

Gender Differences in Stroke Across the Lifespan: 2014 AHA/ASA Guidelines for the Prevention of Stroke in Women

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October 18, 2014

Goals of this talk

After this lecture, participants should be able to

- Identify and manage sex specific risk factors for stroke
- Identify and manage which stroke risk factors are higher in women compared to men
- Recognize pre-eclampsia and eclampsia are risk factors for future strokes in both pregnancy and beyond childbearing years
- Identify the risk factors and understand management of cerebral venous thrombosis in women

Stroke in Women

- Stroke is the fifth leading cause of death for MEN but the **THIRD leading cause of death** for women
- More than HALF (53.5%) of ~795,000 strokes occur in women annually in the US
- 59.6% of all stroke-related deaths were in women in 2010
- Thought to be because women live longer than men → lifetime risk of stroke is **HIGHER** in women

Men versus Women

Type of Stroke	Incidence in Men vs. Women	Mortality
Ischemic stroke (IS)	>85 years old: women have higher or similar incidence than men. <85 years: Incidence similar in men and women	>65 years old: women have higher IS mortality than men <65 years old: lower IS mortality in women than men
Subarachnoid hemorrhage (SAH)	>55 years old: women have higher rates of SAH compared to men <55 years old: men have higher rates than women	Women have HIGHER age adjusted SAH mortality than men
Intracerebral hemorrhage (ICH)	Lower rates in women than men in MOST studies	<65 years old: mortality lower in women >65 years: No sex difference

Stroke in Women

- Women are more likely
 - To be living alone and widowed before stroke
 - Institutionalized after stroke
 - Poorer recovery from stroke than men



Why have stroke guidelines specific women?

- Women differ from men in multiple ways including
 - Genetic differences in immunity
 - Coagulation
 - Hormonal factors
 - Reproductive factors including pregnancy and childbirth
 - Social Factors

ALL OF THESE CAN INFLUENCE RISK OF STROKE AND IMPACT STROKE OUTCOMES!!

Risk Factors for Stroke

Table. Risk Factors for Stroke

Risk Factor	Sex-Specific Risk Factors	Risk Factors That Are Stronger or More Prevalent in Women	Risk Factors That Are Similar in Men and Women
Pregnancy, preeclampsia, or gestational diabetes	X		
Oral contraceptive or postmenopausal hormone use	X		
Migraine headache with aura		X	
Atrial fibrillation		X	
Diabetes		X	
Hypertension		X	
Physical inactivity, obesity, or unhealthy			X
Age			X
Prior cardiovascular disease			X
Smoking			X
The metabolic syndrome			X
Depression		X	
Psychosocial stress		X	

Case #1

- 85 y/o RH female with history of hypertension and diabetes woke up with clumsiness and weakness of her left arm and leg. She was able to speak clearly. She was last known normal at 10 pm the night before when she went to sleep.

