Allergol Immunopathol (Madr). 2013;41(1):45–53

Allergologia et immunopathologia

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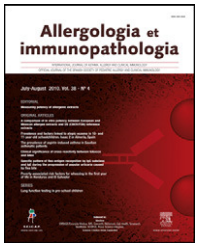

REVIEW

Angio-oedema due to hereditary C1 inhibitor deficiency in children

T. Caballero

Servicio de Alergia, Hospital La Paz Health Research Institute (IdiPaz), Biomedical Research Network on Rare diseases-U754 (CIBERER), Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain

Received 8 November 2011; accepted 2 January 2012
Available online 13 March 2012

KEYWORDS
Angio-oedema;
Hereditary angio-oedema;
C1-inhibitor;
C1 inhibitor deficiency;
Children;
Treatment;
Diagnosis

Abstract Hereditary angio-oedema due to C1 inhibitor deficiency (HAE-C1-INH) is a rare inherited disorder characterised by recurring and debilitating episodes of cutaneous swelling and abdominal pain and less frequent episodes of laryngeal oedema. Symptom onset is usually in childhood and early adolescence, with earlier disease onset associated with greater disease severity. Although HAE-C1-INH attacks are generally less frequent and less severe in children than in adults, they can cause significant physical and psychological impairment and affect advancement in school. There are often significant delays in the diagnosis of HAE-C1-INH due to its variable clinical presentation and because abdominal symptoms can often mimic other common paediatric gastrointestinal disorders. In recent years, several disease-specific agents have become available for the acute and prophylactic treatment of HAE-C1-INH. Although these treatments have not been evaluated rigorously in controlled clinical trials in children with HAE-C1-INH, paediatric data on efficacy and safety are available for some agents. Early diagnosis and initiation of appropriate therapy in children with HAE-C1-INH can help reduce the burden of this illness in the paediatric population.

Introduction

Hereditary angio-oedema due to C1 inhibitor deficiency (HAE-C1-INH) is a rare genetic disorder characterised by recurrent episodes of oedema, usually in the subcutaneous or submucosal tissue of the skin, gastrointestinal (GI) tract and upper airways.[1] There are two types of HAE-C1-INH: type I is characterised by low C1-INH level and activity, whereas type II is characterised by low C1-INH activity in the presence of normal or even elevated C1-INH levels and occurs less frequently (type II disease accounted for only 6.3% of HAE-C1-INH cases in a Spanish registry[2]).

Cutaneous symptoms manifest as non-pitting, non-pruritic swelling of the extremities, face, trunk and genitals. Gastrointestinal symptoms present as recurring attacks of severe abdominal pain, often accompanied by nausea, vomiting and/or diarrhoea. Laryngeal oedema, which may be mistaken for allergic asthma or epiglottal inflammation, may lead to asphyxiation and possibly death if not treated promptly.[1,3–5] Clinical symptoms usually appear in childhood or early adolescence, with ~90% of patients exhibiting

E-mail addresses: mteresa.caballero@idipaz.es, tcaballero.hulp@salud.madrid.org

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doi:10.1016/j.aller.2012.01.002

clinical signs of HAE-C1-INH before the age of 20.[6] Thus, the diagnosis and management of HAE-C1-INH is within the purview of the paediatric allergist/immunologist. This article provides a review of HAE-C1-INH, with a focus on its clinical presentation, diagnosis and management in children.

Epidemiology and pathogenesis

HAE-C1-INH is estimated to occur in 1 in 50,000 individuals, although accurate epidemiological data are lacking.[7,8] A recent study based on a Spanish HAE-C1-INH patient registry estimated the minimal prevalence of HAE-C1-INH in Spain to be 1.09 per 100,000 inhabitants.[2] However, given that HAE-C1-INH is a rare disorder and is often misdiagnosed or undiagnosed, the actual prevalence in Spain is likely higher.[2] All ethnic/racial groups are supposed to be affected equally,[7] although no systematic epidemiological study has been performed. There is no sex predominance in the prevalence of HAE-C1-INH, but women are known to have a more severe disease course and more frequent episodes, possibly due to the effects of oestrogen.[6]

