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Case description of stroke in a female patient with heterozygous MTHFR C677T mutation:

Lessons learned in stroke prevention and the importance of continuity of care for women with multiple risk factors for thrombosis

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ABSTRACT

Case Description: A 58-year-old female with a history of antiphospholipid syndrome (APS) with multiple deep vein thromboses (DVTs), spontaneous abortions, hypertension (HTN), hyperlipidemia (HLD), type 2 diabetes mellitus (T2DM), and tobacco use disorder presented to the hospital with dysarthria and headache for three days. Evaluation revealed a left MCA stroke. Testing at the time of stroke was negative for antibodies associated with APS, but revealed heterozygous mutation of MTHFR C677T. Prior to this stroke, she had recently established care with a new primary care provider and cardiologist. She reported previously following with a hematologist who managed her APS with folic acid and vitamin D. She was prescribed no anticoagulation therapy and was taking 81 mg aspirin daily at the time of this event.

Conclusions: There is mixed evidence regarding the patient's diagnosis of APS as the underlying factor causing multiple DVTs. Nevertheless, the treatment for APS in the setting of multiple prior DVTs is anticoagulation, which was not part of the patient's treatment plan prior to her stroke. A more detailed investigation of the patient's medical history and re-evaluation of appropriate treatment when establishing care with new providers would have helped optimize her care and may have prevented her stroke.

Clinical significance: Compared to men, women experience worse health outcomes after stroke, including increased mortality. When women are establishing care with new providers, this disruption in continuity of care presents an opportunity for re-evaluation of their risk factors and optimal primary prevention of stroke. This case illustrates how immediate investigation of a patient's pre-existing diagnoses and treatment plan after any transition of care may help prevent poor health outcomes for women.

CASE DESCRIPTION

Patient: 58-year-old female

PMH: APS with multiple DVTs, spontaneous abortions, HTN, HLD, T2DM, COPD, GERD, tobacco use disorder

PSH: appendectomy, hysterectomy, cholecystectomy, hip surgery, arm surgery

Medications: albuterol inhaler, aspirin 81 mg daily, atorvastatin 80 mg daily, Basaglar 26 units daily, Breo Ellipta 100 mcg-25mcg 1 puff daily, diltiazem 360 mg daily, folic acid 1 mg daily, lisinopril 20 mg daily, nitroglycerin 0.4 mg q5min prn chest pain, rabeprazole 20 mg daily, spironolactone 100 mg BID, vitamin D3 1000 intl units daily

Family Hx: Father - T2DM, cardiovascular disease, hypertension. Mother - colon cancer, hypertension, TIA. Sister - colon cancer

Social Hx: Retired. Lives with husband. Smoking tobacco, 0.5-1.5 ppd. Drinks alcohol 1-2 times/month. Denies current or previous substance use.

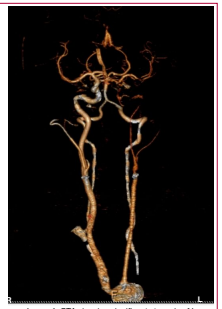
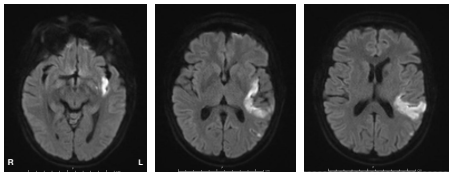


Image 1: CTA showing significant stenosis of L internal carotid artery.



Images 2-4: Non-contrast MRI diffusion-weighted images showing areas of ischemic infarct (axial view).

Patient Presentation: The patient presented to the emergency department with a chief concern of dysarthria and headache onset 3 days prior. She also reported paresthesia throughout the right side of her body. NIH stroke scale = 2 (+ for mild to moderate aphasia and mild to moderate dysarthria). Vital signs within normal limits.

