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ASSOCIATION OF THE CUTANEOUS MARKERS WITH CORONARY ARTERY DISEASE: A CASE CONTROL STUDY

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Abstract

Objectives: To determine the strength of the association of the cutaneous markers described in coronary artery disease (CAD).

Methods: A hospital-based, case-control study was conducted in Christian Medical College, Vellore for the period of 14 months from September 2012 to October 2013. Two hundred patients were recruited from the cardiology in-patients who underwent coronary angiogram.Cases were 153 patients with CAD and controls, 47 without CAD on the basis of coronary angiogram.Patients were examined for the presence of androgenetic alopecia (AGA), acanthosis nigricans (AN), diagonal earlobe crease (DELC), preauricular crease (PAC), corneal arcus (CA), thoracic hairs, acrochordons, premature canities (PC), xanthelasma and xanthomas. A record of the history of onset, morphology, grading and distribution of the lesions was made.

Results: DELC (diagnostic odds ratio - 811.62, sensitivity- 98.69, specificity- 91.49), PAC (diagnostic odds ratio- 97.63, sensitivity- 67.97%, specificity-97.87%), AGA (diagnostic odds ratio - 21.76, sensitivity- 95.42%, specificity- 51.06%), PC (diagnostic odds ratio- 4.45, sensitivity- 47.71%, specificity- 82.98%), AN (diagnostic odds ratio- 4.01, sensitivity- 41.18%, specificity- 85.11%), thoracic hairs (diagnostic odds ratio – 130.76, sensitivity- 92.02%, specificity- 91.89%), corneal arcus (diagnostic odds ratio - 24.61, sensitivity- 86.93%, specificity- 78.72%) and ear canal hairs (diagnostic odds ratio-22.21, sensitivity- 49.67%, specificity- 95.74%) were found to be associated with CAD. But xanthelasma palpebrarum (diagnostic odds ratio - 0.50) and acrochordons (diagnostic odds ratio- 1.13) were not associated with CAD. Multiple logistic regression analysis showed DELC and thoracic hairs were strongly associated with CAD.

Conclusion: The study suggests that diagonal ear lobe crease, preauricular crease, androgenetic alopecia, premature canities, acanthosis nigricans, thoracic hairs, corneal arcus and ear canal hairs are associated with coronary artery disease while xanthelasma palpebrarum and acrochordons are not.

Key Words- Cutaneous manifestations, Coronary artery disease, Thoracic hairs

Introduction

Recognizing dermatological markers suggesting atherosclerosis at an early age may prove to be supportive in early diagnosis and secondary prevention of coronary artery disease.[1] The heart and the skin have much in common due to common changes during aging and degenerative processes.[2,3,4] A meticulous search for the cutaneous markers such as diagonal ear lobe crease, androgenetic alopecia, premature canities, preauricular crease, acanthosis nigricans, acrochordons, xanthomas, xanthelasma palpebrarum, corneal arcus and thoracic hairs which may be associated with coronary artery disease may prove to be worthwhile in recognizing asymptomatic coronary artery disease in a high risk individual.

