Angioedema Hereditario

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Objetivos
Epidemiología
Fisiología
Cuadro clínico
Estudio
Bibliografía

Objetivos

- Conocer el cuadro clínico de un paciente con angioedema hereditario
- Conocer su fisiopatología
- Conocer tratamiento y prevención AH

Definiciones

- El Angioedema se define como una reacción vascular de la dermis profunda o de los tejidos subcutáneos/submucosos con dilatación localizada y aumento de la permeabilidad de los vasos sanguíneos, que produce inflamación del tejido.
- Puede tener causa adquirida o hereditario.

- El angioedema hereditario con deficiencia de inhibidor de C1 se transmite en un patrón genético autosómico dominante que causa una gran variedad de mutaciones diferentes del gen SERPING1.

Clasificación

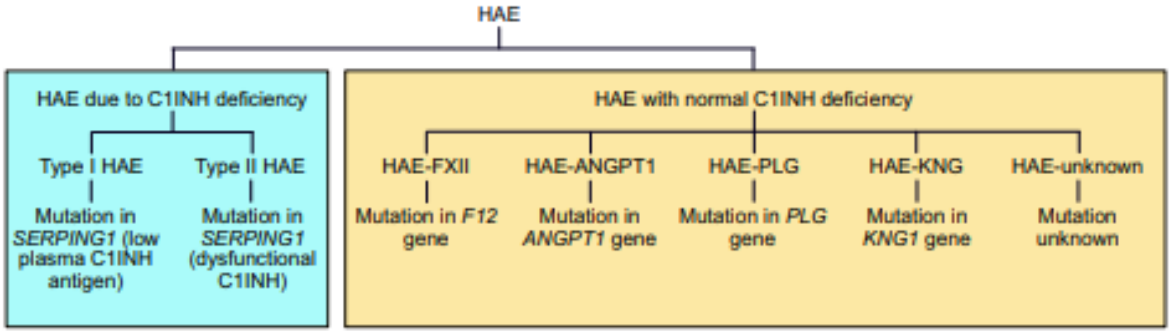


FIGURE 1. Current HAE classification. Schema showing the major grouping of HAE into HAE-C1INH and HAE-nl-C1INH. Within each major group, subgroups are recognized based on the criteria shown. *C1INH*, C1 inhibitor; *HAE*, hereditary angioedema; *HAE-C1INH*, HAE due to a deficiency of C1INH; *HAE-nl-C1INH*, HAE with normal C1INH.

Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021 Jan;9(1):132-150.e3

Epidemiología

- Enfermedad rara

- Incidencia
  - 1:50.000 Australia
  - 1:66.000 Suecia, Italia y Noruega
  - 1:99.000 España, Dinamarca y Grecia
  - 1:140.000 Sudáfrica

