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PRACTICAL DERMATOLOGY

Practical Management of C1 Inhibitor Deficiency

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Abstract. C1 inhibitor deficiency is a rare syndrome clinically characterized by recurrent episodes of swelling of subcutaneous tissue or angioedema. It can involve the skin, upper respiratory airways and abdomen. There are two main types: hereditary and acquired. Angioedema can involve practically any part of the cutaneous surface, it can cause lethal laryngeal edema and can present as gastrointestinal obstruction. The attacks can be triggered, in general, by trauma, drugs or infections. Diagnosis is confirmed by decreased serum levels of C4 and absence or marked decrease of the level or function of C1 inhibitor. Commonly employed drugs for prophylaxis and treatment of these patients include anabolic steroids, antifibrinolytic agents, and infusion of C1 inhibitor concentrate. Fresh frozen plasma is an option to be considered for short term prophylaxis or treatment of the acute attack. It is convenient to know this syndrome as it is a potentially life-threatening disease. Diagnosis of this rare syndrome is based on clinical features and characteristic alterations of laboratory tests. The acute attack should be treated as quickly as possible. Prophylactic therapy is indicated in certain circumstances (dental procedures, oral surgery).

Key words: angioedema, C1 inhibitor deficiency, androgens, antifibrinolytics.

MANEJO PRÁCTICO DEL DÉFICIT DE C1 INHIBIDOR

Resumen. El déficit de C1 inhibidor es un raro síndrome caracterizado clínicamente por episodios recurrentes de tumefacción en el tejido celular subcutáneo o angioedema. Puede afectar a la piel, las vías respiratorias superiores y el abdomen. Se describen principalmente dos tipos: hereditario y adquirido. El angioedema puede afectar a prácticamente cualquier parte de la superficie cutánea, puede causar edema laríngeo mortal y cursar con características clínicas idénticas a una obstrucción del tracto gastrointestinal. Los ataques pueden ser desencadenados, de forma general por traumatismos, fármacos o infecciones. El diagnóstico se confirma mediante la presencia de C4 disminuido en suero y la ausencia o gran reducción del nivel o la función de C1 inhibidor. Los andrógenos atenuados, los agentes antifibrinolíticos y la infusión de concentrado de C1 inhibidor son los fármacos habitualmente utilizados en el manejo profiláctico y terapéutico de estos pacientes. El plasma fresco congelado es una opción a considerar en caso de profilaxis a corto plazo o ataque agudo. Es conveniente conocer este síndrome, ya que se trata de una enfermedad potencialmente mortal. El diagnóstico de este raro síndrome se basa en el reconocimiento de las características clínicas y en las alteraciones características de las pruebas de laboratorio. El tratamiento del ataque agudo se debe realizar lo más rápidamente posible. El tratamiento profiláctico está indicado en determinadas situaciones (manejo dental y cirugía oral).

Palabras clave: angioedema, déficit C1 inhibidor, andrógenos, antifibrinolíticos.

Introduction

Deficiency of the esterase inhibitor of the C1 complement component is characterized by the appearance of subcutaneous and submucosal edema affecting any part of the skin surface, respiratory tract, or gastrointestinal tract. The incidence is estimated as between 1/10 000 and 1/50 000 population,[1] with no racial differences.[2] This syndrome has been associated with a personal or family history of atopy in 24% of adults and 14% of patients over 10 years of age.[3] There are 2 main types of C1 inhibitor deficiency: hereditary (autosomal dominant) and acquired. Their principal characteristics are shown in Table 1. In 2000, Bork et al[4] described a third type within hereditary angioedema, with clinical characteristics identical to the 2 types described previously, but estrogen dependent,

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Table 1. Types of Angioedema

