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The Challenges in the Follow-Up and Treatment of Brazilian Children with Hereditary Angioedema

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Keywords
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Abstract
Introduction: Hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency is a rare autosomal dominant disease. Although the first symptoms can appear in childhood, the diagnosis's delay has a strong impact on the patient's quality of life. We analyzed clinical and laboratory characteristics and the drug therapy of pediatric patients with HAE in Brazil. ***Methods:*** Medical records from 18 reference centers of HAE patients under 18 years of age were evaluated after confirmed diagnosis was performed by quantitative and/or functional C1-INH. ***Results:*** A total of 95 participants (51 M:44 F; mean age: 7 years old) out of 17 centers were included; 15 asymptomatic cases were identified through family history and genetic screening. Angioedema attacks affected the extremities (73.5%), gastrointestinal tract (57%), face (50%), lips (42.5%), eyelids (23.7%), genitals (23.7%), upper airways (10%), and tongue (6.3%). Family history was present in 84% of patients, and the mean delay in the diagnosis was 3.9 years. Long-term prophylaxis (51/80) was performed with tranexamic acid (39/80) and androgens (13/80); and short-term prophylaxis (9/80) was performed with tranexamic acid (6/80) and danazol (3/80). On-demand therapy (35/80) was prescribed: icatibant in 7/35, fresh frozen plasma in 16/35, C1-INH plasma-derived in 11/35, and tranexamic acid in 12/35 patients. ***Conclusions:*** This is the first study on HAE pediatric patients in Latin America. Clinical manifestations were similar to adults. Drugs such as androgens and tranexamic acid were indicated off-label, probably due to restricted access to specific drugs. Educational programs should address pediatricians to reduce late diagnosis and tailored child therapy.

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Introduction

Hereditary Angioedema (HAE) caused by C1 inhibitor (C1-INH) deficiency is a rare disease due to mutations in the *SERPING1* gene, whose prevalence is 1 in 50,000 individuals in the general population [1]. It affects the subcutaneous tissue causing edema of the extremities, face, trunk, and genital organs, as well as the submucosa, resulting in gastrointestinal edema, vomiting, colic, abdominal distension, and diarrhea [1, 2]. The most feared symptom is laryngeal edema, causing asphyxia and death in untreated patients [3, 4].

There are few data on HAE caused by C1-INH deficiency in pediatric patients, and in most reports, attacks were treated with plasma-derived C1-INH [5–12]. Although the symptoms of HAE caused by C1-INH deficiency start early in life, the diagnosis of the disease is delayed and a pediatrician's approach is limited [13, 14]. In addition, several medications, both prophylactic and acute drugs, are restricted to more advanced ages [15, 16].

Questioning has arisen about using drugs, such as androgens, in children and their possible side effects [11]. On the other hand, some medications not available for the pediatric age-group were evaluated and released recently [17]. The access to all the available drugs for HAE in our country, as well as in Latin America, is still limited, with long delays when compared to Europe and the USA [18]. Considering the restricted access to diagnosis and therapy in developing countries, we evaluated the clinical and laboratory characteristics and pediatric patients' drug therapy from Brazilian referral centers.

Materials and Methods

A multicenter, retrospective, cross-sectional, descriptive study was conducted to evaluate data from the first clinical evaluation until December 2018 including 17 HAE reference centers in Brazil. Inclusion criteria are as follows: children above 1 year and adolescents under 18 years of age with laboratory-confirmed diagnosis of HAE caused by C1-INH deficiency, including asymptomatic patients identified by family genetic screening. Patients without a confirmed diagnosis and with other causes of associated angioedema were excluded from the study. The following data were collected: age of diagnosis, age at the onset of symptoms, prodrome, symptoms, triggering factors, severity of the attacks, diagnostic exams and treatments performed as prophylaxis, and/or on-demand. The patient's clinical presentation was classified as follows: (a) mild, when presenting with discomfort and without the need to interrupt daily activities; (b) moderate, with discomfort that reduces or affects daily activities; and (c) severe, when frequently present inability to perform daily activities and/or need for hospital care, according to previously published data [2]. The descriptive analysis of the data is presented through frequency means (*n*) and percentages (%). The protocol was approved by the Research Ethics Committee (CAAE 83143217.0.1001.0082) and the patients were included after signing the Terms of Assent and Consent of those in charge.

