Hereditary Angioedema and Oral Contraception

L.	Luca	Borradori ^a
O.	Odile	Marie ^a
M.	Michel	Rybojad ^a
P.	Patrick	Vexiau ^b
P.	Patrice	Morel ^a
P.	Peter	Späth ^c

^aDepartments of Dermatology and ^bEndocrinology, Hôpital Saint Louis, University of Paris VII, Paris (France); ^cCentral Laboratory of the Swiss Red Cross, Transfusion Service, Berne (Switzerland)

Luca Borradori, Odile Marie, Michel Rybojad, Patrick Vexiau, Patrice Morel, Peter Späth, Departments of Dermatology and Endocrinology, Hôpital Saint Louis, University of Paris VII, Paris (France); Central Laboratory of the Swiss Red Cross, Transfusion Service, Berne (Switzerland)

To the Editor

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by a quantitative or functional deficiency of C1 esterase inhibitor (C1-INH) [1]. Attacks of angioedema may be induced by a variety of factors, such as tissue trauma, infection, anxiety, and fatigue [1]. The condition apparently is further influenced by sexual hormones [2–4].

Case Report. A 20-year-old previously healthy woman was given Diane® (containing 0.035 mg ethinyl estradiol and 2 mg cyproterone acetate) as treatment for acne. Three weeks after institution of the therapy she experienced attacks of poorly circumscribed, nonpitting and nonpruritic cutaneous swellings, along with occasional abdominal pain. The edema involved particularly the extremities, the trunk and further pressure-exposed sites. The episodes lasted for up to 3 days and occurred weekly. After 2 months she changed to Trinordiol® (containing 0.05–0.125 mg levonorgestrel and 0.03–0.04 mg ethinyl estradiol) as oral contraceptive agent (OCA), but attacks persisted. She was therefore given Lutényl® (containing 5 mg of norgestrel acetate) and she was free of symptoms until she discontinued OCA 2 months later.

Responses to repeated pressure challenges were all the time negative. Extensive laboratory investigations, including search for autoantibodies, did not reveal any abnormalities, except of the complement profile (table 1).

Letters to the Editor

79

Table 1. Complement profile 1 month after stop of OCA treatment

Patient

Normal range

gests that progestational agents, such as norgestrel acetate, may be of benefit in young women with hereditary angioedema requiring an oral contraception.

300 SI β /ml

276

Functional assay CH50 Functional CI-INH

Formation of CI-INH-Clr

82

undetectable

1

0.04

114 115 0.93 0.07

70 -135% 80 -125 %4 70 -130%5

0.11–0.26 g/l 75 -125% 67 -127% 0.75–1.40 g/l 0.14–0.35 g/l

complexes2 Exog. Cls (amidolysis)3) Exog. Cls (amidolysis) Protein concentrations6 CI-INH Clr
C2

C3/C3c C4

1 1 U corresponds to the amount of serum (ml) , which lyses 50% of $3 \cdot 10^6$ optimally sensitized sheep erythrocytes within 45 min at 37 °C in a total volume of 0.5 ml.

2 This assay directly measures interaction of CI-INH with its natural substrate, Clr, at physiologic concentrations of Clr and CI-INH [according to 7].

3 Based on inhibition by CI-INH of amidolytic activity of exogenous Cls added to the sample to be tested, using commercially available testkits.

4 Kits from Beringwerke, Marburg, FRG.

5 Kits from Immuno, Vienna, Austria.

6 Assessed by nephelometry or radial immunodiffusion using mono-specific antisera.

The father of our patient, 3 of her paternal uncles and 1 aunt had a history of repeated attacks of angioedema, occasionally in association with the intake of salicylates and insect bites.

Comment. In the present case clinical features, complement profile and family history are consistent with a diagnosis of hereditary angioedema. In this disorder, the first clinical manifestations often occur during puberty and symptoms may be further elicited or aggravated by menstruation, suggesting a direct relationship between hormonal changes and angioedema. In addition, angioedematous attacks induced by OCA have been rarely described [2–5].

In line with previous reports, our patient experienced the first symptoms shortly after institution of the OCA therapy [2–5]. The estrogen-related compounds contained in the OCA appear to precipitate the attacks [2–5]. Cyproterone acetate has not been shown to aggravate clinical manifestations in hereditary CI-INH deficiency [6] , however, it has been recently implicated in the development of angioedema in female patients with normal CI-INH function [5].

Interestingly, the swellings disappeared while the patient was on norgestrel acetate, a progestogen derived from 17-OH progesterone. In fact, in order to avoid the frequent side effects observed in female patients with CI-INH deficiency receiving long-term prophylactic therapy with attenuated androgens, such as danazol, clinical efficacy of synthetic progestatins with anabolic properties has been recently assessed [8].

Our observation thus confirms that OCA containing estrogens may precipitate potentially dangerous attacks of edema, and further sug-

References

Guenther LC: Inherited disorders of complement. *J Am Acad Dermatol* 1983;9:815–839.

Gordon EM, Ratnoff OD, Saito H, Donaldson VH, Pensky J, Jones PK: Rapid fibrinolysis, augmented Hageman factor (factor XII) titers, and decreased C1 esterase inhibitor titers in women taking oral contraceptives. *J Lab Clin Med* 1980;96:762–769. Warin RP, Cunliffe WJ,

Greaves MW, Wallington TB: Recurrent angioedema: Familial and oestrogen-induced. *Br J Dermatol* 1986; 115:731–734.

Böckers M, Bork K: Kontrazeption und Schwangerschaft beim hereditären Angioödem. *Dtsche Med Wochenschr* 1987;112: 507–509.

Pichler WJ, Lehner R, Späth PJ: Recurrent angioedema associated with hypogonadism or anti-androgen therapy. *Ann Allergy* 1989; 63:301–305.

Jamin C, Intrator L, Laurent J, Lagrue G: L'acétate de cyproterone n'est pas actif pour la prophylaxie de l'œdème angioneurotique héréditaire. *Presse Méd* 1985; 14:1559.

Späth PJ, Wüthrich B, Butler R: Quantification of C1-inhibitor functional activities by immunodiffusion assay in plasma of patients with hereditary angioedema – evidence of functionally critical level of C-1-inhibitor concentration. *Complement* 1984; 1:147.

Laurent J, Jamin C, Lagrue G: Oedème angioneurotique héréditaire: la norgestriénone n'est pas active dans tous les cas. *Presse Méd* 1987;16:2132.

About the Association of Lichen planus and Psoriasis

Sir,

W. We read with interest the report by Shiohara et al. about the coexistence of lichen planus and psoriasis in a single patient in a recent issue of *Dermatologica* [1].

Between September 1986 and February 1988 the Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED) conducted a multi-