

## PREMATURE ANDROGENIC ALOPECIA AND INSULIN RESISTANCE. MALE EQUIVALENT OF POLYCYSTIC OVARY SYNDROME?

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**Background.** Polycystic ovary syndrome (PCOS), the most frequent endocrinopathy in women with estimated prevalence of 5-10 %, is characterised by a hormonal and metabolic imbalance of polygene autosomal trait. The complexity of symptoms and genetic base started up the hypothesis on the existence of male equivalent of PCOS. Precocious loss of hair before 30 years of age was suggested as one of the male symptoms of this syndrome.

**Objectives.** The aim was to confirm the association of lower levels of follicle stimulating hormone (FSH) and sexual hormone binding globulin (SHBG) or higher free androgen index (FAI) in premature balding men with a reduced insulin sensitivity.

**Patients/Methods.** The study included 30 men with premature hair loss (defined as grade 3 vertex or more on the alopecia classification scale by Hamilton with Norwood modification) starting before 30 years of age. The hormonal values of the investigated group were compared with those regarded as normal reference values obtained in a group of 256 males in the age of 20-40 years during the Czech population study of iodine deficiency. In all men with premature baldness besides hormonal level determinations insulin tolerance test was carried out.

**Results.** The observed group was divided into two subgroups. The first one showed similar hormonal changes as women with PCOS, namely subnormal SHBG, FSH or increased FAI. The other had either no anomalies in steroid spectrum or only lower SHBG. The groups did not differ either in BMI or in age. The group with hormonal profile resembling that of women with PCOS, showed significantly higher insulin resistance than the group without these changes.

**Conclusions.** The findings are consistent with the hypothesis that at least a part of the men with premature androgenic alopecia could be considered as a male equivalent of the polycystic ovary syndrome of the women. These premature balding men represent a risk group for the development of impaired glucose tolerance or diabetes mellitus type 2.

**Key words.** Premature balding – Androgenic alopecia – Polycystic ovary syndrome – Insulin resistance

The polycystic ovary syndrome (PCOS) in female population belongs to the widest spread endocrine disorders with prevalence between 5-10 % (ASUNCION et al. 2000). PCOS is now recognised as an important metabolic and reproductive disorder. It is associated with substantial defects in insulin action and secretion that confer a markedly increased risk for impaired glucose tolerance or type 2 diabetes mellitus. The insulin resistance modifies reproductive function both by the direct actions of insulin on steroidogenesis and by dis-

ruption of insulin signalling pathways in the central nervous system. Hyperandrogenaemia and insulin resistance cluster in PCOS families, consistent with a genetic susceptibility to these abnormalities. CELA et al. (2003) reported that females with alopecia had a higher prevalence of polycystic ovary (PCO) and hirsutism than the control population. Such females (either with or without PCO) had higher testosterone, androstenedione and free androgen index than controls, even though slightly abnormal androgens had only few

of them. These findings confirm an association between androgenic alopecia and PCO, and other symptoms of hyperandrogenaemia. Thus, most women who present with androgenic alopecia as their primary complaint also have PCOS and have indices of abnormal androgen production. Since PCOS is a well-known risk factor for the development of type 2 diabetes, this association has important implications for long-term management.

In the search for potential male equivalent of PCOS, male premature baldness was suspected to be an apparent clinical sign of this syndrome (for review see LEGRO 2000), as could be derived from the frequency of hair loss in male members of the families with higher frequency of PCOS in female relatives. Recently we reported that men with premature androgenic alopecia showed lower SHBG and FSH and higher FAI than men selected randomly from the control population (STARKA et al. 2004). Now we would like to point out that they are also at higher risk of reduced insulin sensitivity.

### Subjects and Methods

**Patients.** We examined a group of 30 males who searched for hair transplantation because of precocious hair loss in. Only patients where the hair loss started before the 30 year of age were included. Their hair loss was characterised by recess of the frontotemporal hair border or balding at vertex (YOUNG and CRITCHLEY 1996) and was defined as grade 3 vertex or more on the alopecia classification scale by Hamilton with Norwood modification. They did not have any endocrine disease, took neither hormonal therapy nor medication for improving the quality of hair. The BMI of these patients was up to 30 kg/m<sup>2</sup>, i.e. within the range of normal weight or slight overweight. As a control group for hormonal examination a total of 256 healthy males age matched to the patients with alopecia were randomly selected from the subjects examined during the survey of iodine deficiency in the Czech Republic. The study was approved by the local Ethical Committee and all patients signed informed consent form before taking part in the study.