Variant	*Subtype*	*Frequency (%)*	*Enzyme Abnormality*	*Age at Onset*	*Family History (%)*	*Associations*
Hereditary	Type I	85	Low C1-inh levels in plasma (5-30% of normal values)	Childhood (second decade of life)	+ (50%)	–
	Type II	15	Functional C1-inh deficiency with normal plasma levels			
	Estrogen-dependent hereditary angioedema[a]	Exceptional	Normal C1-inh levels/ function Normal C4		–	
Acquired	Type I	5	Increased C1-inh consumption	Adults (fifth decade of life)	–	Lymphoproliferative diseases of B cell origin (monoclonal gammopathy of uncertain significance, chronic lymphocytic leukemia), carcinomas, infections (HIV), autoimmune diseases (arthritis, thyroiditis, glomerulonephritis, inflammatory bowel disease), cold urticaria, lupus erythematosus.
	Type II	5	Anti C1-inh Ab			

[a]Entity recently described by Bork et al.[4] Abbreviations: HIV, human immunodeficiency virus; C1-inh, C1 inhibitor; Ab, antibody.

occurring only in women, and related to pregnancy or hormone therapy in the majority of cases. This variant is possibly linked to the X chromosome as it has only been observed in women.

C1 inhibitor is an enzyme characterized by being the principal regulator of the early activation steps of the classical complement pathway, and of the activation of kallikrein, of plasmin in the fibrinolytic system, of factor XI in the coagulation cascade, and of factor XIIa. In the absence of C1 inhibitor, the classical complement pathway may be activated inappropriately or excessively. The result is an increase in vascular permeability with uncontrolled massive local edema,[2] which causes the specific symptoms of this syndrome. The evidence levels used throughout this article are shown in Table 2.

Table 2. Levels of Evidence Referred to in This Article

Level 1	Randomized clinical trial
Level 2	Nonrandomized clinical trial or case series
Level 3	Case reports
Level 4	Expert opinion
Level 5	No evidence level

Diagnosis

The approach to the 2 main types of angioedema (hereditary and acquired) is similar. An algorithm for the diagnosis of C1 inhibitor deficiency is presented in Figure 1.

Clinical Aspects

1. Recurrent angioedema (swelling) without urticaria and that is not usually pruriginous. Prodromal erythema (erythema marginatum) has been reported in 25% of cases, and may be confused with urticaria.[5,6] Angioedema is not usually painful unless it affects pressure areas or regions in which the subcutaneous cellular tissue is constricted.
2. The swelling usually affects the limbs, face, trunk, gastrointestinal tract, genitourinary region, or upper respiratory tract; however, it can affect any part of the body.
3. The abdominal symptoms can mimic infantile colic, acute appendicitis, or acute abdomen, and include nausea,

