Hereditary Angioedema and Oral Contraception

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To the Editor

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by a quantitative or functional deficiency of Cl esterase inhibitor (Cl-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 normegestrol 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).

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

<table>
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<th>Patient</th>
<th>Normal range</th>
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<td>L. Luca Borradori</td>
<td>300 SIβ0/ml1</td>
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300 SIβ0/ml1
Functional assay CH50 Functional Cl-INH
Formation of Cl-INH-Clr
undetectable
1
0.04
114 115 0.93 0.07
70 -135% 80 -125 % 4 70 -130%
0.11–0.26 g/l 75 -125% 67 -127% 0.75–1.40 g/l 0.14–0.35 g/l
complexes
Exog. Cls (amidolysis)
Protein concentrations
Cl-INH Clr C2
C3/C3c C4
1 1 U corresponds to the amount of serum (ml), which lyses 50% of 106 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 Cl-INH with its natural substrate, Clr, at
physiologic concentrations of Clr and Cl-INH [according to 7].
3 Based on inhibition by Cl-INH of amidolytic activity of exogenous Cls added to the
sample to be tested, using commercially available test kits.
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 Cl-INH deficiency [6], however, it has been recently implicated in
the development of angioedema in female patients with normal Cl-INH function [5].
Interestingly, the swellings disappeared while the patient was on normeestrol acetate, a
progestogen derived from 17-OH progesterone. In fact, in order to avoid the frequent side effects
observed in female patients with Cl-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
Gordon EM, Ratnoff OD, Saito H, Donaldson VH, Pensky J, Jones PK: Rapid fibrinolysis,
augmented Hageman factor (factor XII) titers, and decreased Cl esterase inhibitor titers in
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-