**Methods.** Basic hormonal spectrum was examined in all patients. The following hormonal determinations were carried out (normal range in parenthesis) by standard immunoanalytical methods described in detail elsewhere (STARKA et al 2004): total testosterone (T) (13.5 – 31.1 nmol x l<sup>-1</sup>), androstenedione (1.7 – 8.6 nmol x l<sup>-1</sup>), dehydroepiandrosterone sulphate (DHEAS) (7.2

– 16.1 nmol x l<sup>-1</sup>), dehydroepiandrosterone (DHEA) (10.8 – 32.6 nmol x l<sup>-1</sup>), epitestosterone (epiT) (0.9 – 7.8 nmol x l<sup>-1</sup>), dihydrotestosterone (0.9 – 3.6 nmol x l<sup>-1</sup>), cortisol (135 – 607 nmol x l<sup>-1</sup>), estradiol (0.01 – 0.27 nmol x l<sup>-1</sup>), sexual hormone binding globulin (SHBG) (34 – 66 nmol x l<sup>-1</sup>), prolactin (2.6 – 7.2 mg x l<sup>-1</sup>), thyrotropin (TSH) (0.27 – 4.20 mIU x l<sup>-1</sup>), luteinizing hormone (LH) (0.5 – 10.0 U x l<sup>-1</sup>) and follicle stimulating hormone (FSH) (2.0 – 10.0 U x l<sup>-1</sup>) were determined and the index of free testosterone was calculated (FAI = [(testosterone/SHBG)x 100]) (27 – 90).

In all patients, an insulin tolerance test was carried out according to YOUNG and CRITCHLEY (1996) in the fasting state between 7 and 9 a.m. Regular insulin (Actrapid HM, 0.1 IU.kg<sup>-1</sup>) was applied i.v. The venous blood samples to set glycaemia were taken from an applied cannula in the cubital vein in –3<sup>rd</sup>, 0, 2<sup>nd</sup>, 4<sup>th</sup> and then, each minute up to 15<sup>th</sup> minute. After the end of the test the patient was released no sooner than a normoglycaemia was achieved. The constant rate K<sub>ITT</sub> for plasma glucose disappearance was calculated according to the formula 0.693/t, where t was calculated from the slope of least square analysis of the plasma glucose concentrations at the 4<sup>th</sup> to 15<sup>th</sup> minute (when the glucose concentration declined linearly).

**Statistical evaluation.** The differences between group mean values were evaluated using robust Mann-Whitney test.

### Results

The results of hormonal examinations in 30 men with precocious alopecia were evaluated. These hormonal levels were compared to those found in the control group which consisted of randomly selected men from those participating in the survey on iodine deficiency in the Czech Republic. The balding men differed significantly in higher frequency of subnormal values of SHBG and FSH and in testosterone and epitestosterone values (not given here, see Starka et al 2004).

From the group of premature balding patients we selected a subgroup (n = 19, group A), which either did not show any hormonal changes or only their SHBG was lower than 34 nmol x l<sup>-1</sup>. The second subgroup consisted of balding men (n=11, group B) who had similar hormonal changes, which are typical for women with PCOS. The patients of this subgroup had either low SHBG and low FSH or low SHBG and high free testosterone index (FAI) as compared to controls. These two subgroups differed neither in age nor in BMI.

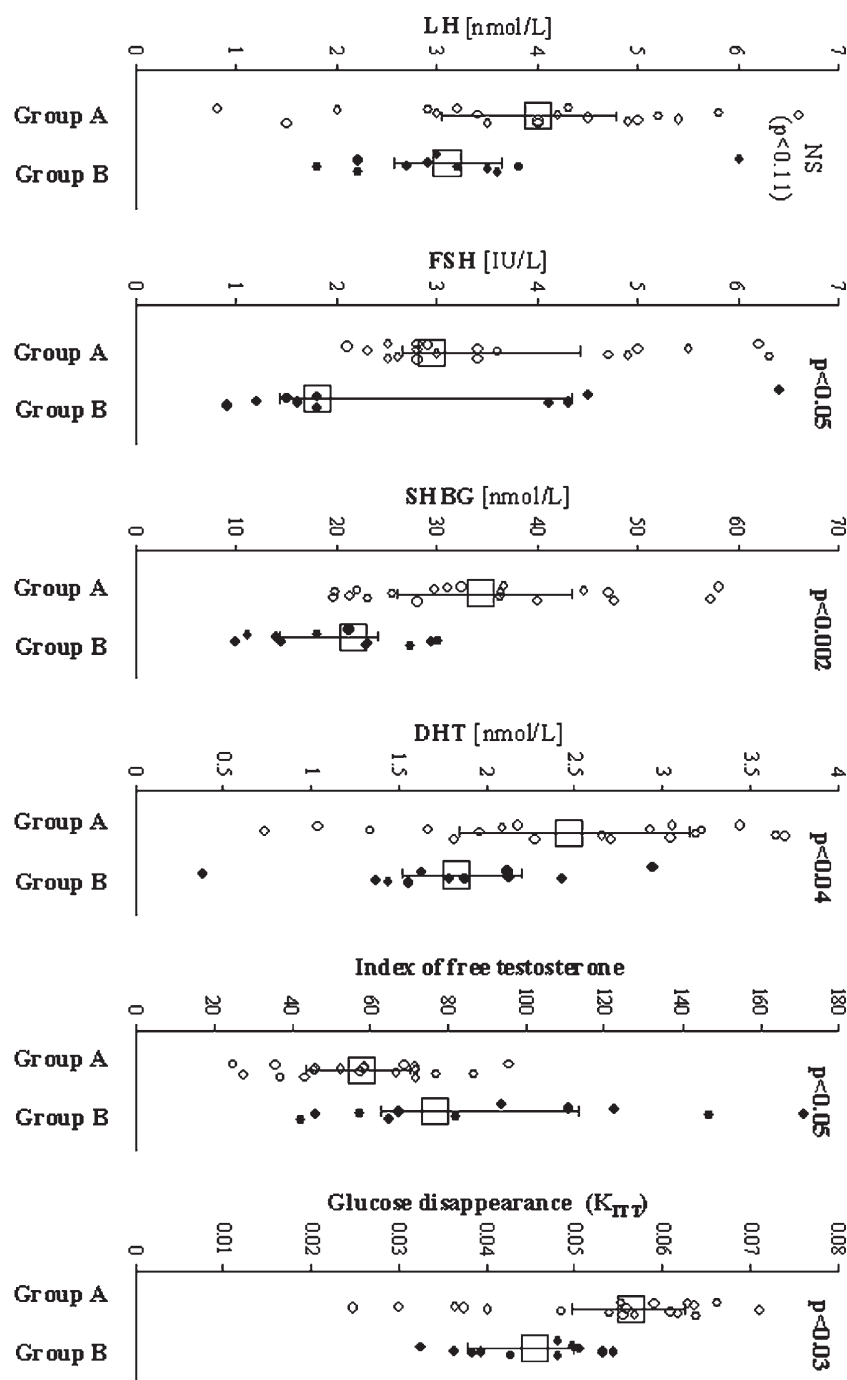
Fig.1 shows the  $K_{ITT}$  value and hormonal parameters in which the subgroup A and B differed significantly. The subgroup B had lower values of SHBG and FSH, but not these of LH, higher FAI and at short insulin tolerance test slower glucose disappearance expressed as  $K_{ITT}$ .