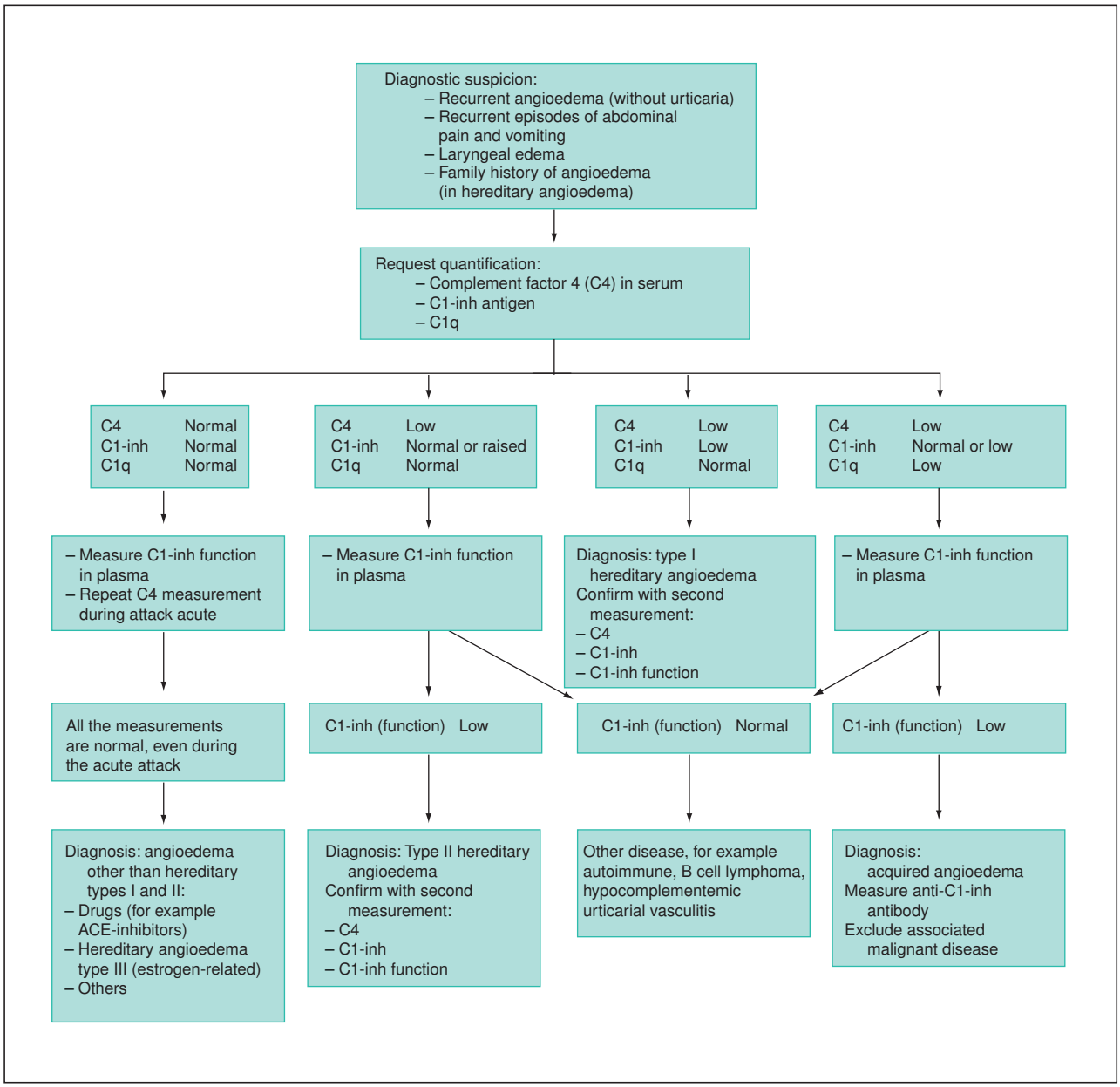

Figure 1. Diagnostic algorithm for C1 inhibitor deficiency.
Modified from Bowen T, et al.[1] C1-inh indicates C1 inhibitor; ACE, angiotensin converting enzyme.

vomiting, abdominal pain, and diarrhea after the acute episode.

4. Respiratory symptoms include dysphagia and alterations of the voice as the disorder can affect both the tongue and the pharynx and larynx.
5. On rare occasions, it can cause cerebral edema or pleural effusion or symptoms suggestive of bladder involvement.
6. The age at onset is variable, and patients can present the initial symptoms before 1 year of age; the main symptoms at this age are colic and, rarely, swelling. The attacks increase in severity with puberty. Episodes affecting the larynx usually begin later than other symptoms, though they can occur in childhood.
7. The acute attack of angioedema has been related to multiple triggering factors, but these are not usually identified (Table 3).
8. Acute attacks tend to be prolonged, usually increasing in intensity over the first 24 hours and then resolving over the following 48 to 72 hours. Some attacks can last more than 72 hours as the swelling migrates from one site to another.

9. Attacks are usually periodic and normally recur after several weeks of remission. They do not usually occur daily.

Laboratory Tests

1. Laboratory tests should be performed in an accredited laboratory with operating procedures that ensure adequate quality. Determinations should be performed when no treatment is being given, ideally less than 7 days after the previous attack.
2. The measurement of protein C4 in serum is a good screening method for C1 inhibitor deficiency, as it is found to be low in untreated patients (C4 <30% of the normal mean values).[14] If the C4 level is normal, it is not usually necessary to go on to measure C1 inhibitor levels as even if these values are low the diagnosis would be doubtful (evidence level 4). It has been observed that the combination of a low C4 and a decrease in C1 inhibitor function has a specificity of 98% and a negative predictive value of 96% for C1 inhibitor deficiency.[15]
3. The low prevalence of this disease indicates that false positives are common.[14] Measurements obtained before 1 year of age may not be reliable as there is a high prevalence of false positives and negatives. In this case, the measurements should be repeated after 1 year of age.[16]
4. Once the diagnosis is established, determination of C4 levels and C1 inhibitor levels and function is useful for monitoring the response to treatment.
5. The measurement of C1q antigen may be of use in the diagnosis of hereditary angioedema as it is usually low in these cases whereas it is normal in the case of acquired angioedema. The various measurements of complement values for the different types of angioedema are shown in Table 4.
6. As in other disorders with autosomal dominant inheritance, genetic studies reveal de novo mutations in 25%-33% of patients. Genetic study is not necessary to confirm the diagnosis.
7. Study of family members is advisable in cases of hereditary angioedema as it is important to detect asymptomatic children.