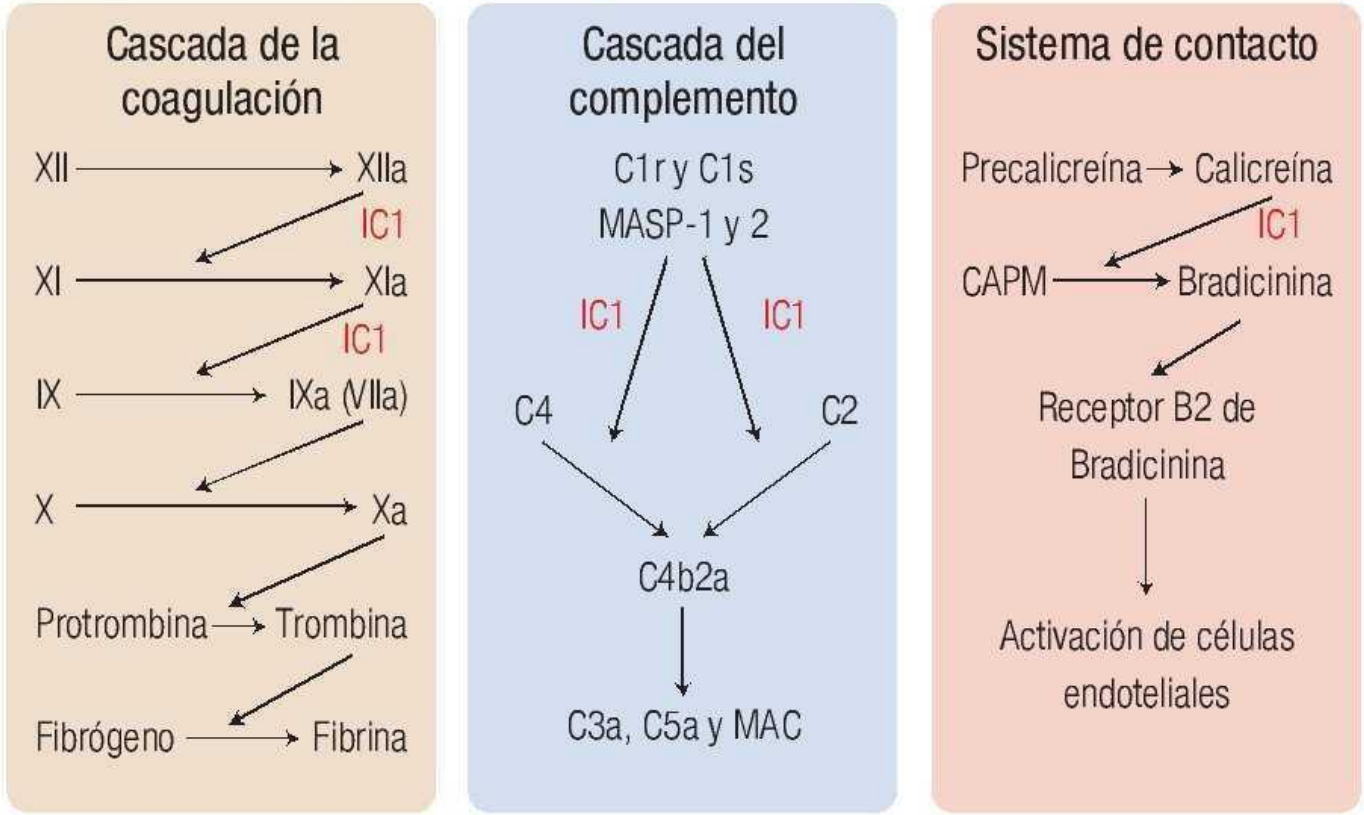
HAE – 1 → 85%
HAE – 2 → 15%

Historia
- 1586 Donati → angioedema, sin urticaria.
- 1883 Quincke → edema angioneurótico.
- 1988 Sir William Osler → carácter hereditario (AD)
- 1963 Virginia Donaldson identificar el defecto molecular del Inhibidor de C1 en 1963.

J Dtsch Dermatol Ges. 2019 Apr; 17(4): 416–423.

Fisiopatología

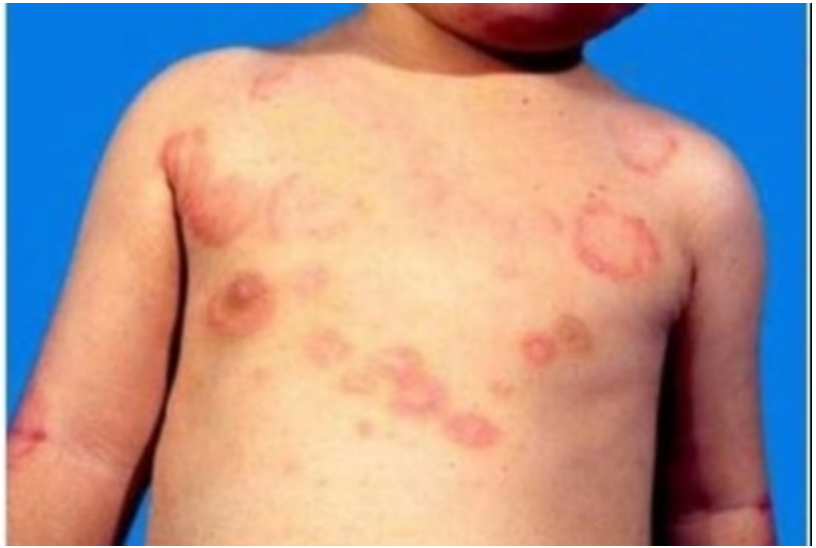
El AH es resultado de mutaciones en el gen del Inhibidor de C1 localizado en el cromosoma 11 (p11.2-q13).[6] Los estudios de genética han identificado más de 150 diferentes mutaciones sin encontrar hasta el momento una correlación clara entre el defecto genético y la severidad de la enfermedad.



Tomado de Zuraw BL. Hereditary Angioedema. New Eng J Med 2008;359:1027-1036.

