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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,