Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 9: 1–4

DOI: 10.1177/2050313X211056419
journals.sagepub.com/home/sco
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Left atrial appendage thrombosis in a patient with Friedreich Ataxia–related cardiomyopathy, left ventricular systolic dysfunction, and atrial fibrillation

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Abstract

Friedreich ataxia is the most common form of hereditary ataxia. Heart involvement in Friedreich ataxia is common and can include increased left ventricular wall thickness, atrial fibrillation, and in the later stages, a reduction of left ventricular ejection fraction. We present the case of a 45-year-old man with a history of paroxysmal atrial fibrillation and a congestive heart failure, hypertension, age ⩾ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, and female sex (CHA2DS2-VASc) score of only 1 (because of reduced left ventricular ejection fraction) who presented with pneumonia and was also found to have atrial fibrillation with a rapid ventricular response. Despite already being on long-term therapy with a non-vitamin K-antagonist oral anticoagulant, a transesophageal echocardiogram showed a mobile floating thrombus in the left atrial appendage. In accordance with previous necropsy evidence of thrombosis and thromboembolism in Friedreich ataxia subjects who likely have had only non-sex-related CHA2DS2-VASc score ⩽1, this case suggests that the risk of thromboembolism in Friedreich ataxia subjects with atrial fibrillation may not be adequately predicted by the sole CHA2DS2-VASc score.

Keywords

Friedreich ataxia, cardiomyopathy, atrial fibrillation, thrombosis, oral anticoagulation

Date received: 26 May 2021; accepted: 12 October 2021

Introduction

Friedreich ataxia (FRDA) is an autosomal recessive multisystem disorder, characterized by prominent spinocerebellar degeneration.[1] It represents the most common autosomal recessive ataxia in Europe.[2] A homozygous GAA repeat expansion in the frataxin gene is considered the cause of the disease in the majority of cases.[1]

Patients with FRDA usually present heart involvement with particular cardiac structural abnormalities.[3,4] In detail, different echocardiographic patterns have been described in FRDA-related cardiomyopathy (FRDA-CM), ranging from symmetrical or asymmetrical hypertrophic patterns to dilated cardiomyopathy.[3] Left ventricular (LV) systolic dysfunction has been frequently observed in the later stages of the disease. Indeed, Weidemann et al.[5] suggested that a left ventricular ejection fraction (LVEF) lower than 50% may be considered as a criterion of severe FRDA-CM. Atrioventricular conduction blocks and atrial arrhythmias such as atrial flutter and atrial fibrillation (AF) have also been reported.[3] Congestive heart failure and arrythmias are common causes of cardiac-related death in FRDA population.[3] In particular, cardiac death was found to represent the most important cause of death in patients with FRDA,[3,6] while stroke mortality associated with AF or mural thrombus accounted for 6.6% of all deaths in patients with FRDA.[3,6]

