FEMALE PATTERN HAIR LOSS MAY BE TRIGGERED BY LOW OESTROGEN TO ANDROGEN RATIO

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Objective. In both sexes the androgenetic alopecia is known to be mediated by the conversion of circulating androgens into dihydrotestosterone within the hair follicle. However, there are a number of differences between male and female pattern baldness with estrogen known to be protective against hair loss in women. Since androgen levels in women with female pattern hair loss are mostly within the normal range, we decided to calculate the ratio of estrogens to androgens in order to find a putative trigger for their hair loss.

Methods. We studied 20 premenopausal women with female pattern hair loss and 9 healthy women for serum levels of LH, FSH, estradiol, free and total testosterone, sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEAS) on the first day of their menstrual cycle.

Results. Although the absolute levels of androgens were normal in both groups, the ratio of estradiol to free testosterone and the ratio of estradiol to DHEAS were significantly lower in patients than in the control group.

Conclusions. We put up a hypothesis that in the presence of a genetic susceptibility, it is the estrogen to androgen ratio, as represented by the ratio of estradiol to free testosterone that might be responsible for triggering female pattern hair loss in women.

Key words: Androgenetic alopecia – Female pattern baldness – Estrogens – Androgens

Androgenetic alopecia (AGA) is known to originate via the conversion of circulating androgens into dihydrotestosterone (DHT) by 5α-reductase within the hair follicles, which facilitates their miniaturization and the following hair loss. However, it is known that women with AGA have significantly lower amounts of 5?-reductase as well as more aromatase in their follicles as compared to men (SAWAYA and PRICE 1997). Aromatase, by metabolising androgens into estrogen, naturally counteracts the process of miniaturization (HOFFMAN et al. 2002). However, the question whether AGA is the same disease in two different sexes or whether the underlying mechanisms of AGA in women are different from those in men still remains unanswered. NORWOOD and LEHR (2000) summarized the differences between men and women as follows: 1. Male pattern baldness (MPB) begins with the recession of the hairline and results in complete hair loss across the top of the scalp, while female pattern baldness (FPB) results in diffuse thinning behind the hairline, but there is no recession of the hairline; 2. MPB begins in the late teens and early twenties when testosterone levels are high. In contrast, FPB tends to begin in the late thirties and reaches its peak after fifty when testosterone levels are falling; 3. MPB affects up to 70 % of all males, while FPB affects up to 30 % percent of women; 4. Females with a predisposition for an-

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drogenetic hair loss rapidly develop typical male pattern baldness if given high doses of androgens.

Some studies published so far failed to show androgen excess in AGA (SCHMIDT et al. 1991; TOSTI et al. 2005). Also estrogen levels were repeatedly shown to be within normal limits (SCHMIDT et al. 1991) and routine testing for hormonal imbalances is currently being discouraged in women with hair loss (PRICE 2003). However, as based on a clinical observation, we decided to examine women with FPB for the estrogen to androgen ratio, which might be, at least hypothetically, the trigger for female hair loss.

The aim of this study was to test the hypothesis that, in the presence of genetic susceptibility it is the estrogen to androgen ratio, as represented by the ratio of estradiol to free testosterone (E2/fT), that triggers female pattern hair loss in women.

Subjects and Methods

Patients. We examined 20 premenopausal women (age range 18-52 years, mean 38 years) with normal menstrual patterns (cycle duration between 26-34 days) and no symptomatic hormonal disturbances. All of them were referred to us with the diagnosis "female pattern hair loss". Such diagnosis was further verified clinically and the severity of the disease was classified according to the Ludwig scale. Based on 468 cases, LUDWIG (1977) developed the following grading system that shows a progressive increase in diffuse hair loss from the top of the scalp: Grade I – perceptible thinning of the hair on the crown, limited by a line situated 1-3 cm behind the frontal hair line; Grade II – pronounced rarefication of the hair on the crown within the area seen

in Grade I; Grade III – full baldness within the area seen in Grades II and III.

Control group of 9 healthy women (age 18-45, mean 23 years) without hair loss or thinning was examined for the same parameters.

