Early Onset Male Androgenetic Alopecia and Cardiovascular Risk Factors: A Case Control Study.

Authors: Dr. Ann Mary Jose and Dr.Raghavendra B.N.

Abstract

Introduction: Several studies have investigated the relationship between male androgenetic alopecia (AGA) and cardiovascular involvement. Some studies have found an increase in cardiovascular risk, especially in patients with early-onset alopecia. Authors have also found that the pattern of male baldness is related with the cardiovascular risk present.

Objectives: The objective of this study was to determine if early onset androgenetic alopecia (occurring before the age of 35 years) in males, is associated with cardiovascular risks.
To determine the type of male pattern baldness that acts a marker for cardiovascular risk in early onset male androgenetic alopecia

Materials and Methods: In this study, 60 cases (with androgenetic alopecia) and controls of age 18-35 years were enrolled in the study and cardiovascular risk factors were measured in both groups.

Results: the cases had a higher risk of cardiovascular risk factors with respect to carotid intima media thickness ($p = 0.01$), metabolic syndrome ($p = 0.01$), measures of obesity such as Body Mass Index - BMI ($p = 0.0003$) and abdominal circumference ($p =0.002$) , systolic blood pressure ($p=0.01$) and diastolic blood pressures ($p= 0.02$), as well as LDL values ($p=0.0007$) and cholesterol values ($p= 0.0009$). However only the values for BMI fell into the abnormal range. Also the group with moderate to severe androgenetic alopecia had a significantly higher percent of smokers compared to the group with mild androgenetic alopecia ($p= 0.02$).

Conclusion: Early onset male androgenetic alopecia, especially the more severe grades, can serve as a marker for cardiovascular risks including metabolic syndrome, atheromatous plaques, hypertension, obesity and hyperlipidemia. They should also be advised about the cessation of smoking. Hence patients with early onset male androgenetic alopecia should be screened for those cardiovascular risk factors and monitored for the same.

Abbreviations:

AGA: androgenetic alopecia; BMI: Body Mass Index; CIMT: Carotid Intima Media Thickness; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; IDF: International Diabetes Federation; HDL: High Density Lipoprotein; LDL: Low density lipoprotein.

Introduction

Early onset male androgenetic alopecia (before age of 35 years) is genetically different from late onset of alopecia[1]. There has been an inconsistency in studies regarding using androgenetic alopecia as a surrogate marker for cardiovascular risk factors and events[2]. This discrepancy in results, creates a need to investigate whether cardiovascular risk factors do indeed have a significant association with early onset male AGA. The pattern of AGA has also been suggested as a significant marker for cardiovascular risks[3], but the results are conflicting as to which pattern of AGA is the more significant marker. So the objective of this study was to determine if early onset androgenetic alopecia (occurring before the age of 35 years) in males, is associated with cardiovascular risks. This study also aimed to determine the type of male pattern baldness that acts a marker for cardiovascular risk in early onset male androgenetic alopecia.

Material and Methods

Sixty males between the ages of 18-35 years, with androgenetic alopecia were taken as cases and an equal number of males without androgenetic alopecia were enrolled as controls. The relevant history that was asked to elucidate risk factors for cardiovascular disease included: smoking, history of chest pain, history of any hypertension (including the intake of any anti-hypertensive medication), history of any cardiovascular events such as stroke or myocardial infarction, whether the patient exercised or not, family history of cardiovascular disease or events or predisposing risk factors for cardiovascular disease.

The diagnosis of AGA was based on the pattern of hair loss of the participants. Assessment of the degree of hair loss was performed by 2 designated post graduate dermatology students and the grade of AGA was classified as per the Hamilton Norwood classification. The presence of miniaturized hair was confirmed using dermascopy.

The patients who had a history of all systemic diseases (other than cardiovascular disease) were excluded from study. Also patients who had a history of medications that could cause hair loss, those already treated for baldness, patients who had received chemotherapy recently and patients with other types of alopecia were also excluded from the study.

