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National survey on clinical profile and management of patients with hereditary angioedema due to C1-Inhibitor deficiency in Colombia

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4. Conflict of Interest.

Author	COI declaration
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Margarita Olivares	Has received speaker fees from Takeda, CSL Behring, Pint Pharma, Novartis, Aztra, is a medical advisor for Takeda.
Mauricio Sarrazola	No conflict of interest declared
Jairo Rodríguez	Has been speaker for Takeda, CSL behring, Pint pharma, has received a grant from Shire
Camilo Daza	No conflict of interest declared
Jaime Ocampo	Has received support in academic activities from CSL Behring and takeda.
Alejandro Carreño	Speaker and receive fes from Sanofi, Takeda, GSK, Aztra Zeneca, CSL Behring, Novartis
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Carlos Olmos	Has received speaker fees from: Takeda, CSL, GSK, Sanofi, Novartis, AstraZeneca, Abbvie, Pfizer
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Hereditary Complement Deficiency Diseases, Hereditary Angioedema Types I and II, Surveys and Questionnaires, Health Care Surveys, Cross-Sectional Studies, Health Status Indicators.

8. Compliance with Ethical Standards.

The absence of formal review by an IRB is justified by the classification of this study as “no-risk” (exempt) research, in accordance with Colombian Resolution 8430 of 1993, as it involved non-sensitive data collected under conditions ensuring anonymity. The study was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki. All participating physicians provided informed consent prior to completing the survey.

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List any abbreviations/acronyms and their definitions. If no abbreviations/acronyms were used, indicate "Abbreviations: none."

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13. Abstract

Background

Hereditary angioedema (HAE) is a rare, often misdiagnosed disorder. Epidemiological data on this condition are scarce in Latin America, particularly in Colombia. This study aimed to describe the demographics, clinical features, and treatments of Colombian HAE patients to address data gaps.

Methods

A web-based survey (Sept 2021–Mar 2023) of Colombian physicians managing HAE patients collected anonymous data on demographics, clinical features, and treatments. Statistical analyses compared patients receiving long-term prophylaxis (LTP) versus those who did not.

Results

The survey included 42 physicians from 19 Colombian departments, covering 274 HAE patients. Median age at symptom onset was 13 years, with a diagnostic delay of 8 years. Most

patients were female (59.85%) and had a family history of HAE (83.58%). Attacks mainly affected peripheral, abdominal, and facial areas; common triggers included stress, trauma, and menstruation. Hospitalization was reported by 46.24% of patients, with23.77% hospitalized in the past year and 4.96% requiring intubation. All had on-demand therapy, mainly icatibant (91.41%). Long-term prophylaxis was prescribed in 52.14% of cases, with danazol (66.67%), tranexamic acid (31.21%), and lanadelumab (17.02%). These patients had longer diagnostic delays and higher hospitalization rates compared to those not receiving prophylaxis ($p<0.01$ and $p=0.01$, respectively).

Conclusions

This study reveals significant diagnostic delays and treatment challenges for HAE in Colombia. Underreporting and geographic disparities suggest an underestimated prevalence. The findings underscore the urgent need for greater awareness, equitable access to therapies, and robust patient registries to address unmet needs and reduce the burden of HAE on affected individuals.

14. Manuscript Text File

INTRODUCTION

Hereditary angioedema (HAE) is a genetic disease with an autosomal dominant pattern whose pathophysiological feature is the deficiency or dysfunction of the C1 inhibitor protein, which plays a modulating role in the complement, coagulation, and fibrinolysis cascades and whose defect generates the overproduction of bradykinin, a vasoactive peptide that, when acting on the endothelium, leads to vascular leakage and generation of angioedema[1,2].

HAE is a rare genetic disorder with an estimated prevalence of 1 in 50,000 to 1 in 100,000 individuals worldwide[3], though underdiagnosis and misdiagnosis make accurate epidemiological data difficult to ascertain[4]. This condition affects men and women across various ethnicities, with no significant geographical predilection[5]. HAE is typically inherited in an autosomal dominant manner, however, approximately 20-25% of cases arise from *de novo* mutations[6]. The HAE symptoms can occur at any age and include episodes of severe, recurrent swelling affecting various parts of the body, including the extremities, gastrointestinal tract, and airways, which can be life-threatening[7]. Early and accurate diagnosis is essential to prevent morbidity and improve quality of life through targeted therapies[8].

