



Diagonal Earlobe Crease (Frank's Sign): A Predictor of Cerebral Vascular Events

Saleh Nazzal, MD, Basem Hijazi, MSc, Luai Khalila, MD, Arnon Blum, MD

Department of Medicine, Baruch Padeh Poria Medical Center, Faculty of Medicine in the Galilee, Bar-Ilan University, Tiberias, Lower Galilee, Israel.

ABSTRACT

BACKGROUND: Frank's sign was first described in 1973 by an American physician (Sonders T. Frank). It is a diagonal crease in the earlobe that starts from the tragus to the edge of the auricle in an angle of 45° in varying depths. Frank's sign was described as a predictor of future coronary heart disease and peripheral vascular diseases. The aim of the study was to examine the association between Frank's sign and the development of ischemic stroke.

METHODS: This was a prospective study that enrolled consecutive patients admitted with an acute ischemic stroke. Frank's sign was tested in both ears. Clinical data included age, gender, type 2 diabetes mellitus, and hypertension. The study was approved by the institutional review board (the institutional ethics committee).

RESULTS: A total of 241 consecutive patients who were hospitalized with an acute stroke and were eligible to take part in the study were recruited. Frank's sign was present in 190 patients (78.8%). Patients were divided according to clinical findings and the findings from brain computed tomography. There were 153 patients with transient ischemic attacks (63.6% of the patients) and 88 with cerebrovascular accidents (36.4% of the patients). A total of 112 patients with transient ischemic attacks had Frank's sign (73.2%), and 78 patients with cerebrovascular accidents had Frank's sign (88.6%), with a statistically significant difference ($P < .01$).

DISCUSSION: Frank's sign could predict ischemic cerebrovascular events. Patients with classical cardiovascular risk factors had Frank's sign at a higher frequency.

© 2017 Elsevier Inc. All rights reserved. • *The American Journal of Medicine* (2017) 130, 1324.e1-1324.e5

KEYWORDS: Cerebrovascular accident; Frank's sign; Transient ischemic attack

Advanced, sophisticated diagnostic techniques are considered the gold standard for diagnosis and clinical evaluation and prediction. Still, physical examination is considered a key factor in patient evaluation and clinical assessment. Physical examination is still used as a reliable tool to diagnose early subclinical stages of atherosclerosis, including physical traits and signs like obesity,¹ Achilles tendon thickness,² xanthelasma,³ short stature,⁴ and alopecia in young men.⁵ Frank's sign was first described in 1973 by an American physician (Sonders T. Frank).⁶ It is a diagonal

crease in the earlobe that starts from the tragus to the edge of the auricle at an angle of 45° in varying depths. This sign is also called diagonal ear lobe crease.⁶ Several studies described Frank's sign as a predictor of future coronary heart disease,⁶⁻¹¹ cerebrovascular disease,¹²⁻¹⁵ and peripheral vascular diseases.¹⁶⁻¹⁸ The aim of the present study was to examine the association between Frank's sign and the development of ischemic stroke.

METHODS

This was a prospective study that enrolled consecutive patients (men and women) over the age of 18 years who were admitted with an acute ischemic stroke and signed a consent form to participate in the study. The diagnosis was confirmed by a senior neurologist within the first 24 hours. Medical history and physical examination were done for all patients, and data were collected also from their medical

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to data and had a role in writing the manuscript.

Requests for reprints should be addressed to Arnon Blum, MD, Department of Medicine, Baruch Padeh Poria Medical Center, Faculty of Medicine in the Galilee, 15208 Tiberias, Lower Galilee, Israel.

E-mail address: ABlum@poria.health.gov.il

history electronic files. Frank's sign was tested in both ears. Clinical data included age, gender, type 2 diabetes mellitus, and hypertension. The study was approved by the institutional review board (the institutional ethics committee).

Definitions

Transient ischemic attack was defined as a stroke with neurologic symptoms that fade within 24 hours, without any signs of brain damage demonstrated on the computed tomography scan of the brain. Cerebrovascular accident was defined as neurologic symptoms that lasted more than 24 hours and/or any signs of brain damage demonstrated on the computed tomography scan, irrespective of the duration of symptoms. Frank's sign was defined as a diagonal ear lobe crease extending diagonally from the tragus across the lobule to the rear edge of the auricle at a 45° angle in varying depths.