Cuadro clínico

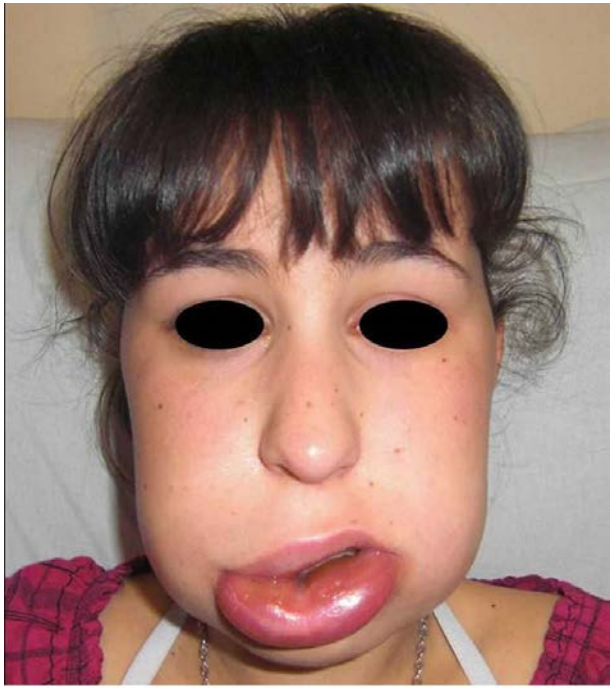
- Pródromo: 1/3 de los casos
  - parestesias
  - eritema marginado
  - rash no pruriginoso



Cuadro clínico

- Edema
  - se desarrolla en 24h
  - cede 48-72h

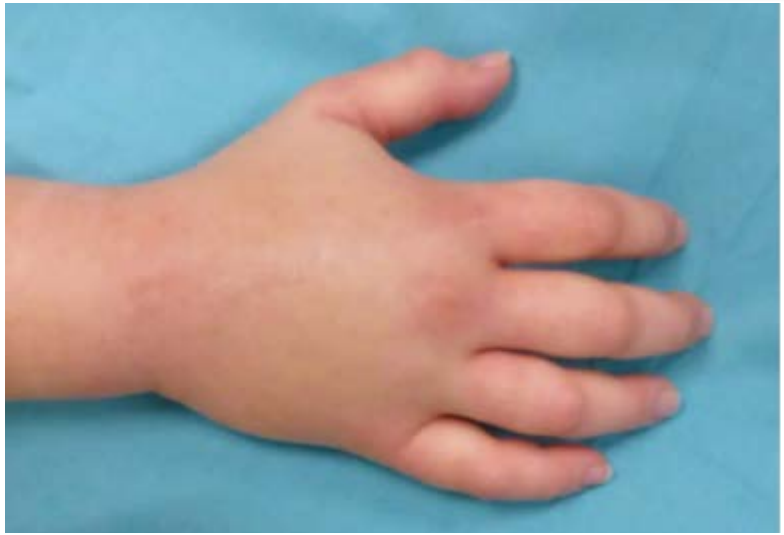
Zonas más afectadas
- cara
- brazos y piernas
- manos y pies
- Abdomen

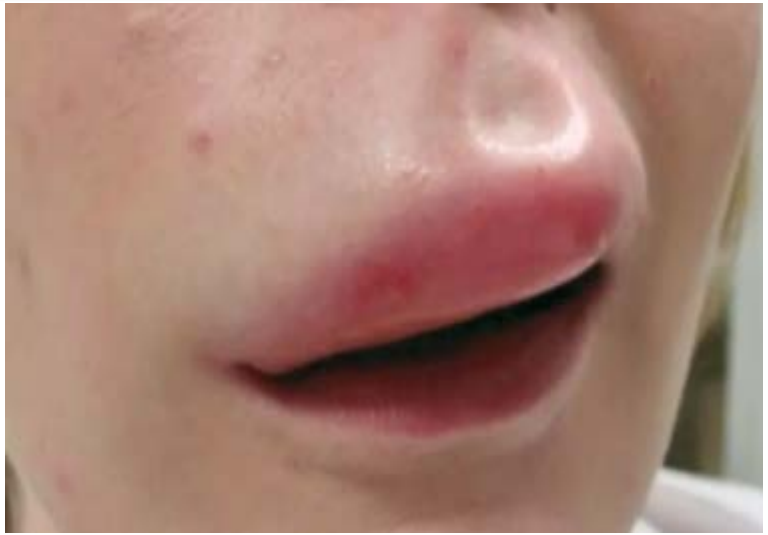


An Pediatr (Barc). 2011;74:283–4

Sin urticaria ni prurito

Cuadro clínico





Cuadro clínico

- Otros

Dolor abdominal 90% de los casos
41% Diarrea
71% Nauseas y vómitos

50% de los pacientes pueden al menos una vez presentar edema laríngeo

30% de las muertes en pacientes con AH se deben a edema laríngeo y asfixia

En quienes sopechar

- a) Antecedentes Familiares: se requiere confirmación diagnóstica de al menos un familiar consanguíneo del paciente de angioedema hereditario con deficiencia de inhibidor de C1.