As is common with rare and orphan diseases, obtaining comprehensive epidemiological data presents significant challenges[9]. In the case of HAE in Colombia, precise figures remain elusive due to underdiagnosis and limited reporting. However, current estimates suggest that the country has a minimum of 650 individuals affected by HAE[10]. One of the key global strategies to address the challenges in obtaining reliable epidemiological data for rare

diseases like HAE has been the implementation of patient registries[11] and surveys. These tools have proven invaluable in providing insights into demographic patterns and therapeutic trends in HAE, both in cases related to C1 inhibitor deficiency and in those with normal C1 inhibitor levels[4,12,13]. Furthermore, these strategies have been instrumental in capturing patient perceptions, unmet needs, and quality of life issues, helping to guide clinical practice and inform the development of targeted therapies[14].

Based on these previous reports this national survey aimed to describe the sociodemographic, clinical characteristics, and treatment patterns of patients with HAE in Colombia, compiling a representative group of patients in the country's estimated cases.

METHODS

Data collection

This study was a web-based survey targeting Colombian physicians specializing in the management of patients with HAE due to C1-inhibitor deficiency. Identification of potential participants ensued through direct invitations conveyed via communication channels established for allergists and immunologists affiliated with the Colombian Association of Allergy, Asthma, and Immunology (ACAAI - By its acronym in Spanish). Subsequently, additional participants from diverse medical specialties were identified by direct consultation with the allergists and immunologists who had initially committed to responding to the survey. To be eligible, each specialist had to confirm their role in overseeing the follow-up care and treatment of at least one patient with hereditary angioedema within the year preceding the survey's completion date. The participants did not receive any form of financial

compensation for their involvement in this study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. In line with Resolution 8430 of 1993, it was classified as minimal-risk research and was therefore exempt from Institutional Review Board (IRB) review. Each participating physician provided their consent to participate at the beginning of the form.

The distribution of the survey occurred via email to each interested participant, spanning the period from September 2021 to March 2023. Each potential participant received up to two follow-up emails containing the invitation. The survey instrument was formulated through collaborative discussions among three authors of the study (MOG, MS, JAR) and encompassed inquiries about general, sociodemographic, and clinical data concerning patients with Hereditary Angioedema who had been under the care of each participating physician. It is noteworthy that the survey did not ask for specific patient identification information, thereby obviating the need for an institutional ethics committee review.

Data analysis

Demographic and clinical information data were analyzed using descriptive statistics and parametric or nonparametric analysis, according to whether they presented a Gaussian distribution. The dataset underwent partitioning based on the necessity for long-term prophylaxis (LTP), prompting a dichotomous categorization of responses. Subsequently, a series of comparative evaluations ensued, employing the Chi-square test and Wilcoxon rank sum test to assess the distinctions between clinical and sociodemographic variables within the delineated dichotomous groups. All data were analyzed using STATA version 17 (StataCorp.2021. Stata Statistical Software: Release 17. College Station,TX: StataCorp LLC) and GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

General characteristics

A total of 42 physicians from 19 of the 32 departments of Colombia responded to the survey, who were responsible for the care of 274 patients with hereditary angioedema due to C1-Inhibitor deficiency (Figure 1). The observed demographic composition exhibited a female preponderance (59.85%), the median age of onset of symptoms was 13 years (IQR 12 years); while the median age of diagnosis was 26.5 years (IQR 26 years) with a median diagnostic delay of 8 years (IQR 21 years). Remarkably, 83.58% of the patients had a family history of HAE. Regarding hospital history, 46.24% of patients have a history of some hospitalization in their life, but 23.77% had been hospitalized during the last year and 4.96% have required orotracheal intubation. Notably, a substantial disease burden associated with HAE was evidenced, with 25.53% of patients documenting disability related to their condition. Additionally, approximately 79% of individuals reported experiencing some degree of limitation attributable to their HAE. Table 1 summarizes the general characteristics of the patients collected through the survey.

