II) patients received rescue treatment and prophylaxis for those who had 2 or more attacks per month.

Results: Of 48 patients, 22 (45.8%) patients with HAE (I or II) were identified. 45.5% of those HAE patients were on prophylaxis and 77.3% were on rescue therapy. Treatment effects were reported as percentages of the HAE patients in each attack/month category: Before treatment, 41.2% of the patients had 0 to 1 attack; after treatment, 84.2%. Similarly, 23.5% had 2 to 3 attacks before treatment, fell to 17.6%, after treatment. Finally, 35.3% experienced more than 3 attacks prior to treatment; and none after treatment. The number of ER visits in 6 months decreased from 64 (3.8 per patient) to 7 (0.4 per patient), and hospitalizations in 6 months decreased from 35 (2.1 per patient) to 7 (0.4 per patient) after treatment. The diagnosis delay averaged 4.3 years; patients diagnosed on or before 2012 averaged 8.6 years; patients diagnosed after 2012 averaged 0.4 years.

Conclusion: HAE patients showed improved treatment responses as documented by decreased diagnostic delay, attack rates, ER visits and hospitalizations and improved QOL in treated patients. [*P R Health Sci J 2019;38:248-254*]

Key words: Hereditary Angioedema, Acquired Angioedema, C1 Inhibitor, Puerto Rico, Icatibant, Ecallantide

Type I and type II hereditary angioedema (HAE) are rare diseases caused by the autosomal dominant inheritance of mutations in the C1-INH gene (1,2). Clinical manifestations of HAE involve intermittent attacks of subcutaneous edema, commonly involving the respiratory and gastrointestinal systems (2). Involvement of the upper airways can result in severe life-threatening symptoms, including asphyxiation, unless the appropriate measures are taken. Skin and visceral systems may be involved by the typically massive local edema. There is a significant humanistic burden associated with HAE, particularly due to the heterogeneity and unpredictability of HAE attacks, making them difficult to characterize and manage effectively (3,4,5). Attacks can occur in the absence of an identifiable event. The severity, frequency, and location of HAE attacks vary greatly, both among and within patients, and are unrelated to the magnitude of C1-INH dysfunction. The ultimate goal of HAE treatment is to enable the patient to live a normal life by reducing the number of HAE attacks and improving safety and quality of life.

Over the past 5 years, there has been an increasing number of identified cases of HAE and acquired angioedema (AAE) in Puerto Rico (PR). This increase is linked to various factors: the recovery of previously diagnosed cases and identified families (6), augmented disease awareness (among patients and physicians), and improved access to diagnostic laboratory testing. Perhaps these are early signs of an undiagnosed increased prevalence of this condition on our island, where we could have inbreeding because of our geographic circumstances. This substantial increase in identified cases is worrisome for the allergists/immunologists around the island because of the phenomenally high cost of the newly available therapies. Also, of concern is the fact that the government has not included HAE on the list of primary immunodeficiency disorders, which means that it is not considered to be a catastrophic illness and

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so is not covered by the state insurance fund (7). It was in order to evaluate the real-world effectiveness of some of the newly approved therapies for this orphan condition that we did this observational exercise within our patient population.

The purpose of this prospective observational study of patients of an allergist's private practice in PR identified as having HAE was to assess their responses to therapy (before and after initiation) and evaluate the effectiveness of newly developed therapies, as measured by HAE attack rate, the number of hospitalizations and emergency room (ER) visits, and the impact of the disease on quality of life.

Patients and Methods

Subjects

Patients ranged in age from 3 to 79 years; all had recurrent angioedema without urticaria. From 2013 through 2016, the patients of an allergist in PR were, first, evaluated and, then, surveyed using a validated HAE assessment and Quality of Life (QOL) Questionnaire (8). The group consisted of all the consecutive patients who had been referred to the practice for the evaluation and further management of recurrent angioedema (the main diagnosis). The severity of the angioedema diagnosis varied depending on the location, degree of impairment associated with, length, and recurrence of symptoms and the individual patient's previous response to treatment with acute or rescue drug therapy. Most of the patients presented swelling of the lips, larynx, face, extremities, abdomen, and genitals during an attack, with or without acute or rescue treatment provided.