HAE-C1-INH is due to mutations in the *C1INH* gene (*SERPING 1*) that codes for C1-INH, a serine protease that regulates vascular permeability by inhibiting various factors in the complement, coagulation and contact (kinin-forming) pathways.[8] C1-INH regulates the initial step of the complement cascade by preventing autoactivation of C1; blocks both MASP-1 and MASP-2; inhibits factor XI in the coagulation system; and inhibits factor XII and kallikrein in the contact system.[8] Hundreds of *C1INH* gene mutations have been described, and these may be spontaneous in up to 25% of cases.[7,9–11] Mutations of the *C1INH* gene can give rise to either absolute deficiency of C1-INH (type I HAE-C1-INH) or production of a non-functioning C1-INH protein (type II HAE-C1-INH).[7]

Deficiency or reduced function of C1-INH leads to cleavage of C4, cleavage of high-molecular-weight kininogen (HMWK) by kallikrein, and uninhibited plasmin generation, all of which result in the release of bradykinin and other vasoactive peptides.[8] Bradykinin, thought to be the primary mediator of swelling in HAE-C1-INH, plays an important role in the regulation of many inflammatory responses and mediates pain by stimulating nociceptive C-fibres. Excess production of bradykinin results in increased vascular permeability, vasodilation, nonvascular smooth muscle contraction, and oedema[12] and the symptoms typically associated with HAE-C1-INH, including oedema and swelling, erythema, hypotension and cramps and pain.

Clinical presentation of HAE-C1-INH in children

Symptoms of HAE-C1-INH typically begin in childhood—generally between 5 and 11 years of age.[13] In a study performed in Spain, 86.3% of patients had a history of symptoms, with a mean age at beginning of clinical symptoms of 12.6 ± 10.5 years (range 0–65 years).[2] Patients with early symptom onset have more severe disease than those with later onset, although the reasons for this observation are not known.[6] Oedema may occur in subcutaneous and/or submucosal tissue of any organ, but it most commonly affects the skin, GI tract and upper airways.[1]

The most common and earliest manifestation of HAE-C1-INH in children is subcutaneous non-pitting, non-pruritic oedema of the extremities, neck, face, torso and genitals (Table 1).[13] Although subcutaneous oedema of the extremities does not progress to a more serious condition and generally resolves within two to four days, such episodes are a common cause of absenteeism from school and can affect a child's advancement in school.[13] Severe oedema of the extremities can be painful and restrict circulation in the affected limb.[13] Oedema of the neck and chest may be complicated by compression and difficult and painful breathing.[13] Facial oedema is known to progress to laryngeal oedema in about one-third of patients.[6]

Table 1 Special considerations in children with HAE-C1-INH.

Clinical presentation
• Patients with early symptom onset have more severe disease than those with later onset
• Recurrent, colicky abdominal pain is observed in 40% to 80% of children with HAE-C1-INH
• Children are particularly susceptible to obstruction from laryngeal oedema
• Most common presentation is cutaneous oedema of the extremities, neck, face, torso, and genitals
Prodromal symptoms
• Attacks in children are commonly preceded by a non-pruritic, non-raised rash (erythema marginatum)
Frequency and severity
• Children generally have less frequent and less severe attacks compared with adults and adolescents
• Frequency and severity of symptoms appears to increase between three and six years of age and during puberty
Most common triggers
• Mechanical trauma
• Mental stress
• Airway infection
• Menses
Comorbidities
• Prevalence of celiac disease among children with HAE-C1-INH is significantly higher than in the general population
• *H. pylori* infection may exacerbate HAE-C1-INH attacks
Diagnosis
• Complement levels can be measured initially in infants of any age with a family history of HAE-C1-INH, but should be repeated at one year of age to avoid false diagnosis.
• Children who present with recurrent episodes of subcutaneous swelling and/or severe abdominal pain should be evaluated for HAE-C1-INH

Gastrointestinal HAE-C1-INH attacks are often associated with colicky, cramping abdominal pain, nausea, vomiting, dehydration and diarrhoea.[14] Abdominal oedema is a common presenting symptom in children with HAE-C1-INH, and recurrent, colicky abdominal pain is observed in 40–80% of children with HAE-C1-INH.[15] Because these symptoms overlap with those of other paediatric acute abdominal disorders, GI HAE-C1-INH attacks are often mistaken for other disorders such as appendicitis, with one in five patients undergoing unnecessary surgery secondary to misdiagnosis.[16] Therefore, recurrent abdominal pain without known cause in a child, particularly a child with family history of such symptoms, should raise suspicion of HAE. GI attacks of HAE-C1-INH are not accompanied by pyrexia or increases in laboratory measures of inflammation, distinguishing them from common intestinal infections.[13] However, leucocytosis is often detected, together with haemoconcentration due to fluid loss.[1] Abdominal ultrasound obtained during an attack can help in the differential diagnosis.[17] Free peritoneal fluid, intestinal wall oedema and structural abnormalities of the liver are characteristic signs.[13]

