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Original Article

Frank sign may predict more advanced coronary artery disease in patients admitted with a first time acute coronary syndrome

Frank sign ilk kez akut koroner sendromla başvuran hastalarda daha ileri koroner arter hastalığını öngörebilir

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ABSTRACT

Aim: Diagonal ear lobe crease (DELC), also called as Frank's sign, is a diagonal fold or wrinkle-like line in the skin of the earlobe. This sign detected on the physical examination was proposed as a surrogate marker for individuals at high risk of cardiovascular disease. The aim of our study was to assess the relationship between presence of DELC and the severity of coronary artery disease according to the SYNTAX score in patients with firstly diagnosed acute coronary syndrome (ACS).

Material and Methods: 356 patients admitted to the emergency department with the diagnosis of ACS from November 2015 to December 2016 were enrolled into the study. Patients were stratified into 3 groups: low SYNTAX score (< 23), high SYNTAX score (≥23) and patients with normal coronary.

Results: Patients with DELC as percentage were statistically significantly different between all groups ($p < 0.001$). Higher number of DELC (OR = 0.497; 95% CI: 0.246-1.001; $p = 0.043$) was an independent predictor for a high SYNTAX score in the ACS patients after multiple linear regression analysis.

Conclusion: Frank's sign can help primary practitioners to predict severity of CAD.

Keywords: Acute coronary syndrome; Diagonal ear lobe crease; Frank's sign; SYNTAX score.

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ÖZ

Amaç: Frank Sign olarak da adlandırılan diyagonal kulak memesi kırışıklığı (DELC), kulak memesinin derisinde çapraz kıvrım veya kırışık benzeri bir çizgidir. Fizik muayenede tespit edilen bu işaret, yüksek kardiyovasküler hastalık riski taşıyan bireyler için prognostik bir belirteç olarak önerilmiştir. Çalışmamızın amacı, ilk kez akut koroner sendrom (AKS) tanısı almış hastalarda DELC varlığı ile koroner arter hastalığı şiddeti arasındaki ilişkiyi SYNTAX skoruna göre değerlendirmektir.

Gereç ve Yöntem: Kasım 2015-Aralık 2016 tarihleri arasında AKS tanısı ile acil servise başvuran 356 hasta çalışmaya alındı. Hastalar 3 gruba ayrıldı: düşük SYNTAX skoru (< 23), yüksek SYNTAX skoru (≥23) ve normal koroner hastaları.

Bulgular: DELC'li hastalar yüzde olarak tüm gruplar arasında istatistiksel olarak anlamlı derecede farklıydı ($p < 0,001$). Daha yüksek DELC sayısı (OR = 0.497; %95 CI: 0.246-1.001; $p = 0.043$), çoklu lineer regresyon analizinden sonra AKS hastalarında yüksek SYNTAX skoru için bağımsız bir öngörücüydü.

Sonuç: Frank Sign, birincil uygulayıcıların CAD'nin ciddiyetini tahmin etmelerine yardımcı olabilir.

Anahtar kelimeler: Akut koroner sendrom; Diyagonal kulak memesi kırışıklığı; Frank Sign; SYNTAX skoru.

Introduction

Diagonal ear lobe crease (DELC), also called as Frank's sign, is a diagonal fold or wrinkle-like line in the skin of the earlobe (Figure 1). This sign detected on the physical examination was proposed as a surrogate marker for individuals at high risk of cardiovascular disease (CVD).[1] In 1973, DELC was firstly reported by Frank to be associated with coronary artery disease.[2] Since then, DELC's association with not only for coronary artery disease has been shown but also for generalized atherosclerosis.[3,4] Various studies have shown no independent relationship of DELC with CVD and mooted that it is basically a marker of senility. But, there is still some controversy that some studies supported Frank's study while some withstood against it.[5,6]

Figure 1: Diagonal ear lobe crease (Frank's sign)

SYNTAX [The anatomical synergy between percutaneous coronary intervention (PCI) with taxus and cardiac surgery] score, an angiographic scoring system, shows the grade and complexity of coronary artery disease (CAD). Patients with a relatively high SYNTAX score have worse prognosis and this score system independently predicts major advanced cardiovascular events (MACE) for percutaneous coronary intervention (PCI). [7,8]

The aim of our study was to assess the relationship between presence of DELC and the severity of CAD according to the SYNTAX score in patients with firstly diagnosed acute coronary syndrome (ACS). To our knowledge, no studies have investigated the association between DELC and the severity of CAD in patients with first diagnosis of ACS.