The investigations done on the patients to assess presence of cardiovascular risk included an electrocardiograph and a B- mode ultrasound of the common carotid artery to detect the presence of atheromatous plaques. The presence of plaque was detected by measuring the common carotid intima media thickness (CIMT). Both the left and right common carotid arteries CIMT was measured 1.5cm below the carotid bulb and an average of the two values was taken. Each patient's lipid profile and the fasting blood sugar levels were also obtained.

Measurements taken for each patient included the abdominal circumference just below the navel, height, weight in kilograms and blood pressure. The blood pressure was measured with the patient in sitting position. Blood pressure was measured twice- when the patient arrived to the OPD and when the patient left the OPD and an average of the two readings was recorded.

For categorical variables chi square was used for analysis. The averages of quantitative variables were determined using t-test. The correlation between different parameters was determined using Spearman's Rank Correlation Coefficient.

For analysis of the correlation between the grades of AGA and the parameters measures, the grades of AGA were classified according to Lotufo et al[3]. The grades of AGA were classified into Mild (Hamilton Norwood grades I, II), Mild frontal (Hamilton Norwood IIa, III, IIIa, IVa), Mild vertex (Hamilton Norwood III vertex, IV), Moderate vertex (Hamilton Norwood V, Va), Severe vertex (Hamilton Norwood VI, VIII).

The Adult Treatment Panel III criteria levels of lipids[4] and fasting blood sugar[5] were used as cut-offs in this study. An abdominal circumference of more than or equal to 94cm in men was considered as an abnormal abdominal circumference, as per the IDF criteria[6]. A BMI (Body Mass Index) of greater than or equal to 23kg/m^2 was considered abnormal for Indian men[7]. For blood pressure a value greater than or equal to 140mmHg and 90mmHg for systolic and diastolic blood pressure[8] respectively were considered to be abnormal.

Metabolic Syndrome was considered to be present, if any 3 out of the following 5 criteria were met[6]: fasting glucose level ≥100 mg/dL or antidiabetic therapy; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg; high-density lipoprotein cholesterol < 40 mg/dL in men and < 50 mg/dL in women; triglyceride levels ≥ 150 mg/dL and/or a waist circumference >≥94 cm for men and ≥80 cm for women (IDF criteria which is to be followed for non-Europeans).

Results

In the family history obtained from the patients, there were no significant difference between the case and control groups with respect to family history of myocardial infarction (p= 1.0), hyperlipidemia (p= 0.7), diabetes (p=0.82) and hypertension (p=0.32).

Among the personal history parameters, no significant difference was found between the controls and cases with regards to chest pain (p= 0.07) and exercise habits (p = 0.86).

With regards to smoking, there was no significant difference in the percent of cases (AGA patients) who smoked versus the controls (p = 0.08). However, when a similar analysis as done by Su and Chen[9] was done within the AGA patient (cases) group in our study, a significant difference was noted. Su and Chen[9] studied the relation between AGA and smoking by dividing the AGA group into mild and moderate to severe baldness. In this study, the cases in the moderate to severe vertex baldness group had a significantly higher percent of smokers as compared to the mild baldness group (p = 0.02).

Table 1: Distribution of smoking habits in the group with mild baldness (Hamilton AGA Grades I-III) and in the group with moderate to severe baldness (Hamilton AGA Grades IV-VII).

	History of Smoking		
	Mild AGA (I-III)	**Moderate to Severe AGA (IV-VII)**	
Smokes	1 (3.7%)	8 (25%)	
Doesn't Smoke	26 (96.29%)	24 (75%)	
	27	32	59 (total)

Note: there was one case who was a former smoker and his information has not been included in the calculations. Therefore the total number of patients is 27+32 = 59 and not 60.

Table 2: table showing the average values (and standard deviations) in the case and control group.

