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## Association of androgenetic alopecia and hypertension

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Androgenetic alopecia is considered to be associated with coronary heart disease but the explanation of this association remains unknown. Hypertension is highly prevalent in patients with coronary heart disease. Essential hypertension is linked to hyperaldosteronism and spironolactone, an antihypertensive drug which is a mineralocorticoid receptor antagonist, has been used for a long time in the treatment of androgenetic alopecia. We recently observed in a double transgenic mouse model that overexpression of a mineralocorticoid receptor targeted to the skin induced the development of alopecia. We prospectively studied the association of hypertension and androgenetic alopecia in Caucasian men. Two hundred and fifty Caucasian men aged 35-65 years were consecutively recruited by 5 general practitioners (50 per practitioner). Data collected included age, androgenetic alopecia score with a simplified Norwood's score (0-4), blood pressure or history of hypertension, smoking, history of diabetes mellitus or hyperlipidemia, familial history of androgenetic alopecia, and treatment. Chi-square, Fisher exact tests and linear regression model were used for statistical analysis. Hypertension was strongly associated to androgenetic alopecia ( $p < 0.001$ ). Linear regression tests confirmed that this association was independent of age : odds ratio was 2.195 (95% CI : 1.1-4.3). Familial history of androgenetic alopecia was also strongly associated with androgenetic alopecia : odds ratio was 10.870 (95% CI : 4.3-27.1). Other variables (diabetes mellitus, hyperlipidemia, smoking, treatment) were not associated with androgenetic alopecia. We were limited by a relatively small study sample but in this study androgenetic alopecia was strongly associated with hypertension. Association of androgenetic alopecia and hyperaldosteronism warrants additional studies. The use of specific mineralocorticoid receptor antagonists could be of interest in the treatment of androgenetic alopecia.

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An association between androgenetic alopecia and severe coronary heart disease has been reported in many epidemiological studies [1-7]. In the Framingham Heart Study development of alopecia during adulthood was associated with coronary heart disease [3]. But the mechanism underlying this association remains unclear.

Many explanations have been proposed including insulin resistance, atherosclerotic processes, higher levels of androgen that may contribute to both atherosclerosis and thrombosis, adverse effects of lipid-lowering or antihypertensive drugs.

Recently we observed that overexpression of mineralocorticoid receptors targeted to the skin induced the development of alopecia in a double transgenic mouse model (Yannis Sainte-Marie, personal communication, ESDR 2006, manuscript in preparation). Mineralocorticoid receptors have been found in skin epithelium [10]. But the role of mineralocorticoids in the skin remained unknown. The role

of mineralocorticoid pathways may be discussed in the development of androgenetic alopecia. Essential hypertension is now considered to be associated with primary hyperaldosteronism. It was recently demonstrated that increased aldosterone levels within the physiological range predisposed people to the development of hypertension [9]. We evaluated in a prospective practice-based study the association between androgenetic alopecia and hypertension.

### Methods

White men aged 35-65 years were consecutively included in this study by five physicians (general practitioners). A total population of 250 Caucasian patients were recruited (50 per physician). The physicians were informed that the aims of this study were to evaluate the prevalence of androgenetic alopecia in this population and to study the association with cardiovascular risk factors (history of personal

hyperlipidemia, blood pressure or history of hypertension, history of personal diabetes mellitus, smoking), familial history of androgenetic alopecia and antihypertensive drugs.

A pre-printed examination form with a scheme of a simplified version of the Norwood's classification of androgenetic alopecia in 5 grades (0-4) was used to collect standardized information [8].

Anonymously collected data included age, 5 grades of androgenetic alopecia (0-4), hypertension, history of familial androgenetic alopecia, history of personal diabetes mellitus, smoking, history of personal hyperlipidemia, antihypertensive drugs (name). Excluding criteria included history of cancer, some treatments (corticosteroids, interferon, antimetabolic, retinoid, lithium, finasteride, testosterone, danazol).

Hypertension was defined by a systolic and diastolic blood pressure over 140 and 90 mmHg, respectively. Patients with normal blood pressure but treated for hypertension were considered as hypertensive. Hyperlipidemia was defined by history of abnormal values (cholesterol or triglycerides).

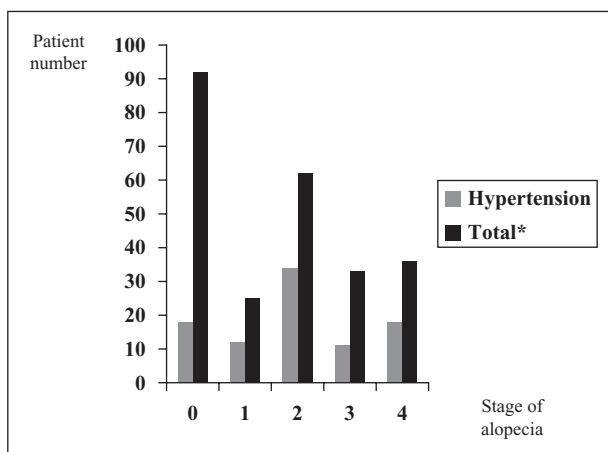
Three groups of patients were defined 35-45 years, 46-55 years, and 56-65 years.