Study protocol

This was a prospective, observational cohort study of patients diagnosed with HAE I and II. The patients were enrolled in the study for 36 months. Comprehensive data from routine patient visits were entered by trained personnel into the electronic case report forms (eCRFs) via electronic data capture at baseline and at follow-up (every 6 months). Standardized patient-reported outcomes (PROs) before and after therapy initiation.

After the consent was acquired, every patient underwent a complete history, took the Angioedema Quality of Life Questionnaire, had a physical examination, and underwent complement testing, which included C4 levels, protein and functional C1-INH, and, in some patients, C1q (antigen and immune complexes binding) and IgE levels. Once the diagnosis of either condition was established, treatment with 30mg of subcutaneous icatibant (9) (a bradykinin B2 receptor antagonist), as needed, every 6 hours (up to 90mg in 24 hours) or 30mg of subcutaneous ecallantide (10) (a plasma kallikrein inhibitor), as needed, every 12 hours (up to 60mg in 24 hours) was always offered as rescue therapy, at the discretion of the physician. In addition, as prophylactic therapy, 1000 U of intravenous C1-INH (human) (11), every 3 to 4 days, was offered if the patient was enduring 2 or more attacks of angioedema per month or in the presence of a life-threatening attack (e.g. laryngeal angioedema) (13), regardless of the frequency, per standard practice of care. Subsequently, the subjects were informed that they should go to the nearest hospital if their prophylactic and rescue therapies were not sufficiently managing the HAE attacks, because such attacks could have lethal consequences if not controlled. Each patient's medical records were also reviewed for recurrent attacks of angioedema, previous diagnosis, treatment, laboratory results, and family background, in order to provide a complete understanding of the condition for the study.

Assessing Angioedema attack severity

The patients were asked to assess the severity of their most recent angioedema attack, taking into account location, impairment, length, and the need (or not) of rescue medications; using a validated visual analog scale (VAS) of 0 (least severe) to 10 (most severe), and to assess if they have observed a most common area of inflammation during the attacks by choosing "YES" or "NO." The list of possible most common areas included: extremities, abdomen, throat, face and lips, and genitals.

Primary endpoint

It was our goal to evaluate the real-world effectiveness of newly developed therapies by measuring each patient's rate of HAE attacks before and after therapy initiation.

In addition, the patients had to state their rate of HAE attacks per month by choosing 1 of the following 3 survey responses: "0 to 1 attack A MONTH," "2 to 3 attacks A MONTH," or "MORE THAN 3 attacks A MONTH."

Secondary endpoint

Secondarily, we wanted to describe healthcare resource utilization by patients suffering from HAE attacks before and after therapy initiation, including hospitalizations and ER visits.

Exploratory Endpoint

As an exploratory endpoint, all the angioedema types were evaluated based on their IgE levels.

Laboratory analysis

Blood for complement testing—including C4 levels, C1q antigen levels and immune complexes binding, C1, protein and functional C1-INH, and IgE levels—was required to determine and diagnose the proper type of HAE: HAE type I, HAE type II, HAE with NL C1-INH, AAE due to C1-INH deficiency, angiotensin-converting enzyme inhibitor–induced angioedema (ACEI-AAE), histaminergic acquired angioedema (H-AAE), or idiopathic non-histaminergic acquired angioedema (InH-AAE) (7). The blood tests were ordered by the primary physician of the study, and the blood analyses were conducted at the clinical laboratory of the patient's choosing.

