THE STATE OF MANAGEMENT OF HAE IN LATIN AMERICA

HAEi

These pictures are of the same woman; during a facial attack and outside of an attack.

Introduction

The first Latin American (LATAM) HAE Patient Advocacy Forum organized by HAEi (the international umbrella organization for the world's HAE patient groups) was held in the city of Buenos Aires, Argentina, in December 2013. Nine countries from the region participated: Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Panama, Uruguay and Venezuela. Also in attendance was a representative from Spain, which, as a Spanish speaking country, collaborated in the coordination and contributed to the meeting with the experience gained from the first European HAE Patient Advocacy Forum.

The concepts shared herein are the result of a survey conducted among the representatives of the 9 LATAM patient organizations that attended the forum, as well as the discussions held during the meeting and the final conclusions reached. The aforesaid survey was conducted prior to the meeting, in November 2013, and its results analyzed beforehand. The surveyed countries covered a population of 434,001,510 people, in which the number of people with Hereditary Angioedema is estimated to be nearly 15,500 patients.

The purpose of this document is to reveal the state of management of HAE patients in Latin America and the multiple and diverse problems that the region faces in dealing with the problems of Hereditary Angioedema.

1. This estimation was extrapolated based on a prevalence of 1 person in 35,000.

Chapter 1

Introduction to Hereditary Angioedema

Hereditary Angioedema (HAE) is a rare, serious, potentially life-threatening genetic disorder that clinically manifests itself with the spontaneous onset of painful episodes of edema (swelling) of unpredictable frequency.

Because of its low prevalence and symptoms that mimic other more common diseases, HAE is often misdiagnosed or under-diagnosed. Patients are usually treated late and ineffectively and suffer for many years until they finally obtain an accurate diagnosis. Many of them have even undergone unnecessary surgery due to the lack of knowledge about the disease.

However, even though it is a serious, debilitating and in some cases fatal disease, an intelligent use of the new therapeutic options radically improves the quality of life of these patients by enabling them to control their disease and thus achieve independence in their daily life and a better quality of life.

Hereditary Angioedema: what Is It?

Hereditary Angioedema due to C1 inhibitor deficiency is an autosomal dominant disorder with an estimated prevalence of approximately 1 in 10,000 to one in 50,000 people.[1]
It affects both sexes equally and there are no differences between ethnic groups or predominance by geographical region.

HAE is transmitted on an autosomal dominant basis and it is hereditary because the genetic defect is transmitted within families. If one of the parents has HAE, their children will have a 50% chance of inheriting the disorder. However, the absence of family history does not rule out the HAE diagnosis, since it has been reported that up to 25% of the cases results from a spontaneous mutation of the C1-inhibitor gene at conception (de *novo* mutation). These patients can pass on the defective gene to their offspring.[2]

HAE manifests itself with recurrent, painful and frequently unpredictable bouts of edema that affect that mucous membranes or subcutaneous tissue of the abdomen, extremities, face, stomach and intestine (abdominal colic), upper airway and urogenital region. A laryngeal (throat) edema is extremely serious and can obstruct the upper airway and cause death by suffocation. HAE attacks are associated with a high rate of morbidity, alteration of the quality of life and death in the case of laryngeal episodes.[3]

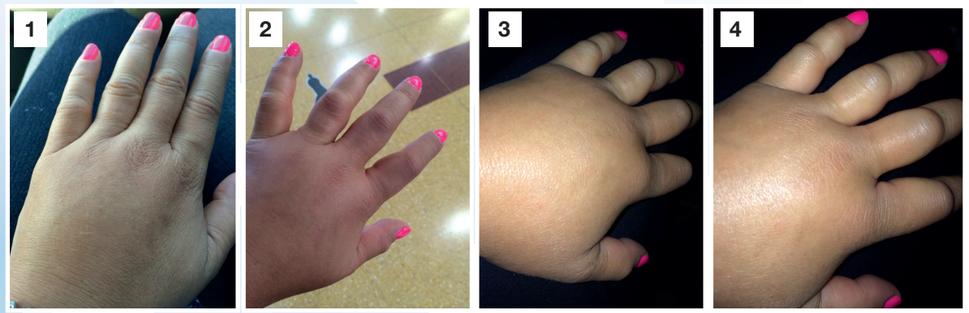
Laryngeal episodes should be considered a medical emergency and urgently treated with the specific treatments at the proper doses. It is estimated that more than 50 percent of patients will endure at least one throat attack in their lifetime. Historically, the mortality caused by throat attacks was 25-30% in untreated patients.[4,5]

