

FRANK'S SIGN AS A RISK FACTOR FOR CEREBROVASCULAR DISEASE

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SUMMARY – Frank's sign is a dermatological marker, which has in many studies correlated with coronary heart disease. The aim of the study carried out in a sample of 60 subjects was to define whether Frank's sign belongs to the group of risk factors for cerebrovascular disease. The subjects with the presence of Frank's sign were assigned to group A, and those without Frank's sign to group B. All study subjects underwent color Doppler examination of carotid arteries and determination of their common carotid artery intimal wall thickness (ACC IMT). The value exceeding 0.9 mm was considered as an ACC IMT increase. Statistical analysis by use of Pearson's χ^2 -test yielded a value of 11.279 and $p=0.001$. Assessment of the Frank's sign value in predicting increased ACC IMT showed a sensitivity of 73%, specificity of 70%, positive predictive value of 71% and negative predictive value of 72%. The study indicated a statistically significant correlation between Frank's sign and increased ACC IMT, supporting the hypothesis according to which this marker is an uncontrollable risk factor for cerebrovascular disease.

Key words: *Ear, external – anatomy and histology; Coronary disease – epidemiology; Cerebrovascular disorders – pathology; Cerebrovascular disorders – etiology; Risk factors; Incidence*

Introduction

Frank's sign (diagonal incisure of ear lobe) is a dermatological marker extending from the tragus usually at an angle of 45 degrees to the rear edge of the auricle¹. Many studies published so far have defined a correlation of Frank's sign and coronary heart disease occurring due to advanced atherosclerosis¹⁻⁷. Since atherosclerosis is a generalized disease, it could be concluded that Frank's sign occurs more frequently in patients with cerebrovascular disease. However, studies of this type have not yet been carried out. Increased common carotid artery intima media thickness (ACC IMT) is a substitute marker of atherosclerosis, meaning that its increased value represents a risk for the occurrence of heart attack and stroke. The aim of our study was to determine whether Frank's sign belongs to the group of risk

factors for cerebrovascular diseases such as race, sex or age. The null hypothesis was that there was no statistically important link between Frank's sign and increased ACC IMT, and accordingly that there was no risk of cerebrovascular disease.

Subjects and Methods

This prospective case-control study was carried out during April 2006 in a group of 60 patients undergoing examination at cerebrovascular laboratory of the Glavić Polyclinic of Neurology in Dubrovnik. Two groups were created, each containing 30 (11 female and 19 male) patients. Consecutive patients with ear lobe crease were included in the study. Women with earrings were not included in the study, due to the possibility of potential false Frank's sign. After including one patient with ear lobe crease (Frank's sign) in the first group, a consecutive sex- and age-matched control was included in the other group. In all subjects, one or more risk factors for the development of atherosclerosis were recorded. The two groups were comparable according to mean age. All

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Received July 19, 2006, accepted in revised form November 7, 2006

subjects underwent carotid Doppler examination using a high-resolution ultrasound system Aloka 3500 Prosound plus (Aloka GmbH, Meerbusch, Germany) and semi-automated computer program for IMT evaluation. IMT values were measured by B-mode on ACC placed 1.5 cm proximally from carotid bifurcation. The ACC IMT above 0.9 mm was considered increased.

Result analysis was done by use of Mann-Whitney test, Pearson's χ^2 -test and contingency tables.

Results

The mean age was 65.7 ± 12.2 (range 53.5-77.9) years in group A (Frank's sign present) and 65.4 ± 11.59 (range 53.8-76.9) years in group B (Frank's sign absent). Statistical analysis using Mann-Whitney test (comparison of data on two independent samples) yielded $z = -0.155$ and $p = 0.877$, indicating that there was no statistically significant between-group difference according to age. Statistical analysis using Pearson's χ^2 -test assessing statistical significance of frequencies in two samples was employed to estimate the possible correlation between Frank's sign and ACC IMT. This testing yielded values of 11.279 and $p = 0.001$, showing statistical significance with a risk level of 0.1%. Using the same test we checked whether there was either sex predominance in the presence of Frank's sign. This testing yielded $\chi^2 = 0$; $p = 1.0$, meaning there was a comparable number of men and women with the sign. Assessment of the Frank's sign value in predicting increased ACC IMT by use of contingency table (Table 1) indicated a sensitivity of 73%, specificity of 70%, positive predictive value (PPV) of 71% and negative predictive value (NPV) of 72%. The results obtained demonstrated that there was a statistically significant correlation between Frank's sign and increased ACC IMT as a marker of atherosclerosis. The sign itself was found to be a good predictor of the risk of cerebrovascular disease.