Material and Methods

Consecutive patients with first-time diagnosis of ACS who underwent urgent coronary angiography (CA) and 120 randomly chosen patients with normal coronary artery detected in CA were enrolled into the study. To have a more homogeneous study group, patients with history of previous myocardial infarction, prior stent implantation or bypass grafting were excluded from the study. The study protocol was approved by Turkiye Yuksek Ihtisas Training and Research Hospital Ethics Committee (15/11/2018-29620911-929). Consent form was obtained from all patients. Procedures were carried out in accordance with the 2013 Helsinki Declaration.

469 consecutive patients admitted to the emergency department with the diagnosis of ACS from November 2015

to December 2016 were included into the study. Of these, 236 patients (59%) had an admission for ACS as a first time. Among those cases, 213 patients with previous CAD and coronary angiography and 20 patients with only medical treatment without diagnostic coronary angiography were excluded from the study. Patients with previous coronary artery bypass grafting (CABG) were also excluded from the study because SYNTAX score is suitable only for patients with native coronary artery lesions. Patients were stratified into 3 groups: low SYNTAX score (< 23), high SYNTAX score (≥23) and patients with normal CA. Before discharge of the patients, all patients were examined for DELC by 2 trained physicians. By a consensus, they determined whether unilateral or bilateral DELC were present or not. Observers were blinded to the results of CA and history

Demographic data, procedural details, and CAD severity of patients were analyzed. Other risk factors for CAD and demographic parameters [age, gender, and body mass index (BMI)] at the time of enrollment into the study were evaluated by history-taking and physical examination results. The CAD risk factor profile comprised of history of cigarette smoking, dyslipidemia (low-density lipoprotein cholesterol ≥70 mg/dL; 1.8 mmol/L), family history of CAD (first degree relatives before the age of 55 years in men and 65 years in women), and hypertension (systolic blood pressure≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or on antihypertensive treatment).

Peripheral venous blood was drawn from an antecubital vein on admission and on the first morning after admission. Admission glucose level, fasting blood glucose, baseline creatinine lipid profile, troponin I, C-reactive protein, and other biochemical parameters were measured using standard methods.

Patients with normal CA were selected from those to whom was performed CA as a result of a positive stress test (exercise stress test or myocardial perfusion scintigraphy test) or clinically high suspicion of CAD (e.g. patients with strong family history of CAD or early death with or without associated risk factors, and patients with unexplained chest pain after careful clinical and laboratory evaluation if there was strong suspicion of ischemic heart disease). Normal coronary arteries were defined as no visible disease or luminal irregularity (less than 50%) by judging visually on CA.

Acute coronary syndrome comprises non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). After a diagnosis of ACS, coronary arteries were cannulated on the same day using either standard techniques with femoral or radial approach. During cardiac catheterization, nitroglycerin was used in all patients in case of suspected coronary artery spasm. Each coronary artery was displayed on at least 2 different planes. Images of coronary angiogram were recorded using digital media (DICOM viewer, MedCom GmbH, Darmstadt, Germany). Percutaneous coronary intervention (PCI) procedures were performed using standard techniques. Coronary artery disease was defined on the quantitative coronary angiography as a coronary stenosis ≥50% luminal diameter narrowing. On the ground of CA, two experienced interventional cardiologists unaware of the patients' clinical or laboratory results calculated the SYNTAX score for all patients. SYNTAX score was computed for all coronary lesions with > 50% diameter stenosis in a vessel > 1.5 mm based on SYNTAX score calculator 2.1 (www.syntaxscore.com). Patients with ACS were stratified into 2 groups: low SYNTAX score (< 23) (129 patients), and high SYNTAX score (≥23) (107 patients).

To define intra-observer variability, 20 patients were randomly selected from the study group. Measurements were repeated under the same basal conditions, and reproducibility of the SYNTAX score by CA was assessed according to the coefficient of variation between measurements. Intra-observer variability was 5.9 % for SYNTAX score.

Statistical Analysis

Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, Il, USA). Continuous variables were reported as mean ± SD, and categorical variables were reported as percentages and counts. The Student's t-test was used for comparisons of normally distributed variables, and the Mann-Whitney U test was used for nonnormally distributed variables if 2 groups existed. Oneway analysis of variance was used to compare normally distributed variables between 3 groups. Tukey's test was used for post-hoc analysis. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test, as appropriate.

Pearson's correlation coefficients were used to assess the strength of relationship between continuous variables, and Spearman correlation analysis was performed for non-continuous and categorical variables. Major clinical factors and predictors of SYNTAX score ≥ 23 as displayed in Table 1 were used in univariate and multiple linear regression analysis. In all analyses, a p value of < 0.05 was considered to be statistically significant and the confidence interval was 95 %.