HAE attacks characteristics

Because the main characteristic of HAE is its swelling attacks, the survey asked about special characteristics of these. As seen in Figure 2a, 39.51% of the patients had multiple triggers for their attacks identified, while 37.86% of the patients considered a single trigger for their flares; it is noteworthy that 22.63% of the patients could not identify any type of trigger for their attacks. The most frequently affected during attacks were peripheral, followed by

abdominal and facial (Figure 2b). Regarding patients who had the triggers for their crises identified, stress, followed by trauma and the menstrual cycle were the most frequently documented (Figure 2c).

Therapeutics data

The survey collected information about the treatment modalities patients received. Regarding to on-demand treatment, 100% of the patients had a prescription for some treatment measure, with icatibant being the most frequently prescribed treatment (91.41%) (Figure 3a). Conversely, regarding long-term prophylaxis (LTP), 52.14% of the patient cohort had undergone specific therapeutic interventions for this purpose. Notably, 17.12% of the patients recorded having received two or more distinct therapeutic modalities for long-term prophylaxis (Figure 3b). Danazol was the most frequently prescribed medication for LTP (66.67%), followed by tranexamic acid (31.21%), and lanadelumab (17.02%) (Figure 3c).

Differences according to the need for long-term prophylaxis

Given that half of the patients identified in this survey necessitated long-term prophylaxis (LTP) treatment, we decided to conduct an in-depth analysis of the prevailing characteristics among individuals with this requirement. Table 2 summarizes the findings of the comparison between patients according to their need for LTP. No differences were documented regarding gender or age at onset of symptoms. However, the age at diagnosis was significantly higher in patients who required LTP (30 years IQR 21years vs 20 IQR 28 years; $p<0.01$) as was the delay in diagnosis (13 years IQR 22 years vs 5 years IQR 19; $p<0.01$). Strikingly, a family history of HAE was more common in the group of patients who did not receive LTP (89.87% vs 77.10%; $p=0.01$). Conversely, history of hospitalization, both overall and in the last year,

was significantly more frequent in the LTP group. Regarding the burden of the disease, patients with LTP more frequently presented disability and limitation due to their disease.

DISCUSSION

This survey collected data from 42 physicians of various specialties who cared for 274 HAE patients identifying significant findings on the epidemiology, sociodemographic, and clinical characteristics of these cases. The total number of cases included was below what was expected according to the previously estimated prevalence of HAE. For an estimated 50 million inhabitants, the prevalence in Colombia would be around 0,55:100000 inhabitants. This is notably lower than the globally reported prevalence range of 1 in 50,000 to 1 in 100,000. The discrepancy likely reflects underdiagnosis and limited awareness, which are common challenges in rare disease epidemiology. Not all allergists and immunologists registered with the ACAAI responded to the survey and, in addition, some patients are treated by other specialties, which would explain why they are below previous short reports of HAE estimation in Colombia[10]. Figure 1 reveals that data collection was limited to 19 of the 32 departments of Colombia. Remarkably, the most significant clusters of cases are not concentrated in the most densely populated urban centers but are in some considered remote regions of the country. This geographic distribution raises the possibility of a higher prevalence of consanguinity as a contributing factor. Moreover, it underscores the need for a more systematic and proactive case-finding approach in similar areas underrepresented in this study.

The results highlight several important trends and challenges regarding HAE in Colombia. The median age of symptom onset (13 years) and the diagnostic delay of 8 years underscore the persistent challenges in recognizing and diagnosing HAE, a finding consistent with studies from other regions that report significant diagnostic delays due to the variability of the disease[15]. These data also highlight significant advancements in the management of HAE patients in Colombia, marking a shift from the absence of previous data on this crucial epidemiological aspect[16] to figures that are comparable to those reported in other regions. This progress can likely be attributed to the successful implementation of diagnostic awareness strategies[17], as well as proactive efforts to identify and investigate family members following the diagnosis of index cases[18], leading to earlier detection and improved patient outcomes. The substantial disease burden, with 25.53% of patients reporting disability and approximately 79% experiencing some degree of limitation, underscores the profound impact of HAE on quality of life. These findings are consistent with previous reports demonstrating the physical, emotional, and social toll of HAE, necessitating comprehensive management strategies that address both acute attacks and long-term patient well-being[14].

