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Primary antiphospholipid syndrome in the elderly: Four strokes and mechanical thrombectomies until the diagnosis - A case report

Anatoli Anastasiadi[1], Chiara Bott[1], Daniel Kitterer[2], Elke Roser[3], Hans Henkes[4], Hansjörg Bäzner[1,5], Marc E. Wolf[1,5]

Abstract:

Antiphospholipid syndrome (APS) is known as a rare etiology of embolic ischemic stroke. In individuals below 50 years, up to 20% of strokes are associated with APS, whereas in patients >50 years, it is considered a very seldom cause of stroke. We describe the course of a 66-year-old white woman, who experienced four embolic strokes with large vessel occlusion over a period of 2 years, which were repeatedly and successfully treated by mechanical thrombectomy. Initially attributed to atrial fibrillation and treated with direct oral anticoagulants, the patient was finally diagnosed with primary APS due to isolated anti-beta 2-glycoprotein antibodies and successfully treated after several stroke recurrences. After initiation of Vitamin K antagonist therapy, no further strokes occurred. For recurrent embolic stroke despite oral anticoagulation, late-onset APS might be considered a rare etiology also in the elderly.

Keywords:

Antiphospholipid syndrome, etiology, mechanical thrombectomy, stroke

Introduction

Antiphospholipid syndrome (APS) is considered a relevant cause of embolic ischemic stroke (IS) in young patients,[1] particularly in women with previous pregnancy loss.[2] Patients often present with secondary APS with the background of autoimmune diseases such as systemic lupus erythematosus.[3] Screening for APS is generally recommended in patients ≤60 years of age with cryptogenic embolic IS.[4]

In older patients >60 years of age, extensive screening for coagulopathies in embolic IS is not routinely performed, because cardioembolism is fairly common; therefore, the detection of (paroxysmal) atrial fibrillation (AF) is the goal in subjects suffering an embolic stroke of undetermined source (ESUS). However, rare cases of APS in the elderly have been reported and in cases of recurrent embolic IS, the etiology should be critically reviewed.[5]

Case Report

A 66-year-old white woman sought help in our emergency room with acute nonfluent aphasia (NIHSS score 2). She had a previously known type 2 diabetes mellitus, and Multiple endocrine neoplasia (MEN) type 1 syndrome (chronic autoimmune thyroiditis, bilateral adrenal adenomas, and chronic pancreatitis with chronic diarrhea), diverticulitis, peptic ulcers, and gastroesophageal reflux disease I. Imaging showed

Departments of [1]Neurology, [2]Nephrology, [3]Cardiology and [4]Neuroradiology, Klinikum Stuttgart, Katharinen Hospital, Stuttgart, [5]Neurologische Klinik, Medizinische Fakultät Mannheim, Universität Heidelberg, Germany

Address for correspondence:
Prof. Dr. Marc E. Wolf, Department of Neurology, Klinikum Stuttgart, Katharinen Hospital, Kriegsbergstraße 60, 70174 Stuttgart, Germany.
E-mail: ma.wolf@klinikum-stuttgart.de

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an acute occlusion of the left middle cerebral artery (MCA) in the M1 segment with good collateral vascularization [Figure 1, index stroke]. Mechanical thrombectomy (MTE) was performed with an excellent result (NIHSS 0, modified Rankin scale (mRS) 0 at discharge). A standardized etiologic IS work-up was not conclusive and an ESUS was retained. In the meantime after discharge, the patient was diagnosed with paroxysmal AF, and medication with the direct oral anticoagulant (DOAC) Rivaroxaban was initiated. The patient was subsequently perfectly compliant regarding the regular intake of the medication in