More than 80% of patients with HAE suffer from abdominal attacks that cause severe and excruciating pain, often accompanied by vomiting and diarrhea and in some cases symptoms of hypovolemia.[6] Approximately one third of patients with undiagnosed HAE undergo unnecessary surgery during abdominal attacks because the symptoms mimic a surgical emergency.[7] Swelling of the face, hands, feet and other soft body parts can be disfiguring and also extremely painful and debilitating. HAE attacks often involve more than one body part.

An average attack lasts for between 24 and 72 hours, but some attacks may last for up to five days or more.[8] The majority of patients experience their first attack during childhood or adolescence.

Anxiety, stress, minor trauma, certain medical, surgical and dental procedures and illnesses such as colds and flu have been cited as triggers of a severe attack. ACE inhibitors (a blood pressure control medication) and estrogen-derived medications (birth control pills and hormone replacement drugs) have also been shown to increase the frequency and severity of the attacks. However, a high percentage of attacks occur spontaneously for no apparent reason.

Patients often report a “tightness” sensation at the site where the swelling will then occur, between thirty minutes to several hours before the attack. In some cases, this sensation can be felt around 12 to 24 hours before the swelling begins. Approximately one quarter of HAE patients experience a flat, non-itching skin rash both before and during an attack.



These pictures are of the same hand and show an example of the progression of a hand swelling without treatment. Image 1 is at 2 hours and image 4 is at 8 hours.

What Causes HAE?

HAE is a genetic disease caused by the functional deficiency of a blood protein called C1-inhibitor (C1-INH), and thus the name of hereditary angioedema due to C1-inhibitor deficiency. Unlike allergic angioedema, the swelling in Hereditary Angioedema is caused by the deficiency or malfunction of the C1-inhibitor blood protein which, due to its inability to adequately perform its regulatory function, results in an uncontrolled action of kallikrien and excessive production of bradykinin, the latter being the most important chemical mediator of angioedema attacks. The increased vascular permeability caused by bradykinin induces the capillaries to release fluids into the surrounding tissues, thereby causing the edema (swelling).

As shown in Table 1, there are three types of HAE. The most common form of the disease – Type I – is characterized by low quantitative levels of C1-inhibitor and affects about 85% of patients. Type II HAE affects the other 15 percent of patients who have normal or elevated levels of C1-inhibitor, but in this case the protein does not function properly. The two types are symptomatically indistinguishable and affect men and women equally. Several investigators have reported a familial (and therefore inherited) angioedema in patients with normal levels of C1-inhibitor. This type of angioedema is often designated “HAE with normal C1-inhibitor or HAE Type III”. In some of these patients, a mutation in coagulation Factor XII has been found. The percentage of patients is not known.

Table 1: Subtypes of Hereditary Angioedema[1]

Type	Cause	Affects
Type 1	Low quantitative/antigenic levels of C1-inhibitor	85 percent of cases
Type 2	Normal or raised quantitative/ antigenic levels of C1-inhibitor, but the protein is non-functional (as measured by the C1-inhibitor functional assay)	15 percent of cases
Hereditary Angioedema with Normal C1-inhibitor (Type 3)	Normal antigenic and functional levels of C1-inhibitor. Some cases related to a mutation in coagulation F12	Percentage still not determined

How Does HAE Affect Patients?

The frequency and severity of the attacks vary considerably between patients and even for the same patient throughout his/her lifetime. The manifestations of the disease differ, even among members of the same family.