Statistical analysis

This was a self-controlled study design. HAE patients before and after treatment initiation were enrolled in this prospective

observational study. The primary effectiveness endpoints were the attack rates before and after treatment initiation. A paired t-test and conditional Poisson regression were used to evaluate and compare the attack rates of the following observation periods: 1. prior to treatment initiation; 2. after treatment initiation; 3. after initiation in previously non-treated HAE patients. The data were collected on Excel spreadsheets, and a multivariable analysis was performed using Stat Suite and Learn Stat for single and cross-variables analysis. The variables were entered into the program, marked, described, and coded according to what the program requested. In total, 22 HAE out of 48 cases. Each variable was taken as the mean and the standard deviation of the mean. Secondary outcomes included HAE attack characteristics (e.g. location, frequency, and healthcare resource utilization) and PRO questionnaire responses. Covariates such as demographics and laboratory tests will be described, herein. Other covariates, such as attack severity, concomitant medications, and comorbidities, will not be described in this paper. Variable crosschecks were made only for variables of exploratory importance, such as the types of angioedema vs. IgE levels.

Trial oversights

To ensure the safety of all the patients in the study, all the researchers in the study had updated certifications for human research, good clinical practice, and health information privacy and security. All the data collected were compliant with the requirements of all 3 certifications and the Copernicus Group, an independent Institutional Review Board (IRB).

Safety

This study was purely observational, using expert panel guidelines for treatment, and all the patients with HAE were offered rescue, prophylactic, or both treatments (12). Safety and tolerability were monitored throughout the study, in addition to vital signs, physical status, and laboratory parameters. All the patients were provided with immediate personal care by the attending allergist and physicians, in addition to having access to a 24-hour ER with all the prophylactic and rescue treatments as might be needed.

Results

Patient characteristics

In the observational study, a total of 48 patients were surveyed to determine the interval from onset to diagnosis; the response to current HAE treatment—acute (rescue), prophylactic, or both—the impact of treatment on HAE attack rates; the number of ER visits, hospitalizations, or both; and the impact of the treatment on their lives and their satisfaction with it.

Forty-eight consecutives cases were evaluated for recurrent angioedema without urticaria over a period of 36 months; the ages of the participants ranged from 3 to 79 years, with a mean age of 40 years; 39 (81%) were females (Table 1). In the 48 cases, the interval from documented onset to diagnosis averaged 4.3 years; in cases prior to 2012 (23), the average interval from onset to diagnosis was 8.6 years; after 2012 (25), the average interval was 0.4 years (Fig. 1).

Table 1. Patient demographics and clinical characteristics

Average age in years: 40		
Age group, no. (%)	**No.**	**%**
<18 years	7	15
18 to 65 years	35	73
≥ 65 years	6	13
Female, no. (%)	39	81
HAE type, no. (%)	**No.**	**%**
Type I	18	37.5
Type II	4	8.3
Type III HAE with NL C1-INH	14	29.2
C1-INH AAE	1	2.1
ACEI-AAE	1	2.1
V-AAE (vasculitic)	3	6.3
H-AAE (histaminergic)	7	14.6
No. of attacks in 6 months before screening	291	
No. of attacks in 6 months after screening/meds	69	
	No.	**%**
No. of ER visits 6 months prior to screening	64	50
No. of ER visits 6 months after screening/meds	7	15
No. of Hosps. 6 months prior to screening	35	
No. of Hosps. 6 months after screening/meds	7	
Attack-rate category prior to medication, no. (%)	**%**	
0-1	41.2	
2–3	23.5	
>3	35.3	
Attack-rate category after medication, no. (%)	**%**	
0-1	82.4	
2–3	17.6	
>3	0	
Current HAE Tx	**%**	
Totally satisfied	12	
Mostly satisfied	76	
Somewhat satisfied	12	
Dissatisfied	0	

Values are mean ± SEM or n (%). Patient (48) demographics in the study alongside the responses of the QOL Questionnaire, which were essential to determine the treatments given. It describes the percentage (%) of the 48 patients in the study along with the number (no.) of patients in years (yrs.).