Oedema of the upper airways may lead to asphyxiation and death if not treated promptly. Children are particularly susceptible to obstruction from laryngeal oedema due to the smaller airway diameter, decreased physiological reserve and weaker respiratory muscles.[18] The risk of laryngeal oedema is highest between the ages of 11 and 45, although laryngeal attacks have been reported in children as young as three years of age.[4,13] About 50% of patients experience a laryngeal attack during their disease course.[6] In children with HAE-C1-INH, oedema has a propensity for the face and neck, where it can expand to include the uvula, soft palate, or larynx.[5] Laryngeal oedema in an HAE-C1-INH patient may be misdiagnosed as allergic asthma or epiglottitis.[13,19,20] One factor that can help in the differential diagnosis is the response to standard therapy with glucocorticoids, antihistamines and epinephrine. Although these agents are highly effective in treating airway oedema due to allergic/inflammatory factors (e.g. anaphylaxis, allergic asthma), they are ineffectual in relieving airway oedema associated with HAE-C1-INH.[13]

The majority of patients report prodromal symptoms such as unusual fatigue, rash, muscle aches, abdominal pain and nausea 12–24 h before an HAE-C1-INH attack.[21] In up to 58% of cases, an HAE-C1-INH attack is preceded by a non-pruritic, non-raised rash called erythema marginatum.[13] This characteristic sign is even more common in children with HAE-C1-INH but may be mistaken for signs of a bacterial or viral infection or be misdiagnosed as urticaria.[13]

The frequency, severity and duration of HAE-C1-INH attacks is highly variable, with some patients experiencing one or more severe attacks per week and others experiencing long attack-free periods lasting several years. The attack pattern may vary significantly, even within the same family. Children generally have less frequent and less severe attacks compared with adults and adolescents.[15,22] Frequency and severity of symptoms appears to increase between three and six years of age and during puberty, probably due to the various physiological changes occurring during these developmental stages.[13]

Various factors can trigger HAE-C1-INH attacks, including trauma; emotional stress; surgical, medical, or dental procedures, particularly those that involve manipulation of the head or neck; hormonal changes (e.g. puberty, menses, pregnancy); infections; and certain drugs (e.g. angiotensin-converting enzyme [ACE] inhibitors, oestrogen-containing oral contraceptives).[7] In children, the most common triggers of attacks were found to be mechanical trauma (52%), mental stress (36.8%), airway infection (36.8%) and menses (26.7%).[13] Infection with *Helicobacter pylori* has also been shown to exacerbate abdominal attacks of HAE-C1-INH.[23] Eradication of *H. pylori* has been shown to reduce the frequency and severity of GI attacks in HAE-C1-INH patients who are positive for *H. pylori*.[23,24] Dentition is a specific trigger of attacks in children.[5] The prevalence of celiac disease among children with HAE-C1-INH is significantly higher than in the general population (18.1% vs. 1.2%).[25] Because both HAE-C1-INH and celiac disease are associated with abdominal symptoms, diagnosis of both diseases may be complicated by overlapping symptoms. Management of celiac disease through dietary changes (i.e., switching to gluten-free diet) has been found to help mitigate the abdominal symptoms of HAE-C1-INH.[25]

Diagnosis of HAE-C1-INH in children

A family history of disease is present in about 75% of patients with HAE-C1-INH. Therefore, children with immediate or extended family members with HAE-C1-INH should be screened for the disease, even if they are asymptomatic. Analysis of complement levels, specifically C4 level, C1-INH level and C1-INH functional activity can help establish the diagnosis of HAE-C1-INH. Measurement of C4 level may be an effective screening tool since C4 levels are almost always low in those with HAE-C1-INH, even between attacks.[1,7]

Acquired C1-inhibitor deficiency may occur among paediatric patients. Therefore, the laboratory screening of children without family history should also include the measurement of C1q along with the detection of autoantibodies against the C1-inhibitor.