Laboratory analyses. In all women we measured serum levels of LH (IU/l), FSH (IU/l), estradiol (E2) (pg/ml), testosterone free (fT) (pg/ml) and total (ng/dl), SHBG (nm/l) and dehydroepiandrosterone sulfate (DHEAS) (ng/ml) on the first day of their menstrual cycle. We paid attention to collect all blood samples at 10 AM to avoid the impact of diurnal fluctuations. Further, the ratios of estradiol to free testosterone (E2/fT ratio) and the ratio of estradiol to DHEAS (E2/DHEAS), respectively, were calculated. For easier reference we firstly multiplied the results of the E2/DHEAS ratio by 100 (E2/DHEAS x100) and then the ranges and means for each variable were calculated.

Statistical evaluation. All nine variables obtained in the patient group were compared with these in control group using one-sample t-test (Stat View for Windows, SAS Institute Inc., Version 5.0).

Results

All 20 women had clinical thinning, which could be classified as Ludwig grade I (11 patients) and grade II (9 patients).

The results of the laboratory findings are presented in Table 1. In patients with FPB the gonadotropin values were at the premenopausal level except one patient (mean FSH = 10.25 IU/l, mean LH = 5.6 IU/l). The levels of testosterone were within normal female range and not significantly different from controls. In fact,

Table 1: The summary of laboratory findings

CONTROLS	FSH (IU/l)	LH (IU/l)	E2 (pg/ml)	fT (pg/ml)	Total T (ng/dl)	SHBG (nm/l)	DHEAS (ng/ml)	**E2/fT**	**E2/DHEAS x100**
Mean	8.36	5.4	111.8	5.0	46.8	73.6	950.0	23.7	14,1
Min.	3.0	3.0	75.1	3.4	15.2	40.2	400.0	15.0	7,00
Max.	17.0	9.0	220.0	8.1	80.0	120.1	2800.0	27.5	22,5
SD	4.4	2.2	41.4	2.1	20.3	26.9	725.7	6.5	4.7
PATIENTS									
Mean	10.25	5.6	40.7	5.7	32.5	91.0	1388.9	7.9	4.9
Min.	5.59	1.6	5.0	1.5	7,2	30.2	110	1.46	0.54
Max.	27.0	9.5	125	24	70,0	191.0	3539	26.9	25.0
SD	5.7	2.4	29.6	5.2	19.3	58.6	940.6	7.3	6.1
P			<0.001					<0.001	<0.001

Table 2: Exemplary patient-control pairs matched by age

Matching by age	FSH (IU/l)	LH (IU/l)	E2 (pg/ml)	fT (pg/ml)	Total T (ng/dl)	SHBG (nm/l)	DHEAS (ng/ml)	E2/fT	E2/DHEAS x100
Patient age 18	7.8	8.2	22.7	4.6	39.2	191.1	1083	4.93	2.09
Control age 18	8.0	6.3	150.1	9.4	50.2	180.0	1200	15.97	12.51
Patient age 19	5.9	3.2	44.7	5.5	40.9	84.8	3539	8.13	1.26
Control age 20	13.9	7.8	100.1	3.0	40.0	50.9	900	33.34	11.12
Patient age 33	8.0	4.7	28.4	7.6	19.1	49.2	754	3.74	3.77
Control age 30	9.9	6.9	75.4	5.5	61.0	90.1	400	15	18.85
Patient age 38	9.8	5.1	20.2	6.5	29.8	45.5	1108	3.11	1.82
Control age 36	12.1	4.3	80.2	3.3	30.4	97.7	453	24.30	17.70
Patient age 45	8.5	1.6	35.4	24.3	70.1	34.7	1638	1.46	2.16
Control age 45	4.3	3.2	89.8	3.5	15.6	45.6	423	25.66	21.23

the values of total testosterone (tT) were lower in patients (range of 7.2-70.0 ng/dl, mean 32.5) than in controls (range of 15.2-80.0 ng/ml, mean 46.8, but the difference was not significant. Also the levels of DHEAS were normal, and if slightly higher than in controls (mean 1388 ng/ml versus 950 ng/ml), the difference was statistically not significant. The levels of SHBG were within normal range and even higher in patients (range 30.2-191.0 nmol/l, mean 91.0) than in controls (range 40.0-120.0 nm/l, mean 73.6).