- b) Edema subcutáneo o submucoso recurrente: no pruriginoso, sin urticaria, auto-limitado, duración mayor a 12 horas.

- c) Dolor abdominal recurrente inexplicable: a menudo acompañado de vómitos y diarrea que se resuelve espontáneamente entre 24 a 72 horas que requirió atención médica en servicio de urgencia.

- d) Edema oral, faríngeo o laríngeo recurrente

Diagnóstico

- **Alta sospecha clínica**
  - alta variabilidad

- **Complemento → C4**
- **Niveles cuantitativos y funcionales de C1INH**
  - HAE tipo I: ambos menos 50%
  - HAE tipo II: solo funcional menos del 50%
- **Pruebas genéticas no son necesarias**
  - solo en diferenciación de la deficiencia adquirida de C1INH en pacientes sin antecedentes familiares
  - cuadro clínico sugerentes con pruebas normales

Recordar realizar prueba
Padres, hermanos, hijos, y menores de 12 meses

Diagnóstico

TABLE II. Criteria for the diagnosis of HAE

Weight	Criteria
HAE-C1INH	
Required	A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
Required	Low (<50% of normal) C1INH antigenic or functional level
Required	Low C4 level (either at baseline or during an attack)
Supportive	Demonstration of a pathologic SERPING1 mutation (not required for diagnosis)
	Family history of recurrent angioedema
	Age of symptom onset <40
HAE-nl-C1INH	
Required	A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
Required	Documented normal or near normal C4, C1-INH antigen, and C1-INH function
Either (at least 1 required)	(1) Demonstration of a mutation associated with the disease; OR (2) A positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (ie, cetirizine at 40 mg/d or the equivalent) for at least 1 mo or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer
Supportive	(1) A history of rapid and durable response to a bradykinin-targeted medication; AND (2) Predominant documented visible angioedema; or in patients with predominant abdominal symptoms, evidence of bowel wall edema documented by CT or MRI

C1INH, C1 inhibitor; *CT*, computed tomography; *HAE*, hereditary angioedema; *HAE-C1INH*, HAE due to a deficiency of C1INH; *HAE-nl-C1INH*, HAE with normal C1INH; *MRI*, magnetic resonance imaging.

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Diagnóstico

Confirmación Diagnóstica

Se confirmará el diagnóstico en los siguientes casos:

- **Personas mayores de 1 año, con "Antecedentes familiares" y "Un examen Bajo nivel cuantitativo de inhibidor de C1 o Nivel funcional de inhibidor de C1 Anormal o Alterado"**.

- **Personas mayores de 1 año, sin "Antecedentes familiares" y "Dos evaluaciones que indiquen Bajo nivel cuantitativo de inhibidor de C1 o Nivel funcional de inhibidor de C1 Anormal o Alterado"**, las evaluaciones de ambos exámenes deben realizarse con una diferencia mínima de 2 meses entre evaluaciones.

- **Personas mayores de 1 año, con "Antecedentes familiares" y dudoso nivel cuantitativo de inhibidor de C1**. Estas personas tendrán una confirmación diagnóstica por 6 meses. Se confirmará el diagnóstico indefinidamente con un segundo examen que indique "Bajo nivel cuantitativo de inhibidor de C1", el cual deberá realizarse con una diferencia mínima de 2 meses respecto al primer examen. En caso de no presentarse el segundo examen dentro de 6 meses posteriores al primer examen con resultado dudoso, el diagnóstico se descartará.