In these two subgroups we compared the insulin resistance by calculating  $K_{ITT}$ . Subgroup B (resembling the hormonal pattern similar to women with PCOS) was more insulin resistant than the group (A), as evaluated by Mann-Whitney test ( $p < 0.03$ ) (Fig.1).

### Discussion

Polycystic ovary syndrome represents the most frequent endocrine disorder in females. It is characterised by hormonal and metabolic imbalance. In a number of communications dealing with this syndrome its interrelation with insulin resistance is described. It is obvious from our results that the males with precocious hair loss starting under the age of 30 and exhibiting similar hormonal changes as females with PCOS (e.g. low SHBG and low FSH or low SHBG and high FAI) show higher frequency of reduced insulin sensitivity, which is also reported in a part of females with PCOS. These males might therefore represent a male equivalent of PCOS.

In our study there was about one third of such affected men. If we take into account the prevalence of precocious hair loss being about 30 % of male population, it corresponds approximately to the prevalence of PCOS in women. Recently in women with androgenic alopecia, a very high, nearly 90 % frequency of PCOS was described (CELA et al. 2003).



**Figure 1**  
The differences in hormonal spectrum and index ( $k_{ITT}$ ) of glucose disappearance in insulin tolerance test between men with premature androgenic alopecia with (group B) or without (group A) the hormonal signs of PCOS.

Provided that polycystic ovary syndrome has an autosomal oligogene or polygene trait (GOVIND et al. 1999; XITA et al. 2002; SAM et al. 2003), it is evident that the genetically determined signs may occur also in close rel-

atives of patients with manifested PCOS (YILDIZ et al. 2003) and that in males these genetic predispositions may occur as well. However, there are only a few references in the literature that deal with male phenotype of PCOS. Precocious hair loss or marked hypertrichosity were suggested as possible male symptoms of this syndrome (LEGRO 2000; GOVIND et al. 1999; CAREY et al. 1993). Unfortunately, the signs were not followed systematically in families with PCOS occurrence and records of laboratory findings of typical disturbances of steroids and gonadotropins and data on insulin resistance in men suspected having potentially the male phenotype PCOS are rare. The exact identification of male phenotype PCOS may be at the same time facilitated with the aid of genetic studies (XITA et al. 2002; ELLIS and HARRAP 2001).

It should be pointed out that, similarly to PCOS, the androgenic alopecia is associated with an increased risk of cardiovascular diseases and glucose metabolism dis-

orders (LESKO et al. 1993; HERRERA et al. 1995; FORD et al. 1996; LOTUFO et al 2000; LIVINGSTONE and COLLISON 2002). Balding represents also an increased risk of prostate carcinoma (DENMARK-WAHNEFRIED et al. 2000; Giles et al. 2002), particularly when the loss of hair starts prematurely (HAWK et al. 2000).

Irrespective whether a part of males with premature balding represents the male phenotype of PCOS or not, the occurrence of androgenic alopecia especially before 30 years of age, may be considered as a mark of increased risks of serious diseases in later age.

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