Bilateral diagonal earlobe crease (DELC) has been designated as Frank's sign,[5] which develops in relation to CAD, as the heart and the ear lobe are supplied by "end arteries" without the chance for collateral circulation.[6,7,8] Preauricular crease (PAC) is a well formed crease in front of the auricle of the ear. This is easily identifiable during clinical examination.[9] Androgenetic alopecia (AGA) is a genetically determined baldness which is linked to CAD by mechanisms such as increased peripheral sensitivity to androgens,[10] hyperinsulinaemia[11] and chronic inflammation.[12] Premature canities is graying of scalp hairs before the age of 30 in Africans and Asians and may be a surrogate marker of premature atherosclerotic changes.[13,14] Acanthosis nigricans (AN) is characterized by hyperpigmented, velvety thickening of the skin in the axillae, groin and back of the neck.[15] AN has been shown to be associated with insulin resistance and premature atherosclerosis.[15, 16] Thoracic hairs (chest hairs) are androgen dependent hairs which grow on the anterior part of chest of males.[17,18] At present scientific literature is lacking to support its existence as a marker of CAD. Corneal arcus is an easily visualized lipid-rich deposit at the corneoscleral limbus that shares similarities with the lipid deposition of CAD.[19] Acrochordons are asymptomatic pedunculated skin lesions. Acrochordons were found to be associated with atherogenic lipid profile in a few earlier studies.[20,21] Xanthomas are caused by faulty lipid metabolism. Xanthelasma palpebrarum is a type of specific form of xanthoma which presents as soft, velvety, yellow, flat, polygonal plaques around the eyelids.[22,23,24] They are associated with hyperlipidemia, and as hyperlipidemia is characterized by elevated concentrations of circulating

atherogenic lipids, this leads to the process of accelerated atherosclerosis.[25] It was shown in one Indian study that 60.6 % of the patients with xanthelasma palpebrarum had dyslipidemia and 12 % patients had family history of xanthelasma palpebrarum.[26]

Astute assessment of various dermatological markers linked to coronary artery disease would assist physicians to suspect disease in the early phase, and thus make it simpler to judge who requires further detailed investigation. There are multiple studies in the literature showing the significance of Frank's sign,[6,27,28,29,30] androgenetic alopecia,[30-33] premature canities,[13,14,34,35] preauricular crease,[9] xanthomas,[22,23,24] xanthelasma palpebrarum,[24,36] corneal arcus[37,38] and thoracic hairs[18] as cutaneous markers of CAD. But there is no study in the past in which all these above mentioned markers were evaluated simultaneously to establish their diagnostic value. We thus decided to assess these cutaneous markers of coronary artery disease prior to coronary angiogram to establish their role in predicting coronary artery disease. We also assessed the correlation between the severity of coronary artery disease and grades of androgenetic alopecia, pattern of thoracic hairs and grades of diagonal earlobe crease (Frank's sign).

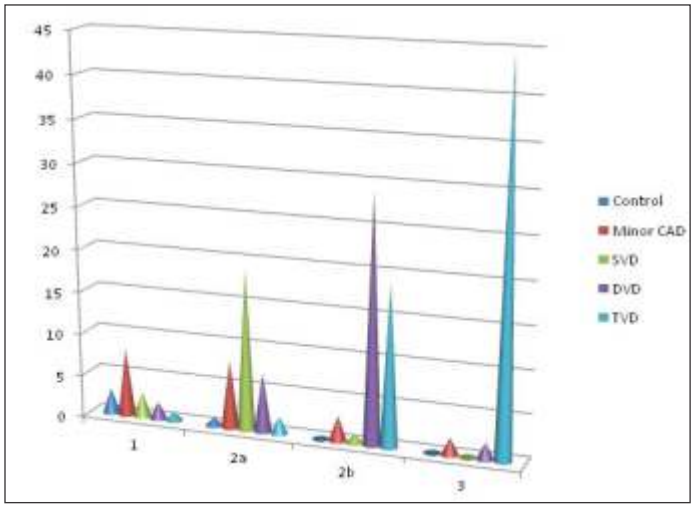

Figure 1: Distribution of various grades of diagonal ear lobe crease among various groups of cases and controls.

Aims and Objective

This study was conducted to assess the association of the cutaneous markers with coronary artery disease. The primary objective was to determine the strength of the association of the cutaneous markers described in coronary artery disease. Other objectives were to assess; 1) the correlation of clinical grading of androgenetic alopecia and severity of coronary artery disease, 2) the correlation of clinical grading of diagonal ear lobe crease and the severity of coronary artery disease and 3) the correlation of pattern of distribution of thoracic hairs with severity of coronary artery disease.