This survey provides valuable insights into the characteristics and triggers of HAE attacks, aligning with findings from previous studies in this field. A significant proportion of patients (39.51%) identified multiple triggers for their attacks, while 37.86% attributed their flares to a single trigger. Interestingly, 22.63% of patients were unable to identify any specific trigger, highlighting the unpredictable nature of HAE, which has been previously documented[19]. The most affected areas during attacks were peripheral regions, followed by abdominal and facial areas, consistent with the literature indicating that peripheral swelling is among the most frequently reported manifestations of HAE[20]. For those patients who identified triggers,

stress emerged as the most common factor, followed by trauma and hormonal changes related to the menstrual cycle. This finding is consistent with existing evidence showing that psychological stress and physical trauma are key exacerbating factors in HAE episodes[21]. Hormonal influences, particularly during menstruation, have also been widely recognized as a trigger in women, reflecting the hormonal sensitivity observed in this population[22,23]. These observations underscore the need for tailored management strategies that address the diverse and multifaceted nature of HAE triggers and attack patterns, potentially improving patient outcomes and quality of life[24,25].

Regarding treatment data, it is evident that 100% of cases adhere to those stipulated in international management guidelines[26], which specify that all patients must have on-demand treatment, with icatibant being the most frequently prescribed medication (91.41%). In terms of long-term prophylaxis (LTP), 52.14% of patients were receiving specific therapies for prevention. This data aligns with the 45-60.3% range reported in previous studies[13,27], and it underscores the significant challenge posed by the need for LTP in developing countries, where first-line therapies are often associated with high costs. Among the LTP treatments, danazol was the most common, prescribed to 66.67% of patients, consistent with its long-standing use in HAE prevention, and reinforcing its usefulness in this type of management[28], especially in developing countries where it is a valuable alternative for the management of patients with HAE[29].

The analysis of patients needing LTP reveals significant differences in diagnostic timelines, with those requiring LTP having a significantly later age of diagnosis and a longer delay in diagnosis. These findings are consistent with previous reports showing that delays in diagnosis are common in HAE, partly due to its rare and episodic nature[15,30]. Additionally,

patients requiring LTP had a higher frequency of hospitalizations and a greater disease burden, as indicated by increased disability and limitations associated with their condition[27,31]. Interestingly, the survey also noted a lower incidence of family history in the LTP group, suggesting that sporadic cases of HAE, often with more severe presentations, may have more pronounced treatment needs.

This study poses several limitations inherent to its design. First, response bias may occur, as individuals who choose to participate may not be fully representative of the broader population, potentially leading to skewed results[32]. Additionally, in studies using online surveys, there is a risk that individuals with certain biases may self-select into the sample, further influencing the generalizability of the findings[33]. Nonetheless, to mitigate these issues, the survey invitation was exclusively sent to clinical specialists who had confirmed their involvement in the management and follow-up of HAE patients during the year preceding the survey. Additionally, clinical specialists from fields outside of Allergy and Immunology who participated also had relevant experience with HAE. To further ensure data accuracy, the questionnaire incorporated multiple quality control questions.

CONCLUSION

This national survey offers valuable insights into the epidemiology and clinical characteristics of HAE patients in Colombia. The data suggests an estimated prevalence of 0.55 per 100,000 inhabitants; however, this figure may be affected by underreporting, given the study's design. Notably, more than half of the patients require long-term prophylactic (LTP) treatment, which poses a significant challenge for healthcare systems in Colombia and other developing countries. Furthermore, a substantial disease burden was observed. These

findings highlight the urgent need for improved documentation, registration, and follow-up systems for HAE patients in Colombia.

4. References

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5. Tables

Table 1. General characteristics of the patients documented.