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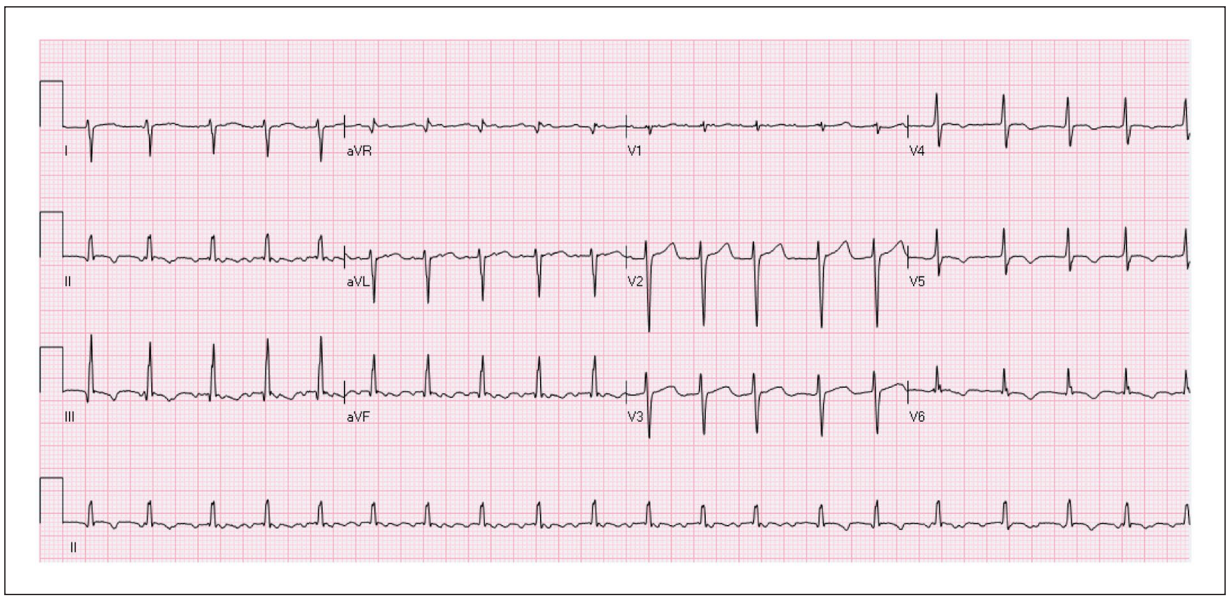

Figure 1. High ventricular response atrial fibrillation (AF) on admission electrocardiogram. Patient's electrocardiogram on admission showed AF with a high ventricular response and diffuse T-waves abnormalities. Electrocardiogram paper speed: 25 mm/s.

Current European guidelines recommend to start oral anticoagulation (OAC) for cerebrovascular events prevention in patients with AF with a CHA2DS2-VASc (congestive heart failure, hypertension, age ⩾ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, and female sex) score ⩾ 2 for men and ⩾ 3 for women, while OAC should be considered in patients with AF and CHA2DS2-VASc score of 1 in men and 2 in women.[7,8] Currently, only few data are available about the best timing to start OAC in patients with AF and FRDA. Hence, we describe the clinical case of a patient with FRDA-CM, LV systolic dysfunction, and AF with CHA2DS2-VASc score of only 1 (due to LVEF reduction) on long-lasting non-vitamin K-antagonist oral anticoagulant (NOAC) therapy, showing left atrial appendage thrombosis (LAA) on transoesophageal echocardiogram (TOE) examination.

Case presentation

The patient gave written informed consent for his case publication in line with the Commitee on Publication Ethics (COPE) best practice guidelines. A 45-year-old man with FRDA was admitted to our hospital for infectious pneumonia and high ventricular rate AF. FRDA-related symptoms began at the age of 12 years with gait difficulties due to lower limbs ataxia and rigidity progressing over time, so that the patient became wheelchair bound at the age of 27 years. The diagnosis of FRDA was performed shortly after the onset of neurological symptoms through genetic testing, showing pathological homozygous GAA trinucleotide repeat expansion in the *FXN* gene. FRDA-CM with septal asymmetrical hypertrophic pattern was diagnosed at the age of 35 years. In addition, the patient had history of two episodes of symptomatic AF (both occurring 3 years before current admission). Transthoracic echocardiogram performed at the time of the first AF episode showed reduction of LVEF (LVEF = 42%). Neither cardiovascular risk factors and vascular disease nor previous cerebrovascular events were reported. CHA2DS2-VASc score was of 1 point (due to reduced LVEF);[8] CHADS2 (congestive heart failure history, hypertension history, age ⩾ 75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously) score was also of 1 point.[9] Apixaban 5 mg twice daily and metoprolol were started 3 years before with a good adherence to treatment.