Methods

A hospital-based, case-control study was conducted in our institution. Two hundred patients were recruited by random sampling from the cardiology in-patients who were admitted for coronary angiogram with the probable diagnosis of CAD. Cases were the patients with CAD and control those without CAD on the basis of coronary angiogram. Patients were examined for the presence of androgenetic alopecia (AGA), acanthosis nigricans (AN), diagonal earlobe crease (DELC), preauricular crease, corneal arcus, thoracic hairs, acrochordons, premature graying, xanthelasma and xanthomas. A record of the history of onset, morphology, grading, number and distribution of the lesions was made.

Results

There were 153 cases with CAD and 47 controls without CAD recruited during the study period. The baseline characteristics such as mean age, gender and mean body mass index (BMI) were similar in both the groups.

DELC (prevalence - cases 98.69% and controls 8.51%; diagnostic odds ratio - 811.62, p<0.001, sensitivity- 98.69, specificity- 91.49), preauricular crease (prevalence - cases 67.97 % and controls 2.13 %; diagnostic odds ratio- 97.63, p<0.001, sensitivity- 67.97%, specificity-97.87%) (Fig. 1), AGA (prevalence - cases 95.42 % and controls 48.94 %; diagnostic odds ratio - 21.76, p<0.001, sensitivity- 95.42%, specificity- 51.06%) (Fig. 2), premature canities (prevalence - cases 47.71 % and controls 17.02 %; diagnostic odds ratio- 4.48, p<0.001, sensitivity- 47.71%, specificity- 82.98%), AN (prevalence - cases 41.17 % and controls 14.89 %; diagnostic odds- 4.00, p<0.001, sensitivity- 41.18%, specificity- 85.11%), thoracic hairs (prevalence - cases 98 % and controls 27.66 %; diagnostic odds ratio – 130.76, p<0.001, sensitivity- 92.02%, specificity- 91.89%), corneal arcus (prevalence - cases 86.93 % and controls 21.27 %; diagnostic odds ratio - 24.61, p<0.001, sensitivity- 86.93%, specificity- 78.72%) and ear canal hairs (prevalence - cases 49.67 % and controls 4.25 %; diagnostic odds ratio-22.21, p<0.001, sensitivity- 49.67%, specificity- 95.74%) were found to be associated with CAD. But xanthelasma palpebrarum (prevalence - cases 3.27 % and controls 6.38 %; diagnostic odds ratio - 0.50, p>0.05) and acrochordons (prevalence - cases 68.63 % and controls 65.96 %; diagnostic odds ratio- 1.24, p>0.05) were not associated with CAD. Androgenetic alopecia of severe forms (grades 3v and above) according to the Norwood-Hamilton classification was associated with CAD with odds ratio of 33.33 as compared to androgenetic alopecia 3a and below in which the odds ratio was 7.84. Multiple logistic regression analysis showed DELC and thoracic hairs were strongly associated with CAD.

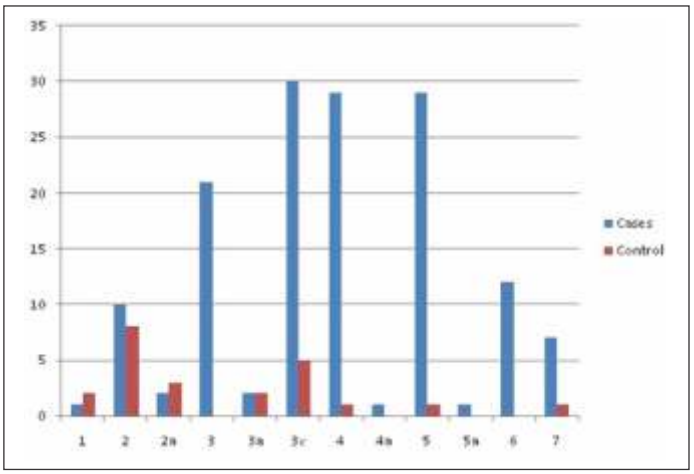

Figure 2: The overall prevalence of various grades of androgenetic alopecia according to Norwood-Hamilton classification and its distribution among cases and controls.