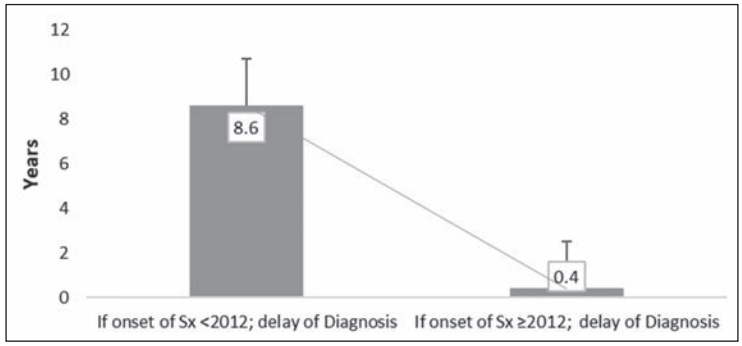
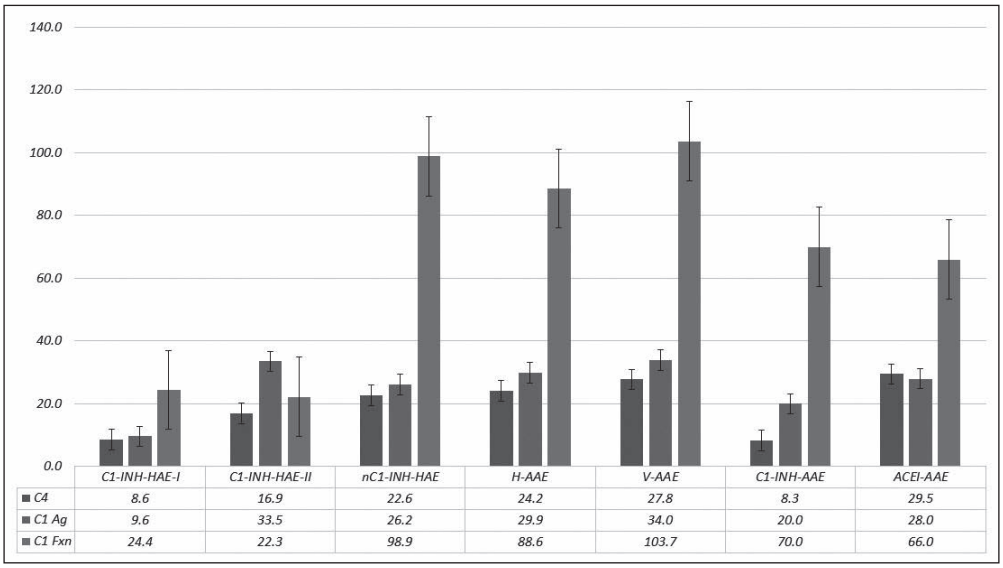


Figure 1. Delay in Diagnosis. Delay in the diagnosis of angioedema patients (from first onset of symptoms), measured in years (mean) before and after 2012.

The overall distribution was 18 (37.5%) with type I HAE, 4 (8.3%) with type II, 14 (29.2%) with type III HAE with NL C1-INH, 1 (2.1%) with C1-INH-AAE, 1 (2.1%) with ACEI-AAE, 3 (6.3%) with V-AAE (vasculitic), and 7 (14.6%) with H-AAE (histaminergic) (Table 1). These specific angioedema types were associated with particular laboratory profiles depicted in Fig. 2 as the mean values of C4, C1-INH antigen, and C1-INH function.



	C1-INH-HAE-I	C1-INH-HAE-II	nC1-INH-HAE	H-AAE	V-AAE	C1-INH-AAE	ACEI-AAE
C4	8.6	16.9	22.6	24.2	27.8	8.3	29.5
C1 Ag	9.6	33.5	26.2	29.9	34.0	20.0	28.0
C1 Fxn	24.4	22.3	98.9	88.6	103.7	70.0	66.0

Figure 2. Angioedema types, laboratory profiles. Laboratory profiles of angioedema types, depicted as mean ± (SEM) values for C4, C1-INH antigen, and C1-INH function.

The treatment distribution for HAE was as follows: Ten (45.5%) patients received C1-INH replacement as prophylaxis; 17 (77.3%) patients received acute (rescue) treatment with icatibant and/or ecallantide; and 5 (22.7%) remained untreated.