Results

We included 95 Brazilian participants (51 M:44 F) from 17 HAE reference centers: 65% from the Southeast, 23% from the Northeast, and 12% from the South. Children and adolescents were self-identified as Caucasians

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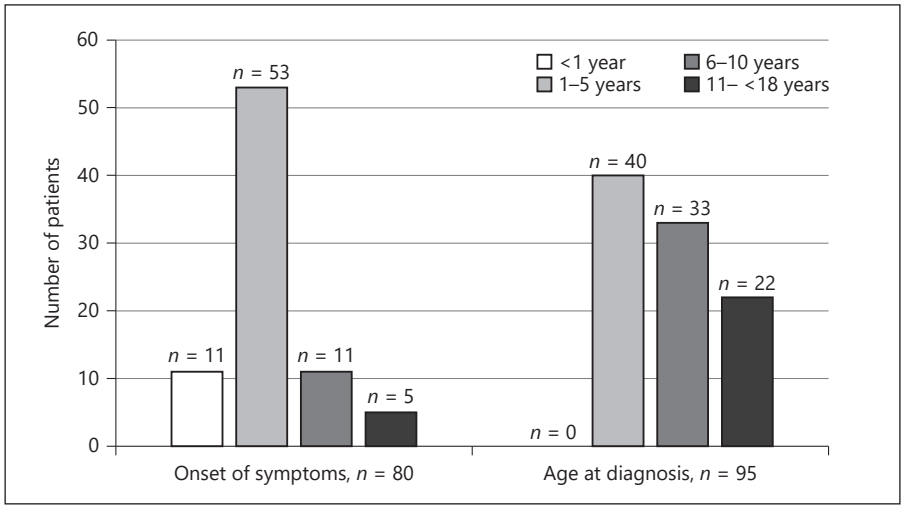

Fig. 1. Distribution by the age of onset of symptoms and age at diagnosis for symptomatic pediatric patients with HAE. HAE, hereditary angioedema.

(44/95), Afro-descendants (26/95), interracial (24/95), and oriental (1). In 15 cases, asymptomatic patients were identified through family history and genetic screening as previously described [19]. Maternal inheritance was present in 55% of patients, and paternal inheritance in 45%. In 77/80 patients, the first symptoms started before 12 years of age. Of the 80 symptomatic patients, 44 were younger than 12 years old (25 M:19 F) and 36 were older than this age-group (17 M:19 F). The onset of symptoms was, on average, 3.3 years and the mean age at the diagnosis was 7.2 years old. The onset of symptoms occurred between 1 and 5 years in 53/80 of patients, and most of the patients (73/95) were diagnosed before 11 years old (Fig. 1). The frequency of angioedema was below one attack per month in 21/80 (26.25%), once a month in 36/80 (45%), from 1 to 6 attacks per month in 20/80 (25%), and above 6 attacks per month in 3/80 (3.75%). Most of the patients had low ($n = 26$) or low to moderate ($n = 4$) clinical presentation (37.5%), followed by 30% of patients classified as having moderate clinical presentation ($n = 24$), and 27.5% with severe ($n = 18$) or moderate to severe ($n = 4$) classification. Four patients reported a similar proportion of low, moderate, and severe attacks. No significant difference in severity was observed between the group of patients below 12 and 12–18 years old. Previous misdiagnoses were reported in 30 patients and included allergy (60%), helminthiasis (20%), gastrointestinal problems (10%), cellulitis, autoimmune disease, and nephritis in one case each.

Most of the patients presented angioedema of the extremities (hands, feet, arms, legs) and 10% of patients experienced at least one episode of upper airways swelling (Table 1). Gastrointestinal edema manifested as epigas-

Table 1. Clinical characteristics of HAE pediatric patients

	N	%
Onset of symptoms (years) (N = 80)		
<1	11	14
1–5	53	66
6–10	11	14
11 to <18	5	6
Mean duration of attacks[a]*(days) (N = 80)*		
<1	4	5
1 ≤2	9	11
2–5	63	79
>5	4	5
Location of symptoms		
Back	1	1
Chest	2	3
Neck	3	4
Ear	5	6
Tongue	5	6
Upper airways	10	8
Legs	15	19
Arms	18	23
Genitalia	19	24
Eyelid	19	24
Lips	34	43
Face	40	50
Intestines	46	58
Foot	47	59
Hands	59	74
Trigger factors (N = 40)		
Trauma	20	50
Stress	10	25
Infections	5	12.5
Exercise	3	7.5
Menses	2	5

HAE, hereditary angioedema; *N*, number of patients. [a] The patients reported "Mean Duration of Attacks" as the mean duration of most of their angioedema attacks.