Untreated patients have attacks every 7 to 14 days on average, with a frequency ranging from practically asymptomatic to episodes every 3 days.[9]

Because a typical attack lasts several days before it subsides, patients may therefore be debilitated and/or find it impossible to resume their normal activities for more than 100 days a year, i.e. more than three months a year. This situation can have a very high impact on the patients' quality of life from a personal, social, professional and economic point of view and can even pose a risk to their continuation or permanence in job posts, professional careers and other activities. These difficulties in turn cause problems of physical and mental health, including depression.[10]

	Percentage of patients who responded yes
HAE has affected professional careers	57.5% n=263
Has not been able to consider certain jobs because of HAE	69.1% n=316
HAE has had an impact on professional options	63.0% n=288
Has not carried on with studies up to the desired level due to HAE	40.5% n=185
HAE has been detrimental to studies	48.4% n=221
HAE has had an impact on educational options	54.5% n=249

Two-fifths of people with HAE are clinically depressed, and they are twice as likely as the general population to be taking psychoactive drugs. The burden of HAE related to productivity impairment is similar to that seen in data from patients with better-recognized chronic diseases such as severe asthma and Crohn's disease.[10]

"Patients with the deficiency of C1-inhibitor are not just an interesting model for study… they are critically ill. Many have ancestors that died suddenly from suffocation. Patients live in constant dread of life threatening laryngeal obstruction."[1]

HAE Daily Impact on Patients

HAE has a devastating impact on patients and their families, and both their quality of life and their daily activities are significantly affected. This impact is not necessarily related to the location and/or severity of the episodes. Not only laryngeal and abdominal attacks impact the daily activities of these patients, but rather all episodes alter their quality of life since it is the attack in itself that interferes in all aspects of the patient's life and wellbeing. It should also be noted that HAE patients experience a high level of anxiety and worry, even in attack-free periods. The fear of the next attack, traveling or being far from a care center, as well as the possibility of transmitting the disease to their children, are some of the most frequently reported factors.[11] This impact on the quality of life dramatically increases if the patient does not have immediate access to the treatments.

These pictures are of the same woman; at the start of an attack and 12 hours later.

The Costs of HAE

The few specific pharmacoeconomic studies available about Hereditary Angioedema agree that the economic burden associated with HAE has a significant effect on patients, healthcare systems and society. A study conducted in the United States of America showed the substantial economic costs associated with both acute attacks and the ongoing chronic (long term) nature of the disorder.[12] However, the study may underestimate the real costs of HAE, as it was performed before acute therapy was available in the US. Over two thirds of patients who took part in the study did not seek immediate medical help for their attacks, probably because of their past experience of frequent misdiagnosis and limited treatment options. Nor did the study take into account the cost of inappropriate procedures or other unnecessary treatments commonly experienced by people with HAE. A more recent study performed in England also underlines the fact that HAE entails high costs for the patient and the healthcare system, but it concludes that more research is needed in this field to be able to more exactly determine the extent of this impact.[13]

Diagnosis

Because of the extreme complexity of the disease and its potential risks, it is essential that HAE patients receive an accurate diagnosis early in life. The risk of death in undiagnosed patients can be as high as 30 to 40 percent.[1]

The delay in diagnosis is a common feature among patients with HAE anywhere in the world. The diversity of symptoms and their similarity to other conditions and/or other types of angioedema lead to confusion among those physicians who are not familiar with Hereditary Angioedema. Numerous studies have reported that this considerable diagnostic delay ranges from 10 to 20 years between the onset of symptoms and an accurate diagnosis.

This diagnostic delay is alarming and creates a situation of concern and total vulnerability for the patient. During this period, many patients are referred for psychiatric evaluation because of the assumed possibility of psychosomatic symptoms.

An HAE diagnosis should be suspected in any patient with recurrent angioedema or abdominal pain in the absence of hives, which could suggest allergic angioedema. Abdominal attacks may be mistaken for acute surgical abdomen, i.e. appendicitis, and it is not unusual for these patients to have been subjected to unnecessary exploratory surgery.

Table 3: Diagnosing Hereditary Angioedema
Typical signs and symptoms of HAE include:
• Recurrent episodes of angioedema and abdominal attacks without urticaria (itching)
• Episodic attacks, with intervals between periods of swelling
• Onset of attacks in childhood or adolescence, worsening around the time of puberty
• Prolonged attacks (typically 76-92 hours in duration)
• Family history of attacks (in 75 percent of patients)
• Attacks do not respond to antihistamines, corticosteroids or adrenaline

An accurate diagnosis is obtained by laboratory tests of a sample of the patient's blood, in which a decreased concentration of C1-INH and/or reduced activity of C1-INH is confirmed. It is also important to determine the concentration of the C4 antigen, as this value is diminished in both HAE Type I and Type II.

