

Frequency of the Diagonal Earlobe Crease (Frank's sign) in Patients with Acute Ischemic Cerebrovascular Events

Mohammad Abdullah¹, Manahil Chaudhry², Ali Nauman³, Ayesha Malik⁴, Noreena Iqbal⁵, Ambreen Tauseef⁶

¹Senior Registrar, Department of Medicine, CMH, Lahore Medical College & IOD, Lahore, Pakistan.

²Medical Officer, Department of Emergency, Hameed Latif Hospital, Lahore, Punjab, Pakistan.

³Resident, Department of Ophthalmology, Layton Rehmatullah Benevolent Trust Free Eye Hospital, Lahore, Punjab, Pakistan.

⁴Medical Officer, Department of Medicine, Hameed Latif Hospital, Lahore, Punjab, Pakistan.

⁵Resident, Department of Medicine, Oxford University Hospitals Trust, NHS, Lahore, Punjab, Pakistan.

⁶Associate Professor, Department of Physiology, CMH, Lahore Medical College & IOD, Lahore, Pakistan.

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ABSTRACT

Background: There exist novel imaging techniques that can quantify underlying atherosclerosis to study its association with the diagonal earlobe crease or the Frank's sign. However, the purpose of this study was to assess the correspondence between the Frank's sign and symptomatic atherosclerotic disease manifested as an acute ischemic stroke (AIS) or transient ischemic attack (TIA) to establish its predictive value as a marker of adverse atherosclerotic complications. **Methods:** This cross-sectional analytical study was held at Combined Military Hospital, Lahore, Pakistan from 1st July, 2019 to 31st December, 2019. A total of 216 patients, aged 40 years and above, were consecutively included in this study. They were divided into two groups, Group A included cases (n=108), which were patients who suffered from a cerebrovascular accident (CVA), AIS or TIA. Group B were controls (n=108), which included age, gender and ethnicity matched individuals who previously had no CVA. Demographics, co-morbidities, and features of the Frank's sign (direction and grade) were recorded for both groups, and descriptive and inferential statistics were drawn. **Results:** Amongst cases, 79 (73.1%) suffered an AIS and 29 (26.9%) had a TIA. Group A had 74 (68.5%) patients, and Group B had 72 (66.7%) patients with a Frank's sign present (p=0.771). The Frank's sign was insignificantly distributed in both genders (p=0.24). Amongst the co-morbidities, which were significantly more prevalent amongst Group A, hypertension had the strongest association with the Frank's sign (p= <0.00001). Both, the grade of the Frank's sign (0-3) and direction had no significance in any group. Lastly, the sensitivity of Frank's sign 50.7%, the specificity was 51.4% with a positive predictive value of 68.5% and a negative predictive value of 33.3%. **Conclusion:** The Frank's sign was a more prevalent finding amongst the cases (p=0.771), however, its presence, regardless of the direction and depth, cannot necessitate the occurrence of an adverse complication such as an AIS or TIA.

Keywords: Acute Ischemic Stroke, Frank's sign, Atherosclerosis, Cerebrovascular accidents.

INTRODUCTION

Atherosclerosis is a lifelong, systemic disease that is the underlying culprit of most cerebrovascular disease processes.^[1] Pathologically, it is a disease of the vascular intima, which may involve the entire vascular system from the aorta to coronary arteries and is characterized by intimal plaques.^[2] Its major clinical manifestations include ischemic heart disease, peripheral arterial disease, and acute ischemic stroke (AIS).^[3] Recent advances in medicine have led to the emergence of novel lab and imaging parameters for the diagnosis of cerebrovascular disease, as well as risk assessment of the aforementioned complications. Nevertheless, the fulcrum of medicine lies in the clinical assessment of patients.