CLINICAL SIGNIFICANCE

- Frank's sign could predict ischemic cerebrovascular events.
- Patients with classical cardiovascular risk factors had Frank's sign at a higher frequency.
- Frank's sign was more prevalent among patients with cerebrovascular accidents compared with patients with transient ischemic attacks.
- An increased rate of Frank's sign was found in patients admitted with an acute ischemic stroke and who suffered from myocardial infarction in the past.

Statistical Analysis

For categorical variables we examined frequencies and quantitative data that were normally distributed (average and standard deviations) by using the Kolmogorov-Smirnov test, whereas data that were not normally distributed were presented as median and interquartile range. We used the χ^2 test in the comparison of categorical data. For the comparison of quantitative data with normal distributions we used the *t* test for independent variables. For quantitative data that were not normally distributed we used the Mann-Whitney *U* test. The significance level was defined as 5% ($P < .05$).

RESULTS

A total of 241 consecutive patients who were hospitalized with an acute stroke and were eligible to take part in the study were recruited. All had to sign a consent form before enrolment. Frank's sign was present in 190 patients (78.8%) (Table 1). Patients were divided according to clinical findings and the findings on brain computed tomography. There were 153 patients with transient ischemic attack (63.6% of the patients) and 88 with cerebrovascular accident (36.4% of the patients) (Table 2).

A total of 112 patients with transient ischemic attack had Frank's sign (73.2%), and 78 patients with cerebrovascular accident had Frank's sign (88.6%), with a statistically significant difference ($P < .01$) (Table 3).

Ischemic Heart Disease

In all, 66 patients admitted with an acute ischemic stroke had prior myocardial infarction. Among them, Frank's sign

was documented in 59 of 66 patients (89.3%). We found 175 patients with stroke who did not suffer from prior ischemic heart disease; 131 of them had Frank's sign (74.9%, $P < .05$) (Table 4).

Hypertension

A total of 163 patients suffered from hypertension and were admitted with an acute ischemic stroke. Among them Frank's sign was present in 142 patients (87%). We found 78 patients with stroke who did not suffer from hypertension. Among them, 48 patients had Frank's sign (61.5%, $P < .01$) (Table 5).

Type 2 Diabetes Mellitus

A total of 115 patients had type 2 diabetes mellitus. Frank's sign was present in 103 patients (87%). We found Frank's sign in 87 of 126 patients who were admitted with stroke but without type 2 diabetes mellitus (69%, $P < .01$) (Table 6).

Gender

There was no gender difference. Frank's sign was present in 97 men with stroke (81.5%) and in 93 female patients with stroke (76%, $P = .315$).

Age

There was a significant correlation between advanced age and the presence of Frank's sign. Patients with Frank's sign were older (70 ± 12.51 years), whereas patients without Frank's sign were younger (55.2 ± 14.67 years, $P < .01$).

DISCUSSION

We found that Frank's sign could predict ischemic cerebrovascular events. Patients with classic risk factors for cardiovascular events had Frank's sign at a higher frequency. We found that Frank's sign was more prevalent in patients with cerebrovascular accidents compared with patients with transient ischemic attacks. An increased rate of Frank's sign was found in patients admitted with an acute ischemic stroke and who suffered from myocardial infarction in the past. On the other hand, Frank's sign was also found in patients who did not suffer from ischemic heart disease before their present admission with stroke, a phenomenon that could represent a subclinical insidious vascular process that would lead eventually to a clinical vascular event.

Hypertension is one of the classic risk factors of atherosclerosis. Indeed we found a higher frequency of Frank's sign in patients who experienced stroke as a result

Table 1 Patients with Frank's Sign

| Variable | Number | Percentage |
|----------|--------|------------|
| Yes | 190 | 78.8 |
| No | 51 | 21.2 |
| Total | 241 | 100.0 |

of long-standing atherosclerosis. Type 2 diabetes mellitus contributed to a higher frequency of Frank's sign in patients who had stroke. There was no gender effect in the presence of Frank's sign.

We found a higher frequency of Frank's sign among older patients. Age is considered a risk factor of atherosclerosis and its different complications.