Discussion

In our study, we examined the correlation of Frank's sign and increased ACC IMT with the consequential risk of cerebrovascular disease. Our results showed that increased ACC IMT was most often found in patients with Frank's sign. In 1973, Frank noticed that many cardiac patients (especially those younger than 60 years of age) had unilateral or bilateral diagonal incisure of ear lobe¹. In their anthropological study, Dharap *et al.* recorded the presence of this phenotypic marker in 31.1% of

healthy men and 3.6% of healthy women in Malay population⁸. Many studies show that Frank's sign can be determined as a marker of atherosclerosis and a sign of elevated risk of coronary heart disease in asymptomatic individuals¹⁻⁷, with the exception of native American Indians, Oriental patients and children suffering from Beckwith's syndrome⁹. According to the results reported by Davis *et al.*¹⁰, and Kenny and Gilligan¹¹, Frank's sign cannot be considered as a predictor of coronary disease. Bahcelioglu *et al.* demonstrated the association of Frank's sign with diabetes, hypertension, myocardial infarction and coronary disease in patients of both sexes¹². Based on the presence of bilateral diagonal incisure of ear lobe on the statues of the Roman Emperor Hadrian, Petrakis poses a hypothesis according to which Hadrian died due to advanced coronary atherosclerosis and heart failure¹³. In the studies carried out by Crouse¹⁴ and Craven *et al.*¹⁵, a connection of coronary heart disease and carotid artery atherosclerotic changes was determined. O'Leary *et al.* found the increased ACC IMT to be directly connected with an elevated risk of myocardial infarction and stroke in adults with a negative history of cardiovascular disease¹⁶. The risk factors for atherosclerosis, which increase the ACC IMT values include arterial hypertension, elevated level of cholesterol and LDL cholesterol, smoking, diabetes, hematological parameters such as fibrinogen level, fibrinopeptide A and D-dimer, tissue plasminogen activator, serum copper value, homocysteine value, while no connection was found with alcohol consumption, triglyceride value or glycosylated hemoglobin (HbA_{1c}) in patients with diabetes¹⁷⁻²⁰. Studies have shown that hormone replacement therapy in menopause has a protective effect, which means that it lowers the ACC IMT values²¹.

A possible limitation of the present study was that the number of patients was too small for multivariate analysis. On literature survey, we found no studies evaluating Frank's sign as a risk factor for cerebrovascular disease. To our knowledge, this was the first study of

Table 1. Evaluation of Frank's sign with identification of increased ACC IMT

ACC IMT	Frank's sign		Total
	Present	Absent	
Increased	22	9	31
Normal	8	21	29
Total	30	30	60

ACC IMT=common carotid artery intima-media thickness

the kind, and we plan to confirm the results obtained in further studies in a larger number of patients. If our observations prove correct in a greater sample of subjects, we could add Frank's sign to the group of risk factors for the development of atherosclerosis. Since Frank's sign is a visible sign, preventive actions could then be taken.

Conclusion

The results of this study revealed a statistically significant correlation between the presence of Frank's sign and increased ACC IMT. The results of Frank's sign validity assessment were higher than those obtained in other similar studies carried out in subjects suffering from coronary heart disease, thus supporting our hypothesis that Frank's sign belongs to the group of uncontrollable risk factors for cerebrovascular disease such as race, sex or age.

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Sažetak

FRANKOV ZNAK KAO ČIMBENIK RIZIKA CEREBROVASKULARNE BOLESTI

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Frankov znak je dermatološki biljeg koji je u brojnim studijama povezan s koronarnom bolešću srca. Cilj istraživanja provedenog na uzorku od 60 ispitanika bio je utvrditi pripada li Frankov znak čimbenicima rizika cerebrovaskularne bolesti. U skupinu A svrstani su ispitanici s prisutnim, a u skupinu B ispitanici s odsutnim Frankovim znakom te je svima napravljen obojeni Doppler karotidnih arterija i određena debljina intimalne stijenke (IMT) na zajedničkoj karotidnoj arteriji (ACC). Kao povećanje ACC IMT uzeta je vrijednost iznad 0,9 mm. Statističkom analizom Pearsonovim χ^2 -testom dobivena je vrijednost od 11,279 i $p=0,001$. Procjenom vrijednosti Frankovog znaka u predviđanju povećanja ACC IMT utvrđena je osjetljivost od 73%, specifičnost od 70%, pozitivna prediktivna vrijednost od 71% i negativna prediktivna vrijednost od 72%. Istraživanje je pokazalo statistički značajnu povezanost Frankovog znaka i povećanja ACC IMT, što podupire hipotezu prema kojoj je ovaj znak čimbenik rizika cerebrovaskularne bolesti na koji se ne može utjecati.

Ključne riječi: Uho, vanjsko – anatomija i histologija; Koronarna bolest – epidemiologija; Cerebrovaskularne bolesti – patologija; Cerebrovaskularne bolesti – etiologija; Čimbenici rizika; Incidencija