Imaging Results:
- CT without contrast of the head: negative for intracranial hemorrhage.
- CTA of the head and neck w/ contrast *(Image 1, above)*: **critical stenosis of greater than 90% in the left internal carotid artery** with a recommendation for vascular surgery consultation for carotid endarterectomy.
- MRI without contrast *(Images 2-4 above)*: moderate amounts of increased signal intensity on diffusion imaging in left subinsular region and posterior aspect of left frontal lobe with at least one focus in the left parietal-occipital junction, compatible with recent infarction.

Labs:
- **Negative** for factor V Leiden mutation, PT gene mutation, MTHFR A1298C mutation, cardiolipin IgG/IgM, beta 2 glycoprotein IgG/IgM, ANA
- **Positive** for heterozygous **MTHFR C677T** mutation

MTHFR MUTATION

What is a MTHFR mutation?
- 5,10-Methylenetetrahydrofolate reductase (MTHFR) catalyses the reduction of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, thereby producing a methyl donor for the conversion of homocysteine to methionine.[1]
- The MTHFR gene is located on chromosome 1 (1p36.3).[2]
- Several known mutations exist, including over a dozen rarer mutations causing severe enzyme deficiency, e.g., P764L, T692M, R985C, and various splice site mutations.[2]
- The most common polymorphism, C677T, is a missense mutation causing a substitution of alanine to valine, thereby altering MTHFR's thermolability and activity, leading to milder enzymatic deficiency.[1]
- Several diseases have been found to be associated with MTHFR C677T polymorphisms, including coronary artery disease, essential hypertension, psoriasis, infertility, neuropsychiatric diseases, diabetic nephropathy, and some cancers.[2]

Does a C677T MTHFR mutation increase the risk of CVA?
- The reduced activity of MTHFR leads to elevated levels of homocysteine, which has been shown to be a risk factor for small vessel and large vessel stroke.[1]
- Thus, it has been posited that the C667T MTHFR polymorphism is an independent genetic risk factor for stroke.
- In their 2015 meta-analysis, Kumar et al. found that there is an associated between MTHFR C677T and stroke in Asian populations. However, evidence connected the polymorphism with stroke for more diverse populations is still lacking.

STROKE RISK FACTORS IN WOMEN

The incidence of stroke in women is increasing worldwide, as is the prevalence of associated risk factors,[3] such as:

- Age
- Atrial fibrillation
- Obstructive sleep apnea
- Smoking
- Obesity
- Physical inactivity
- Arterial hypertension
- Dyslipidemia
- Heavy alcohol consumption
- Diabetes mellitus
- Pregnancy
- Estrogen exposure

Although most of these are seen in both men and women, the strength of their respective associations with stroke differs between the sexes; this is demonstrated in the table below from Madsen, et al.[4] Moreover, women are subject to sex-specific risk factors, such as the hypercoagulable state that is pregnancy as well as estrogen exposures, which is higher than men at baseline and further increased with several contraceptive methods.

Risk Factor	Prevalence	Association With IS	Treatment Disparity
Hypertension	Lower in women (vs men) in younger age groups, higher in older age groups	Similar in women (vs men) in younger age groups, higher in older age groups	In younger age groups, women more likely to have BP controlled; in older age groups, women less likely to have BP controlled
Dyslipidemia	Data conflict; either similar between sexes or lower in women	Lower in women	Women less likely to be on statins and have LDL controlled
Atrial fibrillation	Higher in women	Higher in women	Women less likely to be prescribed oral anticoagulants, less likely to have cardiac ablation, and receive lower doses of NOACs
Migraine	Higher in women	Higher in women	Unknown if migraine treatment reduces stroke risk
Diabetes mellitus	Similar women vs men	Higher in women	Data conflict on sex differences in meeting HbA1c goal
Cognitive impairment	Higher in women	Unknown whether there is a sex difference	Women less likely to be treated with antidementia drugs

BP indicates blood pressure; HbA1c, glycated hemoglobin; IS, ischemic stroke; LDL, low-density lipoprotein; and NOAC, novel oral anticoagulant.

