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EC NEUROLOGY
Case Series

Serological Gap in Patients with Recurrent Stroke and Delayed Prothrombotic State Diagnosis

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Received: May 14, 2020; **Published:** June 29, 2020

Abstract

Background: Patients diagnosed with ischemic stroke undergo extensive investigations to find out the cause for the vascular event, which optimizes the secondary stroke prevention. In stroke patients under age 50 without other vascular risk factors, the investigations, includes screening for inherited and acquired hypercoagulable disorders. A group of patients with recurrent thrombotic events, and persistently negative hypercogulable testing that could be classified as SN-APS (Seronegative Antiphospholipid Antibody Syndrome).

Case Report: We are reporting two young patients with recurrent ischemic stroke, embolic stroke of undetermined etiology (ESUS), underlying etiology (embolic stroke of undetermined source-ESUS) despite extensive testing including hypercoagulable screen, the aPL and the other immunological tests were done in each with delayed positive aPL test, in the first case, the patient had a recent history of acute limb ischemia strongly suggests active prothrombotic state.

Conclusion: There is debate as to whether routinely order costly additional tests in the attempt to identify those novel aPL, or to establish the diagnosis of SN-APS and start a treatment, given the potential risk of thrombosis, on the part of those who would possibly benefit from the treatment. However, to date, there is no quality evidence that can establish the benefit.

Keywords: *Stroke; Thrombosis; Stroke Prevention; Risk Factors; Stroke Treatment*

Introduction

Patients diagnosed with ischemic stroke undergo extensive investigations to find out the cause for the vascular event, which optimizes the secondary stroke prevention. In stroke patients under age 50 without other vascular risk factors, the investigations, includes screening for inherited and acquired hypercoagulable disorders [1,2].

The actual benefit of routine testing for thrombophilic disorders in ischemic stroke patients remains uncertain [3]. However, the yield of performing extensive diagnostic tests is often low [3,4].

The accuracy of these tests results depends on its timing in relation to the acute thrombotic event as well as concurrent medications, especially vitamin K antagonists and heparin [4,5]. In addition, to other factors like old age and concomitant medical conditions [5,6].

Here we present two young patients with recurrent ischemic stroke of undetermined source as initial diagnosis found later to have positive hypercoagulable test results which doesn't fulfill the diagnostic criteria of APS, debating whether or not their clinical picture will justify starting anticoagulation.

Case Report

Patient 1

38 years old right handed woman, known to have DM type 1, HTN, ESRD on peritoneal dialysis, she was well till 2017, when she developed sudden right homonymous hemianopsia, when PCA ischemic stroke was found in her brain CT, she was started on Aspirin, in January 2018 she developed sudden left sided moderate weakness, and dysarthria with worsening of her right sided visual field defect, she was ambulating with cane, thorough investigations were done, including vasculitis and thrombophilia screen, on September 2019, she had 3rd stroke presented as sudden right hemiplegia and expressive aphaisa she was beyond the therapeutic window for thrombolysis, and endovascular treatment was not done, she was diagnosed to have left MCA ischemic stroke, and incidentally found to have chronic superior sagittal thrombosis, her current functional status she is wheel chair bound, needs assistance for most of her daily activities.

Upon neurological examination, Impaired fluency, naming and repetition, visual fields: blinks to threat on the left sided upper visual field, extra-ocular movement was intact, right facial palsy (UMN), weak gag reflex, no tongue deviation. Motor exam of (upper and lower extremities): right 0/5 UE, LE 2/5, left +4/5 of both UE and LE, plantars response upgoing in the right side. NIH stroke scale: 12 (Moderate dysarthria, mild dysphasia, right hemiplegia, right hemianopsia).

Her brain Imaging, the brain parenchymal shows interval development of acute infarction involving the left middle cerebral artery territory, this is corresponding to high signal intensity on diffusion weighted imaging with low signal intensity on ADC, the T2 and FLAIR shows high signal intensity, the remaining brain parenchyma shows stable appearance of the multiple old infarctions involving the supra and infratentorial compartment (Figure 1-3). MRA brain and neck: the left internal carotid artery shows faint opacification, the intracranial left middle cerebral artery and right A1 segment are not visualized, cervical segment of the left internal carotid is poorly visualized on the non-contrast MRA secondary to the slow flow, the left common and external carotid artery show no flow-limiting stenosis.