Efficacy results

The effect of treatment on the per-month rate of attack before and after treatment: 0 to 1 attack/months from 41.2% to 82.4%; 2 to 3 attacks from 23.5% to 17.6%, and >3 from 35.3% to 0% (Fig. 3). The total number of attacks in the 6 months before treatment was 291 and after treatment was 69 (Table 1).

Secondary endpoint results

The effect of treatment on the HAE patients in terms of their ER visits in the 6 months after that treatment: The number of ER visits decreased significantly, falling from 64 (mean = 3.8/patient) to 7 (mean = 0.4/patient; p-value = 0.0186). The number of visits of non-treated HAE patients fell from 14 (mean = 2.8/patient) to 5 (mean = 1.0/patient; p-value = 0.3852: not significant) (Fig. 4).

The effect of treatment on the number of hospitalizations in the 6 months after treatment: The number of hospitalizations decreased significantly, from 35 (mean = 2.1/patient) to 7 (mean = 0.4/patient; p-value = 0.0026). For non-treated HAE patients, the number of hospitalizations decreased from 7 (mean/patient = 1.4) to 5 (mean = 1.0/patient; p-value = 0.3739: not significant) (Fig. 5).

When asked (through the QOL Questionnaire) how much HAE had affected their lives, 63% responded, significantly, plenty or a lot; however, when asked how little HAE had affected their lives, 27% responded very little or not at all. Ninety percent of the HAE patients responded that they were totally or mostly satisfied with the treatment they had received, 8% responded that they were somewhat satisfied with the treatment, and none responded that they were dissatisfied ; 16.7% did not respond because they never made use of any of the treatments under study (Table 1).

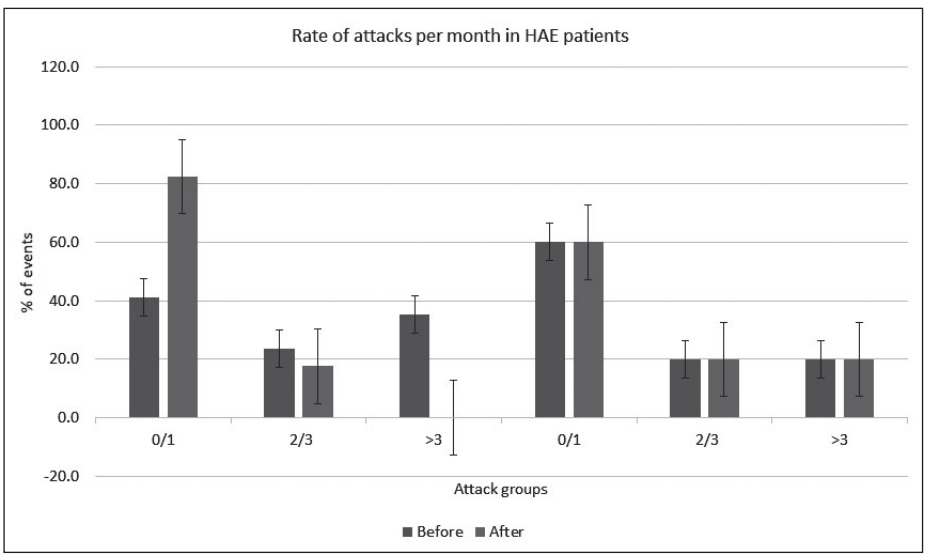


Figure 3. Rate of attacks per month in HAE patients, before and after treatment; treated vs. non-treated groups. The effect of treatment on HAE patients expressed as the rate of attacks per month, before and after treatment: 0 to 1 attack/month; 2 to 3 attacks/month; and >3 attacks/month. Treated vs. non-treated groups.