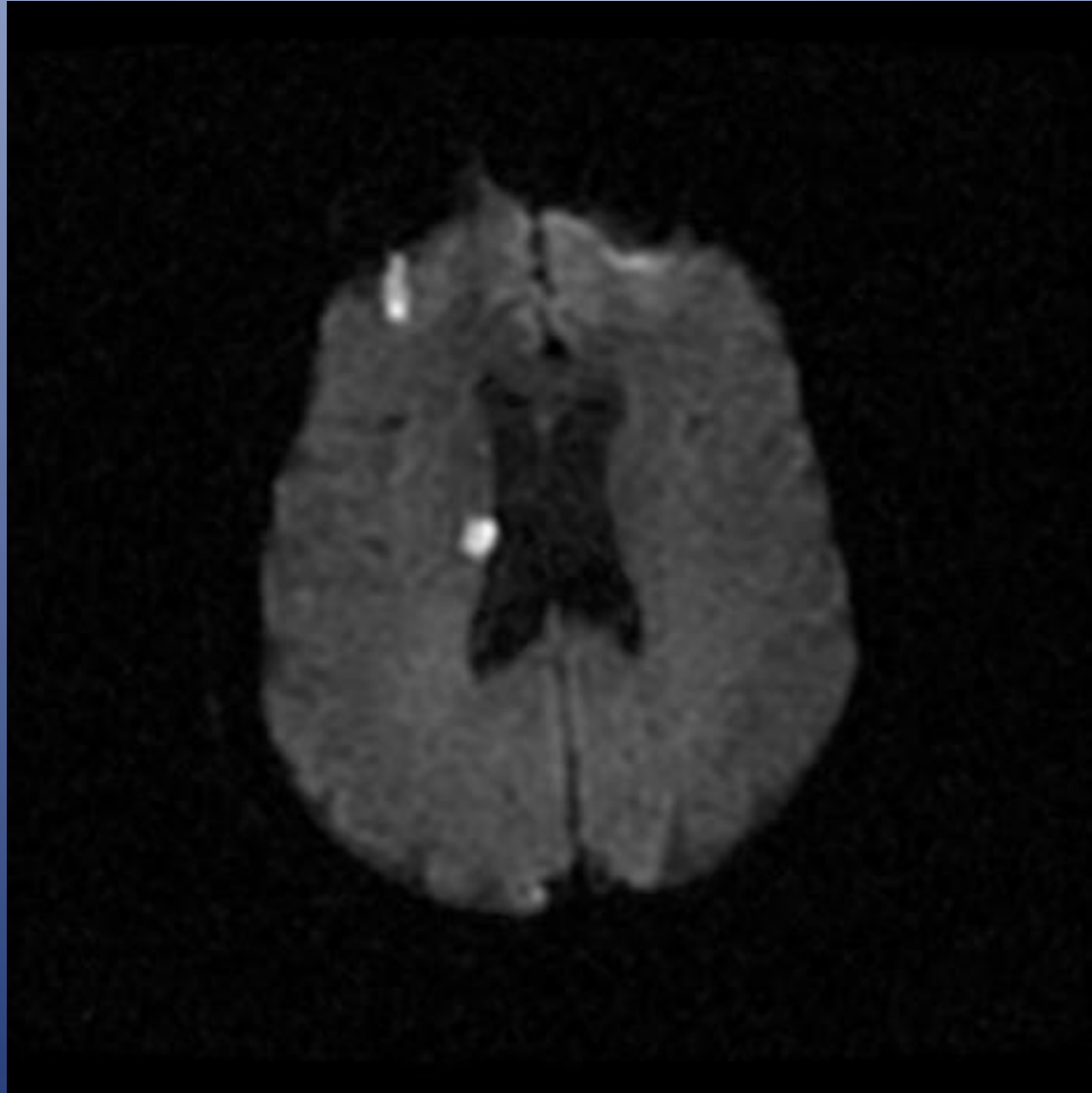
History and Physical

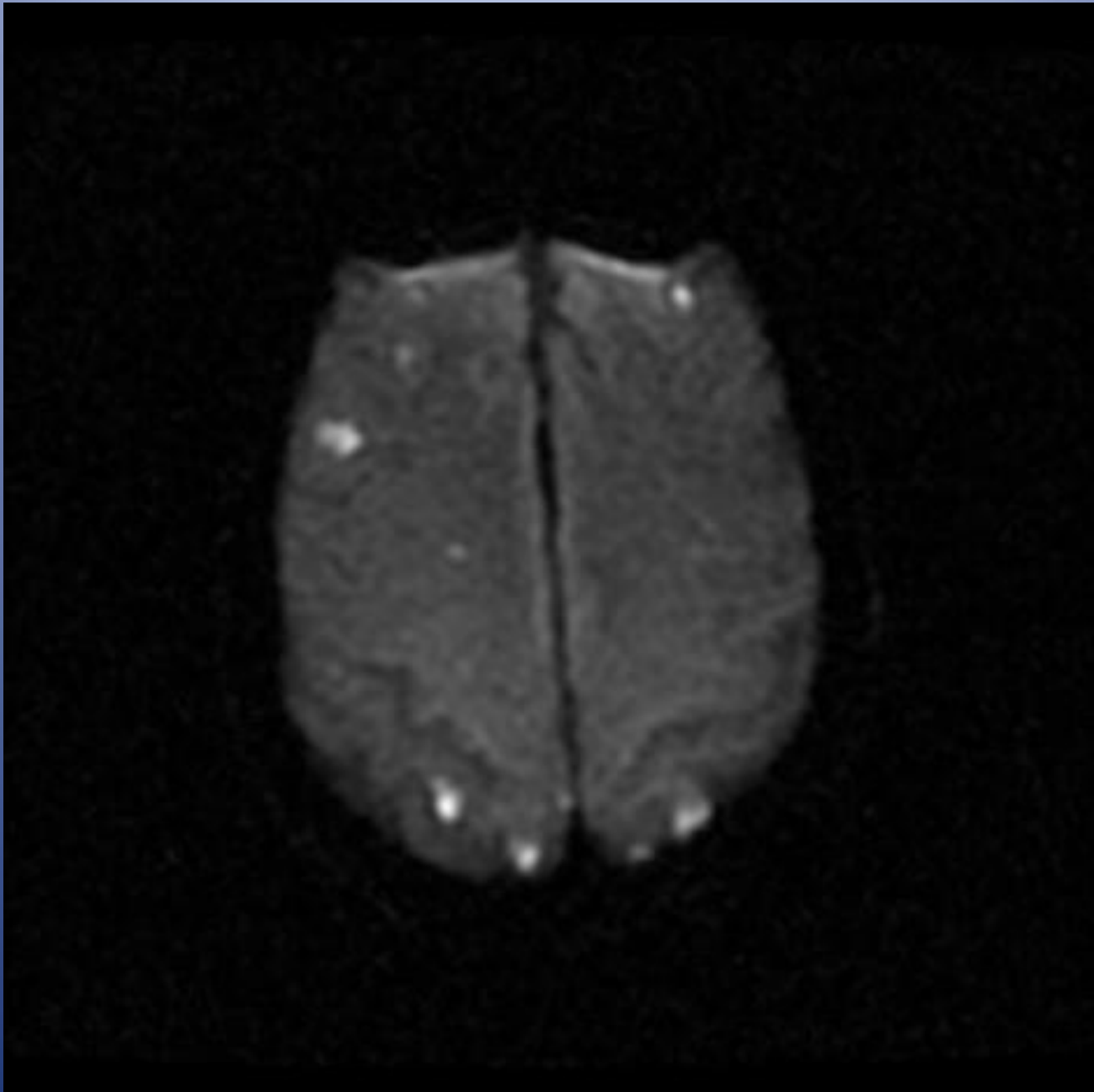
- **PMH:** Non-insulin dependent Type II diabetes, hypertension, dyslipidemia, gout, no complications during her pregnancy
- **FH:** Stroke in brother
- **SH:** Former smoker, 20 pack year history, does not drink alcohol, no illicit drugs, widowed and lives alone
- **Medications:** Metformin, Lisinopril
- **Allergies:** None