The concentration of C1-INH in the umbilical blood of healthy neonates is approximately two-thirds that of a normal adult.[26] The normal values of C1-INH and complement proteins show age-dependent changes, and concentrations reach levels for mature adults between 6 and 36 months for C1-INH and between two to three years of age for C4.[27,28] Therefore, complement levels can be measured initially in infants of any age with a family history of HAE-C1-INH, but should be repeated at one year of age to avoid false diagnosis.[1,5,13] A normal C1-INH level does not rule out an HAE-C1-INH diagnosis, as HAE-C1-INH type II is characterised by normal or high C1-INH levels. The distinction between type I and type II HAE-C1-INH is merely a diagnostic one. Clinical presentation and the treatment approach are the same for both types of HAE-C1-INH. Molecular genetic analysis is not necessary for a diagnosis but may be of help in cases where complement levels are borderline low.[1,13] Although C1-INH antigen level does not correlate with severity of disease, baseline C1-INH functional activity does appear to correlate with disease severity scores.[29]

Table 2 Therapeutic options for the acute and prophylactic treatment of children with HAE-C1-INH.

Product/manufacturer	Dosage/administration	Use in children
Acute treatment		
Plasma-derived, pasteurised C1-inhibitor (Berinert®, CSL Behring)	20 U/kg administered via IV injection	Approved dose in children: 20 U/kg for the treatment of acute attacks
Plasma-derived, pasteurised, nanofiltered C1-inhibitor (Cinryze®, ViroPharma)	1000 U administered via IV injection or infusion	Approved for acute treatment in adolescents; paediatric data (0–12 years) available
Recombinant human C1-inhibitor (Ruconest®, Pharming)	50 U/kg (for body wt $\leq$84 kg) administered via slow intravenous injection	Not approved for use in children or adolescents; adolescent data (13–17 years) available; no paediatric data (0–12 years) available
Icatibant (Firazyr®, Shire)	30 mg by subcutaneous injection	Not approved for use in children or adolescents (0–18 years); no paediatric data available
Ecallantide (Kalbitor®, Dyax)	30 mg by subcutaneous injection as 3 injections of 10 mg (1 mL) each	Not approved in the EU; approved in the US for adolescents >16 years
Fresh frozen plasma		
Routine prophylactic treatment		
Attenuated androgens (e.g. danazol, stanozolol)	Danazol: 2.5 mg/kg/d	Not recommended for prophylaxis until pubertal growth complete
Pasteurised, nanofiltered C1-inhibitor (Cinryze®, ViroPharma)	1000 U administered via IV injection or infusion	Approved for preprocedural and routine prophylactic treatment in adolescents; paediatric data (0–12 years) available
Antifibrinolytic agents (e.g. tranexamic acid [TXA], epsilon aminocaproic acid [EACA])	TXA: 20–40 mg/kg/d EACA: 0.17–0.43 g/kg/d	Preferred to androgens due to more favourable safety profile

In about 25% of cases, HAE-C1-INH is due to spontaneous genetic mutations[9,10]; thus, absence of a family history does not exclude the diagnosis. Children who present with recurrent episodes of subcutaneous swelling (e.g. extremities, face, trunk, genitals) and/or recurring severe abdominal pain with or without nausea, vomiting, and diarrhoea should be evaluated for HAE-C1-INH using laboratory assessment of complement levels.

Treatment of HAE-C1-INH in children

Treatment begins with the identification and possible elimination of factors that can trigger or exacerbate HAE-C1-INH attacks (Table 2). As discussed, dentition, mechanical trauma, psychological stress and airway infection are common triggers of HAE-C1-INH attacks in children. Restriction of physical activities is not recommended, but should be decided on an individual basis.[30] Prompt treatment of upper airway infections is an important step in reducing the frequency of attacks.[13] Screening for *H. pylori* infection or celiac disease may be considered for children with frequent abdominal attacks.[24,25] Oestrogen-containing oral contraceptives should not be prescribed for adolescents with HAE-C1-INH.[30–32] Children with HAE-C1-INH should also be up to date with all recommended immunisations.[13] Hepatitis B immunisation is especially recommended, as patients with HAE-C1-INH are often treated with plasma derivatives.[7,30]