Table 1 shows that diagonal ear lobe crease, preauricular crease, androgenetic alopecia, premature canities, acanthosis nigricans, thoracic hairs, corneal arcus and ear canal hairs are associated with coronary artery disease by univariate analysis.

Cutaneous marker	Sensitivity	Specificity	Diagnostic odds ratio	Positive likelihood ratio	Negative likelihood ratio	Sig.
Diagonal ear lobe crease	98.69	91.49	811.620	11.59	69.83	0.000
Premature canities	47.71	82.98	4.48	2.80	1.58	0.000
Acanthosis nigricans	41.18	85.11	4.000	2.76	1.44	0.002
Xanthelasma	NA	NA	0.495	NA	NA	0.349
Thoracic hairs	92.02	91.89	130.769	11.34	11.51	0.000
Corneal arcus	86.93	78.72	24.605	4.09	6.02	0.000
Acrochordons	NA	NA	1.240	NA	NA	0.539
Ear canal hairs	49.67	95.74	22.210	11.67	1.91	0.000

Table 1: Cutaneous Markers Of Coronary Artery Disease.

Discussion

The patients recruited into the study were from different states in India however predominantly hailing from Tamil Nadu and West Bengal and few from the neighboring country of Bangladesh. There was no significant difference in the baseline characteristics of cases and controls. The mean age of the cases was around 59 years and of the controls was 54 years and their mean BMI was also similar. The commonest presenting symptom among cases was chest pain (58.82%) followed by dyspnoea on exertion (13%) and the least common symptom was post meal angina (0.65%). Similarly the commonest presenting symptom among controls was also chest pain (31.9%) followed by dyspnoea on exertion (21.27%).

Diagonal ear lobe crease (DELC) is a well acknowledged cutaneous marker for CAD in the literature.[6, 27,28,29,30] There are multiple theories supporting the relationship between DELC and CAD. Majority of them postulate that microvascular disease affects both ear lobes and coronary vasculature simultaneously. Our study showed that prevalence of DELC among cases (98.69%) was almost 11 times more than in controls (8.51%) (Fig. 3). This was high in contrast to the prevalence shown by earlier studies like Christiansen et al[28] (46.8%), Frank[5] (47 %) and Kaukola et al[6] (69%) in their respective studies. The reason for the higher prevalence of DELC in our study could be attributed to the fact that we included even the early grades of diagonal ear lobe crease. So we were able to compare the prevalence of DELC among cases and controls as well as correlate the association of the different grades of DELC with the severity of coronary heart disease. Studies conducted in the past confirmed the association between DELC and CAD but the methodology was not similar.[6, 27,28,29] We also did univariate and multiple logistic regression analysis, which showed its individual diagnostic value. Multiple logistic regression analysis of various cutaneous markers in our study showed DELC as a strong marker of coronary artery disease. The results of this study add to the knowledge available in understanding the association between DELC and CAD status. Such information will be a valuable background data to support future studies for screening vulnerable populations with CAD risk.

Figure 3: Grades Of Diagonal Ear Lobe Crease; A - Grade 1, B - Grade 2a, C - Grade 2b, D - Grade 3

Preauricular crease (PAC) is a well formed crease in front of auricle of the ear (Fig. 4). There is scarcity of evidence in literature to support preauricular crease as a cutaneous marker of CAD. Our study showed high prevalence of preauricular crease (PAC) among cases (67.97 %) as compared to controls (2.13 %). So it revealed a strong association between preauricular crease and CAD with a diagnostic odds ratio of 97.63($p<0.001$). The odds ratio of PAC was high in our study as compared to Miot et al[9] (OR-5.5, $p<0.05$). This study was conducted similar to our methodology but the controls selected were not completely free of CAD as patients with <50% stenosis of all coronary arteries were considered as controls.[9] The sensitivity and specificity of PAC in our study was 67.97 % and 97.87 % respectively. The sensitivity of PAC in our study was high in contrast to the study done by Miot et al,[9] which showed sensitivity of 59.3%. The positive and negative likelihood ratios were 31.91 and 3.055 respectively. So it can be said to be a marker of CAD with a good diagnostic value.