Results

Baseline clinical characteristics and laboratory parameters of the study population according to SYNTAX score are demonstrated in Table 1. No significant difference in terms of the age, sex, hyperlipidemia, diabetes mellitus, hypertension, ACS subtype and smoking were detected between the groups (Table 1). Patients with DELC as percentage were statistically significantly different between all groups (p < 0.001). The ACS patients with a high SYNTAX score (score ≥23) had more DELC (n=60, %=56.1) compared to the ACS patients with a low SYNTAX score (score < 23)(n=53, %=41.1)and the control group (n=35, %=29.2). There were also significant differences between the high SYNTAX score group and control group (p < 0.001), low SYNTAX score group and control group (p= 0.049), and high SYNTAX score group and low SYNTAX score group (p=0.023). There were significant differences between the patients with DELC and without DELC regarding of age (p<0.001), Body mass index (BMI) (p=0.007), multi-vessel disease status (p<0.001), lymphocyte (p=0.023) and SYNTAX score (p<0.001) (Table 2).

Table 1. Baseline characteristics and laboratory parameters of the study groups (n=356).

Variables	ACS SYNTAX score ≥23 (n=107)	ACS SYNTAX score <23 (n=129)	NCA (n=120)	P value*	P value[a]	P value ☐	P value☐
Age,years	61.6 ± 11.7	60.9 ± 12.0	61.2 ± 11.7	0.544	-	-	-
BMI, kg/m2	27.7 ± 3.5	27.4 ± 3.6	25.4 ± 2.3	<0.001	0.588	<0.001	<0.001
Male, n(%)	79 (73.8)	64 (49.6)	75 (62.5)	0.110	-	-	-
Hyperlipidemia, n(%)	24 (22.4)	23(17.8)	19 (15.8)	0.389			
Diabetes Mellitus, n(%)	39 (36.4)	39 (30.5)	23 (19.2)	0.013	0.332	0.004	0.040
Hypertension, n(%)	44 (41.1)	57 (44.2)	40 (33.3)	0.201	0.637	0.227	0.080
Smoking, n(%)	41 (38.3)	59 (45.7)	41 (34.2)	0.167	-	-	-
Multi-vessel disease, n (%)	41 (52.6)	16 (14)	0 (0)	-	<0.001	-	-
ACS subtype NSTEMI (%) STEMI (%)	 57 (47.2) 58 (54.2)	 49 (45.8) 72 (55.8)	 0 (0) 0 (0)	-	 0.805 0.805	-	-
Stent implantation, n (%)	68 (63.6)	114 (88.4)	0 (0)	-	<0.001	-	-
Decision for CABG, n (%)	38(35.5)	12 (9.3)	0 (0)	-	<0.001	-	-
Glucose, mg/dL	155.21 ± 84.9	144.8 ± 67.4	98.8 ± 33.3	<0.001	0.319	<0.001	<0.001
Creatinine, mg/dL	1.97 ± 8.3	1.0 ± 0.34	0.99 ± 0.12	0.213	-	-	-
Total cholesterol, mg/dL	203 ± 42.0	189.5 ± 50	165.8 ± 43.1	<0.001	0.030	<0.001	<0.001
LDL-C, mg/dL	131.7 ± 35.4	123.5 ± 35.0	100.2 ± 30.1	<0.001	0.120	<0.001	<0.001
HDL-C, mg/dL	45.1 ± 10.7	43.4 ± 10.1	45 ± 13.7	0.306	-	-	-
Hemoglobin, g/dL	15.2 ± 1.8	14.8 ± 1.6	14.4 ± 1.3	0.71		-	-
WBC,10^3/mm^3	11.2 ± 2.7	11.1 ± 2.9	10.3 ± 2.5	0.117	-	-	-
Platelet, 10^3/mm^3	236.7 ± 70.9	238.1 ± 61.4	238.2 ± 66.5	0.982	-	-	-
Neutrophil, 10^3/mm^3	8.27 ± 3.5	8.45 ± 5.5	7.8 ± 6.6	0.690	-	-	-
Lymphocyte,10^3/mm^3	2.1 ± 1.2	2.5 ± 1.3	2.4 ± 1.1	0.035	0.017	0.043	0.528
CRP,mg/L	19 (12-34)	11 (5-21)	4 (2-9)	<0.001	0.089	<0.001	0.001
LVEF, %	44.6 ± 10.1	48.9 ± 8.9	60.6 ± 6.9	-	0.001	-	-
Peak troponin-T, ng/mL	5.3 (2.4-14.5)	4.6 (1.8-12.3)	-	0.744	-	-	-
SYNTAX score	29.1 ± 5.39	15.1± 5.1	0 ± 0	-	<0.001		
Patients with DELC n (%)	60 (56.1)	53(41.1)	35(29.2)	<0.001	0.023	<0.001	0.049

