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Hereditary angioedema in children and adolescents

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Abstract
Hereditary angioedema is a genetic disease with autosomal dominant inheritance and, in most cases, caused by C1 inhibitor deficiency. Patients present with recurrent edema affecting subcutaneous and mucus membranes with variable onset and severity. More than 50% of patients may become symptomatic before 10 years of age. Family history can help with the diagnosis; however, approximately 25% of the cases are *de novo* mutations. Biochemical diagnosis should be delayed until after 1 year of age. Children were often excluded from advances in therapy for hereditary angioedema since most of the new medicines were tested in adults and thus excluded by the Food and Drug Administration (FDA) and other agencies for approval to be used in children. Treatment of attacks is available for the pediatric patient; however, barriers still exist for the use of long-term prophylaxis in young children.

Introduction

Hereditary angioedema (HAE) is a genetic disease characterized by isolated (without urticaria), self-limited, and recurrent episodes of edema of the deep layers of skin and mucosa, commonly causing swelling of extremities (hands, feet, limbs), face, lips, tongue, genitalia, bowels, and the upper airway. Swelling attacks are transitory and usually last from 2 to 5 days, but their severity and frequency vary widely from patient to patient. Attacks can range from one debilitating attack per week to as little as one mild attack per year, with some patients being totally asymptomatic.[1] In the most frequent subtype, HAE with C1 inhibitor (C1-INH) deficiency (HAE-C1INH, OMIM #106100), the first HAE episodes occur at a mean age of 10 years.[2] However, the onset of symptoms may occur at an early age, including

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a recent report of an in-utero swelling of lips and legs just before delivery.[3]

The development of new drugs for the treatment of HAE has potentially prevented many fatal attacks and has significantly reduced morbidity. Although there are many novel therapies and improvement of the knowledge about HAE, the influence on the care of the child has been limited.[4,5] One of the main reasons for the exclusion of children from these advances is that most of the clinical trials have recruited mainly adults.

When the patient is a child, research and clinical interventions must take into account the needs and engagement of both the child and family caregivers. In chronic diseases, caregivers play a crucial role in assisting children to adjust physically and psychologically to a disease state.[6] Above all other aspects, the issue of uncertainty, which is intrinsic to the HAE experience, is often considered more distressing than the impact of physical symptoms.[7,8] Lack of adherence to therapy is a well-recognized factor reducing the quality of life (QoL) in adults, and we must assume that the lack of adherence to therapy, whether or not the result of the caregiver or the child, would also decrease the QoL of a child. The aim of this manuscript was to improve awareness about HAE in children for both health care providers and caregivers.

Pathophysiology and Diagnosis

The diagnosis of HAE-C1INH is confirmed by the presence of classical clinical symptoms and family history of the disease, associated with low plasma levels of C4 and low C1-INH function. In most of the patients with HAE-C1INH (85%), the quantitative plasma levels of C1-INH will also be decreased, usually below 50% of the normal values, characterizing the HAE-C1INH type I, in which deleterious mutations in the gene encoding to C1-INH (*SERPING1*) cause a reduction in the secretion of the inhibitor to the circulation. Less frequently (15% of cases), HAE-C1INH is characterized by a functional defect of C1-INH, which is secreted in a molecular conformation not able to inhibit its targets, but present in normal or even high concentrations in plasma (type II). Although HAE-C1INH is a genetic disease transmitted in an autosomal dominant inheritance, approximately 5 to 25% of cases are due to *de novo* mutations in the gene *SERPING1*,[9,10] and the absence of family history should not discourage the measurement of C4 and C1-INH in plasma.

International guidelines recommend the measurement of C4 and C1-INH in two independent samples collected on different days and out of attacks to confirm the diagnosis of HAE-C1INH.[11,12] Although not necessary for most of the patients,[13] the genetic sequencing of the *SERPING1* gene can be supportive in cases where there are inconsistent assessments of C4 and/or C1-INH, or in patients below 1 year of age.[2] *SERPING1* analysis may also be helpful in the differential diagnosis of patients presenting with a late onset of symptoms (>40 years old) and without family history, in which C1-INH deficiency may be acquired.