Typically, HAE-C1-INH pharmacological treatment includes treatment of acute attacks, short-term prophylaxis (also known as preprocedural prophylaxis) and long-term prophylaxis (also called maintenance treatment or routine prevention). The indications for acute treatment, short-term prophylaxis and long-term prophylaxis in children are the same as for adults.[30]

Acute treatment of HAE-C1-INH in children

An acute HAE-C1-INH attack should be treated as soon as possible after symptom onset. All episodes of upper airway oedema and cervicofacial oedema should be treated to avoid asphyxia secondary to glottis oedema. Most episodes of abdominal oedema should also be treated to avoid progression and the risk of hypovolemic shock. It may be argued that peripheral oedema (e.g. of the extremities) does not require immediate treatment, but peripheral oedema can be debilitating, particularly if it affects the ability to walk and the ability to write. Although several agents have recently become available for the treatment of HAE-C1-INH, including three formulations of C1-INH, icatibant and ecallantide, there is a lack of controlled data in paediatric HAE-C1-INH patients (Table 2).

Pasteurised, plasma-derived human C1-INH concentrate (pdhC1-INH) (Berinert®, CSL Behring) has been in use in Europe for more than 25 years. The product is administered by intravenous injection and is used for the treatment

of acute attacks of HAE-C1-INH. In Europe, this product is approved at a dose of 20 U/kg for acute treatment of HAE-C1-INH attacks in children and adults.[33] In the United States, Berinert is indicated for the treatment of facial and abdominal attacks in adult and adolescent patients. The FDA considered that clinical trials did not enrol sufficient numbers of children 0–12 years of age to assess safety and efficacy in this population.[34] Nevertheless, pdhC1-INH has been widely used in children in Europe and has been proven to be efficacious and well tolerated.[5,35,36]

In two clinical trials (one randomised, double-blind, placebo-controlled trial and an open-label extension study), pdhC1-INH treatment at a dose of 20 U/kg was found to provide symptom relief during facial, abdominal and laryngeal attacks, with a median time to onset of symptom relief of 0.46 h after administration.[37,38] In the two trials, one child <12 years of age and six adolescents <17 years of age were included, but data were not analysed independently, as the sample was too small.[37,38]

Thrombosis has been reported with off-label use of pdhC1-INH in neonates with conditions other than HAE-C1-INH at doses above 200 U/kg,[39] which are much higher than those used for HAE-C1-INH.[37] The pro-coagulatory effect of high doses of pdhC1-INH has been confirmed in an animal model.[40] However, this effect has not been observed when pdhC1INH is used as acute treatment at recommended doses in patients with HAE-C1-INH or acquired angio-oedema (AAE-C1-INH) or in studies conducted with doses of 100 U/kg in infants undergoing surgery to correct transposition of the great arteries.[41,42]

A plasma-derived, pasteurised, nanofiltered C1-INH formulation (nfC1-INH, Cinryze®, ViroPharma Incorporated) was recently approved in Europe for the acute, preprocedural and routine prophylactic treatment of oedema attacks in adults and adolescents with HAE-C1-INH. It is already approved in the United States for routine prophylaxis against oedema attacks in adults and adolescents with HAE-C1-INH. Although no recommendations on posology for children under 12 years has been made in the European labelling for this product, clinical data from paediatric patients are available.[43,44] In a multicentre, open-label trial, nfC1-INH was evaluated in HAE-C1-INH patients aged $\geq$1 year, 22 of whom were <18 years of age.[44] In this study, nfC1-INH 1000 U was administered intravenously after an attack, with a second dose administered 60 min later if required. Symptoms were assessed at 15-min intervals within the 4-h post-treatment period. Symptom relief was defined as three consecutive assessments of improvement within the 4-h treatment period. The 22 paediatric patients in the study experienced a total of 121 attacks of HAE-C1-INH; gastrointestinal attacks were the most common manifestation. In 89% of HAE-C1-INH attacks, symptom relief was achieved within 4 h of nfC1-INH administration. Of the 64 gastrointestinal attacks, 97% of those occurring in children 6–11 years of age and 89% of those occurring in children 12–17 years of age improved within 4 h after nfC1-INH administration. None of the children who experienced a laryngeal attack required intubation. No treatment-related adverse events occurred, and no subjects discontinued treatment. In addition, no subject had clinically relevant anti-C1-INH antibodies or evidence of transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).[44] Venous thrombosis is listed as an uncommon adverse reaction with suspected relationship to nfC1-INH in clinical trials.[43]