Pathophysiology of Frank's Sign

In the early 1970s through the 1980s the suggested theory of Frank's sign was poor blood supply in arteries to the earlobes, which lacked end arteries.^{19,20}

Another theory was that Frank's sign could represent a microvascular disease with loss or degeneration of elastin fibers with rupture of the elastic fibers, as was shown in biopsies from ear lobes in patients who were suffering from ischemic heart disease.⁸ Another study investigated Japanese men with Frank's sign who were suffering from metabolic syndrome. In those men shorter telomeres were found, which is indicative of accelerated aging, and an accelerated atherosclerosis.²¹ The first theory is that there is an increased prevalence of both conditions—aging and ischemic heart disease; the second theory is a common genetic background of Frank's sign and ischemic heart disease; the third theory is that there could be acquired anatomic changes in patients with cardiac disease—could indicate specific lying and sleeping forms, which cause pressure on the ear lobe, and the fourth theory is that there could be common innervation of the heart and the auricle through the vagus nerve.⁶

Frank's Sign and Ischemic Heart Disease

Many studies have considered Frank's sign as an independent risk factor for coronary heart disease. First it was described in 1973 by Frank, who described this finding in a patient with ischemic heart disease.⁶ Later it was suggested to add Frank's sign to the classic risk factors (type 2 diabetes mellitus, hypertension, and smoking) to the list of risk

Table 2 Transient Ischemic Attack (TIA) and Cerebrovascular Accidents (CVAs)

| Variable | Number | Percentage |
|----------|--------|------------|
| TIA | 153 | 63.6 |
| CVAs | 88 | 36.4 |
| Total | 241 | 100.0 |

Table 3 Presence of Frank's Sign in Patients with Transient Ischemic Attack (TIA) and Cerebrovascular Accidents (CVAs)

| Frank's Sign | TIA | CVAs | Total |
|-----------------|------|------|-------|
| Yes | | | |
| Number | 112 | 78 | 190 |
| Percentage | 73.2 | 88.6 | 78.8 |
| No | | | |
| Number | 41 | 10 | 51 |
| Percentage | 26.8 | 11.4 | 21.2 |
| Total | 153 | 88 | 241 |
| <i>P</i> < .01. | | | |

factors of ischemic heart disease.⁷ In a survey that was published describing 421 patients who experienced myocardial infarction and 421 healthy subjects were recruited as the control group, Frank's sign was found in 77% of the patients with myocardial infarction, whereas only 40% of the healthy subjects had Frank's sign. A statistically significant association was even stronger in patients with diabetic retinopathy, hypertension, and in patients of Ashkenazi descent. An earlobe biopsy from 12 patients with Frank's sign found tears in the elastic fibers and thickening of the arteries.⁸ A study that evaluated the association between coronary artery disease and Frank's sign using coronary computed tomography found that it was present in 71% of the patients with documented coronary artery disease. This study demonstrated that Frank's sign was a statistically significant predictor of the presence of coronary artery disease.⁹

In 2011 a review was published describing Frank's sign as an indicator of ischemic heart disease.¹⁰ Among 956 patients with ischemic heart disease who underwent coronary intervention catheterization the prevalence of Frank's sign was strongly associated with ischemic heart disease, mainly in patients with who had more than 4 risk factors. Patients who had Frank's sign in both ears had an increased rate of cardiovascular complications after coronary catheterization.¹¹

The association between Frank's sign and cardiovascular diseases was also studied in 2015, with 89.6% likelihood of

Table 4 Presence of Frank's Sign in Patients with Ischemic Heart Disease

| Ischemic Heart Disease | Frank's Sign | | Total |
|------------------------|--------------|------|-------|
| | Yes | No | |
| Yes | | | |
| Number | 7 | 59 | 66 |
| Percentage | 10.6 | 89.4 | 100.0 |
| No | | | |
| Number | 44 | 131 | 175 |
| Percentage | 25.1 | 74.9 | 100.0 |
| Total | 51 | 190 | 241 |
| <i>P</i> < .05. | | | |

Table 5 Presence of Frank's Sign in Patients with Hypertension

| Hypertension | Frank's Sign | | Total |
|--------------|--------------|------|-------|
| | Yes | No | |
| Yes | | | |
| Number | 21 | 142 | 163 |
| Percentage | 12.9 | 87.1 | 100.0 |
| No | | | |
| Number | 30 | 48 | 78 |
| Percentage | 38.5 | 61.5 | 100.0 |
| Total | 51 | 190 | 241 |

P < .01.