Data are given as mean ± SD, n (%) or median (lower-upper limit). BMI, body mass index; CABG, coronary artery bypass grafting; CRP, C-reactive protein; DELC, Diagonal earlobe crease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NCA; normal coronary artery; NSTEMI, Non ST-segment elevation myocardial infarction;MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; SYNTAX, The anatomical synergy between percutaneous coronary intervention (PCI) with taxus and cardiac surgery; WBC, white blood cell.

* p value between all groups
☐ p value between NSTEMI SYNTAX score ≥23 and NSTEMI SYNTAX score <23groups
☐ p value between NSTEMI SYNTAX score ≥23 and NCA groups
☐ p value between NSTEMI SYNTAX score <23 groups and NCA groups groups

Table 2. Baseline characteristics and laboratory parameters of the study groups according to the diagonal earlobe crease (n=356).

Variables	Patients with DELC (n=148)	Patients without DELC (n=208)	P value
Age,years	(n=148)	51.8 ± 8.6	<0.001
BMI, kg/m2	27.4 ± 3.2	26.4 ± 3.5	0.007
Male, n(%)	98 (66.2)	150 (72.1)	0.233
Hyperlipidemia, n(%)	30 (20.3)	37 (17.8)	0.555
Diabetes Mellitus, n(%)	44 (29.9)	57 (27.4)	0.603
Hypertension, n(%)	66 (44.6)	75 (36.1)	0.105
Smoking, n(%)	71 (47.9)	90 (43.2)	0.475
Multi-vessel disease, n (%)	37 (30.1)	20 (11.2)	<0.001
Glucose, mg/dL	127.26 ± 62.1	141.2 ± 73.6.4	0.080
Creatinine, mg/dL	1.4 ± 4.3	1.0 ± 0.3	0.420
Total cholesterol, mg/dL	188.3 ± 46.9	185.4 ± 47.9	0.613
LDL-C, mg/dL	121.8 ± 40.6	117.0± 40.5	0.323
HDL-C, mg/dL	45.6 ± 10.7	43.4 ± 10.1	0.07
Hemoglobin, g/dL	14.7 ± 2.1	14.6 ± 1.6	0.508
WBC,10^3/mm^3	10.9 ± 3.5	10.8 ± 3.4	0.615
Platelet, 10^3/mm^3	240.8 ± 67.2	236.5 ± 65.4	0.596
Neutrophil, 10^3/mm^3	9.1± 5.3	7.9 ± 3.3	0.08
Lymphocyte,10^3/mm^3	2.1 ± 1.5	2.4 ± 1.3	0.023
CRP,mg/L	16.4 (7-37)	8.5 (3-20)	0.147
LVEF, %	46.1 ± 9.6	48.3 ± 9.4	0.083
SYNTAX score	17.9 ± 7.3	11.5± 6.5	<0.001

Data are given as mean ± SD, n (%) or median (lower-upper limit). BMI, body mass index; CRP, C-reactive protein; DELC, Diagonal earlobe crease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; SYNTAX, The anatomical synergy between percutaneous coronary intervention (PCI) with taxus and cardiac surgery; WBC, white blood cell.

We performed univariate and multiple linear regression analyses for the predictors of SYNTAX ≥ 23 score as depicted in Table 3. In univariate regression analysis, BMI (OR = 1.114; 95% CI: 1.041-1.191; p = 0.050), Diabetes Mellitus (DM) (OR = 0.581; 95% CI: 0.357-0.946; p = 0.029), glucose (OR = 1.007; 95% CI: 1.004-1.011; p = 0.043), C-reactive protein (CRP) (OR = 1.014; 95% CI: 1.004-1.024; p = 0.049) and patients with DELC (OR = 0.428; 95% CI: 0.270-0.679; p <0.001) were associated with a higher SYNTAX score. Higher number of DELC (OR = 0.497; 95% CI: 0.246-1.001; p = 0.043) was an independent predictor for a high SYNTAX score in the ACS patients after multiple linear regression analysis.

