Hepatitis C and recurrent treatment-resistant acute ischemic stroke

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Since the introduction of recombinant tissue plasminogen activator and thrombolysis, acute ischemic stroke has become a treatable disorder if the patient presents within the 4.5-hour time window. Typically, sporadic stroke is caused by atherosclerotic disease involving large or small cerebral arteries or secondary to a cardioembolic source often associated with atrial fibrillation. In the over-65-year age group, more rare causes of stroke, such as antiphospholipid syndromes, are unusual; such stroke etiologies are mostly seen in a younger age group (<55 years). Here we describe acute ischemic stroke in three patients >65 years with hepatitis C–associated antiphospholipid antibodies. We suggest that screening for antiphospholipid disorders in the older patient might be warranted, with potential implications for therapeutic management and secondary stroke prevention.

The risk factors for ischemic stroke have been well categorized by major epidemiological studies, such as the Framingham population-based study established in the 1950s. Such epidemiological studies particularly highlight modifiable risk factors of ischemic stroke such as hypertension, diabetes mellitus, smoking, alcohol usage, and dyslipidemia. The contribution of other risk factors for ischemic stroke, such as hypercoagulable states, is typically found in persons <55 years old (1). The typical antiphospholipid patient with acute ischemic stroke is a young woman of childbearing age with recurrent miscarriages (2). The etiology of stroke is customarily defined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, with the presumption that the main attributable stroke risk factors are derived in the general stroke population from the presence of atherosclerotic vascular disease (3). The occurrence of other modifiable risk factors in the multifactorial etiology of acute ischemic stroke is an area of active study. In this report, we present three patients >65 years where we found an association between hepatitis C and the occurrence of antiphospholipid antibodies more typically found in younger patients.

CASE REPORTS

In all patients, coagulation screens were performed, including factor 8, homocysteine, antiphospholipid, factor V Leiden, antithrombin III, Russell viper venom assay, and protein C and

S. Only the antiphospholipid screen was found to be abnormal in our patients. The *Table* summarizes patient demographic data and results of the antiphospholipid screens.

Case 1

Six months prior to his third hospital admission, a 72-year-old right-handed African American man presented with a past medical history of hyperlipidemia and a 2-day history of left leg weakness, dizziness, and left-sided facial numbness with a National Institutes of Health Stroke Scale (NIHSS) score of 3. Evaluation for acute stroke with diffusion-weighted magnetic resonance imaging (MRI) demonstrated a subacute lesion in the right posterior internal capsule. The extended symptom time course precluded use of recombinant tissue plasminogen activator (rt-PA) or another neurovascular intervention. The patient was admitted to address secondary stroke prevention and was found to have a cholesterol of 142 mg/dL; high-density lipoprotein cholesterol of 9 mg/dL; low-density lipoprotein cholesterol of 71 mg/dL; triglycerides of 639 mg/dL; cardiac ejection fraction of ~60%; regular cardiac rhythm; and no persistent foramen ovale or pulmonary hypertension. In addition, blood cultures showed no growth, and cerebral computed tomographic angiography showed minimal atherosclerotic disease in the carotid bulbs with a hypoplastic left vertebral artery. A diagnosis of small vessel stroke was made and the patient was encouraged to be more compliant with his hypertension regime and adopt a heart and stroke–healthy diet together with smoking cessation. Secondary prevention therapy included lisinopril, aspirin, and atorvastatin. An albumin-immunoglobulin protein gap was noted, and the patient was subsequently screened and diagnosed with hepatitis C; he was referred to gastroenterology for further evaluation.

Approximately 5 months later, the patient presented with sudden onset of right facial numbness, slurred speech, and right

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Table 1. Patient demographics and antiphospholipid screen in the three described male patients

Variable	Case 1	Case 2	Case 3
Age (years)	72	67	65
Blood pressure (mm Hg)	treated 147/74	treated 140/90	189/100
NIHSS score	3	19	5
Total cholesterol (mg/dL)	142	141	146
LDL cholesterol (mg/dL)	71	92	85
HDL cholesterol (mg/dL)	9	47	25
Triglycerides (mg/dL)	639	57	219
Smoker	1–3 packs/day	1–2 packs/day	N/A
Hemoglobin A1C (%)	<4.5	<3.5	10.7
IgM anticardiolipin antibody (0–12 MPL U/mL)*	13	<9	13
IgG anticardiolipin antibody (0–14 GPL U/mL)*	21	12	20
IgA anticardiolipin antibody (0–11 APL U/mL)*	31	10	<9
IgM β -2 glycoprotein (GPI IgM units)	<9	<9	9
IgG β -2 glycoprotein (GPI IgG units)	<9	<9	<9
IgA β -2 glycoprotein (GPI IgA units)	18	<9	10
IgM phosphatidylcholine (0–25 MPS IgM)*	29	6	23
IgG phosphatidylcholine (0–11 GPS IgG)*	7	48	24
IgA phosphatidylcholine (0–20 APS IgA)*	21	10	1

*Units indicate the value showing absence (versus low, moderate, or high positivity).