Treatments

Because HAE is not an allergic form of angioedema, symptoms do not respond to treatments for allergic reactions, such as antihistamines, corticosteroids and epinephrine. In the past, treatment was limited to tranexamic acid and pain medicines (including morphine) for acute attacks and anabolic steroids or attenuated androgens (such as danazol) for long-term attack prevention.

Fortunately, the development of new, safe and effective therapeutic options offers patients the possibility of implementing an individual treatment plan for their specific needs.

There are currently five modern therapeutic drugs or medicines to prevent or treat acute HAE attacks.

Table 4: Treating Hereditary Angioedema

Acute Treatment / On Demand		
Class of Drug	**Name of Drug**	**Administered**
Plasma-derived C1-inhibitor concentrate	Berinert / Cinryze/ Cetor	Intravenous (in the vein)
Recombinant C1-inhibitor	Ruconest	Intravenous (in the vein)
B2 bradykinin receptor antagonist	Firazyr (icatibant)	Subcutaneous (under the skin)
Kallikrein inhibitor	Kalbitor (ecallantide)	Subcutaneous (under the skin)
Prophylactic Treatment		
Plasma-derived C1-inhibitor concentrate	Cinryze	Intravenous (in the vein)
Anabolic steroids	Danazol (danocrine). Stanozolol	Oral

Attenuated androgens / anabolic steroids, which include danazol, are effective in reducing the frequency of attacks in many patients, but they are associated with significant side effects. Because they are male hormones, these side effects can be particularly severe in female patients. In addition, these drugs cannot be given to pregnant women and children.

Many patients still receive treatment to prevent or treat their attacks in a clinic or hospital. However, there is an increasing worldwide trend towards home treatment. Several studies have confirmed that home treatment is safe and effective and that it considerably reduces the severity and duration of attacks because it enables faster treatment of the episodes, helping patients to regain control of their lives and minimize the negative impact of the disease on their daily activities.[14]

For this reason, the international consensus documents for HAE treatment and management indicate that all patients diagnosed with HAE should be motivated to learn self-administration of the various medications and to self-administer them early, during and/or prior to the attack.[15,16,17] It has been demonstrated that home treatment can help patients to regain control of and improve the quality of their lives and in many cases avoid costly admission to the hospital.3 However, it is recommended that in all cases patients seek prompt medical attention when the attack compromises the airways or face and, in the case of abdominal attacks, does not respond to the initial treatment.

"Important advances in diagnosis and treatment of C1 inhibitor deficiency have been made in recent years, and today we can rely on different therapeutic options to prevent symptoms or to treat those already present. Because of these advances, in patients properly diagnosed and treated, the mortality for the disease has dropped close to zero, and the quality of life for these patients approaches that of normal subjects.[18]"