Table 3. Multivariate linear regression analysis showing the predictors for the SYNTAX score

	Univariable		Multivariable	
Variables	Beta (95% CI)	P value	Beta (95% CI)	P value
BMI	1.114 (1.041-1.191)	0.050	1.074 (0.991-1.165)	0.212
Diabetes Mellitus	0.581 (0.357-0.946)	0.029	0.933 (0.492-1.652)	0.831
Glucose	1.007 (1.004-1.011)	0.043	1.006 (1.002-1.010)	0.311
Total cholesterol	1.002 (0.997-1.007)	0.420	-	-
LDL-C	1.004 (0.999-1.010)	0.141	-	-
Lymphocyte	0.758 (0.608-0.944)	0.160	-	-
CRP	1.014 (1.004-1.024)	0.049	1.001 (0.991 - 1.011)	0.478
Patients with DELC n (%)	0.428 (0.270-0.679)	<0.001	0.497 (0.246-1.001)	0.043

BMI, body mass index; CRP, C-reactive protein; DELC, Diagonal earlobe crease; LDL, low-density lipoprotein.

Discussion

According to our best knowledge, this is the first study demonstrating the association of DELC and CAD severity according to SYNTAX score in patients with first diagnosis of ACS. The present study indicated that DELC was independently and significantly associated with extent and severity of CAD in patients with first diagnosis of ACS. Above all, DELC continued its relation with the extent, and severity of CAD even after adjusting for age, BMI, DM and CRP.

This wrinkle-like line extending diagonally in the skin of the ear-lobe was firstly described by Frank in 1973. Then by, various studies have revealed not only the relation between the

existence of DELC and CAD, but also a significant correlation with the extent and severity of CAD regardless of major risk factors such as hypertension, hyperlipidemia, diabetes or obesity for cardiovascular system. DELC, which is a physical sign, can early detect high risk individuals for atherosclerosis.[9]

But a certain pathophysiologic explanation underlying this association has not been cleared up. It has been proposed that the same genetically originated end-arterioles supply the myocardium and ear lobe and so share a common final pathway. It was assumed that DELC was an external sign of a microangiopathic lesion of terminal vessels in CAD. This was determined in biopsy specimens of earlobe creases which described vasculature morphology as in the coronary bed in patients with CAD.[10,11]

Sapira demonstrated that earlobe collagen was formed by peptide chains with a repeating specific triplet of amino acids similar to those present on the surface of scavenger macrophages at the receptor used for the ingestion of atheromatous cholesterol. This was the most clear explanation which reported the pathophysiologic relation of DELC with CAD by now.[12] According to some studies, DELC was not a predictor of CAD in some ethnicities while some had a significant association with CAD.[13,14] In addition, DELC was independently and significantly associated with increased prevalence, extent, and severity of CAD in patients imaged with computed tomography (CT) coronary angiography.[15] Disruption of collagen to elastin ratio and the degenerative process of elastin fibers may clarify to a degree for the relationship between CAD and DELC.[16] DELC is rare in infants and skin ageing also shows correlation with the ageing process of the coronary arteries; thus, DELC may externalize skin ageing[11,17] Also, DELC was associated with shortened telomere indicating ageing in a study consisting of Japanese male participants with metabolic syndrome.[18]

On the grounds of CA, SYNTAX score is utilized to grade CAD complexity by considering the number of lesions and their functional and anatomic components including location, presence of bifurcations, tortuosity, total occlusions, collaterals, thrombus and calcification. It is helpful for physicians to decide the optimal revascularization strategies especially among patients with complex CAD. A high SYNTAX score indicates a more complex disease and is an indicative of a therapeutic compelling. Patients with a high SYNTAX score have been shown to have more major adverse cardiac or cerebrovascular events.[19-23] There were more DELC in patients with a high SYNTAX (≥23) score in this study population than both low SYNTAX (<23) score and normal CA group in this study population.

This is the preliminary study investigating the relationship of DELC and CAD severity according to SYNTAX score in a population consisting of ACS. This physical sign had a strong association with CAD severity.We have revealed that the coronary atherosclerosis burden was more advanced in patients with DELC detected on the physical examination at first presentation of ACS. It is a costless method but, is not used commonly in the daily practice.

Our study should be interpreted with some limitations. The present study is a cross-sectional study with a relatively small sample size. We do not know Frank Sign's association with MACE. Because, we did not have follow-up MACE data. That is why, our study should be proved in multi-center prospective longitudinal studies with a larger sample size. We also did not divide patient population into different groups based on whether they have unilateral or bilateral DELC. So, this may also affect the results of our study. The limitations of this study should be considered when interpreting the results.

Concslusion

Frank's sign is an easy physical sign to detect. In our study we found an association with Frank's sign and SYNTAX Score. SYNTAX is a scoring system detects the severity of coronary artery disease severity and complexity, but it can be used by expertized clinicians. Frank's sign can help primary practitioners to predict severity of CAD.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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