The safety of nfC1-INH in children has been evaluated. Across the nfC1-INH clinical trial program, 46 unique paediatric subjects were enrolled and exposed to nfC1-INH (2–5 years, $n = 3$; 6–11 years, $n = 17$; 12–17 years, $n = 26$). Among these children, the only adverse reactions were headache, nausea, pyrexia and infusion-site erythema. None of these adverse reactions were severe, and none led to discontinuation of nfC1-INH.[43]

A recombinant human C1-INH formulation (rhC1-INH, Ruconest®, Pharming), produced by expressing the C1-INH protein in the milk of transgenic rabbits, is approved in Europe for the acute treatment of oedema attacks in adults with HAE-C1-INH. The safety and efficacy of rhC1-INH in children 0–12 years of age have not been established.[45] The product has a very short half-life compared with other plasma-derived C1-INH products ($\sim$3 h vs. >20 h). The safety and efficacy of rhC1-INH were evaluated in North American and European trials.[46] HAE-C1-INH patients >12 years of age were randomised to receive rhC1-INH 100 U/kg, rhC1-INH 50 U/kg, or saline placebo. Treatment with rhC1-INH at either dose resulted in significant reduction in time to beginning of symptom relief and time to minimal symptoms compared with saline placebo. The therapeutic failure rate was 59% in the saline group versus 0% and 10% in the 50 and 100 U/kg groups, respectively. Treatment-related adverse events in the rhC1-INH groups included headache and vertigo.[46] In the clinical trial program for rhC1-INH, nine adolescent HAE-C1-INH patients (aged 13–17 years) were treated with 50 U/kg for 26 acute angio-oedema attacks, and seven (aged 16–17 years) were treated with a single 2100-U dose for 24 acute angio-oedema attacks, but these data were considered insufficient to allow a posology to be recommended.[45]

Icatibant (Firazyr®, Shire) is a bradykinin-2 receptor antagonist approved in Europe for the acute treatment of HAE-C1-INH attacks in patients >18 years of age and has been recently approved by the FDA for the same indication.[47] Icatibant is administered by subcutaneous injection at a dose of 30 mg and may be self-administered after adequate training in self-injection technique by a healthcare professional. However, the safety and efficacy of icatibant have not been evaluated in patients 0–18 years of age, and, to date, no paediatric data from clinical trials are available for this product.[48]

Ecallantide (Kalbitor®, Dyax) is a potent inhibitor of plasma kallikrein, the enzyme that converts HMWK to bradykinin. Ecallantide is approved in the United States for the treatment of acute attacks of HAE-C1-INH in patients $\geq$16 years of age[49] and is currently under review in Europe for the same indication. Ecallantide is also administered as a subcutaneous injection but is associated with hypersensitivity reactions, including anaphylaxis, in about 3.9% of treated patients; it must therefore be administered by a healthcare professional.[49]

Fresh frozen plasma is an alternative in those countries in which pdhC1INH, nfC1INH, ecallantide, or icatibant are not available.[30] However, fresh frozen plasma contains

complement components that have the potential to exacerbate the HAE-C1-INH attack.[12]

In summary, in the absence of controlled data in children, the treatment of choice for acute oedema attacks in children is pdhC1-INH at 20 U/kg. The dose can be repeated 1 h later if the response is insufficient.[30]

Long-term prophylaxis (routine prophylaxis, maintenance therapy) in children with HAE-C1-INH

Long-term prophylaxis attempts to reduce the frequency and severity of acute oedema attacks. Children who have frequent attacks at any location, recurrent laryngeal oedema and/or abdominal pain causing distress and disability are candidates for long-term prophylaxis. Traditionally, attenuated androgens and antifibrinolytics have been used for this purpose. Attenuated androgens, which have been found to be very effective in controlling HAE-C1-INH attacks in adults,[50–52] are associated with increased risk of virilisation, premature puberty, growth retardation, liver disorders, atherogenesis and behavioural problems.[15] These adverse effects (i.e., growth retardation, premature puberty) may be particularly problematic in children. For this reason, long-term prophylaxis with attenuated androgens is not recommended for children until after pubertal growth is complete.[7,30] Androgens may be used intermittently (e.g. dosing every other day or every three days) to reduce the risk of virilisation side effects and effects on growth and development.[5] Although danazol has been found to be effective in preventing attacks in children with HAE-C1-INH, its effect may wane after four to five years of use.[13]