The diagnostic criteria for C1 inhibitor deficiency were established in 2004 during the Third C1 Esterase Inhibitor Deficiency Workshop (Table 5).

Table 3. Principal Triggering Factors of an Acute Attack of Angioedema

Minor trauma	Dental procedure (> 50%)[7,8] – Local anesthetic – Others
Drugs (evidence level 3)	Estrogens (contraceptives, hormone replacement therapy)[9] Angiotensin converting enzyme inhibitors Angiotensin II receptor antagonists Plasminogen activators Antibiotics
Emotional stress	
Infections[10]	Dental Other foci of infection *Helicobacter pylori* (evidence level 3)[11,12]
Hormonal changes	Menstruation Pregnancy (evidence level 3)[13]

Table 4. Measurement of the Complement Fractions in C1 Inhibitor Deficiency.

	Type of Angioedema	*C1q Concentration*	*C1-inh Concentration*	*C1-inh Function*	*C4 Concentration*	*C3 Concentration*
Hereditary	Type I	N	↓	↓	↓	N
	Type II	N	N/↑	↓	↓	N
	Estrogen-dependent	N	N	N	N	N
Acquired	Type I	↓	↓	↓	↓	N/↓
	Type II	↓	N/↓	↓	↓	N/↓
Others	Related to hormonal changes	N	N	N	N	N
	ACE-inhibitor induced	N	N	N	N	N
	Induced by other drugs	N	N	N	N	N
	Idiopathic	N	N	N	N	N

↓: low value; ↑: raised value. Abbreviations: N, normal; ACE, angiotensin converting enzyme; C1-inh, C1 inhibitor. Modified from Werter et al.[17]

Table 5. Diagnostic Criteria for the Diagnosis of C1 Inhibitor Deficiency

Clinical Criteria		*Laboratory Criteria*
Major	*Minor*	
Self-limiting noninflammatory subcutaneous angioedema with no urticarial rash, usually recurrent and with duration > 12 hours	Family history of recurrent angioedema or abdominal pain or laryngeal edema	C1-inh antigen levels < 50% of normal values in 2 separate determinations with the patient in basal conditions and after the first year of life
Self-limiting abdominal pain with no obvious organic cause, usually recurrent and with duration > 6 hours		C1-inh function < 50% of normal values in 2 separate determinations with the patient in basal conditions and after the first year of life
Recurrent laryngeal edema		Mutation in the C1-inh gene affecting protein synthesis or function

The diagnosis is established by the presence of 1 mayor clinical criterion and 1 laboratory criterion. Abbreviation: C1-inh, C1 inhibitor.

Management

First, primary prevention consists of avoiding the triggering factors of an acute attack of angioedema in so far as is possible. In general, the management of patients with C1 inhibitor deficiency will include long- and short-term prophylaxis and treatment of the acute attack (Table 6). This is a condition that must be kept in mind as, without treatment, mortality can reach 30%-40%, and is due to airway obstruction in the majority of cases.[25] The adverse effects of the different treatments are shown in Table 7.

Long-Term Prophylaxis

Indications:

1. More than 1 severe episode per month or more than 5 days per month unable to perform usual activities
2. More than 1 episode of severe abdominal pain in a year
3. Occasional episodes of angioedema affecting the head or neck
4. Frequent episodes of peripheral or genital angioedema
5. Need for more than one C1 inhibitor concentrate per year

Attenuated androgens are considered to be the treatment of first choice as, in general, they are more effective than other treatments. If they are ineffective or cause adverse effects, antifibrinolytic agents should be used or, as a last resort, C1 inhibitor concentrates. The antifibrinolytic agents have been shown to be more effective in acquired angioedema than the other treatments available (evidence level 2).[26] Antifibrinolytic agents are contraindicated in active thromboembolic disease.

