# Idiopatic angioedema treated with dapsone

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## ABSTRACT

The most commonly identified causes of angioedema are medications, allergens and physical agents, but most cases of angioedema are idiopathic. Treatment depends on identification of the causative agent and, especially when the mechanism is not identified, on the clinician's knowledge and experience with innovative therapeutic regimens.

*Case report:* A 48-year-old man presented with a 3-month history of recurrent severe episodes of angioedema affecting the lips, tongue and throat. A fiberoptic examination revealed laryngeal edema during some episodes. He did not report abdominal pain, nausea or vomiting. No precipitating factors were identified. The patient was not receiving angiotensin-converting enzyme inhibitors.

For the previous 4 years, the patient had been receiving levothyroxine for autoimmune thyroiditis. There was no history of facial palsy or hereditary angioedema.

*Allergy study:* Skin prick test with aeroallergens, food, latex, Anisakis and patch test to a standard series (true test) were negative. Laboratory investigations revealed normal complete blood count (CBC), erythrocyte sedimentation rate, urinalysis, blood biochemistry, serum protein electrophoresis and serum immunoglobulins. IgE concentration was 30 UI/ml. Antiperoxidase antibodies were positive (535 UI/ml). Antinuclear antibodies serum immune complexes and rheumatoid factor were negative. Complement study during acute and asymptomatic periods revealed normal values of C1 esterase inhibitor, C1q, C3, C4, functional activity of C1 inhibitor and CH50.

No pathologic findings were observed in a lip biopsy.

The patient was treated with sedating and nonsedating H1 antihistamines and corticosteroids (prednisone 30 mg/day for 3 months) with no clinical improvement and treatment with 50 mg of dapsone daily was started. Glucose 6 phosphate dehydrogenase deficiency had previously been ruled out. The patient improved and antihistamine and corticoid treatment was withdrawn 1 month after starting the dapsone regimen. No episodes of angioedema appeared during the subsequent year. No reductions in hematologic parameters or adverse events were detected.

Dapsone may be an alternative drug in extreme cases of idiopathic angioedema in patients with poor response to conventional therapy.

***Key words:*** Idiopathic angioedema. Glucocorticoids. Antihistamines. Dapsone. Sulfone. Complement. Glucose 6 phosphate dehydrogenase.

## RESUMEN

Los elementos más frecuentemente implicados en la etiología del angioedema son fármacos, alergenos y agentes físicos, si bien la mayoría de los casos son de carácter idiopático. El tratamiento se basa en la identificación del agente causal y en la experiencia del clínico en el manejo de estos cuadros, siendo preciso en algunas ocasiones recurrir a regímenes terapéuticos novedosos.

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*Caso clínico:* Paciente varón de 48 años de edad, que 3 meses antes de acudir a nuestra consulta comienza con episodios de angioedema que afectan labios, lengua y región faringo-laríngea. La laringoscopia reveló edema laringeo durante las crisis. No presentaba síntomas digestivos acompañantes. No identificamos ningún desencadenante. No recibía inhibidores del enzima de conversión de la angiotensina (IECA).

Los últimos 4 años seguía tratamiento con levotiroxina por tiroiditis autoinmune. No refería antecedentes de parálisis facial ni angioedema hereditario.

*Estudio alergológico:* prick test con bateria de inhalantes, alimentos, latex, anisakis: negativo. Prueba del parche estándar (true test): negativo. No se detectaron alteraciones en hemograma, velocidad de sedimentación, bioquímica con perfil hepático, electroforesis sérica e inmunoglobulinas. IgE total 30 UI/ml. Anticuerpos antiperoxidasa: positivos (535 UI/ml). Inmunocomplejos séricos, ANA, factor reumatoide: negativos. Estudio de complemento normales (C3, C4, C1 inhibidor, actividad funcional de C1, C1 q, CH50) realizado en fase asintomática y durante las crisis: dentro de los valores normales.

No se detectaron alteraciones patológicas en biopsia de labio.

Se inicia tratamiento con antihistamínicos y corticoides (prednisona 30 mg/día) durante un periodo de 3 meses persistiendo los brotes de angioedema con la misma intensidad y frecuencia, por lo que decidimos iniciar tratamiento con dapsona 50 mg/día, previamente se descartó déficit de glucosa 6 fosfato deshidrogenasa. El paciente presentó mejoría clínica, pudiendo suspender el tratamiento con corticoides y antihistamínicos al mes de iniciar el régimen terapeútico con dapsona. En los 12 meses posteriores no presentó nuevos episodios de angioedema, tampoco detectamos efectos adversos tras dicho tratamiento, ni reducción en las 3 series hematológicas.

La dapsona puede ser un fármaco alternativo en casos de angioedema idiopático que no se controlan adecuadamente con la terapia convencional.

***Palabras clave:*** Angioedema idiopático. Glucocorticoides. Antihistamínicos. Dapsona. Sulfona. Complemento. Glucosa 6 fosfato deshidrogenasa.

