Neurological Sciences (2024) 45:5947–5949
https://doi.org/10.1007/s10072-024-07799-9

LETTER TO THE EDITOR

Ischemic stroke despite direct oral anticoagulation: what is hidden?

A. De Martino[2] · V. Andreone[1] · I. Mormile[3] · F.W Rossi[1] · Giorgia Teresa Maniscalco[1,2,3]

Received: 11 May 2024 / Accepted: 3 October 2024 / Published online: 28 October 2024

Introduction

Cardioembolism due to non-valvular atrial fibrillation (AF) accounts for about 13–26% of ischemic stroke etiology. Prophylactic anticoagulation treatment (whether direct oral anticoagulants, DOAC, or vitamin K antagonists) was demonstrated able to lower the risk of ischemic stroke in this category of patients. Nevertheless, the risk of stroke, despite treatment, ranges from 0.7% in patients in primary prevention to 2.3% in those in secondary prevention [1].

To date, little data is available in literature about stroke occurring in patients with ongoing oral anticoagulation therapy. Most of these studies were conducted on patients affected by AF treated with oral anticoagulants [1]. In a recent analysis of 2946 patients, 1674 treated with direct oral anticoagulants (DOAC) and 1272 in vitamin K-antagonists (VKA), the most common failure mechanism was cardioembolism, followed by poor adherence or insufficient anticoagulant dose and presence of competing mechanisms (large artery atherosclerosis, small vessel disease, coagulopathy, peri-interventional stroke endocarditis, other cardioaortic causes, cervical artery dissection and vasculitis) [1]. We hereby report a rare case of stroke occurring in a young woman on DOAC treatment.

Case report

A 37-years-old female was admitted to the Stroke Unit of "Antonio Cardarelli" Hospital of Naples (Italy) for a sudden onset of difficult in speech. Her medical history revealed chronic anemia, obesity (BMI 30.9 kg/m^2), chronic wrist and finger joint pain and an episode of deep vein right femoral vein thrombosis occurred 6 months earlier (a complete thrombotic panel was not available at the moment), for which she was prescribed with oral Endoxaban 60 mg. Neurological examination showed poor speech production and paraphasia, with intact comprehension, consistent with motor aphasia. Emergency head CT scan showed a mild left frontal cortical-subcortical area of hypodensity consistent with an acute ischemic stroke. CT angiography highlighted the occlusion of the distal left middle cerebral artery (M3-M4 tract) without signs of large vessel occlusion or atherosclerosis. Magnetic Resonance Imaging (MRI) disclosed an increased diffusion weight image (DWI) signal (Fig. 1A) with a corresponding reduction of apparent diffusion coefficient (ADC) value (Fig. 1B), and Fluid Attenuated Inversion Recovery (FLAIR) hyperintensity in the left frontal area (Fig. 1C), confirming the diagnosis of acute ischemic stroke. Due to the ongoing anticoagulation therapy and the (M3-M4) site of occlusion, the patient was not eligible for recanalization treatment. DOAC therapy was suspended and high dose of acetylsalicylic acid (300 mg/die) was introduced. She underwent a full blood panel which showed low red blood cells (3.08×10^6/uL) and platelets (59×10^3/uL) counts, low hemoglobin (10.1 g/dL) and hematocrit (27.6%) level, with increased mean corpuscular volume (101.5 fL). Autoimmune blood test screening revealed positive antinuclear antibody (ANA), at a titer of 1:640, (n.v. <1:80) with homogeneous pattern, high antiextractable nuclear antigen (ENA) (6.6 U/mL n.v. <0.7), anti B2-glicoproteine1 (aβ2GP1) IgG (9.7 UI/mL, n.v. <10) and IgM (432 UI/mL, n.v. <10 UI/mL), anti-double stand DNA (347 U/mL, n.v. <15 UI/mL) and anti-cardiolipin antibodies (ACA), (344 U/mL, n.v. <15). Positive lupus anticoagulant antibodies (LAC) were also found. Complement level (C3: 0.38 g/L,