In childhood patients, the antifibrinolytic agents should be considered to be first choice due to the lower number and severity of adverse effects; if they are not effective, the second choice is C1 inhibitor concentrate. If neither of these works, antiandrogens can be used; these agents are particularly indicated if there is more than 1 abdominal attack per month, though they should be used with caution due to their potential effects on growth.

Combinations of different treatments can be used (for example, fibrinolytic agents with synthetic attenuated androgens), and use of the minimum effective dose is recommended.

The efficacy of attenuated androgens in the treatment of type II acquired angioedema is not clear. Likewise the efficacy of the antifibrinolytic drugs and attenuated androgens in estrogen-dependent hereditary angioedema has not been fully confirmed, although at least 1 patient with such disease has responded to danazol.[27]

There are 2 internationally accepted regimens for the long-term use of danazol for prophylaxis (Table 8).

Hepatitis B virus vaccination is recommended in all patients who frequently receive blood derivatives (C1 inhibitor concentrates or fresh frozen plasma).

Short-Term Prophylaxis

Indications for short-term prophylaxis:

1. Dental procedures
2. Oral surgery
3. Intubation
4. Other procedures, principally those involving areas in which angioedema is clinically manifest

In this situation, C1 inhibitor concentrate is considered to be the first choice treatment and, if this is not available, attenuated androgens or antifibrinolytic agents can be used.

Table 6. Summary of the Therapeutic Management of Patients With C1 Inhibitor Deficiency

Intervention	*Treatment*	*Dose (adult)*	*Dose (child)*	*Monitoring Tests*
Long-Term Prophylaxis	Synthetic attenuated androgens (evidence level 2/3[18-20])	Oral danazol (see Table 8)	Oral danazol 100-200 mg/24-72 h (only if specifically indicated)	Biannual: blood test with liver function[a] Annual: lipid profile, PSA, rectal examination Biannual: Liver ultrasound (annual after 10 y of treatment). Evidence level 4[21]
		Oral stanozolol 2-12 mg/24 h		
		Oral oxandrolone 2.5-20 mg/24-72 h. Divide daily dose into 2-4 doses		
		Oral methyltestosterone 10-30 mg/d		
	Antifibrinolytic agents (evidence level 2[22])	Oral tranexamic acid In general: 25-75 mg/kg/d. Divide daily dose into 2-3 doses Initial: 1-1.5 g/8-12 h Maintenance: 0.5 g/12-24 h	Oral tranexamic acid In general: 50 mg/kg/24-72 h Regimen: 1-2 g/24 h	Biannual: liver function tests (evidence level 4) Annual: eye check
		ε-Aminocaproic acid 8-10 g orally, divided into 2-4 doses/d	ε-Aminocaproic acid. Not more than 6 g/d if < 11 years old and not more than 12 g/d if > 11 years old	
	C1-inh concentrate	500-1000 U IV 2 times/wk		Biannual: liver function tests, viral serology (HIV, HTLV 1 and 2, HBV, HCV)
Short-Term Prophylaxis	C1-inh concentrate	500, 1000, or 1500 U IV in the previous 24 hours (preferably 1 h before), respectively according to weight < 50, 50-100, or > 100 kg. Have 2 more doses available	< 10 years old: 500 U IV > 10 years old: 1000 U IV in the previous 24 hours	
	Synthetic attenuated androgens	Danazol 100-600 mg/24 h orally for 5 days before and 2 days after In general 10 mg/kg/d	Danazol 300 mg/24 h orally for 5 days before and 2 days after	
		Stanozolol 2-6 mg/24 h orally for 5 days before and 2 days after		
	Antifibrinolytic agents	Tranexamic acid 1 g/6 h orally/IV for 48 hours before and after In general 75 mg/kg/d	Tranexamic acid 500 mg/6 h orally/IV for 48 hours before and after	
		ε-Aminocaproic acid 10 mg/d orally, divided into 2-3 doses		
	Fresh frozen plasma	2 units (400 mL) IV 1-24 h before surgery	10 mL/kg IV 1-24 hours before surgery	