		Case	Controls	p value
Carotid atheromas	CIMT (mm)	0.54 ± 0.1	0.48 ± 0.08	0.01
Measures of obesity	Abdominal Circumference (cm)	95.26 ± 15.8	87.88 ± 9.6	0.002
	BMI (kg/m^2)	24.86 ± 3.08	22.92 ± 2.55	0.0003
Blood pressure	Systolic blood pressure (mmHg)	125.46 ± 13.06	120.63 ± 7.19	0.01
	Diastolic blood pressure (mmHg)	84.37 ± 7.8	81.37 ± 5.57	0.02
Lipid Profile	Total cholesterol (mg/dl)	166.95 ± 33.98	145.85 ± 31.52	0.0009
	HDL (mg/dl)	42 ± 15.57	40 ± 9.15	0.32
	LDL (mg/dl)	100.38 ± 27.2	84.32 ± 22.81	0.0007
	Triglycerides (mg/dl)	146.23 ± 75.35	145.29 ± 82.64	0.9
Fasting blood sugar levels	FBS (mg/dl)	91 ± 15.53	90 ± 12.75	0.6

As can be seen from Table 2, the cases had a significantly higher value with respect to carotid intima media thickness (CIMT) (p=0.01) , abdominal circumference (p=0.002), BMI (p=0.0003), systolic (p=0.01) and diastolic(p=0.02) blood pressure . Among the lipids, only the cholesterol (p= 0.0009) and LDL levels (p=0.0007) were significantly different between the cases and controls with the cases having higher values. No difference was seen between the cases and controls with respect to HDL, triglyceride and fasting blood sugar levels. Despite the significant differences only the values for BMI fell into an abnormal range.

As seen from table 3, there were a significantly higher percent of cases compared to controls who had an abnormal abdominal circumference (p=0.003), BMI (p=0.04), systolic (p=0.04) and diastolic (p=0.03) blood pressure. Among the lipids, only the cholesterol (p< 0.0001) and LDL levels (p=0.0086) had a higher percent of cases compared to controls who had an abnormal value. There were a significantly higher percent of cases who had the metabolic syndrome when compared to controls (p =0.01). There was no significant difference in the average values of fasting blood sugar levels (p=0.3), HDL (p=0.46) and Triglyceride (p=0.57) levels.

The cases also had a higher percent of subjects with abnormal ECGs when compared to the controls (p=0.02). The ECG changes seen in the case and control group are mentioned in Table 4.

Table 3: table showing the percent of subjects in the cases (n=60) and controls (n=60) who had an abnormal value

		Case	Controls	p value
Measures of obesity	Abdominal Circumference (cm)	45%	20%	0.003
	BMI (kg/m^2)	70%	62%	0.04
Blood pressure	Systolic blood pressure (mmHg)	6.67%	0	0.04
	Diastolic blood pressure (mmHg)	20%	6.67%	0.03
Lipid Profile	Total cholesterol (mg/dl)	13%	3%	<0.0001
	HDL (mg/dl)	55%	48%	0.46
	LDL (mg/dl)	50%	27%	0.0086
	Triglycerides (mg/dl)	40%	35%	0.57
Fasting blood sugar levels	(mg/dl)	10%	5%	0.3
Metabolic Syndrome		45%	23.33%	0.01
ECG Abnormalities		13%	1.7%	0.02

Table 4: Table showing the ECG changes in the AGA Group (Cases) and Controls

	AGA Grade as per Lotufo et al[3]	ECG Changes
Cases	Mild (I, II)	Nil
	Mild Frontal (IIa, III, IIIa, IVa)	1) Evolved anterior wall MI 2) STEMI (Antero-lateral wall), mild LV dysfunction
	Mild vertex (III vertex, IV)	STEMI (Inferior wall): 2 cases
	Moderate vertex (V, Va)	1) Inferior wall MI 2) Borderline ECG (mild ST segment depression)
	Severe vertex (VI, VII)	1) STEMI 2) Anterior wall MI, Sinus tachycardia
Control	----------	ST segment depression

As seen from table 5, the strongest correlation between an advancing grade of AGA was with the metabolic syndrome (r =1), followed with a very strong correlation with carotid intima media thickness (r =0.9), abdominal circumference (r=0.9), hypertension (r = 0.9), and abnormal lipid profile (r = 0.9). A strong correlation was also found with BMI (r =0.7) and ECG changes (r= 0.6).