Patients presenting with normal C1-INH but with clinical symptoms and family history of angioedema are diagnosed as having HAE with normal C1-INH (HAE-nl-C1INH), previously described as HAE type III. Symptomatically, HAE-nl-C1INH is very similar to HAE-C1INH, with higher mean age at the onset of symptoms (around 20 years of age), incomplete penetrance in affected males, and a remarkable influence of estrogens as trigger of attacks in female patients.[14-17] In HAE-nl-C1INH, the most common affected gene is *F12*, coding for the factor XII protein (HAE-F12). All the pathogenic mutations described in HAE-F12 are located at the exon 9 of the gene, and its sequencing is currently the only method to confirm the diagnosis, since no biochemical changes can be identified in the circulant factor XII of HAE-F12 patients.[13] In the last 3 years, rare mutations found in five new genes were associated with HAE-nl-C1INH: angiopoietin 1 (*ANGPT1*),[18] plasminogen (*PLG*),[19] kininogen (*KNG1*),[20] myoferlin (*MYOF*),[21] and heparan sulfate 3-O-sulfotransferase 6 gene (*HS3ST6*).[22] None of these new variants associated with HAE-nl-C1INH are recommended to be included in the routine molecular diagnosis,[13] since they were found in single families, with the exception of the variant p.Lys330Glu in *PLG*, which has been identified in many families from different nationalities.[17] Therefore, the analysis of the *PLG* variant may be considered in the absence of mutations in the exon 9 of *F12*.

Treatment of HAE

The understanding of the pathophysiology of HAE I/II enabled the development of more specific and effective treatments for HAE.[1] These treatments are approved in several countries for adults and adolescents and, in some, for children (Table 1). Moreover, data on the efficacy and safety, as well as guidelines for the management of pediatric HAE remain, to date, limited.[2,23,24] As in adults, the approach to HAE therapy in children includes the treatment of attacks, referred to as on-demand, short-term prophylaxis (STP), often referred to as preprocedural, and long-term prophylaxis.

Treatment of attacks

Early treatment of attacks is advocated to reduce the severity, duration, morbidity, and possible mortality of HAE attacks, as well as the need for hospitalization and emergency department treatment.[25] For these reasons, all patients and/or caregivers must be encouraged and trained to self-administer their prescribed therapy.[25] Therefore, drugs approved for self-administration are preferred to improve QoL and decrease the burden of disease.[1,26-28]

Intravenous plasma-derived C1-INH (pdC1-INH) has been used for decades in Europe and has proved to be safe and effective even in pregnancy and in very young children for the treatment of HAE attacks. pdC1-INH is recommended for attacks at the dosage of 20 IU/kg for all ages.[29-31] The recommended dose not based on patients' weight and based on 10 IU/kg showed less efficacy, even needing a second dose for laryngeal attacks.[29,30,32]

Special consideration is that pdC1-INH is a human blood product, a limiting factor in some religious communities.[12] Intravenous recombinant human C1-INH (rhC1-INH), obtained from rabbit milk, was demonstrated to be safe

Table 1 Drugs for acute treatment, short-term prophylaxis, and long-term prophylaxis in the management of pediatric HAE.

Drug	Acute treatment	Short-term prophylaxis	Long-term prophylaxis
Androgens (danazol, oxandrolone, stanozolol)	Not recommended	Avoid use. 10 mg/kg/d and ≤ 200 mg/d for danazol, 5 d before & 2-3 d after procedure/trigger. Oral	Avoid use. If necessary, 10 mg/kg/d and ≤ 200 mg/d for danazol, after puberty (Tanner 5). Oral
Antifibrinolytics (tranexamic acid, Epsilon aminocaproic acid)	Not recommended	Not recommended	Tranexamic acid: 10 mg/kg/d bid to 25 mg/kg/d tid. Limit dosage 3g/d. Oral
Berotralstat	Not approved	Not recommended	Approved in some countries for 12 y or older. 150 mg/d. Oral
Ecallantide	Approved in some countries for ≥12 y. 30 mg SC. Self-administration is not allowed due to anaphylaxis	Not recommended	Not recommended
Fresh frozen plasma	May be used, if other on-demand medications are not available. 10 mL/kg IV. No age limit	May be used, if other STP medications not available. 10 mL/kg IV. No age limit	Not recommended
Icatibant	Approved for ≥18 y in some countries, ≥2 y in others. 30 mg/3mL. Dose adjustment is needed for adolescent/children <65 kg/≥2 y. SC	Not approved	Not approved
Lanadelumab	Not approved	Not approved	300 mg every 2 weeks. After 6 months, if no attacks: 300 mg every 4 weeks. >12 y. SC
pdC1-INH nanofiltrated*	20 IU/kg IV (No age limits)	20 IU/kg IV (No age limits) 1 to 6h before procedure/trigger. IV	Approved for ≥12 y in some countries, ≥6y in others. 1000 IU in ≥12 y. 6 to 12 y 500 UI. q 3-4 d. IV
SC pdC1-INH nanofiltrated	Not approved	Not approved	60 IU/kg twice weekly. >12 y. SC
rhC1-INH/conestat alfa	Approved for ≥12y in some countries, ≥2y in others. 50 IU/kg, max. 4200 IU (50 IU/kg <84 kg, 4200 IU >85kg) IV	Not approved	Not approved