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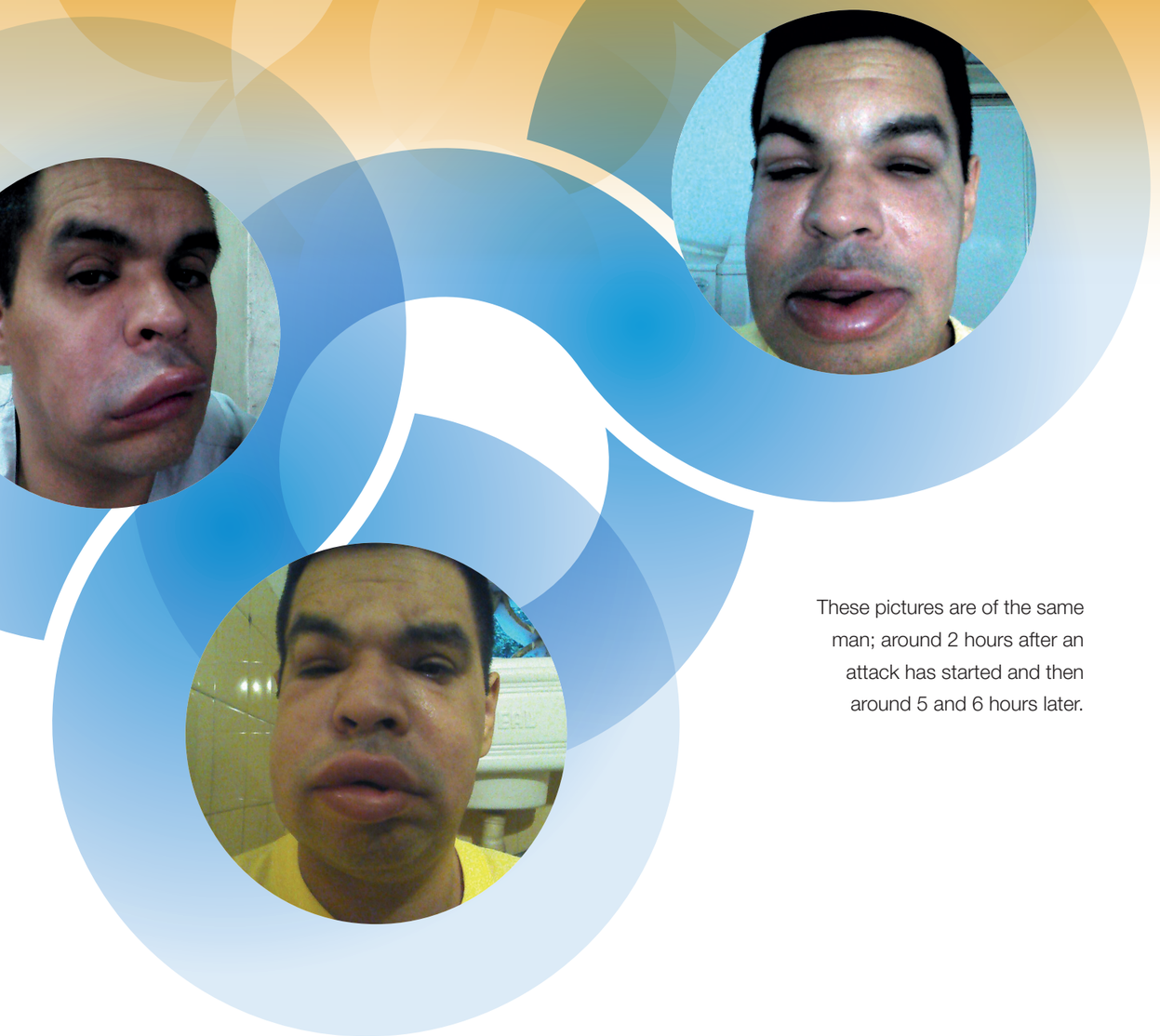


These pictures are of the same man; around 2 hours after an attack has started and then around 5 and 6 hours later.

Chapter 2
Survey

The Reality of Hereditary Angioedema in Latin America

Although Hereditary Angioedema cannot still be cured, a great deal of scientific and research work has been carried out in recent years on this disease, and this has led to the approval of new drugs which, added to the already existent ones, have radically changed the HAE treatment paradigm. The intelligent use of these modern treatments helps patients to prevent the onset of symptoms and/or treat them promptly, thus enabling them to achieve a full and productive life.

However, the results of a survey conducted among representatives of HAE patient associations and groups from 9 Latin American countries reveal that the situation throughout the region is far from acceptable and that in only two of the surveyed countries are HAE patients gradually approaching the optimal treatment and management model for this disease. The survey also reveals that the quality of diagnosis, patient care and treatment availability varies significantly between the region's countries but that, in all cases, it is clearly deficient and calls for immediate, radical change.