PROTOCOLO TRATAMIENTO CON INHIBIDOR DE C1 ESTERASA PARA ANGIOEDEMA HEREDITARIO LEY 20.850 – MINISTERIO DE SALUD 2018

Tratamiento

No se cuenta con evidencia para recomendar el uso de antihistamínicos, corticosteroides o epinefrina

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Tratamiento agudo

Vm 2h

Vm 32-46h

TABLE III. FDA-approved on-demand medications for HAE attacks

Drug (trade name, manufacturer)	Regulatory status	Self-administration	Dosage	Mechanism	Anticipated potential side effects
Ecallantide (Kalbitor, Dyax)	Approved in the United States for patients ≥12 y of age	No	30 mg SC	Inhibits plasma kallikrein	Uncommon: antidrug antibodies, risk of anaphylaxis
Icatibant (Firazyr, Takeda)	Approved in the United States for patients ≥18 y of age; approved in Europe for patients ≥2 y of age	Yes	Pediatric (EU): 12-25 kg, 10 mg SC; 26-40 kg, 15 mg SC; 41-50 kg, 20 mg SC; 51-65 kg, 25 mg SC; >65 kg, 30 mg SC Adults: 30 mg SC	Bradykinin B2 receptor antagonist	Common: discomfort at injection site
Plasma-derived nanofiltered C1INH (Berinert, CSL Behring)	Approved in the United States and Europe for children and adults	Yes	20 U/kg IV	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and Xla, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Recombinant human C1INH (Ruconest, Pharming)	Approved in the United States and Europe for adolescents and adults	Yes	50 U/kg up to 4200 U IV	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and Xla, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon: risk of anaphylaxis in rabbit-sensitized individuals Theoretical: transmission of infectious agent

C1INH, C1 inhibitor; *FDA*, Food and Drug Administration; *HAE*, hereditary angioedema; *IV*, intravenous; *MASP-1, -2*, mannose-binding lectin–associated serine proteases 1, 2; *SC*, subcutaneous.

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Efecto 60min

Tratamiento general

- Identificar factores desencadenantes

- trauma físico
- procedimientos quirúrgicos, médicos y dentales
- bipedestación prolongada
- Infecciones
- estrés emocional
- algunos fármacos

Tratamiento profiláctico

TABLE IV. FDA-approved prophylactic medications for HAE

Drug (trade name, manufacturer)	HAE regulatory status	Self-administration	Dosage	Mechanism	Anticipated potential side effects
Plasma-derived nanofiltered C1INH (Cinryze, Takeda)	Approved in the United States and Europe for patients ≥6 y of age	Yes	Pediatric (6-11 y): 500 IU every 3-4 d IV Adolescents and adults: 1000 U IV every 3-4 d Doses up to 2500 U IV every 3-4 d may need to be considered based on individual patient response	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived nanofiltered C1INH (HAEGARDA, CSL Behring)	Approved in the United States for adolescents (≥12 y) and adults	Yes	60 IU/kg SC twice-weekly	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Lanadelumab (Takhzyro, Takeda)	Approved in the United States for adolescents and adults	Yes	300 mg SQ every 2 wk 300 mg every 4 wk may be considered if a patient is well controlled (eg, attack free) for more than 6 mo	Inhibits plasma kallikrein	Rare: risk of anaphylaxis Common: injection site reactions
Danazol (Danocrine, Sanofi-Synthelabo)	Approved in the United States for adults	Yes	Adult: 200 mg/d PO (100 mg every 3 d to 600 mg/d) Pediatric: 50 mg/d PO (50 mg/wk to 200 mg/d)	Unknown	Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile Uncommon: decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma

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Tratamiento

Stanozolol (Winstrol, Winthrop)	Approved in the United States for adults and children	Yes	Adult: 2 mg/d PO (1 mg every 3 d to 6 mg/d) Pediatric: 0.5 mg/d PO (0.5 mg/wk to 2 mg/d		Same as danazol
Oxandrolone	Not approved for HAE indication	Yes	Adult: 10 mg/d PO (2.5 mg every 3 d to 20 mg/d) Pediatric: 0.1 mg/kg/d PO (2.5 mg/wk to 7.5 mg/d	Unknown	Same as danazol
Methyltestosterone (Android)	Not approved for HAE indication	Yes	Adult men: 10 mg/d PO (5 mg every 3 d to 30 mg/d) Women and pediatric: not recommended	Unknown	Same as danazol
Epsilon aminocaproic acid (Amicar, Xanodyne Pharmaceuticals)	Not approved for HAE indication	Yes	Adult: 2 g PO tid (1 g bid to 4 g tid) Pediatric: 0.05 g/kg PO bid (0.025 g/kg bid to 0.1 g/kg bid)	Inhibits activation of plasminogen and activity of plasmin	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes Theoretical: thrombosis
Tranexamic acid (Cyklokapron, Pfizer; Lysteda, Ferring)	Not approved for HAE indication	Yes	Adult: 1 g PO bid (0.25 g bid to 1.5 g tid) Pediatric: 20 mg/kg PO bid (10 mg/kg bid to 25 mg/kg tid)	Inhibits activation of plasminogen and activity of plasmin	Same as epsilon aminocaproic acid

C1INH, C1 inhibitor; *FDA*, Food and Drug Administration; *HAE*, hereditary angioedema; *IV*, intravenous; *SC*, subcutaneous.