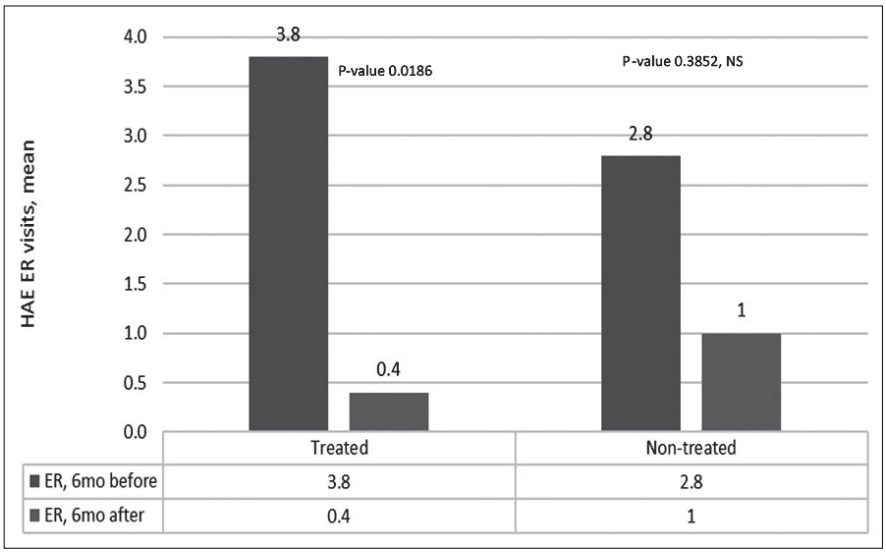


Figure 4. Effect of treatment on HAE patients' ER visits; treated vs. non-treated groups. The effect of treatment on HAE patients' ER visits in a 6-month period; treated vs. non-treated groups.

Exploratory endpoint results

As expected, the H-AAE patients were found to have significantly higher quantitative total IgE levels (mean = 762.1). Interestingly, the HAE groups (HAE-I, HAE-II, and HAE with NL C1-INH) were found to have higher-than-expected IgE values (means = 133.6, 142.7, and 112.2, respectively). The least significant, clinically speaking, were V-AAE (mean = 82.1), C1-INH-AAE (mean = 5.1), and ACEI-AAE (mean = 66.0) (Fig. 6).

Safety

The most frequently observed adverse events were injection-site reactions (29.4%), which occurred in 5 patients; overall, the most frequently reported adverse events were nasopharyngitis, upper respiratory tract infections, localized injection-site pain, and headaches.

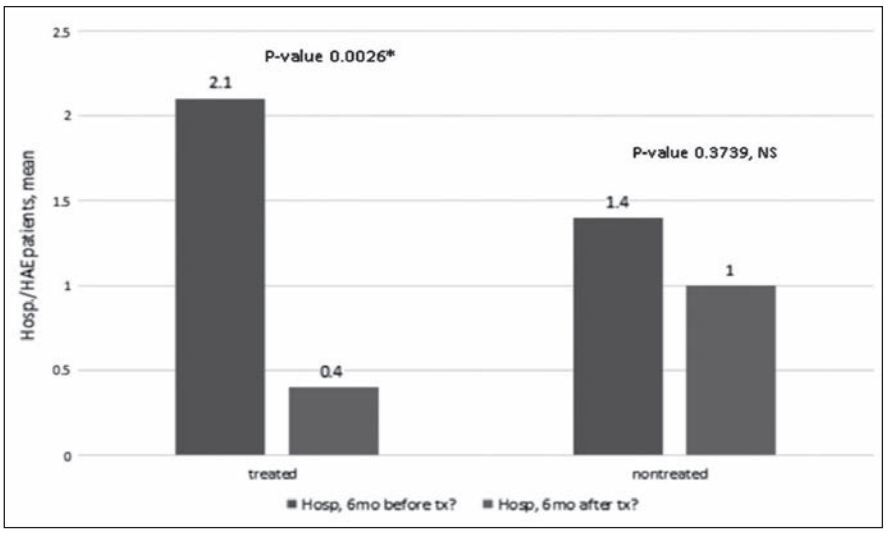


Figure 5. Effect of treatment on HAE patients' hospitalizations; treated vs. non-treated groups. The effect of treatment on HAE patients' hospitalizations in a 6-month period (depicted as mean per patient).