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Table 2. Treatments received by HAE symptomatic pediatric patients

Medication	Patient's age					
	<12 years, *N* = 44		>12 years, *N* = 36		total, *N* = 80	
	N	%	*N*	%	*N*	%
Long-term prophylaxis						
Danazol	2	4.6	5	13.9	7	8.8
Tranexamic acid	23	52.3	16	44.4	39	48.8
Oxandrolone	1	2.3	5	13.9	6	7.5
Short-term prophylaxis						
Danazol	0	0.0	3	8.3	3	3.8
Tranexamic acid	5	11.4	1	2.8	6	7.5
Medication in attacks						
Icatibant	3	6.8	4	11.1	7	8.8
Fresh-frozen plasma	7	15.9	9	25.0	16	20.0
C1 esterase inhibitor	8	18.2	3	8.3	11	13.8
Others	10	22.7	4	11.1	14	17.5

HAE, hereditary angioedema; *N*, number of patients.

tric and/or abdominal pain (66.3%), abdominal distension (57.5%), vomiting (35%), and diarrhea (18.7%). Prodromes have been reported as serpiginous erythema in 8.8%, and fatigue, nausea and irritability in 5% of patients. Triggering factors were identified by half of the patients (40/80) as trauma (20/40), stress (10/40), infections (5/40), exercise (3/40), and menses (2/40). 54/80 symptomatic patients reported previous visits to the emergency room. Surgical intervention, like appendectomy, occurred in 10% of patients before the diagnosis of HAE.

From 80 symptomatic patients, 44 were younger than 12 years old. Long-term prophylaxis was introduced in 52/80 (65%). Most of the patients under long-term prophylaxis were treated with tranexamic acid 39/80, followed by danazol (7/80) and oxandrolone (6/80) (Table 2). Long-term prophylaxis tranexamic acid doses ranged from 100 to 1,500 mg/day. Among the 23 patients younger than 12 years-old under tranexamic acid prophylaxis, 6 were treated with <250 mg/day, 9 were treated with 250–500 mg/day, 5 were treated with 500–750 mg/day, and 3 were treated with >1,000 mg/day (9%). Among the 16 patients above 12 years-old, 4 received 250 mg/day, 3 received 500 mg/day, 6 received 750 mg/day, 2 received 1,000 mg/day, and only 1 patient required a dose as high as 1,500 mg/day. As for danazol prophylaxis, 1 patient under 12 years was treated with doses between 100 and 200 mg/day and the other with 200–375 mg/day. Among the group of patients over 12 years, 4 used danazol 100 mg/day and one used 200 mg/day. Regarding long-term oxandrolone prophylaxis, doses varied from 2.5 to 5 mg/day.

Short-term prophylaxis was prescribed in 9/80 patients (11.3%). Tranexamic acid was used in 6/80 cases (7.5%), in doses ranging from 500 mg to 1,500 mg. Danazol was prescribed for 3 patients older than 12 years-old in doses from 100 to 200 mg (Table 2).

On-demand treatment was reported by 35/80 patients: icatibant in 7/35 (20%) with only 1 dose per attack (30 mg subcutaneous injection), fresh frozen plasma in 16/35 (45.7%) patients (10–20 mL/kg), and plasma-derived C1-INH in 11/35 (31.4%) patients with doses ranging from 300 UI to 1,000 UI. Among the drugs used on-demand, tranexamic acid was used by 12/35 (34.2%) patients at doses ranging from 250 to 2,000 mg/day.

Discussion

The early diagnosis and management of pediatric patients with HAE are challenging. Observational studies have been published with a limited number of children. We evaluated 95 HAE pediatric patients in our collaborative study after an intensive search in various reference centers. There is only one study with a similar number of patients, which is multicentric and reporting the experience of 16 centers in the UK [20]. In addition, the report

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here resulted from a collaboration of 17 reference centers on HAE in Brazil, which represents the diversity of conditions and approaches on HAE pediatric patients in our country.

The first obstacle faced by the different groups was laboratory diagnosis. Conflicting data are available to perform the diagnosis of HAE early in life [21, 22]. Considering that the mean age that the onset of symptoms occurs is approximately 8–10 years old [14] and that the delay in the diagnosis of HAE caused by C1-INH deficiency is still estimated around 10 years [1], we may presume that many pediatric patients spend most of their childhood without proper diagnosis and treatment worldwide. Furthermore, C4 screening is not recommended for patients younger than 1 year [23], and the therapy is restricted to plasma-derived C1-INH [1].

When assessing the regions in which patients were identified, the Northern and Central-West region did not present any pediatric patient. This fact probably reflects the difficult access to laboratory diagnosis and to carry out the screening of patients even if an adult family member has manifested the disease. There were no restrictions on collaboration, and the request was made to all the states belonging to these regions. It is important to note that only patients with confirmed laboratory diagnosis were included.

The family history was helpful for the diagnosis of pediatric patients. However, there was still an average time of 3.9 years until the diagnosis was confirmed. In a previous study, evaluating the specialist who identifies patients with HAE, pediatricians represented a low percentage, confirming the delay of diagnosis by pediatricians [13]. Fourteen percent of the children already had the first symptoms before 1 year of age and 53% between 1 and 5 years of age. The delay in the identification of HAE was associated with misdiagnosis, which included allergy or helminthiasis, corresponding to 30% of the cases.