(Continued)

In the case of minor procedures (for example, dental manipulations), a possible course of action if C1 inhibitor concentrate is available is not to give any prophylaxis and to use the treatment only if an acute attack occurs. If C1 inhibitor concentrate is not available, prior prophylaxis with attenuated androgens or antifibrinolytic agents should be given. The use of fresh frozen plasma is accepted, though the possibility of the transmission of viral diseases must always be taken into account. Caution should be observed in the case of dental procedures as attacks can occur up to 36 hours later.

In the case of major procedures or intubation, prophylaxis should be given from the outset, using

Table 6. Summary of the Therapeutic Management of Patients With C1 Inhibitor Deficiency. *(Continued)*

Intervention	*Treatment*	*Dose (adult)*	*Dose (child)*	*Monitoring Tests*
Treatment of an Acute Attack	C1-inh concentrate (evidence level 2)[23]	500-1500 U IV (according to weight. See above). Reinfusion/re-evaluation if symptoms persist for more than 2 hours	< 10 years old: 500 U IV > 10 years old: 1000 U intravenous	Baseline: liver function tests Hepatitis viruses
	Synthetic attenuated androgens	Danazol maximum 1 g/24 h orally		
		Stanozolol maximum 16-12 mg/24 h orally		
	Antifibrinolytic agents	Tranexamic acid 1 g/6 h orally/IV for 48 hours		
		ε-Aminocaproic acid IV		
	Fresh frozen plasma (evidence level 3)	2 units IV		Baseline: liver function tests Hepatitis viruses
Pregnancy	Synthetic attenuated androgens	Contraindicated (may be considered in third trimester)		
	Antifibrinolytic agents	Can be used with caution (class B)[24]		
	C1-inh concentrate	Treatment of attack acute (see above) Severe cases: use is common Prepartum: 500-1000 U IV		

[a]Liver function tests include measurement of aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin, alkaline phosphatase, creatine phosphokinase, urea, creatinine, lactate dehydrogenase.
At diagnosis include complete blood count, urinalysis, thyroid hormones, and antithyroid antibodies.
Abbreviations: IV, intravenous; HIV, human immunodeficiency virus; HTLV, human T-lymphotrophic virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PSA, prostate specific antigen; C1-inh, C1 inhibitor.
Modified from Gompels MM, et al.[2]

Table 7. Adverse Effects of the Drugs Used in the Management of Patients With C1 Inhibitor Deficiency

Drug	*Adverse Effects*	
	Adults	*Children*
Synthetic attenuated androgens (dose-dependent)	Weight gain, virilization (acne, alopecia, and hirsutism), reduced libido, muscle pain and cramp, hypertension, headache, depression, fatigue, nausea, constipation, menstrual cycle disturbances, abnormal liver function, masculinization of a female fetus, hepatocellular adenoma, peliosis hepatis, liver necrosis, cholestasis, adenocarcinoma of the prostate (evidence level 3)[20,21]	Androgenization, precocious puberty, premature epiphyseal fusion with growth limitation, liver disturbances, atherogenesis, behavioral changes
Antifibrinolytic agents	Nausea, vertigo, diarrhea, orthostatic hypotension, fatigue, thromboses, muscle cramps with a rise in muscle enzymes, elevated CPK, rhabdomyolysis, possible teratogenicity, tumors of the retina or liver in experimental animals (evidence level 2/3)[22]	Arteriosclerosis

Abbreviation: CPK, creatine phosphokinase.