Antifibrinolytics such as tranexamic acid or epsilon aminocaproic acid (EACA) have also been used with some success in children and may be preferable to attenuated androgens in this population due to their more favourable safety profile.[7,30] Antifibrinolytics are generally well tolerated, but they are not devoid of secondary effects. Thrombosis, extensive muscle necrosis, transient increases in creatine phosphokinase and aldolase associated with muscle pain, weakness and fatigue have been described with EACA use.[30] Muscle cramps, nausea, diarrhoea, hypotension, dizziness and fatigue and thrombosis have been described with use of tranexamic acid.[30] Long-term use of these agents may affect plasma inhibition and predispose to arteriosclerosis.[15]

In Europe, nfC1-INH is approved for routine prevention against oedema attacks in adolescents and adults with HAE-C1-INH with severe and recurrent attacks who are intolerant to or insufficiently protected by oral prevention treatments (e.g. attenuated androgens, antifibrinolytics) or patients who are inadequately managed with repeated acute treatment.[43] In the United States, it is indicated as routine prophylaxis against angio-oedema attacks in adolescents and adults with HAE-C1-INH.[53] The safety and efficacy of nfC1-INH as prophylactic treatment have been evaluated in a double-blind crossover study of 22 HAE-C1-INH patients. In this trial, patients were randomised to receive 12 weeks of placebo or nfC1-INH 1000 U every three to four days (twice a week) and then crossed over to the opposite treatment for 12 weeks. A total of 22 patients were evaluable. During treatment with nfC1-INH, patients experienced reduced number, frequency, duration and severity of oedema attacks.[54]

The safety and efficacy of nfC1-INH prophylaxis have also been evaluated in an open-label, multicentre trial enrolling 146 subjects $\geq$1 year of age experiencing at least one HAE-C1-INH attack per month or with a history of laryngeal oedema.[55] A total of 23 children aged <18 years were enrolled in this trial. The mean attack rate at baseline was 4.4 ± 5.7 per month. During treatment with nfC1-INH, the mean attack rate decreased to 0.7 ± 0.98 in those aged two to five years, to 0.4 ± 0.45 in those aged six to 11 years, and to 0.7 ± 0.90 in those aged 12–17 years. Of the 23 children, 87% experienced $\leq$1 attack per month on prophylaxis. Adverse events considered to be related to nfC1-INH treatment included headache, nausea and infusion-site erythema. No hypersensitivity reactions occurred. No patients discontinued treatment, had anti-C1-INH antibodies, or had evidence of viral transmission of HIV, HBV or HCV.[55] The studied dose is nfC1-INH 1000 U twice a week. However, experience indicates that the dose should be adjusted on an individual basis.pdhC1-INH has been used off-label in Europe for long-term prophylaxis in some specialised HAE-C1-INH centres for the last two decades.[56–58]

Home therapy

The administration of HAE-C1-INH treatment by the patient, a caregiver or health professional at home or other non-healthcare setting (e.g. home therapy) has the potential to reduce the time between symptom onset and treatment and improve patient quality of life by reducing absences from work and school. An international consensus document based on discussions at the 6th C1 Inhibitor Deficiency Workshop in Hungary and at a 2010 meeting of the Canadian Hereditary Angioedema Network makes several recommendations regarding home therapy for children.[22] This document recommends home therapy with C1-INH for children with frequent or disruptive attacks where a parent or other responsible adult is available and willing to be trained in infusion.[22]

In a retrospective, observational study, Kreuz et al. assessed the feasibility of home therapy with pdC1-INH in 20 paediatric patients who were previously treated by a physician. All attacks were treated successfully at home, and the mean annual number of days of hospitalisation decreased from 3.8 during physician-based therapy to 0.11 during home therapy. There were no side effects or injection-site complications reported.[36]

In a review of a database of patients receiving nfC1-INH as prophylaxis, 47% of patients were able to have their medication administered at home. Although children aged 0–12 years did not report self-administration, ~45% of them were able to receive the medication at home, administered by a caregiver or home healthcare personnel.[59]