Table 5: table showing the correlation between the grades of androgenetic alopecia and the parameters measured.

Parameter		Spearman's Rank Correlation Coefficient (r)
Carotid Intima Media Thickness		0.9
Measures of Obesity	Abdominal Circumference	0.9
	BMI	0.7
Hypertension (either raised systolic or diastolic blood pressure)		0.9
Abnormal Lipid Profile (either abnormal levels of HDL, Triglycerides or Total Cholesterol or LDL)		0.9
Metabolic Syndrome		1
ECG changes		0.6

Discussion

There were several cardiovascular risk factors that were significantly higher in the androgeentic alopecia group when compared to controls.
The lack of significant difference in the percent of cases (AGA patients) who smoked versus the controls (p = 0.08), means that smoking as such would not have contributed significantly to any differences between the control and cases with respect to hair loss. This result is similar to the findings in Santiago et al study. However when smoking habits of AGA patients with moderate and severe hair loss were compared to those of mild hair loss, as done by Su and Chen[9], a significant difference was noted (p = 0.02).This means that in a population susceptible for androgenetic alopecia, smoking has a significant contribution to the severity of androgenetic alopecia. Therefore AGA patients who have baldness should be advised about cessation of smoking habits and its common pathogenesis in the development of both AGA and cardiovascular disease.

In the present study, there was no significant difference between the case and control groups with respect to family history of myocardial infarction (p= 1.0), hyperlipidemia (p= 0.7), diabetes (p=0.82) and hypertension (p=0.32). Santiago et al[2] and Farajzadeh et al[10] however did find a significant difference in the family history of cardiovascular disease between cases and controls. This result of non-significance in the present study could be due to the limitations of this study. The first limitation is that in this study the relevant family history could not be confirmed with the parents either through history or laboratory tests. The second limitation is that the patients being asked for the presence of family history of cardiovascular disease were often unaware of the disease status of the parents. This was especially true among the younger patients. This came to light when the parent accompanying a few young patients would confirm the presence of the disease being screened for, while the patient himself would deny the presence of the disease in the parent.

In the present study, there was a significant difference in the values of carotid intima media thickness between case and control group with p value of 0.01. A similarly significant difference was found by Santiago et al[2]. Though there was a significant difference in the case and control group in this study, the absolute value of CIMT in the cases did not reach the value of 0.75mm which is considered the cut off point for the risk of occurrence of stroke[11]. However the finding cannot be ignored, because a 0.1-mm increase in CIMT represents a 11% increase in risk of myocardial infarction[12].
Kasliwal et al[13] had shown that CIMT of less than 0.55mm predicted absence of coronary artery disease. Although the average value of CIMT for cases was below 0.55mm, the group with severe vertex baldness had an average value of 0.62mm. This means that the absence of cardiovascular disease cannot be ruled out in this subset of cases, since This finding is in accordance with the findings of Lesko et al[14], where they found that as the degree of vertex baldness increased so did the risk for myocardial infarction.

In this study blood pressure was significantly different between the control and AGA patient group in this study, with p values of 0.01 and 0.02 for systolic and diastolic blood pressure respectively with higher blood pressures in the AGA group. This is similar to the study by Santiago et al[2] and Chakrabarty et al[15]. However in both those studies and in this study, the absolute values for systolic and diastolic blood pressures were not abnormal in value. There was a very strong correlation between AGA grade and presence of hypertension (r=0.9)
The role of blood pressure in androgenetic type of hair loss has been suggested by Arias-Santiago et al where they showed that males who had early onset AGA along with high

blood pressures also had a higher levels of aldosterone[16]. A greater amount of aldosterone would stimulate a greater number of mineralocorticoid receptors thus causing a rise in blood pressure. It was also shown that increasing density of mineralocorticoid receptors was shown to be responsible for a reduction in the density of hair follicles in mice. Mineralocorticoid receptors are present in both the skin and hair. Another hypothesis is that androgens involved in AGA bind to the mineralocorticoid receptors directly thus favouring a rise in blood pressure. It has been shown that skin has all of the enzymes required for mineralocorticoid pathways. Higher levels of testosterone also increase the plasma renin activity and renin in turn controls the blood pressure and body fluid volume (ie, pressure-natriuresis) via the renin-angiotensin system[17].