Currently, the patient presented to our emergency department (ED) with fever and palpitations. Blood pressure was in the normal range, while electrocardiogram (ECG) showed high ventricular rate AF (Figure 1). Due to shortness of breath associated with an increase in inflammatory markers, a chest X-ray was obtained revealing a pattern of interstitial pneumonia. Nasopharyngeal swab testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was negative. Cardiological examinations showed tachycardic and arrhythmic heart sounds, systolic heart murmur on auscultation position for mitral valve, absence of lung rales, and no peripheral edema. Neurological examination showed moderate dysarthria, gaze-evoked nystagmus, upper and lower limbs ataxia and dyssynergia, absent vibration, and joint position sense bilaterally. There was severe spastic paraparesis with absent lower limbs tendon reflexes and bilateral extensor plantar responses. The patient was admitted to the hospital, and pneumonia was effectively treated with antibiotics administration for 10 days, achieving a complete resolution of the infectious process. OAC was continued during the entire hospitalization. A transthoracic echocardiography showed septal hypertrophy (septal LV

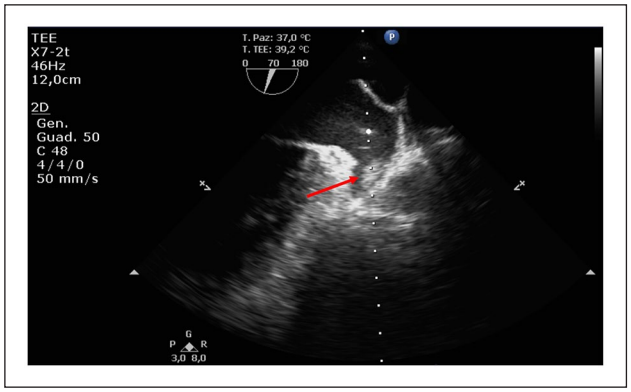

Figure 2. Left atrial appendage (LAA) thrombus on transoesophageal echocardiogram (TOE). TOE performed during hospital stay showed a mobile thrombus (4 mm × 4 mm) floating in the center of LAA (*red arrow*), contraindicating electrical cardioversion.

wall thickness = 13 mm) without LV outflow tract obstruction, no LV dilation, moderate reduction of LV systolic function (LVEF = 40%), moderate diastolic dysfunction, and moderate left atrium dilation. Considering the persistence of a high ventricular rate despite the treatment of infectious pneumonia and beta-blockers titration with metoprolol (up to an oral dose of 100 mg twice daily), electrical cardioversion was proposed. Preliminary TOE revealed severe LAA smoke effect, low LAA velocity (<20 cm/s), and a mobile floating thrombus (4 mm × 4 mm) in the center of LAA, contraindicating electrical cardioversion (Figure 2). A low oral dose of digoxin was added (0.0625 mg per day), achieving a satisfactory heart rate control, and apixaban was replaced with rivaroxaban 20 mg once a day. The patient was discharged in good clinical conditions and without symptoms. Upon clinical follow-up after 3 months, the patient was asymptomatic, normal sinus rhythm was restored on follow-up ECG, and neither cardioembolic events nor major bleedings occurred.

Discussion

We reported a case of LAA thrombosis in a patient with FRDA-CM, LV systolic dysfunction, and AF. It is important to note that our patient (1) had low CHA2DS2-VASc and CHADS2 scores (both of 1 point) and (2) was on chronic NOAC treatment.

FRDA-CM can be detected in the largest portion of patients with FRDA throughout their lives.[3] In FRDA, frataxin protein mutations disrupt mitochondrial metabolism, increasing reactive oxygen species, and inducing iron redistribution with secondary mitochondrial proliferation. Iron-induced inflammation may also play a role.[3] Mitochondrial proliferation, together with the loss of contractile proteins and subsequent myocardial fibrosis, may be responsible for the thickening of LV walls and for the occurrence of typical structural cardiac alterations.[3]