Preprocedural prophylaxis (short-term prophylaxis) in children

Short-term prophylaxis refers to an intervention designed to prevent against an angio-oedema event with the intention of discontinuing the intervention once the indication for prophylaxis has passed.[60] Currently, the only approved agents for short-term or preprocedural prophylaxis are attenuated androgens (e.g. danazol) and nfC1-INH. However, other agents, such as antifibrinolytics and fresh frozen plasma are used, particularly in countries where C1-INH is not available. Medical, dental and surgical procedures, particularly those that involve manipulation of the head and neck, can induce attacks in HAE-C1-INH patients. Thus, patients undergoing such procedures may require short-term prophylaxis. In general, prophylaxis is not necessary before minor procedures provided an acute medication is available for acute treatment. However, for major procedures and for patients with a history of oedema during medical procedures, prophylaxis with C1-INH is recommended. Short-term prophylaxis is less frequently required in children than it is in adults, with the exception of procedures that involve interventions in the head and neck region.[7]

In Europe, nfC1-INH has been approved for preprocedural prevention of angio-oedema attacks in adolescents and adults with HAE-C1-INH.[43] Across the clinical trial programme, nfC1-INH was administered within 24 h before 91 medical, dental or surgical procedures—40 of these procedures were in children. For 98% of procedures, no HAE-C1-INH attacks were reported within the 72 h after the nfC1-INH dose.[43] In adolescents, as in adults, the recommended dose is 1000 U of nfC1-INH administered within 24 h before a medical, dental, or surgical procedure.[43]

Rusicke et al. studied the preprocedural prophylactic efficacy of pdhC1-INH in 51 HAE-C1-INH patients undergoing minor or major surgery, 23 of whom were children (age range: 4.5–17.6 years).[61] All patients received 500–1000 U of pdhC1-INH 1 h before surgery. Surgical procedures included tonsillectomy, adenoidectomy, tooth extraction, orthopaedic surgery and appendectomy. No acute attacks or incidents of laryngeal oedema were observed during or after any of the 71 surgical procedures monitored. In this study, pdhC1-INH appeared to be safe and effective in preventing swelling attacks and laryngeal oedema in adult and paediatric HAE-C1-INH patients both during and after surgery, regardless of the duration of surgery.[61]

Administration of attenuated androgens or antifibrinolytics is another prophylactic option, but therapy must be started five days before the procedure and continued for two days after the procedure.[7] The suggested dose for attenuated androgens such as danazol is 5–10 mg/kg per day, with a maximum of 600 mg/day.[30] Some experts suggest that, given the availability of C1-INH formulations for acute and prophylactic treatment, androgens and antifibrinolytics should play only a minor role in preprocedural prophylaxis in HAE-C1-INH patients.[60]

Once the diagnosis is made, the child and his/her family should be counselled and educated on HAE-C1-INH, the child's school or day care should be informed of the diagnosis and the child should be encouraged to carry a medical information card at all times.[13] Because the severity, frequency, and burden of HAE-C1-INH attacks are so variable, an individualised treatment plan should be developed to address the specific needs of the patient.

Summary

Symptoms of HAE-C1-INH most often manifest in childhood or early adolescence. Because of its variable clinical presentation and frequent abdominal involvement, HAE-C1-INH is often misdiagnosed or remains undiagnosed for years, causing patients undue suffering. Although children generally have less frequent and less severe attacks than adults, it is known that earlier age of onset is associated with a more severe disease course. Moreover, attacks often increase in frequency at the time of puberty, which can compound the difficulties children face during this developmental phase. Recognition of HAE-C1-INH symptoms early in childhood, and prompt testing of complement levels to establish a diagnosis are the keys to reducing the burden of illness on children with HAE-C1-INH.

Conflict of interest

Dr. Teresa Caballero has received sponsorship for educational purposes, has been paid for providing consultancy services, and has taken part in clinical trials sponsored by Jerini AG/Shire, CSL Behring, Dyax Corp, Pharming NV, and ViroPharma Incorporated. Dr. Caballero has also received an honorarium for authorship of this manuscript, which was provided by a grant from ViroPharma Incorporated.

Acknowledgements

The authors wish to thank Viji Anantharaman and Euro RSCG Life Catapult for editorial support in the preparation of this manuscript, which was funded by ViroPharma Incorporated.

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