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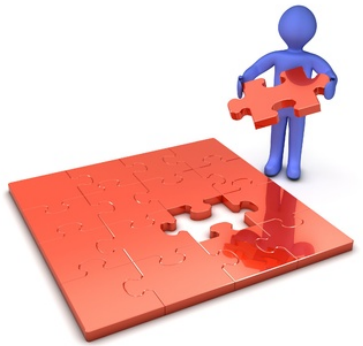
Conclusiones

- El angioedema hereditario es una entidad poco frecuente y potencialmente grave . Aunque la sintomatología puede ser similar a cuadros alérgicos, su manejo es muy diferente.
- Debe considerarse tratamiento profiláctico a largo plazo ante el antecedente de episodio de angioedema grave o episodios recurrentes.



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- **Comparing acquired angioedema with hereditary angioedema (types I/II): findings from the Icatibant Outcome Survey.** Longhurst Clinical and Experimental Immunology 2018, 188: 148–153

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- International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. H. Farkas. Allergy 2017; 72: 300–313.

Clinical manifestations of hereditary angioedema and a systematic review of treatment options

- The mechanism behind HAE is dysregulated by low levels of C1 esterase inhibitor (C1-INH) protein, leading to a bradykinin-mediate increase in vascular permeability.
- During an attack of HAE, abortive treatment with C1-INH replacement is most commonly described, however, icatibant, ecallantide, or fresh frozen plasma are also used.
- Long-term prophylaxis in the form of C1-INH replacement (subcutaneous or intravenous), monoclonal antibodies targeting plasma kallikrein, attenuated androgens, and transexemic acid should be considered for those who suffer from frequent, severe attacks.
- Progressively distal involvement of the upper airway, especially the larynx, has been shown to pose an increased risk of asphyxiation and death in the acute presentation of HAE

Laryngoscope Investigative Otolaryngology. 2021;6:394–403. Rosi-Schumacher

Concepts HAE

- Hereditary angioedema (HAE) is a rare, autosomal dominant disorder that is commonly characterized by repeated episodes of cutaneous or submucosal swelling affecting the skin, gastrointestinal tract, face, upper airway and other organs.
- The incidence of HAE is estimated to be 1 in 50 000, but ranges from 1 in 10 000 to 1 in 150 000.2-5.
- HAE is often classified into three major types, which are defined by the amount or function of C1 esterase inhibitor (C1-INH) present in an individual.
- C1-INH is a serine protease inhibitor that plays an important regulatory role in the complement cascade, coagulation cascade, fibrinolytic pathway and contact pathway.
- Initial presenting symptoms of angioedema are most commonly thought to be related to allergic reactions resulting in mast-cell mediated angioedema.

Laryngoscope Investigative Otolaryngology. 2021;6:394–403. Rosi-Schumacher

Concepts HAE

- Lack of pathognomonic tests available in the acute and emergency setting.
- In the acute setting, a high clinical suspicion may allow for a diagnosis of exclusion made through clinical evaluation and the lack of response to epinephrine, antihistamine, or glucocorticoid treatments in patients with HAE

Laryngoscope Investigative Otolaryngology. 2021;6:394–403. Rosi-Schumacher

- January 1, 2018, and August 31, 2020. Data on 1297 patients from 29 centers in 5 European countries were.
- At least one attack was recorded for 497 patients during the study period.
- Overall, 1182 patients were diagnosed with HAE type 1 and 115 with type 2.
- At the time of database lock, 389 patients were taking long-term prophylactic medication, 217 of which were on danazol.
- Most recorded attacks affected the abdomen, were generally moderate in severity, and occurred in patients who were not on prophylactic treatment (70.6%, 6244/8848).
- The median duration of attacks was 780 min (IQR 290–1740) in patients on prophylactic medication and 780 min (IQR 300–1920) in patients not on continuous prophylactic medication.

¡Gracias!