Characteristics			n or Median	% or IQR
Gender	Female		164	59.85
	Male		110	40.15
Age	Age of onset		13	12
	Age of diagnosis		26.5	26
	Diagnostic delay (years)		8	21
History	Familiar history of HAE		224	83.58
	Hospitalization overall		123	46.24
	Hospitalization in the last year		63	23.77
	Endotracheal intubation		13	4.96
Burden of disease	Disability		24	25.53
	Limitation	None	22	20.95
		Mild	38	36.19
		Severe	39	37.14
		Total	6	5.71
Laboratories	C4 levels		4	4.55
	C1-Inhibitor concentration		5.75	6
	C1-Inhibitor function		20	29

Data are shown as the absolute number of patients and corresponding proportions within each group. Quantitative variables are represented by the median and interquartile ranges (IQR). HAE: Hereditary angioedema.

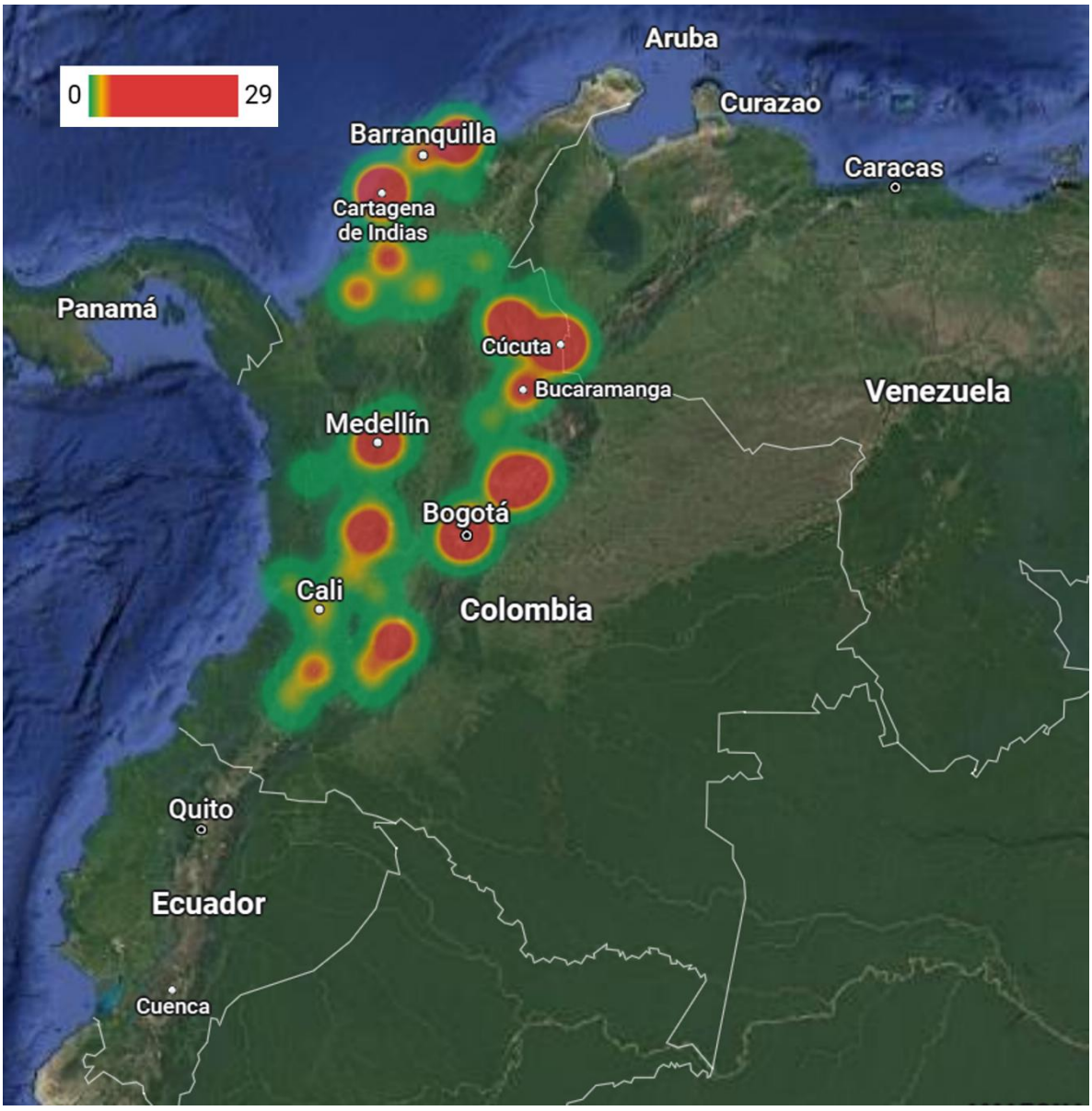
Table 2. Comparisons according to the need for LTP.