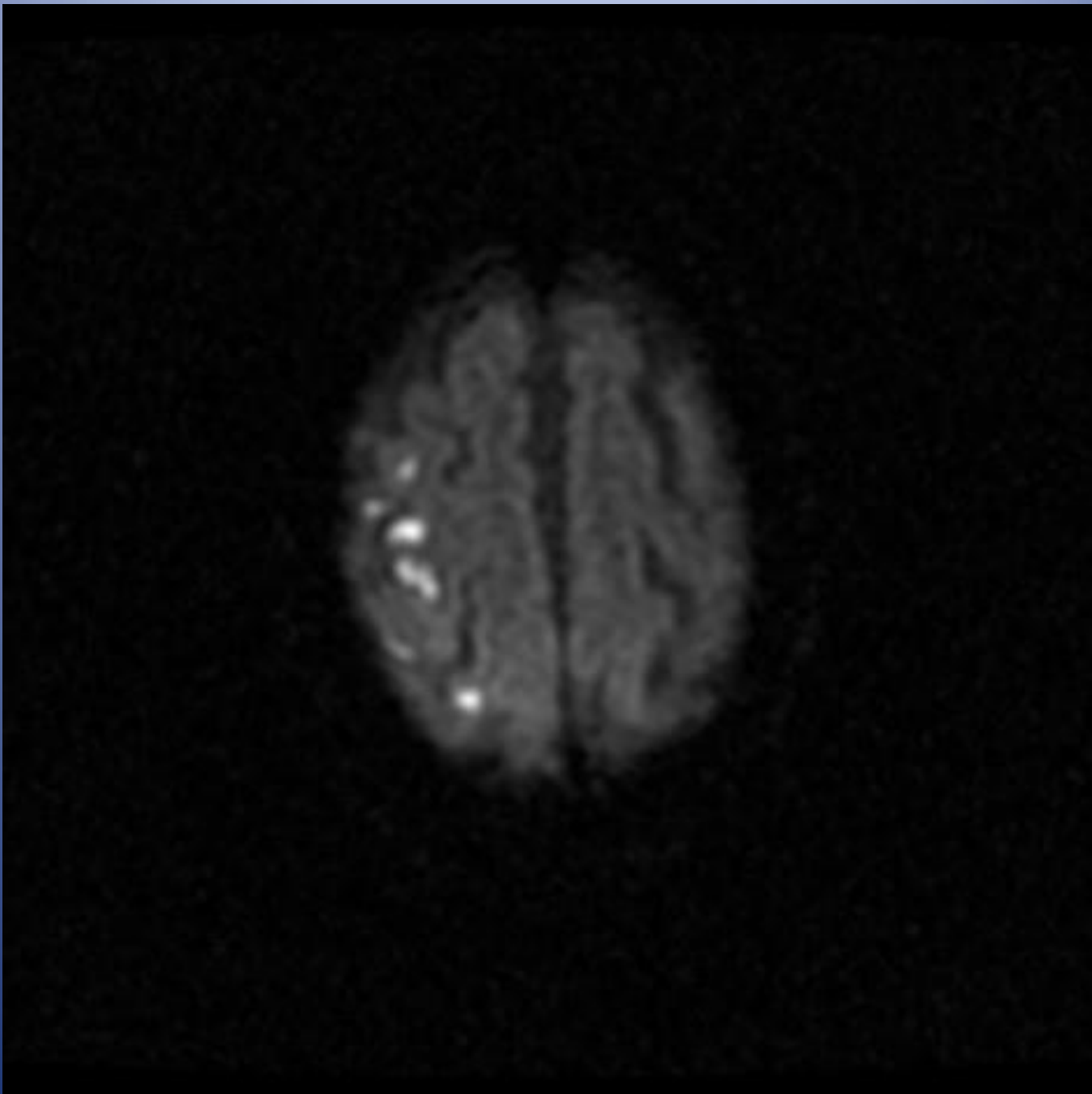
Examination

- Vitals: Temp: 98.6 BP: 175/85 HR: 90 RR: 16
- General: Lying in bed, no acute distress
- CV: Irregularly irregular
- Respiratory: Clear breath sounds bilaterally
- Neurological:
 - HIF: A&O x 3, able to name 6/6 objects, able to follow simple commands
 - CN: 2-12 intact
 - Motor: Left pronator drift present. Mild weakness (4/5 MRC grade) present in left arm and leg. Left finger tapping is slower and more clumsy compared to the right
 - Reflexes: 3+ biceps, BR, triceps, and patellar on the left. Toe is up on the left, down on the right
 - Sensation: Numbness to light touch in the left arm and leg, intact otherwise
- Cerebellar: FTN, HTS normal
- Gait: Strolling gait is normal
- **NIH Stroke Scale: 3**