With respect to measures of obesity, the present study showed that there were a significantly higher percent of cases with abnormal values when compared to controls, with p values of 0.003 for abdominal circumference and p values of 0.04 for BMI . As in this study, other studies by Hirsso et al[18] and Bakry et al[19] have also found significant differences in BMI and abdominal circumference values between cases and controls, with the higher measures of abdominal obesity being found in the cases. There was a very strong correlation between grade of AGA and abdominal circumference (r=0.9) and a strong correlation between grade of AGA and BMI (r=0.7).

In the present study, there was no significant difference between the fasting glucose of controls and AGA patients (p= 0.6). The percent of AGA patients who had an abnormal fasting glucose level was not significant compared to controls (p = 0.3). This was similar to the findings in Santiago et al[2] and Chakrabarty et al[15] where the average fasting sugar levels were not significantly different between the case and control groups and the fasting sugar levels fell into the normal range. However when the levels of insulin resistance as measured by HOMA-IR were significantly different between the case and control groups in both those studies. This could indicate that fasting glucose is a late indicator of insulin resistance and that measures of insulin resistance will detect the problem much earlier.

With regards to lipid parameters, a highly significant difference between the LDL and cholesterol values of control and AGA group (p= 0.0007 and p= 0.0009 respectively). However the averages of these values were within normal limits (LDL: 100.38mg/dl, and Cholesterol: 166.95mg/dl). This was similar to the findings by Chakrabarty et al[15] and Bakry et al[19] where they found a significantly difference between the AGA and control groups lipid parameters. Nonetheless, the average values for lipids fell into the normal range. This was similar to the findings by Santiago et al[2] and Chakrabarthy et al[19].
In this study a very strong correlation (r=0.9) was found between the grade of AGA and the presence of hyperlipidemia. A similar finding was obtained by Sasmaz et al[20] where they showed that men who had vertex baldness (average age = 36 years), had a significantly higher level of triglyceride and lipoprotein (a) when compared to the control group.

In this study the cases had a significantly higher occurrence of metabolic syndrome when compared to the control group (p=0.01). This result implies that patients with AGA (cases) have a significantly higher cardiovascular risk factor when compared to the control group, since metabolic syndrome is a multiplex cardiovascular risk factor. This corroborates the findings of by Santiago et al[2] and Chakrabarthy et al[15].

In the present study, the strongest correlation between AGA and the cardiovascular risk factors was with metabolic syndrome (r=1).

There is a strong correlation between the abnormal ECG/cardiovascular incident and the grade of AGA with r=0.6. This strong correlation is corroborated by Matilainena et al[21], where it was shown that a significantly greater number of men who had early onset of AGA had revascularization procedures done when compared to their counterparts who did not have early onset AGA. In this study, there was a significant difference between the ECG changes in the case and control group (p= 0.02).

In this study, the degree of baldness had a significant correlation with several cardiovascular risk factors, including carotid intima media thickness (r =0.9), abdominal circumference (r=0.9), hypertension (r = 0.9), and abnormal lipid profile (r = 0.9). A strong correlation was also found with BMI (r =0.7) and ECG changes (r= 0.6). Vertex baldness is present only in the more advanced Hamilton Norwood Scaling of AGA. This means that vertex baldness as well correlates strongly with the presence of cardiovascular risk factors corroborating the findings of Lutufo et al[3] and Lesko et al[14] who found that coronary artery disease is associated with male pattern baldness involving the vertex.

Conclusion

Early onset male androgenetic alopecia, especially the more severe grades, can serve as a marker for cardiovascular risks including metabolic syndrome, atheromatous plaques, hypertension, obesity and hyperlipidemia. They should also be advised about the cessation of smoking. Hence patients with early onset male androgenetic alopecia should be screened for those cardiovascular risk factors and monitored for the same.

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