Frank's sign and coronary artery disease or peripheral vascular disease. The bilateralism of the sign was significantly higher in patients with cardiovascular events compared with the control group. Multivariate analysis showed that there is a significant correlation between Frank's sign and cardiovascular events. Cerebrovascular events alone were also significantly correlated with Frank's sign. The authors concluded that bilateral Frank's sign is independently associated with cardiovascular events in hospitalized patients. An independent correlation with ischemic stroke has also been demonstrated in this study.^{22,23}

Frank's Sign and Carotid Arteries

In 1993 Levine et al¹² examined the association between ischemic stroke and Frank's sign in a prospective study. In this study 116 patients with stroke were included and 232 healthy subjects, age and gender matched without stroke. In all participants (n = 348) Frank's sign was significantly associated with advanced age. In patients with stroke Frank's sign was correlated with ischemic heart disease and type 2 diabetes mellitus. In another study it was associated with increased intima-media thickness on multivariate regression analysis (*P* = .0001).¹³ Another study followed 60 subjects who were divided into 2 groups: group "A" with Frank's sign and group "B" without it. All subjects underwent an ultrasound scan of the carotid arteries to evaluate

Table 6 Presence of Frank's Sign in Patients with Diabetes Mellitus

| Diabetes Mellitus | Frank's Sign | | Total |
|-------------------|--------------|------|-------|
| | Yes | No | |
| Yes | | | |
| Number | 12 | 103 | 115 |
| Percentage | 10.4 | 89.6 | 100.0 |
| No | | | |
| Number | 39 | 87 | 126 |
| Percentage | 31.0 | 69.0 | 100.0 |
| Total | 51 | 190 | 241 |

P < .01.

the intima-media thickness. Frank's sign was associated with increased intima-media thickness with a sensitivity of 73% and a specificity of 70%; both represent the progressive atherosclerotic process leading eventually to ischemic stroke.¹⁴

In 2009 Shrestha et al¹⁵ studied the correlation between carotid atherosclerotic changes and diagonal earlobe crease in Japanese patients. The addition of "plaque score" and "plaque numbers" to the regular intima-media thickness measurement created a more reliable and sensitive test to detect atherosclerosis. Frank's sign in those patients was significantly associated with these indices and the development of accelerated atherosclerosis.¹⁵

Frank's Sign and Peripheral Vascular Disease

The prevalence of Frank's sign was significantly higher among 60 men with peripheral artery disease compared with 60 men without peripheral arterial disease. This difference remained statistically significant after adjusting for risk factors for atherosclerosis.¹⁷

Arterial stiffness has been proposed as a tool by the European Society of Hypertension/European Society of Cardiology for the evaluation of subclinical damage to target organs and is considered a measure of atherosclerosis. In 2013 a study examined the relationship between Frank's sign and vascular stiffness by measuring the cardio-ankle vascular index, which reflects the stiffness of blood vessels. In the study 75 patients with Frank's sign were recruited, versus 75 patients adjusted for age and gender who were admitted to the cardiac clinic. In patients with Frank's sign the cardio-ankle vascular index was higher, with a statistically significant difference compared with patients without Frank's sign.¹⁸

Korkmaz et al¹⁹ studied 253 patients without peripheral vascular disease. In these patients the ankle-brachial index (ABI) was measured. In patients with Frank's sign a lower ABI was measured compared with patients without Frank's sign (*P* < .001). Multivariate analysis of the data found that Frank's sign and advanced age were independent factors for abnormal ABI. The patients were divided into 4 groups according to the severity of the disease by ABI. They found increased incidence of Frank's sign associated with increasing severity of the disease.

CONCLUSION

Frank's sign is a sign found in the physical examination that predicts ischemic stroke independently and is found in patients with high risk of developing ischemic stroke even in the absence of ischemic heart disease. It is more common in older age, higher in the presence of cardiovascular risk factors such as hypertension and diabetes, and more frequent in the presence of a previous myocardial infarction or ischemic heart disease. Adding Frank's sign to the list of classic risk factors for the development of ischemic heart disease and stroke in the future should be considered.