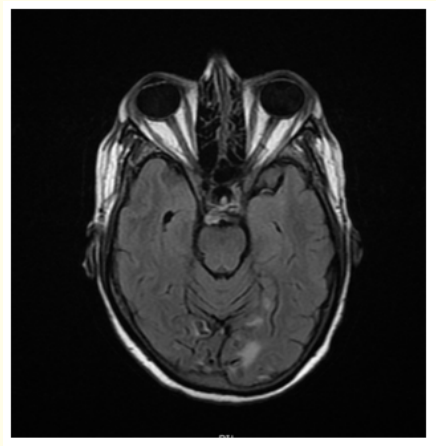

Figure 1: *Fluid-attenuated inversion recovery (FLAIR) sequence of MRI brain, axial view, showed high signal intensity in the left occipital cortex.*

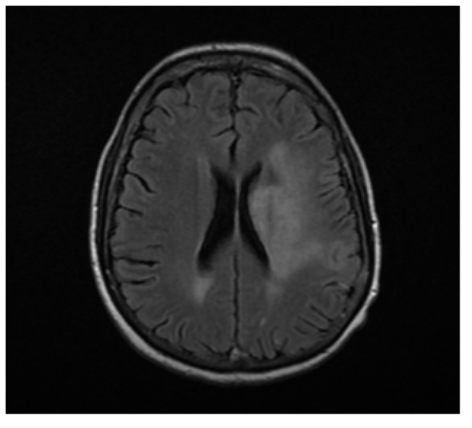

Figure 2: *Fluid-attenuated inversion recovery (FLAIR) sequence of MRI brain, axial view, showed high signal intensity in the left middle cerebral artery territory.*

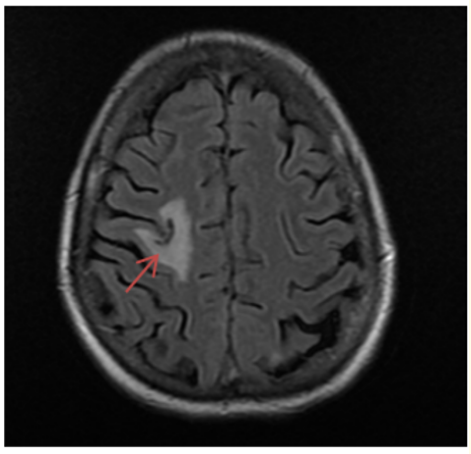

Figure 3: *Fluid-attenuated inversion recovery (FLAIR) sequence of MRI brain, axial view, showed high signal intensity in the right frontal cortex.*

The laboratory investigations shows anti-Thrombin III: -ve, anti-Cardiolipin IGA, IGG, IGM: -ve, anti-DNA: -ve, ANA: -ve, BETA 2 glycoprotein IGG: -ve, BETA 2 glycoprotein IGM: -ve. Lupus anticoagulant: LA1: 48.3 (July 2017) to 66 (November 2019), (normal values: 31-44 sec). LA2: 41.3 (July 2017) to 46 (November 2019), (normal values: 30-38 sec), ratio: 1.1 (July 2017) to 1.4 (November 2019), (normal values: 1.09 - 1.37).

Other investigations: TTE (transthoracic echocardiogram) with bubble study: un-remarkable. Holter monitor 48 hrs: un-remarkable.

She was started on Aspirin then changed to Clopidogrel after recurrent stroke, inpatient and outpatient rehabilitation with physical, occupational therapy, and speech therapy. Her latest stroke on September 2019, left MCA ischemic stroke. On January 2020, right below knee amputation done for lower limb ischemia. On March, 2020 started on anticoagulation (Warfarin 5 mg po od).

Patient 2

He is 30 years old man, on February 2019, while he was driving all of sudden noticed difficulty to see in the left side of his vision, he didn't notice any other sudden neurological symptoms like weakness in both arms or legs, he was not having and trouble walking, he didn't' notice any facial droop, or difficulty swallowing, he went to a private hospital where plain brain CT done and patient discharged home, came to our hospital ER for persistent vision field loss, when he was examined patient found to have left homonymous quadrantanopia, no other language or speech difficulty, without motor or balance problems, he was beyond 24hrs of symptoms onset, Brain MRI and MRA done which revealed subacute right PCA ischemic stroke, with no evidence of vessels occlusion or dissection.