Erythema marginatum is frequently described in children, occurring in approximately 50% of pediatric patients [24, 25]. However, only 8.8% of our patients reported erythema marginatum preceding the attacks. Erythema marginatum can also occur independently of angioedema attacks and may be misdiagnosed as urticaria, delaying the diagnosis [24].

Clinical characteristics during the attacks were very similar to those of adults concerning symptoms and duration of swellings. On the other hand, the percentage of children submitted to surgical procedures was lower than that previously observed by us for the whole population, including adults [23]. Although we are evaluating children, stress was also reported as a trigger for attacks. As expected, the hormonal factor has a significant influence only on adolescents.

Half of the patients used prophylactic treatment. The use of tranexamic acid for long-term prophylaxis in HAE caused by C1-INH deficiency is not effective [16], and only a few studies support its use for this purpose [26, 27]. However, in the absence of the recommended long-term prophylactic drugs, tranexamic acid has been used by a considerable number of pediatric patients described here, with an allegedly decrease in the frequency and severity of attacks. Considering the recommended dose of tranexamic acid for long-term prophylaxis is between 500 and 3,000 mg/day for adults [28], most of the physicians opted to start the prophylaxis in pediatric patients with doses as low as 100 mg/day, increasing it according to the patient's response and tolerance to the drug, reaching a maximum of 1,500 mg/day. Long-term prophylaxis has been very supportive for patients without access to specific on-demand drugs [16]. Attenuated androgens were prescribed as long-term prophylaxis for 7 pediatric patients, including 2 patients younger than 12 years old. Although no effects were reported on these patients' growth, attenuated androgens are contraindicated before puberty due to a series of substantial side effects [2, 16]. The choice of therapy in our country reflects a lack of access to better therapies. These data emphasize the necessity of a better follow-up of pediatric patients treated off-label with attenuated androgens. Furthermore, the large frequency of attacks despite the use of long-term prophylaxis indicates the poor control for these off-label prophylactic drugs in HAE children.

Concerning on-demand treatment, fresh-frozen plasma was the most frequent therapy due to a lack of access to specific drugs. On the other hand, icatibant, released only recently for the pediatric age-group, had already been used "off-label" in our population, probably due to parents' anxiety who had access to icatibant. Although plasma-derived C1-INH is approved by the Brazilian National Health Surveillance Agency (Anvisa), its use is not supported by the public health system and it is not available in emergency rooms. Although tranexamic acid is not recommended for the acute treatment of attacks [16], our real-life situation probably pushed its use. The consequence of all these limitations in our and several other developing countries reflects the misuse of old drugs and a high-risk situation [18].

Thus, we can conclude that educational programs should guide pediatricians to reduce the delay in diagnosis and provide appropriate therapy. It is critical to em-

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phasize that difficulties in accessing laboratory tests and specific drugs result in an often-inadequate approach for our patients.

Acknowledgement

We thank all participating centers for their cooperation.

Statement of Ethics

The protocol was approved by the Research Ethics Committee (CAAE 83143217.0.1001.0082). All the patients signed their written informed consent and the study was conducted according to the Declaration of Helsinki.

Conflict of Interest Statement

J.A.S. received grants from Santander and travel support from Shire/Takeda. F.S.S. received travel support and lecture fees from Shire (Takeda). R.N.C.S. received travel support from Shire. F.G.M. received travel support from Takeda and CSL. L.K.A. received lecture fees from Shire/Takeda. M.P.L.F. received lecture fees from Shire (Takeda). E.C.T. received travel support and lecture fees from Shire (Takeda) and Novartis. H.J.C.N. received travel support and lecture fees from Shire (Takeda), Sanofi, and Mylan. R.C.A. received travel support and lecture fees from Shire (Takeda), C.S.L. Behring, and Novartis. P.R.J. received lecture fees from Takeda and CSL Behring. A.S.G. has been a speaker or consultant for BioCryst, Biotest, CSL Behring, and Shire. The other authors declare no conflict of interest.

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Authors Contributions

J.A.S. and C.L.V. performed data analysis and wrote the manuscript; R.N.C.S. and C.L.V. performed laboratory analysis and interpretation; J.A.S., A.G.P.B., N.T.M.L.F., J.A.P., F.M., R.F.G., S.R.V., M.L.O.A., S.D.J., E.S.G., A.M.R.S., M.M.M., F.S.S., J.H.C.N., N.R., E.M., I.F.M., A.S.M., L.K.A., P.R.J., M.P.L.F., J.S., J.F.S.F., P.G.B., P.M.T., L.F.E., R.C.A., E.T., J.B.P., S.M.U.P., and A.S.G. collected sample data and reviewed manuscript for content; A.S.G. conceived the study and wrote the manuscript.

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