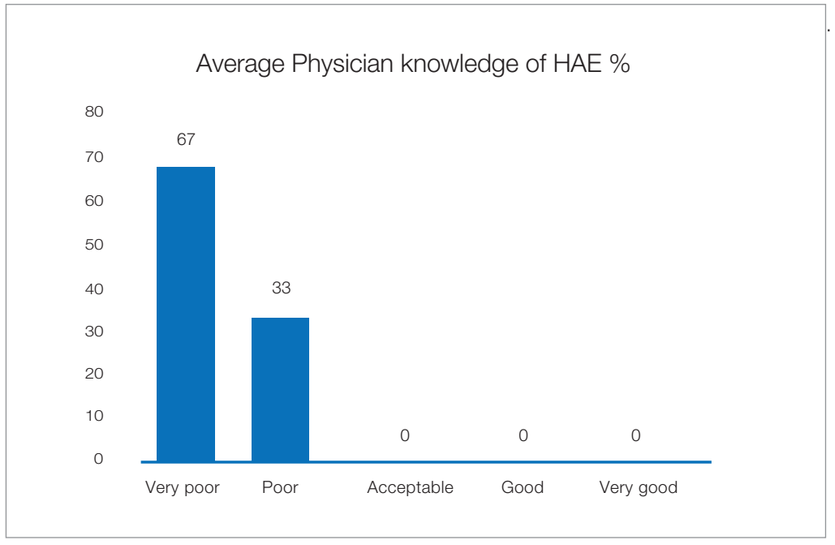
HAE continues to be a highly under-recognized, under-treated disease in this region. Limited knowledge of this condition, diagnostic difficulties and lack of availability of effective treatments pose a constant risk to these patients' lives.

To be sure, the region is well behind other countries where there are better organized models for HAE management and where several therapeutic options are registered and available for use.

Survey Results

Under-recognized and under-diagnosed

100% of the surveyed patients from the participating countries agree that the medical knowledge of HAE in the region is VERY DEFICIENT or DEFICIENT.



None of the surveyed respondents was satisfied with the existing knowledge of HAE in the region.

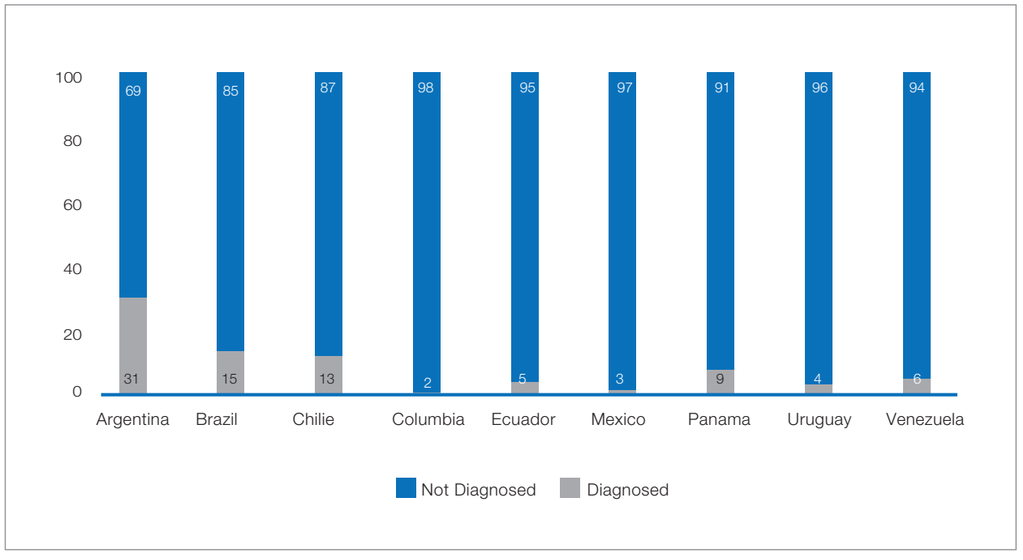
The low levels of professional knowledge and awareness of HAE result in a situation of extreme vulnerability for the Latin American patient community. A potentially life-threatening disease such as HAE requires specific knowledge to promptly prevent and/or treat attacks and thus avoid potentially fatal consequences.

Case history: “There is very little knowledge of HAE in our country and physicians do not believe that we are seriously ill.”

Number of Diagnosed Patients

The lack of knowledge and the shortage of financial, technical and logistic resources for diagnosing HAE result in a very low percentage of diagnosed patients in the region, thus revealing anew the situation of constant risk to the still unidentified patients in Latin America.

In accordance with the survey results and bearing in mind the estimated number of patients per country, Argentina has the highest percentage of diagnosed patients with 31%, followed by Brazil with 15%, Chile with 13% and Panama with 9%. In some countries such as Mexico and Colombia, the percentage of undiagnosed patients amounts to 97 and 98%, respectively, exposing once again an alarming situation for patients.
In all cases, these percentages are also estimations because there are still no national epidemiological registers for the disease.