Upon neurological examination, Unremarkable apart from left homonymous quadrantanopia. His brain Imaging shows right PCA occlusion (P2 occlusion), small right occipital infarct (Figure 4), incidental tiny left MCA infarct. No vasculitic changes of the intracranial vessels.

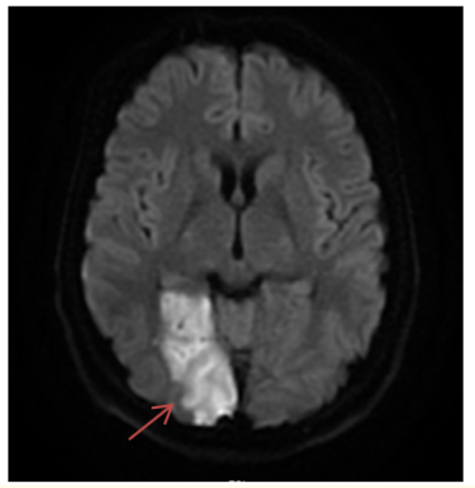

Figure 4: *Diffusion-weighted magnetic resonance sequence of MRI brain, axial view, showed high signal intensity in the right occipital cortex.*

The laboratory investigations was done, lupus anticoagulant: -ve, anticardiolipin IGA, IGM, IGG: -ve. Beta glycoprotein: initially -ve on February 2019 and then +ve on Sep, 2019, others were persistently -ve.

Other investigations which was done, TTE (transthoracic echocardiogram) with bubble study and Holter for 48hrs were un-remarkable.

Patient initially placed on Antiplatelets, then Warfarin was started after repeating the BETA glycoprotein which persistently came back +ve, no reported vascular events stroke or TIA or other thrombotic events.

Discussion

Antiphospholipid syndrome (APS) can be diagnosed based on required clinical criteria of one or more occurrence of pregnancy morbidity or vascular thrombosis, and laboratory criteria of the presence of antiphospholipid antibodies on two or more occasions at least 12 weeks apart [6,7].

Both anticardiolipin antibodies and anti-β2-glycoprotein antibodies can be detected using enzyme-linked immunosorbent assay (ELISA) techniques, but many of these tests are not standardized [5-7]. Consensus guidelines recommend semi-quantitative assays of anticardiolipin antibody results (low, medium, or high titer) [8,9].

In both cases that we reported, ischemic stroke were recurrent without an identified underlying etiology (ESUS) despite extensive testing including hypercoagulable screen, the aPL and the other immunological tests were performed in each with delayed positive aPL, in the first case, the patient had a recent history of acute limb ischemia strongly suggests active prothrombotic state.

There is a group of patients that have recurrent thrombotic events, persistently negative in laboratory tests that could be classified as SN-APS (Seronegative Antiphospholipid Antibody Syndrome) [8]. This concept was introduced for the first time in 2003 by Hughes and Khamashta, who described patients with clinical manifestations highly indicative of APS, in patients who rapidly developed the classical accelerated and progressive multiorgan damage of patients with actively symptomatic APS, but with persistently negative aPL tests [7,8].

However, the hypothesis for the existence of a group of seronegative patients could be that the series of tests is insufficient, either because of the limitations of standard assays or because of different antigenic targets [8,9].

There is debate as to whether routinely order costly additional tests in the attempt to identify those novel aPL, or to establish the diagnosis of SN-APS and start a treatment, given the potential risk of thrombosis, on the part of those who would possibly benefit from the treatment [6,8,10]. However, to date, there is no quality evidence that can establish the benefit.

Management of APS and prevention of its complications mainly the thrombo-embolism phenomena is a challenge for clinicians. During the 14th International Congress the Trends Task Force recommended that vitamin K antagonists (VKAs-warfarin) should be the drug of choice in thrombotic APS. The use of Newer Oral-Anticoagulants (NOACs) safety and efficacy in the management of APS may need more clinical trials [11].

Conclusion

In conclusion, when there are clinical symptoms such as recurrent thrombo-embolism phenomena including arterial and venous occlusive events, without any underlying determined etiology causing thrombosis, the clinicians should suspect APS and investigate for aPL, as early diagnosis may affects patients outcome.

The existence of SN-APS continues to be controversial. Nonetheless, it is important that this entity be considered, since the recurrence of vascular events without clear etiology may benefit from early management. However, there is still not enough evidence to establish a standard for approaching these patients, which should be personalized and multidisciplinary.

Disclosure

Nothing to disclose.

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Volume 12 Issue 7 July 2020