Our study showed that the prevalence of AGA among cases (95.42%) was almost doubles that of controls (48.94%) (Fig. 5). The prevalence of androgenetic alopecia among the controls was found to be similar to that in general population (40%) as given in literature.[39] In our study androgenetic alopecia was found to be associated with CAD (diagnostic odds ratio - 21.76, $p<0.001$).The higher prevalence of AGA among cases and a more robust diagnostic odds ratio in our study as compared to the study done by Miot et al.[9] It was further demonstrated in our study that the prevalence of AGA was highest in cases with triple vessel disease (97.01%) and lowest in minor CAD (17 %). Our

study was different from earlier studies because we compared the grades of AGA according to Norwood Hamilton classification with the sub types of coronary artery disease based on coronary angiogram. The study showed that androgenetic alopecia of severe forms (3v and above) according to the Norwood-Hamilton classification was associated with coronary artery disease with odds ratio of 33.33 as compared to androgenetic alopecia 3a and below in which the odds ratio was 7.84. Thus the relationship between CAD and baldness is probably dependent on the severity of AGA.

Figure 4: Preauricular crease

Figure 5: Vertex Alopecia

There are few studies in literature which have shown the association of premature canities and CAD.[14, 15, 40] In our study prevalence of premature canities among cases and controls was 47.71% and 17.02% respectively. This was low when compared to the study by Eisenstein et al, [40] which showed 100% prevalence of premature canities in patients with proven CAD and 55% in controls. This discrepancy may be attributed to racial difference. Premature canities was confirmed in our study as a significant dermatological marker of CAD with diagnostic odds ratio of 4.48 ($p<0.001$).

Acanthosis nigricans has been proved to be associated with hyperinsulinemia,[41] which in turn leads to an increased risk for CAD. The relationship between acanthosis nigricans and coronary artery disease was also compared among cases and controls in our study. We showed that the prevalence of AN was almost 3 times more among cases (41.18%) than that of the controls (14.89%). Acanthosis nigricans was found to have an association with CAD with a significant diagnostic odds ratio of 4.00($p<0.001$).

Xanthelasma palpebrarum is a type of specific form of xanthoma which presents as soft, velvety, yellow, flat, polygonal plaque around the eyelids.[25] It is known to be associated with hyperlipidemia which is characterized by elevated concentration of circulating atherogenic lipids, this leads to the process of accelerated atherosclerosis.[22, 42, 43] In our study it was observed in 27 % of cases and 6.38 % of controls. However our study did not show an association of the same with coronary artery disease (Diagnostic odds Ratio = 0.50, $p>0.05$). This is in contrast to the only study available in the literature which showed the association of xanthelasma palpebrarum and CAD.[36]

Thoracic hairs are commonly called as chest hairs, which are easily identifiable on clinical examination.[17] There is scarcity of literature supporting the association between thoracic hairs and coronary artery disease. Our study showed that 98 % of cases (see table) had thoracic hairs as compared to 27.66 % in controls (Fig. 6). This was high in contrast to the study by Miric et al, which showed that the prevalence of thoracic hairs was 40 % more in cases as compared to controls.18 However the methodology used to define thoracic hairiness was not given and the types of thoracic hairs were not elucidated. In contrast to our study comparison was done to general patients of the same hospital. As the control group was not evaluated by an angiogram, it cannot be elucidated whether their coronary artery was normal at the time of comparison or not. So the result of the above mentioned study may not be comparable. Our study showed a strong association between thoracic hairs and CAD (diagnostic odds ratio = 64.08, $p<0.001$). This potential relationship should be checked in further studies, including well-designed prospective studies.