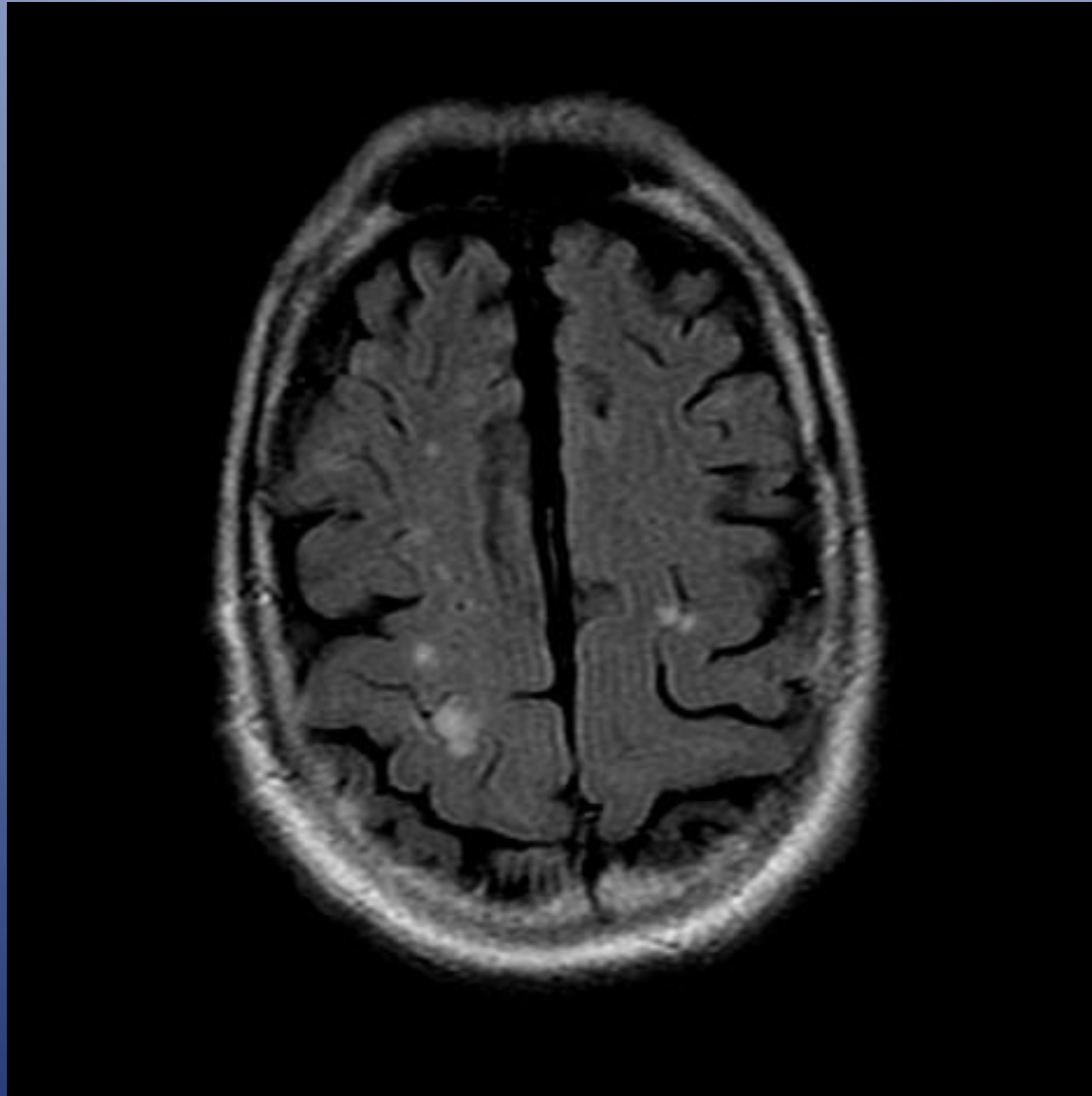
MRI Brain: DWI images







MRI Brain: T2/FLAIR image



Additional Data

- EKG: Notable for Atrial Fibrillation
- Labs: Notable for LDL of 100, HDL 35, A1c: 6.5 Rest of stroke labs were negative
- Did not qualify for tPA as she was outside the window
- Echo: normal left ventricular size, an ejection fraction >65%, and abnormal left ventricular diastolic filling. The left atrium was mild to moderately dilated. There was mild mitral regurgitation, mild pulmonary hypertension, and no evidence of patent foramen ovale with agitated saline
- **CHADS2 Score:** 3 (Hypertension, age, & diabetes)
- **CHA₂DS₂-VASc:** 5 (hypertension, age (2), diabetes, and female sex)