Discussion

In Puerto Rico (PR), there have been an increasing number of patients identified as having HAE. In addition to the abovementioned factors (the recovery of previously diagnosed cases, augmented disease awareness, and more accessible diagnostic testing), we believe that we may have a high prevalence of undiagnosed HAE in PR, possibly caused by our geographic circumstances, increasing the manifestation of a particular genetic variance inherent in the Puerto Rican population, as suggested by the presence in other conditions (13). Therefore, it is crucial to further expand disease awareness and diagnostic testing into different parts of the island to identify undiagnosed patients so that they might receive prompt, appropriate, and cost-effective therapeutic interventions, thereby preventing any unfortunate casualties. In addition, it is important to contact healthcare workers in key areas (e.g. ER and gastrointestinal specialists) so that they might help identify all the currently undiagnosed HAE patients; important, also, is working with all the allergists/immunologists on the island to promptly differentiate between the various causes of recurrent angioedema, develop appropriate treatment action plans, and complete an island wide registry.

The purpose of this study was to prospectively observe the patients of an allergist in PR—which patients had been identified as having HAE—and their pre- and post-therapy responses (measured by HAE attack rate, hospitalizations, ER visits, and impact on quality of life) to newly developed and available therapies.

A remarkable finding of this study was that there was a significant reduction in the delay in diagnosis. The known gap between the onset of angioedema symptoms to a diagnosis by a physician (before and after 2012) was significantly decreased from a mean of 8.6 years to one of 0.4 years (Fig. 1). This finding could be attributed to increased disease awareness (among patients and

physicians) sponsored by the pharmaceutical industry, the US HAE Association, and more accessible diagnostic testing.

The new medications had a significant impact in terms of decreasing the HAE attack rate and the number of ER visits and hospitalizations; in addition, there was a high degree of satisfaction among this patient population regarding them. There was a correlation between patients on prophylactic and rescue treatments (which were offered to all patients) with the decreased attack rate and number of ER visits and hospitalizations, as can be visibly seen in Figures 4 and 5; no significant effects were found in the HAE patients who were not treated. Additionally, the total number of HAE attacks decreased in the 6 months after the onset of therapy, falling from 291 to 69 (Table 1). Unfortunately, there were some patients (those younger than 18 years old) who were too young to receive icatibant and others (those younger than 12 years old) who were too young to receive ecallantide as the acute treatments to prevent the anaphylactic attacks.

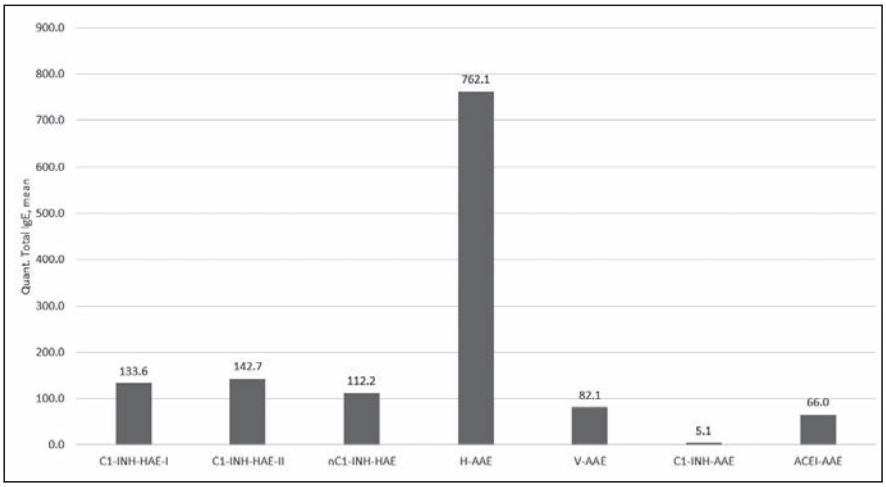


Figure 6. Types of angioedema and their quantitative IgE levels. The types of angioedema and their respective mean quantitative IgE levels.