*There are two commercial drugs in use.
bid, twice a day; C1-INH, C1 inhibitor; d, day; HAE, hereditary angioedema; IU, international unit; IV, intravenous; pd, plasma-derived; q, every; rh, recombinant human; SC, subcutaneous; STP, short-term prophylaxis; tid, three times a day; y, years.[1,20,26,30,53]

and effective as a therapy for HAE attacks. It is important to mention that the difference in glycosylation results in shorter plasma half-life. In addition, the effective dose was 50 IU/Kg, far greater than that required for human-derived C1-inhibitor. Rabbit-derived C1-inhibitor should be avoided in patients with known rabbit allergy. rhC1-INH was approved for patients older than 12 years old in some countries and ≥2 years in others.[32,33]

The subcutaneous kallikrein inhibitor, ecallantide, a 60-amino acid recombinant protein, is effective for acute HAE attacks in adolescents and adults and is available in some countries. Due to the risk of anaphylaxis, in approximately 3-4%, it is not approved for home administration.[2,32]

Subcutaneous icatibant, a synthetic selective bradykinin B2 receptor competitive antagonist, is approved for HAE patients ≥2 years of age in the EU and other countries, but in the USA for adults only. The dose adjustment is needed for adolescents/children (0.4 mg/kg). Approximately, 10% of patients, in some studies, require a second dose for re-emergent symptoms, although in others a smaller proportion of patients needed a second dose.[34,35] Additional injections may be administered after 6 hours of the previous dose, reaching up to a maximum of three in 24 hours. Icatibant is effective and well tolerated, but mild injection site reactions are common and occur in 97% of the patients.[35,36] The recent approval of multiple generic icatibant drugs has significantly reduced the cost of therapy of HAE and hopefully will improve access in lower income counties.

As a last resort, C1-INH replacement with intravenous fresh frozen plasma (FFP) is a reasonable alternative in

all ages, despite the lack of evidence. In addition, there are some theoretical concerns that FFP may aggravate angioedema by providing, apart from C1-INH, substrates for more BK production; however, published data to support this are lacking.[28,37] Finally, antifibrinolytics, such as tranexamic acid, are not recommended as a treatment option for HAE attacks and when used as a comparator to icatibant in the EU, while placebo was used as a comparator in the USA, both comparators were similar in efficacy.[1]

STP of HAE

Manipulating the upper airway is a known trigger of HAE attacks. This includes surgery near the upper airway as well as dental procedures and endoscopy.[38,39] In light of this, STP is suggested to decrease the risk of upper airway swelling and asphyxia. Therapies include FFP, antifibrinolytics, attenuated androgens, and C1-INH with varying degrees of success.[40] Presently, preprocedural prophylaxis with C1-INH 20 IU/kg concentrate intravenously, approximately 1 hour before the procedure, is the recommended option.[41] An observational study described that despite using an established dose of 500 IU or 1000 IU, independently of body weight, attack occurrence after the procedure was not uncommon.[40] For this reason, it is recommended to prescribe plasma-derived C1 inhibitor at a dose of 20 IU/kg. As an example, for a person weighing 80 kg, a dose of 1500 IU should be infused before the procedure. Even with STP, on-demand treatment should be available for breakthrough attacks.[1,11,41,42]