Availability and Access to Modern Treatments

However, the most critical and pressing concern throughout the region is the lack of availability of the medications to prevent and/or treat acute attacks and the continuous difficulties experienced in accessing these drugs in the few countries where one or more of the existing therapies are available.

This causes many professionals to resort to the use of other therapies that are not indicated for HAE but, that in the absence of other therapeutic options, constitute the only possible alternatives to try to improve the current situation.

The complex regulatory and medical systems specific to each country were not evaluated in the survey; however, a table was obtained of the availability of the modern therapeutic options existing in each participating country.

	Berinert®	Firazyr®	Cinryze®	Kalbitor®	Ruconest®
Argentina	✓	✓			
Brasil	✓	✓			
Chile					
Colombia		✓			
Ecuador					
México	✓	✓			
Panamá					
Uruguay					
Venezuela					

The table shows that, on the date the forum was held in December 2013:

- No country had access to all the approved modern treatments
- Five (5) of the participating countries did not have any drugs for the treatment and/or prevention of acute attacks.
- Two (2) countries had only 1 drug for the treatment of acute attacks.
- Only two (2) countries had 2 of the existing modern treatments.

100% of the countries have androgens available to prevent HAE attacks, while 82% of the respondents use tranexamic acid as prophylaxis and/or treatment of acute attacks.

Availability and access to the drugs to treat and/or prevent acute attacks of HAE is vital for patients with Hereditary Angioedema, not only as an option to improve quality of life but also, in many cases, as the only possibility for survival.

According to the international consensuses, all HAE patients should have the necessary doses to treat and/or prevent at least two acute HAE attacks, and all attacks are eligible for treatment. These same documents recommend that attacks be treated as early as possible and that patients be offered the possibility of learning the self-administration techniques that would help them to treat their disease at home.

Taking the above mentioned recommendations into account and after evaluating the results of the survey, it is obvious that the situation in the majority of the participating Latin American countries is one of total defenselessness, vulnerability and extreme risk and that these patients face enormous challenges on having to live every day with HAE under such adverse circumstances.

Case history: “It is devastating to live in a country where there is no medication to treat your disease. We live in constant fear.”

CASE HISTORIES

"I had to pay 5000 dollars for my son's tracheotomy. Last year he had a laryngeal edema and, because there are no available treatments, that was the only thing they could do to save his life. At times I ask myself what would have happened if I hadn't had the money."

"There is only Danazol in my country. I don't take it. My brother takes it and also his five-year old son; they prescribed very small doses for him. The doctors don't know about the disease and we don't have medications for emergencies. There are so many times that I've had to go home to wait for my attack to pass, with no care at all and praying that nothing would happen to me."

"In an emergency, we are the ones who guide the doctors and even then they refuse to believe us and at times we have to be demanding and get angry, since my son and I have undergone several tracheotomies."

"I've been living with the disease for 16 years, suffering and crying without knowing what was wrong and going through the same thing with my mother. Finally, at 75, my mother was diagnosed. She was operated on for a supposed colon cancer, which we now suspect was no such thing."

"I had a serious laryngeal attack in 2001 and it's a miracle I'm alive. They diagnosed the disease one year later thanks to a very active doctor and I, as a patient, was very inquisitive. I traveled to Argentina for the diagnosis. Later we sent my daughter's blood samples abroad and her diagnosis was also confirmed. I was operated on for appendicitis, I don't have a gallbladder and I also underwent a gynecological laparoscopy. All for nothing."

"When my son was diagnosed in 2008, they told me that he had a very rare disease and the doctor said: 'Why give you a prescription if you can't get the medication in this country?', and he warned me that if someday my son had trouble breathing and a cough, I would have to rush him to a healthcare center because he could suffocate."

Chapter 3

HAE: The Latin American Dimension

Because of its geographical vastness and the huge economic and sociocultural differences among countries, the situation throughout the region is notably dissimilar. The inevitable differences in the knowledge of the disease, its management and also the differing regulatory conditions related to the approval of drugs result in a very diverse scenario. For this reason, the challenges faced by the patients in each country are also very diverse and they are directly related to the specific needs of each one.