Characteristics			without LTP		with LTP		p
			n/median	%/IQR	n/median	%/IQR	
Gender	Female		86	61.43	78	58.21	.62
	Male		54	38.57	56	41.79	
Age	Age of onset		13	13	13	11	.24
	Age of diagnosis		20	28	30	21	**<.01**
	Diagnostic delay (years)		5	19	13	22	**<.01**
History	Familiar history of HAE		123	89.78	101	77.10	**.01**
	Hospitalization overall		52	38.24	71	54.62	**.01**
	Hospitalization in last year		24	17.78	39	30	**.02**
	Endotracheal intubation		5	3.79	8	6.15	.49
Burden of disease	Disability		7	15.91	17	30	**.04**
	Limitation	None	18	34.62	4	7.55	**<.01**
		Mild	23	44.23	15	28.30	
		Severe	9	17.31	30	56.60	
		Total	2	3.85	4	7.55	
Laboratories	C4 levels		3.5	4	4	4.4	.06
	C1-Inhibitor concentration		5.75	5.5	5.5	7	.63
	C1-Inhibitor function		23	32	18	24	.06

Data are shown as absolute number of patients and corresponding proportions within each group. Quantitative variables are represented by the median and interquartile ranges (IQR). Statistical comparisons were performed utilizing chi-square or Wilcoxon rank-sum tests. LTP: long-term prophylaxis. HAE: hereditary angioedema. Statistically significant data are shown in bold.