Table 8. Prophylactic Androgen Therapy With Danazol:

High Starting Dose and Reduce (If Attacks Are Common)	*Low Starting Dose and Increase (If attacks Are Relatively Infrequent)*
Starting dose 400-600 mg/d for 1 month	Starting dose 200 mg/d for 1 month
Reduce by 100 mg or one-third at 1 month	If no control, increase to 300 mg/d for 2-4 wk
On reaching 200 mg/d, reduce by 50 mg every 2 months	If no control, increase to 400 mg/d for 2-4 wk
On reaching 100 mg/d, reduce 50 mg every 2 months	If controlled at 200 mg/d, reduce to 100 mg/d for 1 month
If recurrence, reinduce remission and adjust to a higher dose	If controlled at 100 mg/d, reduce to 50 mg/d or 100 mg/48 h If recurrence, double the dose for some days and adjust to a higher dose

Adapted from Weiler CR, et al.[17]

either attenuated androgens or antifibrinolytic agents (if there is sufficient time) or C1 inhibitor concentrate (if this is available). If neither of these options is available, prophylaxis should be given with fresh frozen plasma.

Treatment of the Acute Attack

Treatment of the acute attack is not always necessary. Sometimes, if the episode is not generalized, the best option is to wait for spontaneous resolution of the angioedema or only to give fluid replacement.

All patients should be offered the opportunity to keep C1 inhibitor at home in sufficient quantity to treat a laryngeal emergency, as these attacks are life-threatening in 50%-75% of cases. The product must be reconstituted at room temperature before its administration. It must not be shaken and it must be administered into a peripheral vein over approximately 10 minutes.

Fresh frozen plasma can aggravate the symptoms during the acute phase. The possible transmission of diseases such as hepatitis B and C must be taken into account, but is ever less frequent.

There is no evidence for the effectiveness of epinephrine,[28] though its efficacy compares relatively favorably with other treatments (corticosteroids[29] or antihistamines).

In the event of an acute attack, suitable analgesics should be added to the usual treatment in order to relieve pain if it is present (nonsteroidal anti-inflammatory drugs for abdominal pain).

If the patient has been on treatment with danazol and has an acute episode, the dose may be doubled for several days.

Maintenance of the airway is important. Tracheotomy may be necessary if severe laryngeal edema develops.

Commercial Names of the Different Drugs Employed

Danazol: Danatrol, 50, 100, and 200 mg capsules (Sanofi-Winthrop Pharmaceuticals, New York, USA).

Stanozolol: Winstrol, 2 mg and depot 1 mL 50 mg (Zambon, Vicenza, Italy).

Oxandrolone: Oxandrin (Savient Pharmaceuticals, New Jersey, USA).

Methyltestosterone: Longivol oral, 1, 5, 10, and 25 mg tablets (Medical S.A., Spain).

Tranexamic acid: Amchafibrin, 500 mg tablets and 500 mg ampoules (Fides Rottapharm, Valencia, Spain).

ε-Aminocaproic acid: Caproamin Fides, 2.5 g sachets and 4 g ampoules (Fides Rottapharm, Valencia, Spain).

C1-inhibitor concentrate: Berinert, 500 U vials (Immuno AG, Vienna, Austria). Not marketed in Spain (request as a foreign medicine).

New Treatments

Plasma kallikrein inhibitor, DX88 (Dyax Corp., Cambridge, Massachusetts, USA).

Bradykinin B2 receptor antagonist, Icatibant (Jerini AG, Berlin, Germany).[30]

Serum protease inhibitor. This is not specific as it inhibits antithrombin III, β2-microglobulin, α1-antitrypsin, and α2-antiplasmin, among others.

Recombinant C1-inhibitor (Pharming Group NV, Leiden, The Netherlands).[31]

Conclusions

Although C1 inhibitor deficiency is a rare syndrome, it is worth being aware of its existence due to its potential

involvement of the upper airways, which can cause death of the patient. The most common type of angioedema due to C1 inhibitor deficiency is the congenital type, which usually becomes evident during the second decade of life with abdominal symptoms. The acquired type is less common and may be triggered by various drugs or hormonal changes. Diagnosis of the disease begins with clinical suspicion (skin swelling with occasional involvement of the upper airways or abdomen). Clinical suspicion must be confirmed by measurement of C4 and quantification of C1 inhibitor in plasma; if necessary, C1 inhibitor function may also be measured. The diagnosis is not always easy as false positives are common and there is a wide variability between laboratories. With regard to treatment, a number of drugs are commonly used in the management of an acute attack, and there are other new drugs still not on the market. There are clear indications for prophylaxis and these should be followed.

Conflicts of Interest

The authors declare no conflicts of interest

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