In patients the levels of 17ß-estradiol (E2) on the first day of menstrual cycle as well as the ratio of estradiol to free testosterone (E2/fT) and the ratio of estradiol to DHEAS (E2/DHEAS x 100), respectively, were significantly lower than in the control group (p<0.001). In addition, the levels of E2 in patients with FPB, although still considered normal, were only one third of the mean levels in healthy women (40.7 pg/ml versus 111.8 pg/ml). The mean ratio of estradiol to free testosterone (E2/fT) in patients was almost three-times lower than in controls (7,9 versus 23,7); the mean ratio of estradiol to DHEAS in balding women being less than a half of the value in healthy controls (4,9 versus 14,1). The results of age matching between the patients and the control group are showed in table 2.

Discussion

AGA in women is generally regarded as the female equivalent of male balding and is often referred to as "female androgenetic alopecia". However, there are several questions about the pathomechanism of this disease in women. Our simultaneous study (RIEDEL-BAIMA, to be published) showed that 50 % of women with AGA did not show any miniaturization of hair follicles up to

the point of hair diameter reduction to 40 μm and less, which is ubiquitous in men. Women with AGA certainly show some decrease in hair diameter, especially in the androgen-dependent scalp regions but they seldom present the extent of miniaturization found in men.

Treatment with finasteride that blocks the conversion of testosterone to 5-DHT, improves male pattern hair loss, but has little effect on female pattern hair loss (PRICE et al. 2000). In contrast, several recent reports showed positive results with spironolactone (SINCLAIR et al. 2005) and cyproterone acetate (BRZEZINSKA-WCISLO 2003; SINCLAIR et al. 2005) both of which lower the levels of circulating androgens. There has been also a report describing a young women with hypopituitarism who presented with clinical and histological features of FPB in the absence of detectable androgen levels thus showing that this pattern of hair loss might be not always androgen dependent (ORME et al. 1999). Attempts to show high levels of androgens, low SHBG or both were unsuccessful in the past (SCHMIDT et al. 1991; TOSTI et al. 2005). Also our current study revealed normal levels of fT, tT, DHEAS and SHBG in women with FPB. In fact, total testosterone (tT) and 17ß-oestradiol were lower in patients than in controls. This could represent an age-dependent decline in both hormones as the controls were younger than patients (mean age 38 versus 23 years). However, the results obtained in some age matched pairs of patients and controls as shown in Table 2 indicate that age difference alone cannot explain this phenomenon.

The ratio of estradiol to free testosterone (E2/fT) and the ratio of estradiol to DHEAS (E2/DHEAS x 100) were significantly lower in patients than in the control group. It supported our experience that females with androgenetic hair loss have almost always E2/fT ratio

lower than 10 (unpublished data). Although we calculated also the E2/DHEAS ratio (E2/DHEAS x 100), we cannot say anything about its predictive value, DHEA varies greatly by age and this study was not extensive enough to evaluate its impact.

However, in the light of the current study we dare to put forward a following hypothesis of FPB. Thus, in genetically susceptible individuals (e.g. those with higher levels and/or activity of 5α-reductase and less aromatase in hair follicles), estradiol plays a protective role against androgens. A recent study has showed that under the influence of 17α-estradiol an increased conversion of testosterone to 17ß-estradiol and androstendione to estrone via aromatase takes place (HOFFMAN et al. 2002). We speculate that when the level of circulating estradiol decreases in relation to that of testosterone or DHEA, it unmasks the relative surplus of androgens and facilitates their subsequent conversion into DHT. Resulting from this the female pattern develops. But even then, the process is slower in females than in males, hair follicles abundant in aromatase (frontal hairline) being the most resistant. Why certain women experience the drop in estradiol while having androgen levels well within the middle range (relative imbalance) still remains unclear and should be further studied. A control group of 9 healthy women (age 18-45, mean 23 years), without hair loss or thinning was examined for the same parameters

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