Figure 6: Patterns Of Thoracic Hairs

Corneal arcus is an easily visualized lipid-rich deposit which clinically presents as a grayish white opacity at the periphery of the cornea.[37] Our study showed a high prevalence (86.93%) of corneal arcus among cases as compared to other studies (Fig.

7).[44, 45] The study by Shanoff et al reported a prevalence of 44 % among cases, however none of the controls had corneal arcus.[45] In contrast to this, our study showed a prevalence of 21.27 % among controls. In our study corneal arcus was found to be associated with CAD with diagnostic odds ratio of 24.61 ($p<0.001$). Corneal arcus was found to have a sensitivity and specificity of 86.93 % and 78.72 % respectively. Thus the findings of our study are in accordance with the data given in literature. Our study emphasizes the usefulness of corneal arcus as a clinical marker for coronary artery disease. We suggest that physicians should examine patients for corneal arcus and if present may be a marker of underlying CAD.

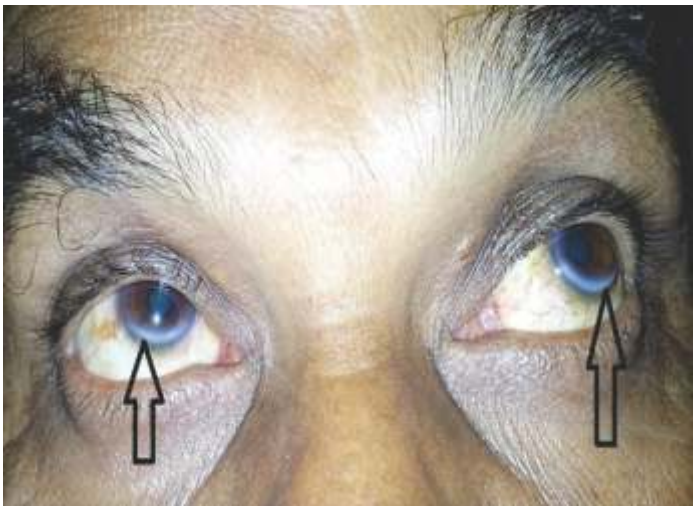

Figure 7: Corneal Arcus

Acrochordons were earlier shown to have a significant relationship with obesity[46] and metabolic syndrome[47] which probably represents a cutaneous sign for impaired carbohydrate or lipid metabolism, liver enzyme abnormalities, and hypertension.[48] Our study showed almost equal prevalence of acrochordons among cases (68.63%) and controls (65.96%) with odds ratio of 1.24 ($p>0.05$). So it is not associated with coronary artery disease. To the best of our knowledge there is no study in literature also to support this association.

Ear canal hairs were found in our study subjects during the clinical examination as an additional observation. Our study showed that ear canal hairs were seen in 49.67 % of cases and 4.25 % of controls. The diagnostic odds ratio was found to be 22.21 $p<0.001$). Thus our study suggests that ear canal hairs should be considered as a marker of CAD. Verma et al[49] and Wagner et al[50] also found a similar association, but comparable data is not available.

Conclusion:

The study suggests that diagonal ear lobe crease, preauricular crease, androgenetic alopecia, premature canities, acanthosis nigricans, thoracic hairs, corneal arcus and ear canal hairs are associated with coronary artery disease while xanthelasma palpebrarum and acrochordons are not. Both presence and severity of diagonal earlobe crease were related to occurrence of coronary artery disease. The grades of AGA with involvement of vertex are more important than just the mere presence of androgenetic alopecia in predicting the risk of CAD. Multiple logistic regression analysis showed DELC and thoracic hairs are strongly associated with CAD. A thorough search for the cutaneous markers of CAD may prove to be a worthwhile exercise in identifying individuals with high risk of CAD.

Limitations

The sample size of this study was small to make a definitive conclusion.

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