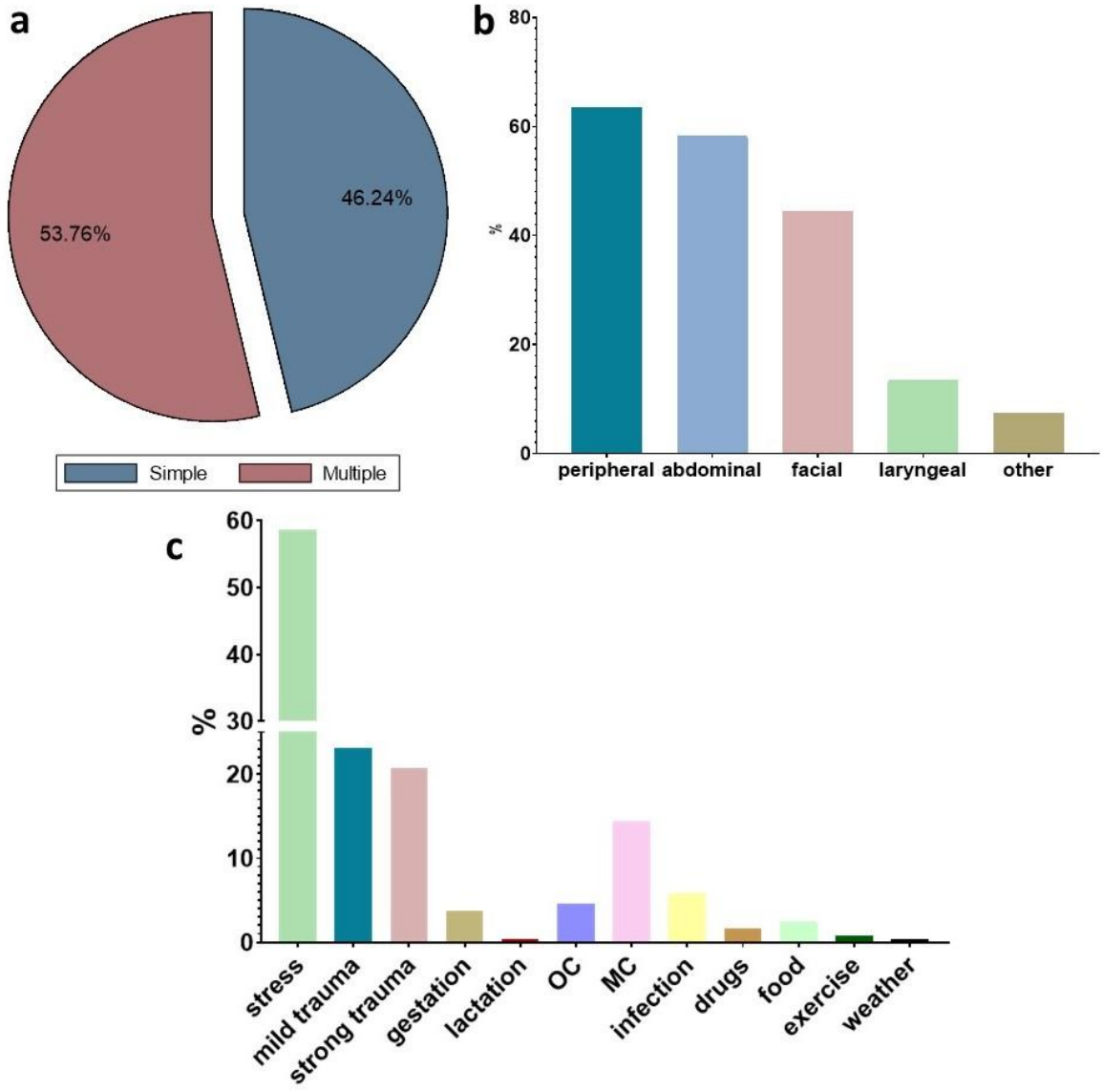
6. Figures legends

Figure 1. Geographic distribution of respondents.



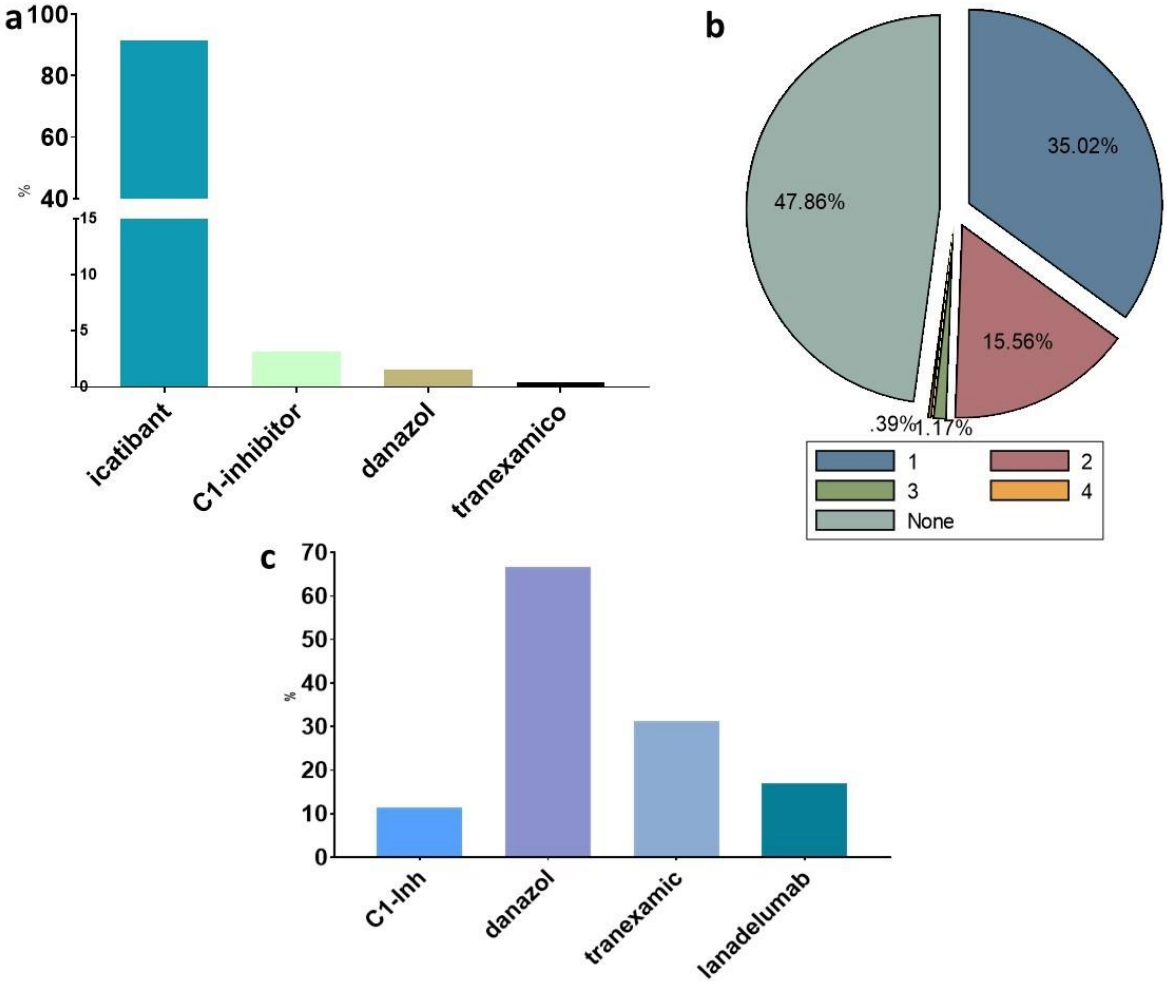
For each region in which a specialist responded, a heat map is shown according to the number of patients followed in the area. The areas correspond to those with the highest population density in the country.