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.

arm and leg weakness. These symptoms were confirmed on physical examination. Presentation to the emergency room was outside the 4.5-hour window, and thrombolysis with rt-PA was not administered. Diffusion-weighted MRI was positive for a left thalamic lacunar stroke, again consistent with small vessel disease. The patient's final admission was due to statin-induced rhabdomyolysis and an associated pancreatitis. During this admission, the patient's creatinine kinase was >8000 mcg/L with an elevated aspartate transaminase of 1735 IU/L and an alanine transaminase of 395 IU/L. Diffusion-weighted MRI was consistent with no new acute ischemic stroke and represented T2 "shine through." During the final admission, the patient was examined for a hypercoagulable state and was found to have elevated values for several antiphospholipid antibodies: IgM anticardiolipin, 13; IgA anticardiolipin, 31; IgA phosphatidylcholine, 21; and IgM phosphatidylcholine, 29. The patient was started on warfarin for antiplatelet failure and has not had any further acute ischemic strokes on extended warfarin therapy for 12 months with an international normalized ratio (INR) goal of 2 to 3.

Case 2

A 67-year-old right-handed African American man with a past medical history of hypertension presented to the emergency department with sudden onset of weakness on the left side of his body. Since he was within the 4.5-hour window,

he received rt-PA with a door-to-needle time of approximately 2.5 hours. Since his NIHSS score was estimated to be 19 and he was noted to be in atrial fibrillation, his stroke was presumed to have a cardioembolic etiology. A diffusion-weighted MRI after administration of rt-PA showed a small ischemic area in the right posterior parietal cortical area. The patient was discharged on warfarin with a therapeutic INR goal of 2 to 3.

Over the next 6 months, the patient's warfarin regime was difficult to maintain within goal despite patient adherence. The patient then presented with a further acute ischemic stroke episode with increased left-sided weakness and problems with gait and balance over a 3- to 4-day period. MRI demonstrated a new lesion in the left cerebellar hemisphere, together with a lesion in the right parieto-occipital region and a further lesion on the left frontal area. The patient's INR at the time of presentation was 1.7, and a diagnosis of cardioembolic stroke secondary to chronic atrial

fibrillation was again made. The patient's warfarin regime was discontinued, and he was started on dabigatran.

Approximately 2 months after this admission, the patient presented with a generalized tonic-clonic seizure, and epilepsy secondary to ischemic stroke structural damage was diagnosed. The patient was started on antiepileptic drugs and at that time was also noted to have an albumin-immunoglobulin protein gap. Screens for hepatitis and HIV were performed with the patient's consent. The hepatitis C screen returned positive, and a full gastroenterology workup was performed. As part of an extended workup for etiological factors associated with the patient's stroke, antiphospholipid screening was performed. Antiphosphatidylcholine IgG returned elevated at 48. The patient was continued on dabigatran, with the introduction of aspirin 81 mg daily as part of his secondary stroke prevention regime.

Case 3

A 65-year-old right-handed Caucasian man with a history of hypertension, dyslipidemia, posttraumatic stress disorder, and hepatitis C contracted during service in Vietnam was admitted with significant left-sided weakness affecting the face, arm, and leg. The patient initially presented at an out-of-state hospital and was not treated with rt-PA. Computed tomography and MRI showed ischemic lesions in the right parietal area. The patient underwent angiographic evaluation and a stent placement in

the right M1 branch of the middle cerebral artery for a critical large vessel stenosis. The stroke was believed to be caused by large vessel disease, and the patient was continued on aspirin 325 mg and clopidogrel 75 mg once daily for secondary stroke prevention. The patient was found to have elevated anticardiolipin antibody at IgG 20, anticardiolipin antibody at IgM 13, and antiphosphatidylcholine at IgG 24.

DISCUSSION

We present a single-center observational case series of hepatitis C and antiphospholipid antibody positivity in the older stroke patient population (>65 years) that altered therapeutic management from antiplatelet therapy to warfarin in two cases and from warfarin to dabigatran in one case. Screening for antiphospholipid antibodies is not part of the usual clinical workup for modifiable stroke risk factors in those >65 years, although it is well described as an independent risk factor for acute ischemic stroke in those <55 years. We suggest that in patients with hepatitis C and acute ischemic stroke, such screening may have a higher yield than in the <55-year demographic.

There are limited references reporting hepatitis C–associated antiphospholipid antibodies and stroke, and most consist of incidental case reports (4–6). One case report described a 43-year-old woman with ischemic stroke, while a further case report described a 54-year-old man with chronic hepatitis C and antiphospholipid-positive serology and ischemic stroke. Of interest, the treatment of hepatitis C with interferon appeared to contribute to the patient's remission from further ischemic stroke events (6). The only case-control patient series came from a Romanian publication, where 58 patients (age range 46–77 years, mean 62 years; 39 women and 19 men) were found to have a higher prevalence ($P < 0.001$) of antiphospholipid antibodies in the hepatitis C–positive group with stroke compared to age- and sex-matched controls (5).

The presence of antiphospholipid antibodies is known to contribute to the development of acute ischemic stroke. Our small

observational case series suggests that no particular type of stroke is favored, since we had patients with both small- and large-vessel disease together with cardioembolic stroke. The additional risk of antiphospholipid-positive serology should suggest optimization of antiplatelet therapy and possibly extension of therapy to anticoagulation with warfarin or direct thrombin inhibitors such as dabigatran. The control of hepatitis C virus expression through interferon therapy is a further therapeutic consideration in these patients and may reduce the risk of stroke (5). Our patients were all noted to have an elevated albumin-immunoglobulin protein gap, suggesting that there is an abnormal immune response to hepatitis C. The infection of vascular endothelial cells by hepatitis C may result in the exposure of previously nonimmunogenic antigens to immunocompetent cells, promoting endothelial dysfunction and potential stroke. However, dysregulation of hepatic synthetic function following hepatitis C infection may also be an important etiologic consideration.

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