There exist certain clinical signs that act as predictors of atherosclerosis, including corneal arcus, xanthelasma, and the diagonal earlobe crease (DELCC) or "Frank's sign".^[4] Morphologically, Frank's sign is a diagonal crease or a wrinkle that extends 45° backward from the tragus to the auricle.^[5] Without discontinuity covering at least 2/3 of its path.^[6] It has previously been studied as a cutaneous marker of underlying atherosclerotic vascular disease, initially correlated in 1973 by the American physician, Sanders T. Frank.^[7]

There are several theories suggesting the underlying mechanism behind the formation of the earlobe crease with no single established interpretation. One theory suggests the presence of underlying microvascular disease leads to the degeneration of elastin fibers, due to end-arterial vascular supply here, which results in the ear crease formation.^[8] A study of Frank sign in patients with metabolic syndrome depicted that these patients had shorter telomeres, which is linked to accelerated aging and accelerated atherosclerosis.^[9]

While existing studies have investigated the correlations between Frank's sign and ischemic heart

Name & Address of Corresponding Author

Dr. Manahil Chaudhry
Medical Officer,
Department of Emergency,
Hameed Latif Hospital, Lahore,
Punjab, Pakistan.
Email. manahilch2307@gmail.com

disease and peripheral arterial disease in detail, there are scarce data on its association with acute ischemic cerebrovascular events.^[10-13] Therefore, the purpose of this study was to assess the correspondence between Frank's sign and underlying atherosclerotic cerebrovascular disease manifested as acute ischemic stroke or transient ischemic attack.

MATERIALS AND METHODS

This cross-sectional study was conducted over 6 months at a tertiary care hospital. A total of 216 patients, aged 40 years and above, were consecutively included. They were divided into two groups, Group A included 108 cases with 40 years of age or above with known atherosclerotic risk factors, who suffered from a cerebrovascular event either an AIS or a TIA. Age, gender, and ethnicity matched individuals who had not previously suffered from any cerebrovascular complications were selected as controls, termed Group B. Co-morbidities including diabetes mellitus, hypertension (on at least one or more hypertensive drug, or with a clinical reading of a systolic ≥ 140 mmHg and/or diastolic of ≥ 90 mmHg), smoking and obesity (BMI ≥ 30) were recorded for both groups. However, patients below 40 years of age, presenting later than 14 days from the occurrence of symptoms of stroke, with non-atherosclerotic causes for ischemic stroke and patients with skin piercings/marks/skin conditions that could confuse the presence of the DELC were excluded from this study.

On presentation, a thorough history and examination were carried out for each patient presenting with signs and symptoms of stroke, after which a plain computed tomography (CT) head was done. The final diagnosis was given by a senior neurologist. For all patients who met the inclusion criteria, demographic data, risk factors, and features of Frank's sign including grade (0-3), unilateral/bilateral presence were recorded with the patient in sitting position. The grades were defined as:

- Grade 1 – wrinkling
- Grade 2a – superficial crease (floor of sulcus visible)
- Grade 2b – crease more than 50% across earlobe
- Grade 3 – deep cleft across whole earlobe (floor not visible)

Frank's sign was considered as present or positive if the wrinkle/crease extended 45° backward from the tragus to the auricle without discontinuity covering at least 2/3 of its path. If there were multiple creases then any one that met the above criteria was considered.

Age, gender matched those who had not previously suffered from any cerebrovascular complications were selected as controls. Similar data and features of Frank's sign were described in this group. A non-probability, consecutive sampling technique was used to induct all cases and controls. Informed consent per the declaration of Helsinki was obtained

from all participants and the study was approved by the hospital's Ethics Review Committee.

Data was analyzed using Statistical Package for Social Sciences (SPSS) v25. A p-value of ≤ 0.05 was considered significant. Continuous data was presented as mean \pm SD and the Chi-square test was used to compare variables amongst cases and controls. A 2x2 contingency table was constructed to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Frank's sign.

RESULTS

Out of total 216 people, group A comprised of 108 cases that suffered from a cerebrovascular accident (CVA), included 79 (73.1%) patients who had an AIS and 29 (26.9%) who had a TIA. The mean age of this group was 63.8 ± 15.6 years which included 76 (70.4%) males and 32 (29.6%) females. Group B included 108 controls, with a mean age of 60.0 ± 10.7 years, and included the same number of males and females as the controls were gender-matched.

