

EDITORIAL

Clinical & Experimental Allergy

Hereditary and other orphan angioedemas: a new prophylactic option at last?

This editorial discusses the findings of the paper in this issue by C. Saule et al. [15], pp. 475–482.

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Progestogens: a new therapeutic option for bradykinin-mediated angioedema?

In this issue Saule and colleagues describe use of progestogens by a sizeable cohort of French women with bradykinin-mediated angioedema, both familial and sporadic, with and without C1 inhibitor deficiency. Progestogens emerge as a potentially effective prophylactic against both pregnancy and angioedema, neatly combining a solution for two unmet needs for this group of patients [15].

In the past 5 years, new acute treatment options for hereditary angioedema (C1 inhibitor deficiency) have led to renewed interest in this disabling and sometimes fatal condition.

Patients with C1 inhibitor deficiency experience angioedema 'attacks' which are unpredictable, affecting almost any part of the body; most commonly the peripheries or intra-abdominal mucosa. Abdominal attacks are painful and typically result in 1–5 days of disablement [1]. Peripheral attacks are disfiguring and impede function of the affected part. Intra-oral attacks are less common but greatly feared by affected families, as they are responsible for the substantial lifetime mortality [1].

Specialists working in allergy and immunology clinics have long been aware of the existence of patients with antihistamine-resistant angioedema. Many have

features similar to the known bradykinin-mediated angioedemas but without identifiable underlying causes such as C1 inhibitor deficiency or angiotensin converting enzyme (ACE) inhibitor use [2, 3]. Where the angioedema is familial, the syndrome is referred to as 'HAE, type 3' or 'HAE with normal C1 inhibitor', to distinguish it from HAE types 1 and 2, which are caused by deficient C1 inhibitor protein or function. Women appear to be affected more frequently and more severely, probably because of the angioedema-promoting role of oestrogen. A minority of affected families carry mutations of the FXII gene which are strongly associated with angioedema susceptibility, at least in women. Patients without a family history or FXII mutation may represent sporadic cases of a similar syndrome [4].

Symptoms occur predominantly in young women, disrupting economic activity and domestic duties. Poor recognition and lack of diagnostic tests for the majority inevitably mean that treatment options are not well defined. It is therefore particularly welcome that Saule and colleagues have included patients with HAE with normal C1 inhibitor in their study. Factor XII mutations are subject to a founder effect and as such may be particularly common in South East France, Italy and Germany. Angioedema services in France are delivered by a national network, therefore, the French have been able to gain unprecedented experience in management of patients with HAEs with FXII mutations and the more numerous patients without known genetic mutations who have a phenotypically similar syndrome.

This group of patients differ from those with histamine associated angioedema both phenotypically and in their aetiology. Overactivation of the contact pathway leads to a stepwise activation of kallikrein, which generates local bradykinin, causing increased capillary permeability and angioedema. Acute treatment options

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recently licensed for HAE1 and 2 may also prove effective for those with other bradykinin-mediated angioedemas [4, 5]. These include replacement of the missing C1 inhibitor, antagonism of kallikrein with ecallantide or inhibition of the bradykinin B2 receptor with icatibant. These options are expensive and require parenteral administration. Moreover, the time to resolution is slow; typically several hours. Thus, for most people with frequent attacks, prophylaxis is desirable to enable normal participation in employment and education [6, 7].

Currently recommended prophylactic options comprise androgens; fibrinolytics such as tranexamic acid; or regular C1 inhibitor replacement. Tranexamic acid is of limited efficacy and does not have a good evidence base [6–8]. C1 inhibitor is administered intravenously, usually twice weekly [9]. Logistic and financial barriers currently limit this option to the most severely affected. 17 alpha-alkylated 'attenuated' androgens, such as danazol and stanozolol, reduce severity and frequency of attacks for the majority but are limited by actual or potential side-effects. In particular, concerns about weight gain or possible androgenic side-effects mean that young women may be reluctant to take these agents [6, 7, 10].

Attenuated androgens probably exert their beneficial action by limiting bradykinin production at multiple sites, including reducing production via increased hepatic synthesis of C1 inhibitor and increased production of bradykinin-metabolizing enzymes [11]. Oestrogen also enhances bradykinin production by several mechanisms, including binding to promoter elements of the factor XII (FXII) gene, thereby increasing contact pathway activation and bradykinin production [4]. Progestogens may theoretically therefore have a beneficial role through their anti-oestrogen and mildly pro-androgenic properties.

Oestrogens, used for their contraceptive effects, or as hormone replacement therapy, have been shown to induce or worsen angioedema in susceptible females with bradykinin-mediated angioedema, with or without C1 inhibitor deficiency. Moreover, once induced, stopping exogenous oestrogen does not necessarily result in a decrease in frequency of angioedema episodes [12, 13]. For this reason, oestrogen-containing 'combined' contraceptives are contraindicated and other birth control options are required [8].

Conventional progestogen-only birth control pills (POP) contain relatively low doses of desogestrel (Cera-zette), Norethisterone (Noriday) or Levonorgestrel (Norgeston). POPs exert their contraceptive effect via induction of changes in the cervical mucus which prevent sperm penetration. Although POPs have antigonadotropic activity, they do not reliably prevent ovulation in every cycle, but may promote development of luteal cysts when ovulation occurs. These cysts produce high levels of oestrogen (and progesterone), with potential paradoxical worsening of the angioedema [8].

Saule's cohort experienced a reduction in frequency of angioedema attacks in 61% of women using POPs, probably because of their antigonadotropic, antiovulatory effect. However, 23% experienced a paradoxical worsening of symptoms, presumably caused by induction of oestrogen-generating luteal cysts. Higher dose progestogens have a more consistent antigonadotropic effect and some, such as norethisterone, may have additional mild androgenic activity which would be predicted to exert additional benefit [8]. Use of higher dose progestagens with antigonadotropic activity (antigonadotropic progestogens; AGPs) was associated with a higher rate of improvement: 81% of women reporting reduced attack frequency and none experiencing worsening of symptoms [15].

High dose progestogens are widely available: Contraceptives such as medroxyprogesterone acetate (Depo-Provera) are available as an intramuscular injection with 12 week duration of action. High dose norethisterone is licensed for endometriosis or dysfunctional uterine bleeding [14].

Women with angioedema may be reluctant to use attenuated androgens because of fear of side-effects. If replicated, Saule's experience is the first report of a new, convenient and well tolerated prophylactic option for this under-resourced group of patients.

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