Cases of cerebrovascular thromboembolism as well as intracardiac thrombosis in young patients with FRDA have been previously reported,[10,11] as well as the occurrence of atrial tachyarrhythmias.[3,12] A milestone ex vivo histopathology study examining hearts from 27 patients with FRDA showed that all cases had conspicuous muscle fiber hypertrophy and interstitial fibrosis; authors also found thrombi in the atria of patients with AF and both enlarged and normal sized LVs. In one case, death was directly caused by cerebral embolism.[11] According to available data from the above-mentioned study,[11] patients with AF and atrial thrombosis likely have had non-sex-related CHA2DS2-VASc scores ⩽ 1.[11] Of note, the only case of cardioembolic stroke in the prospective series of patients with FRDA by Biller et al.[13] (n = 4, mean age: 15 years old) occurred in the presence of both FRDA-CM and AF. Moreover, Pousset et al.[12] followed patients with FRDA for a longer follow-up period (mean follow-up of 10.5 years) and found that 8 out of 133 patients with FRDA (mean age: 31 years old) died for cardiovascular causes, including 2 cases of cardioembolic stroke in the context of progressive heart failure and AF.

Correct timing to start OAC in patients with FRDA and AF is uncertain. 2014 FRDA guidelines suggest that OAC with warfarin or NOAC should be considered in AF if one CHADS2 risk factor is present and is generally indicated if more than one CHADS2 risk factor is present. They also strongly recommend anticoagulation in AF if there is reduced LVEF, although few evidences supporting these recommendations are currently available (level of evidence: C).[14] Latest guidelines on progressive ataxias recommend to consider pharmacological treatment (including the use of OAC) in patients with FRDA with cardiac involvement (level of evidence: good practice point (GPP)).[15] In our case, we observed the presence of LAA thrombosis in a patient with FRDA with AF, FRDA-CM with LV systolic dysfunction, and low thrombotic risk scores. First AF episode in our patient occurred at the age of 42 years, and he did not present any cardiovascular risk factors included in CHA2DS2-VASc score, neither vascular diseases nor prior cerebrovascular events. Therefore, our clinical case may suggest that currently recommended scores (CHA2DS2-VASc score, CHADS2 score) may not be reliable in the prediction of thromboembolic events in patients with FRDA with AF, thus corroborating prior necroscopy findings.[11] The younger age of AF occurrence and the peculiar myocardial abnormalities in patients with FRDA may represent a possible explanation. Anyway, LV systolic dysfunction per se may represent a relevant thrombotic risk factor in patients with FRDA with AF. Indeed, FRDA guidelines recommend to start OAC in patients with FRDA with AF and cardiomyopathy with reduced LVEF, irrespective of thrombotic risk scores.[14]

Finally, it is interesting to note that in our patient LAA thrombosis occurred while he was in long-lasting treatment with NOAC. This event may have different explanations: (1) ineffective anticoagulation despite appropriate NOAC

intake; (2) thrombus development before starting anticoagulation without thrombus lysis after NOAC assumption; and (3) poor patient's adherence to anticoagulation therapy (whereas in our case adherence to treatment was appropriate). Therefore, it was not possible to individuate with certainty the exact mechanism leading to atrial thrombosis. Regarding the efficacy of NOAC in patients with FRDA with AF, FRDA guidelines suggest the potential use of both NOACs and warfarin in patients with FRDA with AF for prevention of systemic thromboembolism,[14] although different anticoagulation regimens have not been extensively studied in FRDA.

Conclusion

In conclusion, we report a case of subclinical LAA thrombosis in a patient with FRDA-CM with LV systolic dysfunction and AF with a low CHA2DS2-VASc score. In agreement with previous autopsy studies showing intracardiac thrombosis in patients with FRDA with non-sex-related CHA2DS2-VASc score $\leqslant 1$, our clinical case suggests that the risk of systemic thromboembolism in subjects with FRDA with AF may not be adequately predicted by the CHA2DS2-VASc score.

Acknowledgements

We thank Dr Andrea Uva (S. Maria delle Croci Hospital of Ravenna) for his help in manuscript revision and English language edit.

Author contributions

M.R. developed the concept, acquired and interpreted the data, prepared the original draft of the manuscript, and approved the final manuscript. A.N., M.F., S.B., S.L., C.T., and P.Q. developed the concept, interpreted the data, performed major revision of the manuscript, and approved the final manuscript. A.R. developed the concept, acquired and interpreted the data, supervised the study, performed major revision of the manuscript, and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical disclosure

The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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