References

1. Singh RB, Niaz MA, Agarwal P, Beegum R, Rastogi SS, Singh NK. Epidemiologic study of central obesity, insulin resistance and associated disturbances in the urban population of North India. *Acta Cardiol.* 1995;50:215-225.
2. Jarauta E, Junyent M, Gilabert R, et al. Sonographic evaluation of Achilles tendons and carotid atherosclerosis in familial hypercholesterolemia. *Atherosclerosis.* 2009;204(2):345-347.
3. Marang-van de Mheen PJ, van Maarle MC, Stouthard ME. Getting insurance after genetic screening on familial hypercholesterolaemia: the need to educate both insurers and the public to increase adherence to national guidelines in The Netherlands. *J Epidemiol Community Health.* 2002;56:145-147.
4. Kee F, Nicaud V, Tiret L, Evans A, O'Reilly D, De Backer G. Short stature and heart disease: nature or nurture? The EARS Group. *Int J Epidemiol.* 1997;26:748-756.
5. Trieu N, Eslick GD. Alopecia and its association with coronary heart disease and cardiovascular risk factors: a meta-analysis. *Int J Cardiol.* 2014;176(3):687-695.
6. Frank ST. Aural sign of coronary artery disease. *N Engl J Med.* 1973;289:327-328.
7. Frank ST. Ear crease sign of coronary artery disease. *N Engl J Med.* 1977;297:282.
8. Shoenfeld Y, Mor R, Weinberger A, Avidor A, Pinkhas A. Diagonal ear lobe crease and coronary risk factors. *J Am Geriatr Soc.* 1980;28:184-187.
9. Shmilovich H, Cheng VY, Rajani R, et al. Relation of diagonal ear lobe crease to the presence, extent, and severity of coronary artery disease determined by coronary computed tomography angiography. *Am J Cardiol.* 2012;109(9):1283-1287.
10. Ohry A. Physical diagnosis: diagonal earlobe crease and atheromatous coronary. [in Hebrew]. *Harefuah.* 2011;150(3):264-265, 303, 302.
11. Hou X, Jiang Y, Wang N, et al. The combined effect of ear lobe crease and conventional risk factor in the diagnosis of angiographically diagnosed coronary artery disease and the short-term prognosis in patients who underwent coronary stents. *Medicine (Baltimore).* 2015;94(26):e815.
12. Levine RL, Daly RF. Diagonal earlobe creases and ischemic stroke: preliminary report. *J Stroke Cerebrovasc Dis.* 1993;3(2):106-111.
13. Celik S, Erdogan T, Gedikli O, Kiris A, Erem C. Diagonal ear lobe crease is associated with carotid intima-media thickness in subjects free of clinical cardiovascular disease. *Atherosclerosis.* 2007;192(2):428-431.
14. Glavic J, Cerimagic D, Lovrencic-Huzjan A, Vukovic V, Demarin V. Frank's sign as a risk factor for cerebrovascular disease. *Atherosclerosis.* 2008;196(1):477-478.
15. Shrestha I, Ohtsuki T, Takahashi T, Nomura E, Kohriyama T, Matsumoto M. Diagonal ear-lobe crease is correlated with atherosclerotic changes in carotid arteries. *Circ J.* 2009;73(10):1945-1949.
16. Friedlander AH. Association between clinically identified diagonal ear lobe crease and panoramic radiographs evidencing calcified carotid artery atheromas: preliminary observations. *J Oral Maxillofac Surg.* 2010;68:227.
17. Ramos PM, Gumieiro JH, Miot HA. Association between ear creases and peripheral arterial disease. *Clinics.* 2010;65(12):1325-1327.
18. Korkmaz L, Ağaç MT, Erkan H, et al. Association between diagonal earlobe crease and cardio-ankle vascular index in asymptomatic hypertensive patients. *Med Princ Pract.* 2013;22:530-534.
19. Korkmaz L, Ağaç MT, Acar Z, et al. Earlobe crease may provide predictive information on asymptomatic peripheral arterial disease in patients clinically free of atherosclerotic vascular disease. *Angiology.* 2014;65(4):303-307.
20. Takahiko T, Izumi I, Yasuo K, Gen T. Histological study on the earlobe crease. [in Japanese]. *Skin Res.* 1982;24(3):352-360.
21. Higuchi Y, Maeda T, Guan JZ, Oyama J, Sugano M, Makino N. Diagonal earlobe crease are associated with shorter telomere in male Japanese patients with metabolic syndrome. *Circ J.* 2009;73:274-279.
22. Smith SW, Johnson SC, hemphill JC. Cerebrovascular Diseases. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Localzo J, eds. *Harrison's Principles of Internal Medicine.* 19th ed. chapter 446. New York, USA: McGraw Hill Education; 2017: 2561-2568.
23. Rodríguez-López C, Garlito-Díaz H, Madroñero-Mariscal R, et al. Earlobe crease shapes and cardiovascular events. *Am J Cardiol.* 2015;116(2):286-293.