Patients' data were recorded in a computerized database. Statistical analyses were conducted using SAS v8.2 (SAS Institute Inc, Cary, NC). The baseline characteristics of the study patients were expressed as numbers and percentages for categorical variables (hypertension, hyperlipidemia, history of familial hypertension, history of familial androgenetic alopecia, diabetes mellitus, smoking, treatment) and as means  $\pm$  standard deviations (SD) for continuous variables. For univariate analysis, the Chi-square and Fisher exact test were used for categorical variables and a Student test was used for the comparison of the age according to the presence or not of alopecia. The variables with the threshold of 0.1 in these univariate analysis were selected, like explanatory variables of the alopecia in a logistic model of regression step by step. Only the results with the threshold of 0.05 were regarded as significant with the logistic model of regression.

## Results

250 patients were recruited by 5 general practitioners. 38% of the patients had hypertension. 65% of the patients had androgenetic alopecia. The distribution of androgenetic alopecia in the different stages is described in *figure 1*. 82% of hypertensive patients had alopecia. 56% of non hypertensive patients had alopecia. The association between hypertension and androgenetic alopecia was highly significant ( $p < 0.001$ ). This association was always highly significant when we only considered the patients belonging to the stages 2-3-4 as compared to the stages 0-1 ( $p < 0.001$ ).

One evident bias was the increase of both hypertension and alopecia with age (*figure 2*). We analysed the association of risk factors with alopecia by logistic regression analysis to calculate the odds ratio and 95% CI for each variable. Odds ratio was 2.195 (95% CI : 1.1-4.3) for hypertension, 10.870 (95% CI : 4.3-27.1) for familial history of alopecia, 1.05 (95% CI : 1.0-1.088) for age (when all scores of alopecia were considered). We confirmed that the association of hypertension and alopecia was independent of age. No

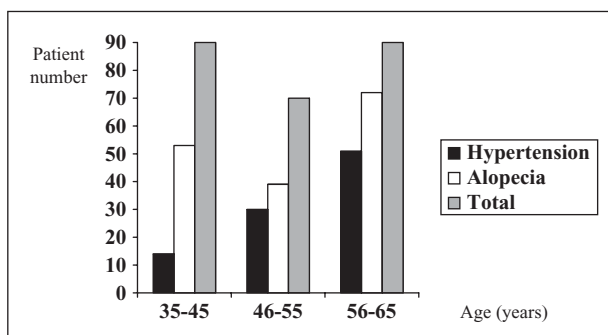


**Figure 1.** Prevalence of hypertension according to the stage of alopecia.

association was demonstrated for other variables (smoking, diabetes mellitus, hyperlipidemia which represented 40.8%, 9.2%, 33% of the patients, respectively). No significant difference was observed between the results of the 5 physicians.

## Discussion

Many studies have reported the association of androgenetic alopecia with severe coronary heart disease without any obvious explanation [1-7]. Few studies have discussed the role of hypertension. In one study vertex baldness was more strongly associated with coronary heart disease risk among men with hypertension (multivariate RR, 1.79; 95% CI, 1.31-2.44) [7]. We demonstrate in this study an association between hypertension and androgenetic alopecia. Androgenetic alopecia could be considered as a clinical marker of a risk for hypertension. It may illustrate the role of the mineralocorticoid pathway in alopecia. Skin and hair follicles normally express mineralocorticoid receptor. We previously demonstrated in our laboratory that skin had all of the enzymes required for mineralocorticoid pathways (11 beta-hydroxysteroid dehydrogenase) [10]. Interestingly, spironolactone, an antagonist of the mineralocorticoid receptor, has been used for a long time to treat androgenetic alopecia in women. It was considered that spironolactone worked



**Figure 2.** Prevalence of hypertension and alopecia in the three groups of patients (35-45, 46-55, 56-65 years).

through its anti androgenic action. We recently developed an original model of double transgenic mice with overexpression of the mineralocorticoid receptor targeted to the skin. In these adult mice, overexpression of the mineralocorticoid receptor in the skin induced the development of alopecia (manuscript in preparation). This observation confirms the role of the mineralocorticoid pathway in hair physiology and suggests that spironolactone could work directly as a mineralocorticoid receptor antagonist.

It is clear that association of androgenetic alopecia and hyperaldosteronism warrants additional studies. On the other hand hypertension may be a consequence of insulin linked disturbance as in diabetes. In a recent report, hypertension and the use of antihypertensive drugs were found more common among Finnish men with androgenetic alopecia (61% versus 45% and 50% versus 26%, respectively) [11]. But the rates of diabetes and hyperinsulinemia were also higher in men with androgenetic alopecia compared to men with normal hair status (21% versus 12% and 61% versus 49%).

But considering our data, two explanations may be proposed to explain the association of hypertension and androgenetic alopecia: (1) androgens which bind to mineralocorticoid receptors might be responsible for the observed difference in blood pressure and for instance may participate in the higher susceptibility to hypertension in men as compared to women [12], (2) hyperaldosteronism which is considered to be responsible for most of primary hypertension may directly participate in the development of alopecia.

In another recent report devoted to androgenetic alopecia in women, a relationship between androgenetic alopecia and high blood pressure ( $p = 0.02$ ,  $RR = 1.69$ ) was also demonstrated [13].

These data may suggest the use of mineralocorticoid antagonists in the treatment of androgenetic alopecia. Spironolactone is a non-selective mineralocorticoid receptor antagonist with moderate affinity for androgen receptors and dose-dependent sexual side effects. New generations of aldosterone receptor antagonists selective for aldosterone receptors alone could be of interest for evaluation in the treatment of androgenetic alopecia. ■

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