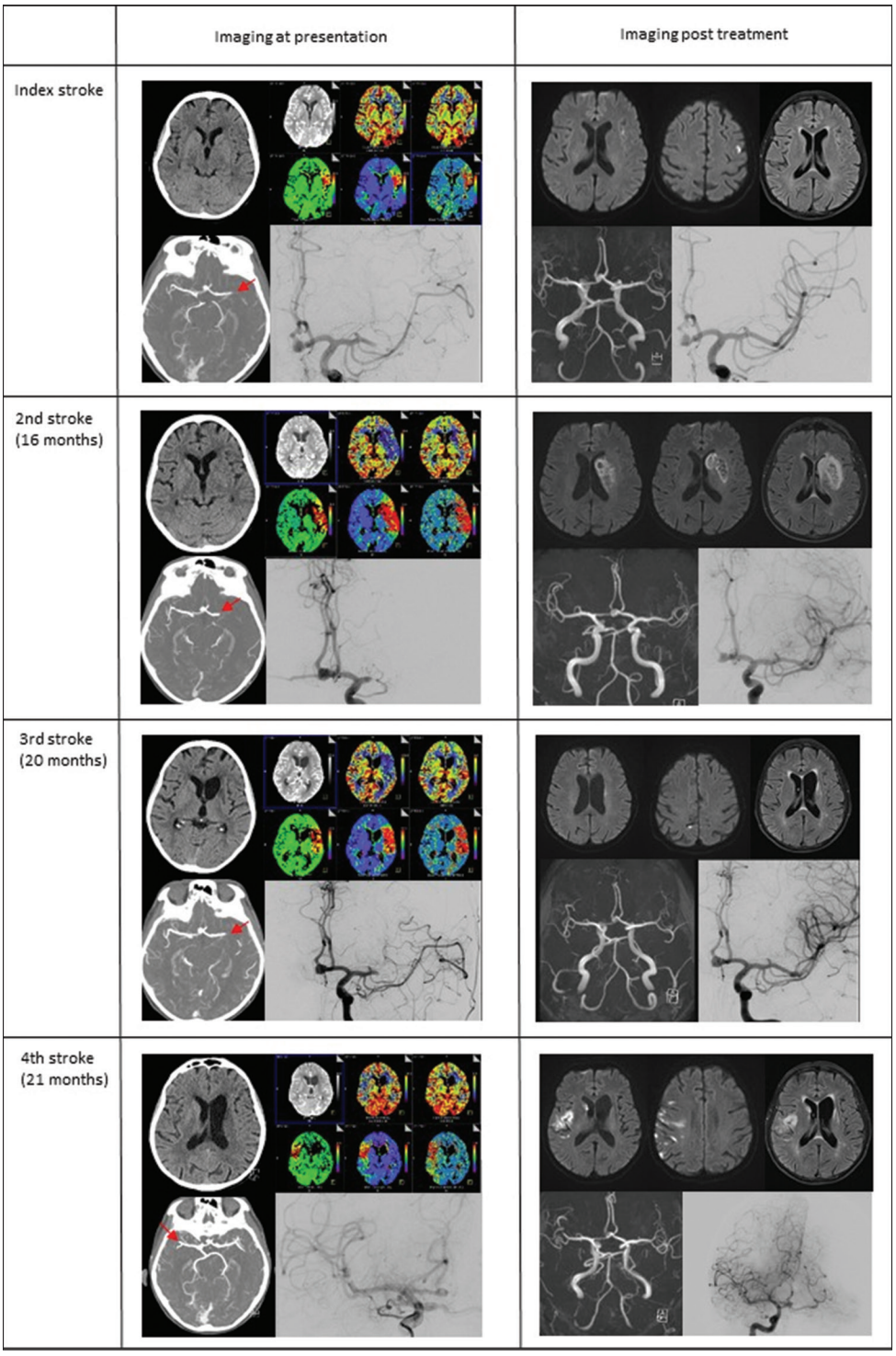

Figure 1: Imaging findings at admission and postmechanical thrombectomy in woman with 4 recurrent ischemic strokes due to primary antiphospholipid syndrome. Left box: Upper left: Native computed tomography (CT); lower left: CT angiography (red arrows indicate the large vessel occlusion); upper right: CT perfusion; lower right: Conventional digital subtraction angiography (DSA), Right box: Upper row: Diffusion-weighted magnetic resonance imaging; lower left: Time-of-flight-magnetic resonance-angiography; lower right: Conventional DSA

combination with food as recommended to ensure full bioavailability.

Sixteen months later, she presented again at our emergency room with global aphasia and hemiparesis on the right side (NIHSS score 16). Again, an acute occlusion of the left MCA in the M1 segment was diagnosed [Figure 1, 2nd stroke] and she received a second MTE with an excellent clinical outcome (NIHSS 0, mRS 0 at discharge). Systemic intravenous thrombolysis (IVT) with alteplase was withheld because of the DOAC therapy. Because she had MEN type 1 syndrome with pancreatic insufficiency, resulting in chronic diarrhea during the days preceding her second IS, we assumed malabsorption of the DOAC with insufficient plasma levels as the most probable cause of her IS recurrence although we were unable to measure factor Xa level at that time. We discharged the patient and proposed the implantation of a left atrial appendage occlusion device (LAAO) as the next possibly best therapeutic decision in view of chronic recurrent diarrhea. This procedure, in addition with the DOAC therapy, was considered to offer maximal protection against future thromboembolic clinical incidents. The LAAO implantation was performed in another hospital, and unfortunately, the DOAC therapy was discontinued.