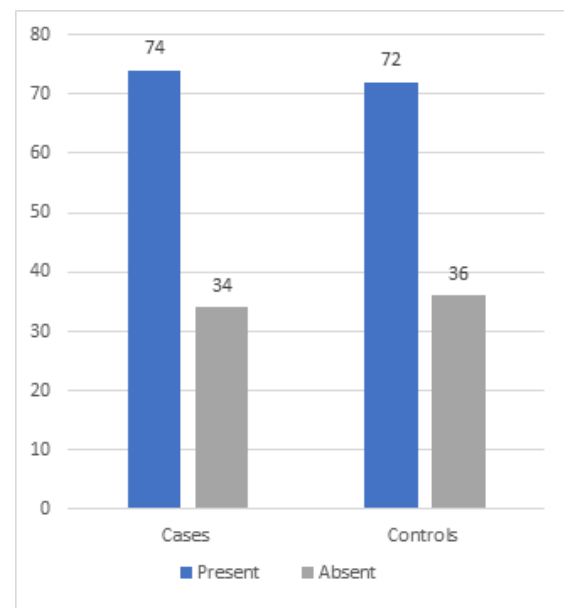


Figure 1: Prevalence of Frank's sign amongst cases and controls (n=216) (p=0.77)

Table 1: Features of patients having Frank's sign

Variable	Cases (n = 74)	Controls (n = 72)	p-value
Age	63.67 \pm 15.41	60.11 \pm 9.27	0.08
Males	53 (71.62%)	45 (62.5%)	0.24
Females	21 (28.38%)	27 (37.5)	
Diabetes mellitus	32 (43.24%)	11 (15.49%)	0.00021*
Hypertension	54 (72.97%)	19 (26.39%)	<0.00001*
Obesity	32 (43.24%)	10 (13.89%)	0.00009*
Smoker	19 (25.08%)	12 (16.90%)	0.183

*p-value ≤ 0.05 is significant

Amongst Group A, 74 (68.5%) patients had a Frank sign present while in Group B, 72 (66.7%) patients had a Frank sign present (p=0.771). Table I shows

that there were 53 (71.62%) males and 21 (23.38%) females in Group A with a positive Frank sign, while for Group B there were 50 (69.44%) males and 22 (30.56%) females with a positive Frank sign. This rendered a p-value of 0.674 for cases and 0.766 for controls.

[Table 1] also shows the comparison of the comorbidities amongst CVA and non-CVA cases in patients with Frank’s sign positive. Diabetes mellitus (p=0.00021), hypertension (p= <0.00001), and obesity (p=0.00009), were significantly more prevalent in CVA patients (with a positive Frank), while the risk factor, smoking, although more prevalent in CVA patients with a Frank sign, was a statistically insignificant finding (p=0.183).

The direction and grade (from 0-3) was noted for all patients and there was found to be no statistical difference in the direction amongst both the groups [Table 2]. In terms of the grade, as shown in Figure 2, the commonest grade found in both cases and controls was 2a (superficial crease, floor of the sulcus visible), which had a prevalence of 24.1% and 25.9%, respectively (p=0.639).

The sensitivity of Frank’s sign as a predictor of CVA was 50.7% (CI 42.3% to 59.1%), the specificity was 51.4% (CI 39.2% to 63.6%) with a positive predictive value (PPV) of 68.5% (CI 62.0% to 74.4%) and a Negative Predictive Value (NPV) of 33.3% (CI 27.4% to 39.8%).

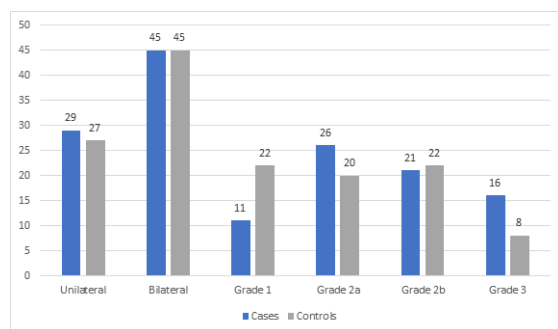


Figure 2: Morphological features of the Frank’s sign amongst cases and controls

Table 2: Grades and direction of Frank’s sign amongst cases and controls

	Cases	Controls	p-value
Direction	Unilateral	29	0.834
	Bilateral	45	
Grade 1	11	22	0.023*
Grade 2a	26	28	0.639
Grade 2b	21	22	0.773
Grade 3	16	8	0.087