Figure 2. Characteristics of HAE attacks.



a) annotation of the perception of the attacks concerning whether they affect multiple locations or only one. b) Locations most frequently affected. c) Identified triggers. OC: oral contraceptives, MC: menstrual cycle.

Figure 3. Data regarding treatments.



a) Frequencies of prescriptions for on demand therapy. b) Number of medications used for Long-term prophylaxis. c) Frequencies of prescriptions for LTP.

RESUMEN:

Caracteres (incluyendo espacios): 3,789

Caracteres (sin espacios): 3,208

Palabras: 573

Abstract

Background

Hereditary angioedema (HAE) is a rare, often misdiagnosed disorder. Epidemiological data on this condition are scarce in Latin America, particularly in Colombia. This study aimed to describe Colombian HAE patients' demographics, clinical features, and treatments to address data gaps.

Methods

A web-based survey (Sept 2021–Mar 2023) of Colombian physicians managing HAE patients collected anonymous data on demographics, clinical features, and treatments. Statistical analyses compared patients receiving long-term prophylaxis (LTP) versus those who did not.

Results

The survey included 42 physicians from 19 Colombian departments, covering 274 HAE patients. Median age at symptom onset was 13 years, with a diagnostic delay of 8 years. Most patients were female (59.85%) and had a family history of HAE (83.58%). Attacks mainly affected peripheral, abdominal, and facial areas; common triggers included stress, trauma, and menstruation. Hospitalization was reported by 46.24% of patients, with 23.77%

hospitalized in the past year and 4.96% requiring intubation. All had on-demand therapy, mainly icatibant (91.41%). Long-term prophylaxis was prescribed in 52.14%, using danazol (66.67%), tranexamic acid (31.21%), and lanadelumab (17.02%). These patients had longer diagnostic delays and higher hospitalization rates compared to those not receiving prophylaxis ($p<0.01$ and $p=0.01$, respectively).

Conclusions

This study reveals significant diagnostic delays and treatment challenges for HAE in Colombia. Underreporting and geographic disparities suggest underestimated prevalence. The findings underscore the urgent need for improved awareness, equitable access to therapies, and robust patient registries to address unmet needs and reduce HAE's burden on affected individuals.