Although the fragile situation of HAE in the region would require a thorough study of the specific deficiencies of each country, since this is the first Latin American Forum for patients with Hereditary Angioedema, the purpose of this document is not to detail the specific problems of each country in particular, but rather to find the points in common between them and thus try to highlight the priorities and alarming deficiencies of the region in general.

Finally, it should be mentioned that there is an obvious close relationship between Patient Associations and improved quality of life for patients, which shows the enormous contribution these groups make to the wellbeing of patients in general by working together and informing. At the time of the forum, only Argentina, Brazil and Mexico had legally established Patient Associations, whereas the other countries were in the process of forming groups such as Chile, Colombia and Venezuela, or had one or two representatives such as the case of Ecuador, Panama and Uruguay.

In spite of the above-mentioned differences, all the participants in the forum agreed that things must change in order to:

- Promote and improve the knowledge of Hereditary Angioedema in all spheres.
- Improve the diagnosis and identification of patients.
- Have access to early diagnosis and the drugs approved in other countries around the world.
- Identify medical professionals and promote the creation of specialized care centers in each country.
- Obtain the proper training to manage attacks at home, thus being able to live life to the full.
- Promote the creation of National Patient Organizations in each country in the region, and at the same time encourage close collaboration with HAEi.

To achieve the above and secure the necessary resources do so, a call to action is proposed.

Call to Action

This first Latin American Forum underlined the enormous difficulties in accessing an HAE diagnosis, the lack of knowledge of professionals in general, the lack of awareness about HAE and the unavailability in the region of the treatments existing elsewhere to manage and/or prevent acute attacks. On addressing this absolutely unacceptable situation, it is concluded that mechanisms should be implemented to drive radical change in the current conditions of HAE in Latin America. Considering that the problems of rare diseases such as HAE are already now priorities for action and collaboration and are on the public agenda in other regions of the world, the same is proposed for Latin America.

In this document, the representatives of the countries participating in the forum formulate a call to action aimed at their governments, medical professionals, health authorities and fellow citizens.

HAE: A CALL TO ACTION IN LATIN AMERICA

HAE patients in Latin America want to have access to an early diagnosis and to the treatments that would allow them to lead a full and productive life. At the same time, they want to be able to safely and quickly treat their attacks, if possible at home, in order to minimize the impact of HAE on their daily activities and to enable them to fulfill their potential in all walks of life: personal, social and professional. HAE patients in Latin America want to achieve an integral, patient-centered approach to HAE that respects their individual needs and personal choices that will allow them to achieve a good quality of life.

Due to the above, the patients in all of Latin American propose a call to action to:

- Raise awareness and improve knowledge of HAE so that governments, health authorities and health professionals will recognize that HAE is a serious, disabling, potentially life-threatening and chronic condition that must receive timely, accurate diagnosis and effective treatment.
- Include HAE in the list of chronic, rare, life-threatening diseases in all the region's countries.
- Facilitate diagnosis and improve identification of patients in the region.
- Ensure that physicians are educated and trained to recognize, diagnose and treat HAE, and understand the importance of specialist referral.
- Procure the availability of the medications approved for HAE management in other countries around the world and implement the mechanisms for access thereto.
- Educate and inform patients about the available therapeutic options and the best ways to manage HAE, including home treatment.
- Draw up specific treatment protocols for each country based on the consensus of international experts, in order to achieve optimal management of the disease and satisfy the individual patient needs and in which home availability of the drugs and self-administration is considered a viable option.
- In each country, ensure cooperation among stakeholders – doctors, patients, industry and governmental decision makers – to jointly develop strategies to improve the quality of life of patients with HAE.
- Organize the communities interested in HAE to produce data that endorse beyond doubt the need for the above described actions, e.g.: treatment guidelines, quality of life surveys, pharmacoeconomic impact studies and patient registers.

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This report was produced by HAEi. For more information on HAE support groups available in Latin America, please look at the resources section of www.HAEI.org

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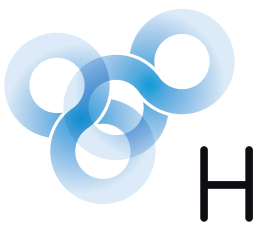

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