It is important to highlight the increased IgE levels in the histamine-dependent angioedema (H-AAE) (allergic) subjects; while the normal upper limit of IgE level is below 180 UI/ml (ideally, this level should be below 100 UI/ml), they had a mean of 762.1 UI/ml, which indicates the atopic nature of these patients. These individuals, in particular, should pay attention to allergens to which they are sensitive, since exposure to such allergens might trigger an allergic cascade, increasing the incidence of angioedema attacks. It is no surprise that all the patients of HAE types had lower than average IgE levels, although those levels were not completely negative; it is interesting that a significant number of HAE type I and type II patients (14 and 17, respectively) had IgE levels that were greater than 100 UI/ml (mean = 133.6 UI/ml and mean = 142.7 UI/ml, respectively) (Figure 6), suggesting that there might be a mixed population with both bradykinin- and histamine-dependent angioedema mechanisms. Another important observation was that there was a significant proportion of patients with HAE with NL C1-INH levels (29.2%), indicating the need for further genetic evaluation in these patients.

It is important to mention that all the diagnosed patients had rescue medication available to treat any acute attack as might occur (unless they had specifically indicated their unwillingness to receive treatment, and had done so by written notification), but patients often did not require (prophylactic) medication if the attacks were infrequent, mild, and/or never involved the larynx. All the patients had specific plans for ER access and understood the risks of undergoing substantial dental work, surgical procedures, or invasive medical procedures. Family members were tested, and genetic counseling was offered. Patients wore or had some sort of identification.

Even though there is no connection between race and gender, there were significantly more symptoms in the female population: The study had 39 women out of the total 48-patient pool.

Finally, the government of PR should add this disorder to the island's list of primary immunodeficiency disorders, under the heading of remediable catastrophic conditions within the health insurance administration law (72-1993), and make the coverage of the diagnosis, treatment, and prevention of this condition compulsory for all health insurance companies on the island.

A limitation of this study was the relatively low number of patients (coming from a single practice); the number of patients was too small to draw any conclusions regarding any effects that might be specific to the patient subgroups. Now, an island wide collaborative effort should be undertaken with all the allergists/immunologists. Ideally, it would include all the identified cases and would consider all the most recent available therapies as well as genetic testing.

Resumen

Objetivo: Fue un estudio de pacientes con angioedema hereditario (HAE) y sus respuestas a nuevos tratamientos medidos en términos de tasas de ataques de HAE, número de hospitalizaciones, visitas a salas de emergencia (ER) y el impacto de la su calidad de vida (QOL). Métodos: Pacientes con angioedema recurrente sin urticaria que asistieron a una práctica privada desde 2013 al 2016. Los pacientes con HAE (tipo I & II) recibieron tratamiento de rescate y profilaxis para aquellos con 2 o más ataques al mes. Resultados: De 48 pacientes, 22 (45.8%) tenían HAE (tipo I & II). El 45.5% de esos pacientes recibieron

profilaxis y el 77.3% terapia de rescate. Efectos de tratamiento fueron reportados como porcentajes de los pacientes con HAE en cada categoría de ataque/mes: el 41.2% de los pacientes tuvo de 0 a 1 ataque antes y 84.2% después del tratamiento. Igualmente, 23.5% tuvo 2 a 3 ataques antes y 17.6% después del tratamiento. Finalmente, el 35.3% experimentó más de 3 ataques antes y ninguno después del tratamiento. El número de visitas a ER en 6 meses disminuyó de 64 (3.8 por paciente) a 7 (0.4 por paciente) y las hospitalizaciones en 6 meses de 35 (2.1 por paciente) a 7 (0.4 por paciente) después del tratamiento. El retraso del diagnóstico promedió 4.3 años; pacientes diagnosticados en o antes de 2012 promediaron 8.6 años; pacientes diagnosticados después de 2012 promediaron 0.4 años. Conclusiones: Los pacientes de HAE demostraron una mejor respuesta al tratamiento con disminución: en retraso diagnóstico, tasas de ataque, visitas a ER, las hospitalizaciones y la mejor QOL en los pacientes tratados.

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