Long-term prophylaxis of HAE

Nonpharmacological preventive measures are suggested to be instituted whenever possible. Rigorous exercise, trauma, infections, and stress are known triggering factors and avoiding them, if possible, is advisable. However, the prevention of attacks based on this approach is quite difficult and affects QoL.[43,44] For this reason, long-term prophylaxis (LTP) is indicated to allow children to have a normal life and do the same activities as the other children. In addition, it is recommended to keep preventive therapy up to date to include vaccines and dental procedures.[1]

LTP in children and adolescents, like in adults, is indicated to reduce the frequency, duration, and severity of HAE attacks, and to improve QoL.[45] As in adults, LTP is not 100% effective and as such, on-demand therapy is always essential to be readily available. It is important to keep in mind that children and adolescents are influenced by stressors, hormonal and lifestyle changes differently than adults, so LTP must be flexible and adjusted accordingly.[1,23,46] The main concerns in prescribing LTP for children is that androgens have a possible impact on growth, likely leading to early epiphyseal closure. Moreover, other side effects observed in adults, such as weight gain, menses irregularity, hyperlipidemia, and aggressive behavior have also been observed in children.[23,24,47]

Intravenous nanofiltrated pdC1-INH has been used for over a decade and has proved to be highly safe and effective. For that reason, it is considered the first-line treatment for LTP of HAE in children. The recommended dose is 20 units per kg[48] and objective evidence suggests that a dose of 20 IU/kg may be more effective than a fixed one of either 500 or 1000 units.[49]

A subcutaneous pdC1-INH nanofiltrated for HAE LTP for adults and adolescents 12 years or older was recently approved in some countries. This treatment proved to be safe and effective at the dose of 60 IU/kg twice weekly (every 3 to 4 days).[50] The reduction of attacks was demonstrated by a median reduction of about 95% and a mean reduction of approximately 85%.[45,50] Presently SQ-C1-INH is approved for patients aged ≥6 years.[28]

Lanadelumab, a human kallikrein inhibitor monoclonal antibody, is a subcutaneous LTP for HAE patients 12 years or older. As with IV or SC pdC1-INH, lanadelumab is considered as the first-line treatment. The dose is 300 mg every 2 weeks; after 6 months, with full control of attacks, the patient may be switched to 300 mg every 4 weeks.[28,42,51]

Berotralstat, a small molecular inhibitor of kallikrein, was recently approved in some countries, for 150 mg once daily oral LTP of HAE in adolescents (≥12 years old) and adults. This drug demonstrated to be safe and reduced the frequency of attacks of HAE by approximately 50%. The main limiting factor was gastrointestinal adverse effects.[52,53]

For countries with limited access to newer, more effective treatments for LTP of HAE, especially in children and adolescents, oral antifibrinolytics, like tranexamic acid, are less likely to induce adverse effects compared to androgens, but in turn are not as effective as androgens. Therefore, their efficacy is low compared to other LTP treatments, and antifibrinolytics are contraindicated in hypercoagulable states. The recommended dose of tranexamic acid ranges from 500 to 3000 mg/day for adults and adolescents, and in children the initial dose was as low as 100 mg/day, increasing as needed to a maximum of 1500 mg/day. In low-income countries this may be the best available therapy; however, in high-income countries antifibrinolytics use is discouraged.[1,2,24]

Oral attenuated androgens (AA), like danazol, oxandrolone, and stanozolol, are considered effective but, due their low safety profile, are not considered as the first-line treatment for LTP of HAE. This is especially true for children where the adverse events supersede the benefit. AA must be avoided, especially before puberty Tanner Stage V and if administered, careful safety monitoring is warranted. Danazol can be started at the dose of 2.5 mg/kg/day and increased as needed to a maximum of 200 mg/day (2.5 to 10 mg/kg/day and ≤ 200 mg/day).[1,2,24,28]

In summary, data on the use of the therapies for on-demand, STP, and LTP in children are mainly extrapolated from data collected from clinical trials that recruited adults. Nonetheless, it appears that the safety of many of the products, especially C1 inhibitor, suggests that their use for STP and LTP in children is acceptable. Despite this comment, more studies are needed to truly assess best therapies in children with HAE.

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