Four months later, the patient presented with transient aphasia as a result of a further MCA occlusion in the M1 segment [Figure 1, 3rd stroke], and received a third consecutive MTE in combination with systemic IVT with alteplase. The clinical outcome was again excellent (NIHSS 0, mRS 0 at discharge). We reinitiated an oral anticoagulation with apixaban. However, in the clinical context of her third large vessel occlusion, we conducted a reevaluation of alternative stroke etiologies including a vasculitis and thrombophilia panel. Anti-beta 2-glycoprotein antibodies (β2GP-Ab) were positive, and a diagnosis of primary APS was strongly suspected (despite negative cardiolipin-immunoglobulin G [IgG] and immunoglobulin M [IgM] antibodies). Considering the potential diagnosis of APS, a switch from apixaban to a Vitamin-K antagonist (VKA) was planned. Before oral anticoagulation witha VKA had successfully reached the therapeutic target of INR 2–3, the patient experienced a fourth embolic stroke as a result of a right MCA occlusion in the M2 segment [NIHSS at admission 5; Figure 1, 4th stroke]. She received her fourth MTE and was discharged with a mild dysarthria and facial palsy to a neurological rehabilitation hospital (NIHSS 2, mRS 1). During the follow-up, diagnosis of primary APS was confirmed (β2GP-Ab was positive again, above the 99th percentile in enzyme-linked immunosorbent assay screening; Cardiolipin-IgG and IgM antibodies remained negative) according to the EULAR guidelines.[6] Ab titer control after an interval of 12 weeks was mandatory to establish the diagnosis of APS and exclude a transient etiologically irrelevant phenomenon. Secondary APS was excluded. Since the successful initiation of VKA within the INR target of 2–3, the patient has not experienced any further strokes or other thromboembolic complications of the APS to date (23 months since the last MTE).

Discussion

Stroke recurrence in patients with AF despite DOAC therapy is not rare. These cases are challenging for clinical management in view of an optimized secondary prophylaxis. In a recent study, every fourth patient with recurrent IS under DOAC therapy had an alternative etiology than AF. In about 5% of these cases, recurrent IS was attributed to a coagulopathy.[7]

IS is a frequent neurological manifestations of APS. Triple positivity for antiphospholipid antibodies (aPL Abs) appears to be associated with a higher risk of recurrent thromboembolism in APS patients.[8] About 10%–20% of stroke patients <50 years of age have APS, thus making screening for aPL Abs particularly important among patients with (recurrent) cryptogenic stroke in this age range.[6] However, the onset of APS as a cause of IS in patients >50 years of age is rare and testing for thrombophilia is not routinely established in the work-up for older stroke patients.

Our case indicates that true primary APS may occur in stroke patients >50 years of age. In the Euro-Phospholipid study with a cohort of 1000 APS patients, APS onset occurred in <13% of patients older than 50 years.[9] Only few descriptions of stroke in late-onset APS have been reported.[5,10] In some of these cases, patients developed a malignancy during follow-up which might explain elevated autoantibody levels (IgM > IgG), probably reflecting a secondary APS. Older patients with primary APS and IS had at least double or triple positive aPL titers (high-risk aPL titers according to the EULAR criteria), whereas our patient was only anti-β2GP positive and therefore had medium-high aPL titers. This seems an important finding when weighing up how to advise a patient concerning potential anticoagulation.

Diagnosis of APS might be difficult in the elderly because aCL prevalence increases with age in normal subjects, and aPL Abs are commonly found in a wide range of conditions that frequently occur in the elderly.[11] Nevertheless, in a recent study with healthy participants, only the presence of aCL and anti-β2GP IgM increased with age, whereas aPL IgG titers remained stable or tended to decrease.[12] In our case, anti-β2GP Immunoglobulin A, IgM, and IgG were elevated, and this was not considered to be due to an older age.

Current guidelines recommend VKAs in APS[13] and a recent meta-analysis has confirmed higher rates of arterial thrombosis in APS patients taking DOACs versus VKAs.[14] Our case with fulminant recurrent large vessel occlusion notably illustrates the need for VKAs for secondary prophylaxis of thromboembolic events in APS, even in a patient with only one abnormal parameter (anti-β2GP-Ab positive, aCL negative).

Finally, this case further illustrates the feasibility of repeating MTE as many as four times (in this case the same vessel was affected three times) with excellent outcomes. Such a frequency had previously been described anecdotally.[15]

In conclusion, in patients with recurrent embolic stroke despite oral anticoagulation, verified compliance, and exclusion of drug interactions, late-onset APS might be considered a rare potential etiology also in the elderly.

Learning points

- Primary APS is a rare but important etiology of IS in the elderly
- Recurrent IS despite preexisting direct oral anticoagulation should trigger a repeated complete etiologic work-up
- In APS, oral anticoagulation with VKA is crucial, and DOACs should be avoided. This applies also to isolated anti-β2GP-Ab positive APS with negative Cardiolipin-Abs.

Author contributions

AA: conception and design of the study, acquisition and analysis of data, drafting of the manuscript; CB, DK, ER, HH, HB: acquisition and analysis of data, revision of the manuscript; MEW: conception and design of the study, acquisition and analysis of data, drafting of the manuscript and figures.

Ethical statement

For this case report no ethical statement was required, since no data was acquired prospectively with the aim to perform a study.

Declaration of Helsinki

We hereby confirm that this study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated and/or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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