DISCUSSION

The Frank’s sign, also stated as the “diagonal earlobe crease (DELIC)” by Ogan et al,^[14] or simply termed as the “earlobe crease (ELC)” by Del Brutto et al. and P. Agouridis et al.^[12,15] was the clinical marker studied in this research. We found that the earlobe crease was more prevalent amongst patients

who had CVA as compared to the control group. Our observation was limited to those individuals having atherosclerotic risk factors and excluded all those where non-atherosclerotic causes for stroke were found, e.g. atrial fibrillation, arterial dissection, fibromuscular dysplasia, thrombophilic disorders, inflammatory and vasculitic conditions were ruled out.

Diabetes mellitus, hypertension, obesity and smoking are established risk factors that lead to atherosclerosis. On par with previous studies comparing the earlobe crease, we found that patients with Frank’s sign positive had a higher prevalence of co-morbidities including diabetes mellitus (p=0.00021), hypertension (p= <0.00001), obesity (p=0.00009), and smoking (p=0.183), though the latter was statistically insignificant. What Nazzal et al.^[4] reported was similar to our study, i.e. hypertension having the strongest association with the Frank’s sign. Additionally, in another study done on a 1000 Japanese patients, the earlobe crease was found to have a significant correlation with hypertension, as well as male gender, age more than 50 years, and smoking.^[16]

A review of our demographics revealed that, the age of both our cases and controls had a mean of 63.8 years (ranging from 40 to 100) and 60.0 years (ranging from 40 to 91), respectively, owing to the two groups being age-matched. In all patients whose Frank’s sign was positive, the comparison of male and female ratios resulted in a statistically insignificant calculation, this was similar to Nazzal et al. (p=.315).^[4] This infers that there both genders have an equal predisposition to developing the Frank’s sign.

Novel advancements have brought forth various non-invasive surrogate markers of detecting atherosclerotic disease such as: carotid artery, coronary and aorta imaging, left ventricular echocardiography, electron beam computed tomography and Ankle-Brachial Index (ABI). While the aforementioned imaging techniques can identify subclinical disease, we studied the occurrence of CVA for clinically defining underlying atherosclerosis, in order to predict the Frank’s sign as an indicator of adverse atherosclerotic complications.

A research by Glavic et al.^[17] used the carotid intima thickness (IMT) to quantify the underlying atherosclerotic disease, defined as an IMT of more than 0.9mm. Shrestha et al. also used the same tool to define atherosclerosis.^[18] Nonetheless, the findings of both studies matched ours in terms of the prevalence of Frank’s in patients in patients with atherosclerosis.

Furthermore, our study showed the presence of the Frank’s sign had a sensitivity of 50.7%, a positive predictive value (PPV) of 68.5% and a negative predictive value (NPV) of 33.3%, as a predictor of CVAs. The values for Glavic et al.’s study (n=60)

were a sensitivity of 73%, PPV of 71% and an NPV of 72%.^[17] We can infer that there still exists large variability amongst the data that exists in comparison with atherosclerosis, whether clinical or subclinical, and there is a need for further research that involves multivariate models. In fact, a meta-analysis done in 2015 that compared previous existing literature also found it difficult to explain why so much variation exists even after so many years. Nonetheless, the Frank's sign should be endorsed as a marker of possible atherosclerotic disease and can prove to be a reminder for clinicians to screen for modifiable risk factors of atherosclerosis.^[15]

There were however some limitations in our study. Firstly, our sample size might have been too small for multivariate analysis, and a larger sample size can produce more generalizable results. Secondly, all of our population was of the South-Asian Pakistani ethnicity, hence, the results cannot be extrapolated to other ethnicities. Lastly, confounding variables that may have led to asymptomatic atherosclerotic disease were difficult to exclude.

CONCLUSION

The Frank's sign poses a significant indicator of underlying atherosclerotic disease as proved by previous researches that studied its association with carotid intima thickness, ABI, and other imaging techniques that quantify atherosclerosis. However, it's limited to being identified as a clinical marker of possible subclinical atherosclerotic disease only. In conclusion, regardless of the grade and severity of the earlobe crease, its presence cannot necessitate the occurrence of an adverse complication such as an AIS or TIA.

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