## INTRODUCTION

Angioedema is a constellation of syndromes that present a challenge to the clinician. The most commonly identified causes of angioedema are medications, allergens, and physical agents, but most cases of angioedema are idiopathic.

The most effective treatment depends on the identification of the causative agent and specially when the mechanism is not identified on the clinician's knowledge and experience with innovative therapeutic regimens.

## CASE REPORT

A 48 year old man, presented to our Allergy Unit in May 02, because recurrent severe episodes of angioedema affecting the lips, tongue, and throat. He often presented at the Emergency room (once or twice a week for the last 3 months) with tongue and lips swelling, dysphonia and dyspnea. A fiber optic examination revealed mild laryngeal edema during some episodes, that resolved within a few hours after treatment with epinephrine, antihistamines or corticosteroids. The patient did not related episodes of abdominal pain, nauseas or vomiting.

No precipitating factor was identified. He had not been taken angiotensin-converting enzyme inhibitors. The last 4 years he was receiving levothyroxine, because an autoimmune thyroiditis. There was no history of facial paralysis or hereditary angioedema.

Physical examination revealed edema limited to the lower lip, the remainder of his examination was unremarkable.

Skin prick tests to a battery of inhalants, foods, latex, Anisakis simplex and patch test to a standart serie (True test, Abelló, Spain) were negative.

Laboratory investigation revealed normal complete blood count (CBC), erythrocyte sedimentation rate, urinalysis, blood biochemistry (liver and renal function tests), C reactive protein, serum protein electrophoresis, serum immunoglobulins. Total IgE was 30 UI/ml. Antibodies anti-peroxidase were positives: 535 UI/ml (normal values up to 34). Serum immune complexes, antinuclear antibodies and rheumatoid factor were negative.

Complement study during acute and asymptomatic periods revealed normal values of C1 esterase inhibitor, C1q, C3, C4 and CH50. Funtional activity of C1 inhibitor was higher than 90 %.

Three different stool samples were negative for parasites. X-ray studies of thorax and paranasal sinuses showed normal findings.

A biopse of the lip was performed to exclude a cheilitis granulomatosa. No pathologic findings were observed in such specimen.

The patient was treated with sedating and nonsedating H1 antihistamines and corticosteroids (prednisone: 30 mg every day during 3 months) with no

clinical improvement. So we decided to start treatment with dapsone 50 mgs daily (previously a deficiency of glucose 6 phosphate dehydrogenase was excluded). Clinically the patient improved and during the subsequent year, no episodes of angioedema appeared. Corticosteroids and antihistamines were stopped one month after starting treatment with dapsone. CBCs were performed weekly during the first month of therapy, monthly for the next 6 months and every 6 months thereafter. No reduction in leukocytes, platelets, or hematopoiesis was detected. No others adverse effects were observed during treatment with dapsone.

## DISCUSSION

The term angioedema describes the localizated, transient episodic edema of the deeper layers of the skin or of the mucosa of the gastrointestinal tract. Angioedema affecting the throat, may lead to obstruction of the airways and death from asphyxiation.

The most commonly identified causes of angioedema are medications, allergens and physical agents, but most cases of angioedema are idiopatic[1]. Rare forms of angioedema associated with either hereditary or acquired faulty activation of the complement and kallicrein-kinin systems have been extensively described[2,3].

After excluding the most probable causes of angioedema, we conclude that our patient presented an idiopatic angioedema. In spite of treatment with antihistamines and a daily scheme of oral corticosteroids for 3 months, the patient continued with recurrent episodes so therapy with dapsone was administered.

Dapsone, a sulfone is an antibacterial drug for susceptible cases of leprosy. It is also a primary treatment for dermatitis herpetiformis and has been used with slightly greater success in urticarial vasculitis[4], bullous eruptions[5], and it has been proposed in cases of severe chronic urticaria to taper off prednisone or in cases of unacceptable side effects of steroids[6].

The mechanism of action of dapsone is poorly understood, its anti-inflamatory effects include reduction in lymphocyte responses to mitogens, suppression of neutrophil chemotaxis, and inhibition of the alternate pathway of complement activation The drug also appears to inhibit spontaneous and induced synthesis of prostaglandin E2 by polymorphonuclear leukocytes[7].

Since dapsone induces severe hemolysis in patients with glucose –6-phosphate dehydrogenase deficiency, this serum enzyme should be measured prior to initiation of such therapy. Others less frequent side effects include headaches, a mild non-hemolytic anemia and most importantly, agranulocytosis. Thereafter a complete blood counts should be monitored periodically in patients treated with dapsone[8].

As in chronic urticaria perhaps some patient with recurrent episodes of idiopathic angioedema may have a good response to dapsone, but the response may be unpredictable in each patient, and side effects must be monitored.

We conclude, that dapsone may be an alternative drug in extrem cases of chronic urticaria or idiopathic angioedema that precise corticosteroids for extended periods as a steroid-sparing drug or in cases with poor response to conventional therapy.

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