STROKE OUTCOMES IN WOMEN

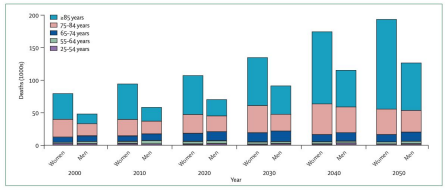


Figure 2: Projected number of deaths from stroke among whites (USA, 2000–2050)
Age-specific and sex-specific mortality estimates were obtained from the US Centers for Disease Control and Prevention WONDER database, and age-specific and sex-specific population projections from the US Census Bureau middle series. Projected deaths were calculated by applying age-specific and sex-specific mortality data to the population projections.

Women are more likely than men to suffer from a stroke and to die as a result; this is largely related to longer life-expectancy in women. This is visualized in the above figure predicting deaths as a result of stroke through 2050.[6] Furthermore, women have **poorer outcomes post-stroke overall:**

- Women are more likely to be disabled at 3 months post-stroke.[6]
- Women have longer door to imaging time than men, which can ultimately affect whether tPA is able to be utilized.[5]
- Women are more likely to present with non-traditional stroke symptoms, which may lead to delay and treatment and poorer overall outcomes.[6]
- Women are less likely to be discharged home, and require long-term care and more extensive rehabilitation therapies.[6]
- Women are more likely to experience post-stroke depression.[6]

ANTIPHOSPHOLIPID SYNDROME

What is antiphospholipid syndrome (APS)?
- APS is an autoimmune disease associated with recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia.
- APS patients are often seropositive for antiphospholipid antibodies, e.g., lupus anticoagulant, anticardiolipin, and anti-beta 2 glycoprotein.
- APS is strongly associated with systemic lupus erythematosus (SLE); 30-40% of patients with APS have concomitant SLE.[7]
- Some studies suggest that over 20% of strokes in patients under 45 years old are associated with APS.[8]

How does APS increase the risk of stroke?
- In patients with APS, strokes are more often thrombotic rather than embolic.[8]
- Seropositivity for antiphospholipid antibodies, particularly lupus anticoagulant, is the most significant factor among APS patients for thrombotic events.
- It is suggested that triple antibody positivity is associated with a significant increased thrombotic risk compared to double- or single-antibody positivity.[7]

What is recommended for stroke prophylaxis in patients with APS?
- Due to the high risk of thrombosis in patients with APS, treatment guidelines recommend life-long anticoagulants, antiplatelets, or both.
- A Cochrane review[7] found insufficient evidence to evaluate the benefit or harm of novel anticoagulants (e.g., rivaroxaban) vs. warfarin, though high doses of the latter are associated with increased risk of bleeding than standard doses.
- The review also found insufficient evidence to demonstrate clear superiority or inferiority of any particular combination of anticoagulants and/or antiplatelet agents.
- Long-term anticoagulation therapy is recommended for patients with a history of unprovoked DVT in the setting of APS.[9]

CONCLUSIONS

- Stroke is more common in women compared to men.[4,6]
- Stroke outcomes are worse in women compared to men.[5,6]
- Some risk factors for stroke are unique to women, including pregnancy and use of combined oral contraceptives.[3]
- **Among risk factors for stroke shared between men and women, atrial fibrillation, migraine, and cognitive impairment are more prevalent among women.[4]**
- Disorders of hypercoagulability, such as antiphospholipid syndrome, increase a person's risk of stroke.
- Guidelines for APS treatment recommend life-long anticoagulation therapy, antiplatelet therapy, or both.[7]
- The C667T MTHFR polymorphism has been associated with increased homocysteine levels and diseases known to increase risk for stroke including CAD and hypertension.[1,2]
- The C667T MTHFR polymorphism has been associated with an increased risk for stroke in Asian populations; further research is needed to describe its relationship to stroke risk in more diverse populations.[1]
- The patient presented in this case had multiple risk factors for stroke, including history of multiple DVTs, tobacco use disorder, and possible diagnosis of APS.
- Despite her history and multiple points of contact with the healthcare system, the patient was not prescribed anticoagulation therapy prior to her stroke.
- **Investigation and evaluation of a patient's past medical history and active treatment plan, while always important in any transition of care, offers an opportunity to minimize stroke risk for women, who experience stroke more often and with worse outcomes than men.**

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