✉ Giorgia Teresa Maniscalco
gtmaniscalco@libero.it

1 Neurological Clinic and Stroke Unit and Multiple Sclerosis Center, "A. Cardarelli" Hospital, Via A. Cardarelli, 9, Naples 80131, Italy

2 Neurological department, Maria SS. Addolorata Hospital, ASL Salerno, Eboli, SA, Italy

3 Department of Translational Medical Sciences, University of Naples Federico II, Naples 80131, Italy

n.v. 0.9–1.8; C4: 0.02 g/L, n.v. 0.1–1.40) were low. Anti-Cardiolipine antibodies were normal. Infectious screening was negative. In the suspect of systemic involvement, a Total body CT was performed to rule out both neoplastic disease responsible for thrombosis and systemic conditions; the exam revealed pleural effusion and enlarged spleen with ischemic signs. Cardiological evaluation and echocardiography showed pericardial effusion and hyperechoic formation in correspondence of the tricuspid valve suggestive of Libman-Sacks endocarditis. We therefore concluded for a diagnosis of ischemic stroke due to antiphospholipid syndrome (aPS) associated to systemic lupus erythematosus (SLE). Due to the progressive worsening of thrombocytopenia, we administered an intravenous bolus of methylprednisolone 500 mg/die for 5 days with an increase in platelet count. Speech also gradually improved during hospitalization. At discharge, acetylsalicylic acid was replaced with VKA. After 4 months antiphospholipid antibodies were retested to confirm the diagnosis of aPS: LAC antibodies and aβ2GP1 IgM were still positive.

Discussion

Herein we report a rare case of ischemic stroke occurring despite DOAC treatment in a young woman affected by SLE complicated by aPS. Antiphospholipid syndrome represents a disease spectrum characterized by venous, arterial and/or microvascular thrombotic events and/or abortion history in the context of persistently positive antiphospholipid antibodies (aPL) [2]. Diagnosis of aPS requires the evidence of persistent aPL: LAC, aβ2GP1 (IgG and/or IgM) and ACA presence on two or more occasions at least 12 weeks apart, in addition to a history of venous and arterial thrombotic events or recurrent abortions. Thrombocytopenia, neurological involvement, and livedo reticularis represent further clinical manifestations [2]. Antiphospholipid syndrome also complicates up to one-third of cases of SLE, with subsequent poor prognosis. Strokes can occur in 2–19% of SLE patients and this risk significantly increases when aPL are present, mainly within the first year after diagnosis. In particular, the presence of LAC antibodies is associated with large cerebral artery thrombosis [3]. The exact mechanism leading to the ischemic event is still unknown. It has been hypothesized that aPL could activate procoagulant factors through the activation of proinflammatory cells, including endothelial cells, monocytes, neutrophils, and platelets leading to cytokines release and suppression of physiological anticoagulant systems. Antiphospholipid antibodies, particularly β2GP1, are thought to induce neutrophils to release prothrombotic neutrophil extracellular traps (NETs), that can activate platelets and endothelial cells. Moreover, aPL seem to interfere directly with protein C and S activity [1]. In SLE patients direct cardiologic involvement represents an additional risk factor. Indeed, sterile fibrinous heart valve vegetation characterizing Libman-Sacks valvular lesion, could dislocate and cause a stroke event. Additionally, SLE-associated cerebral vasculitis could represent another risk factor for stroke, especially in the late disease course [3].

DOAC use to prevent cardioembolism in patients with AF is widely accepted. Our patient presented a single episode of deep venous thrombosis. Anticoagulation treatment after deep venous thrombosis is used to prevent the extension and the recurrence of thrombosis, and to reduce risk of complications such as pulmonary embolism or paradoxical embolism (in the presence of a patent foramen ovale) but specific treatments depend on the etiopathogenesis underlying the thrombotic event. DOAC treatment in APS is still debated. Current evidence is scarce and conflicting. Hence, there is no full agreement between the various society guidelines. The 2019 European Society of Cardiology (ESC) guidelines do not recommend DOAC use in aPS patients but do not take into consideration the role of the different antibody profiles (double or triple aPL positivity) or DOAC type in the decision-making process. International Society on Thrombosis and Haemostasis (ISTH) British Society of Haematology (BSH) and American Society of Hematology (ASH) guidelines suggest avoiding DOAC in aPS. Of note, in the case of patients already undergoing DOAC treatment, ISTH suggests continuing treatment only for patients without high-risk factor (i.i.e, patients without triple antibodies positivity, arterial thrombosis, small vessel thrombosis, organ involvement or heart valve disease). Similarly, European League Against Rheumatism (EULAR) guidelines published in 2019 suggest VKA prescription stating that DOAC must be considered only in case of intolerance to VKA or difficulty in maintaining therapeutic INR range. Finally, DOAC treatment is not suggested to prevent venous thromboembolic events in aPS patients [4]. A recent meta-analysis demonstrated an elevated risk of recurrent arterial thrombosis in APS patients treated with DOAC without increased incidence of venous thromboembolic events. The authors suggest that it is possible to use DOAC therapy in the cases of non-triple positive aPL patients and concomitant absence of previous arterial thrombosis [5]. Several hypotheses have been proposed to explain why DOAC treatment may be inadequate in aPS: one of the most widely accepted theories is that VKAs inhibit a broader range of coagulation factors compared to DOACs [4]. Despite a double antibody positivity, our patient was classified as a high-risk individual, due to her history of venous thrombosis and the diagnosis of SLE with signs of cardiovascular involvement. According to the above guidelines, DOAC therapy was interrupted, and she started VKA

treatment. Moreover, the multi-organ involvement led = to suspicion of a catastrophic antiphospholipid antibody syndrome (CAPS) which can complicate an APS to the point of multi-organ failure. This dramatic condition develops within a few days and can lead to the patient's death. However, our patient does not meet al.l the criteria for CAPS because the clinical course of several weeks and the primary involvement of large vessels make this diagnosis unlikely. In case of suggestive CAPS symptoms or recurrence of APS manifestations, chronic immunosuppressive treatments such as anti-CD20, hydroxychloroquine or eculizumab may be indicated. Nevertheless, a treatment with corticosteroids was administered to reduce the patient's systemic inflammatory state resulting in a gradual improvement of symptoms and laboratory parameters.

Conclusion

This case highlights the importance of extensive clinical evaluation in patients presenting with ischemic stroke despite DOAC therapy. Furthermore, deep venous thrombosis without clear underlying causes can be considered a red flag for systemic involvement that needs to be carefully investigated. Of note, autoimmune disorders, including aPS, should be suspected in case of recurrent thrombotic events and stroke in young patients on DOAC. Patients with SLE and APS carry a higher risk of cerebrovascular disease and, particularly triple positive aPL subjects, require ad hoc treatment with VKA according to the current expert committees of international societies. Further longitudinal studies including data from the international registry of individuals with aPS and a more precise risk stratification may help optimize the therapeutic approach to these patients.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability Data are available upon reasonable request.

Declarations

Ethics approval The study was approved by the local ethical committee.

Conflict of interest None

References

1. Polymeris AA, Meinel TR, Oehler H et al (2022) Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. J Neurol Neurosurg Psychiatry 93(6):588–598. https://doi.org/10.1136/jnnp-2021-328391
2. Garcia D, Erkan D (2018) Diagnosis and management of the Antiphospholipid Syndrome. N Engl J Med 379(13):1290. https://doi.org/10.1056/NEJMc1808253
3. El Hasbani G, Uthman I (2023) Lupus, antiphospholipid syndrome, and stroke: an attempt to crossmatch. Lupus 32(5):593–602. https://doi.org/10.1177/09612033231165151
4. Pastori D, Menichelli D, Cammisotto V, Pignatelli P (2021) Use of direct oral anticoagulants in patients with antiphospholipid syndrome: a systematic review and comparison of the International guidelines. Front Cardiovasc Med 8:715878. https://doi.org/10.3389/fcvm.2021.715878
5. Dufrost V, Wahl D, Zuily S (2021) Direct oral anticoagulants in antiphospholipid syndrome: Meta-analysis of randomized controlled trials. Autoimmun rev 20(1):102711. https://doi.org/10.1016/j.autrev.2020.102711