Stroke Risk Factors and Management

Our patient's risk factors for stroke

- Atrial Fibrillation
- Hypertension
- Metabolic Syndrome (Hypertension, dyslipidemia, diabetes)

Atrial Fibrillation

- Increases 4-5 fold the risk of ischemic stroke
- Associated with higher death and disability
- ~60% of atrial fibrillation patients that are 75 years and over are women



CHADS₂ vs. CHA₂DS₂-VASc

CHADS ₂		CHA ₂ DS ₂ -VASc	
Risk factors	Points	Risk factors	Points
<u>CHF</u>	1	<u>CHF/LVEF ≤ 40%</u>	1
<u>HTN</u>	1	<u>HTN</u>	1
<u>Age ≥ 75</u>	1	<u>Age ≥ 75</u>	2
<u>DM</u>	1	<u>DM</u>	1
<u>Stroke/TIA/embolism</u>	2	<u>Stroke/TIA/embolism</u>	2
	Max 6	<u>Vascular disease (prior MI, PAD, or aortic plaque)</u>	1
		<u>Age 65-74 years</u>	1
		<u>Sex category (Female)</u>	1
			Max 9

Annual Stroke Risk

CHADS₂ → CHA₂DS₂VASc

CHADS ₂ score	Patients (n = 1733)	Adjusted stroke rate %/ year
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

CHA ₂ DS ₂ -VASc score	Patients (n = 7329)	Adjusted stroke rate %/ year
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

From ESC AF Guidelines http://www.esc-rfp.org/guidelines/n/af/esc_guidelines/GuidelinesDocument/afguidelines-fp-F-T.pdf

2014 AHA/ASA Stroke Guidelines re: Atrial Fibrillation

- Use risk stratification tools such as CHADS2 and CHA₂DS₂-VASc scores
- **Screen elderly women (especially women >75 years) using pulse taking followed by ECG in the primary care setting**
- Oral anticoagulation in women <65 years old with AF alone is NOT recommended (CHADS2 =0 or CHA₂DS₂-VASc = 1)
- Novel anticoagulants may be useful alternative

2014 AHA/ASA Stroke Guidelines re: Hypertension



- **MOST** modifiable risk factor for stroke
- **POORLY** controlled in older women
- Women with prehypertension: 93% increased stroke risk compared to men
- Insufficient evidence to warrant different approach for BP treatment in women and men
- BP recommendations for prevention of stroke are the **SAME** for women and men

EARLY treatment of BP is critical!

2014 AHA/ASA Stroke Guidelines re: Obesity, Metabolic Syndrome and Lifestyle Factors

- Maintain healthy lifestyle with regular physical exercise, moderate alcohol consumption, cessation from cigarette smoking, and diet rich in fruits and vegetables (DASH diet) for primary stroke prevention in women with cardiovascular risk factors
- Lifestyle interventions focusing on diet and exercise recommended for stroke prevention in women at HIGH risk for stroke



In our patient....

- Etiology of stroke: Shower of embolus from atrial fibrillation
- Started on dabigatran for anticoagulation
- Hydrochlorothiazide added for better BP control
- Simvastatin added for high LDL
- Doing scheduled physical therapy and rehabilitation for exercise and weakness
- Met with dietician regarding her diet

Case #2

- 35 y/o right handed African American woman G2P1 28 3/7 weeks pregnant presents with a one day history of nausea and vomiting, left-sided headache, blurred vision, weakness of the right side, and incoherent speech.

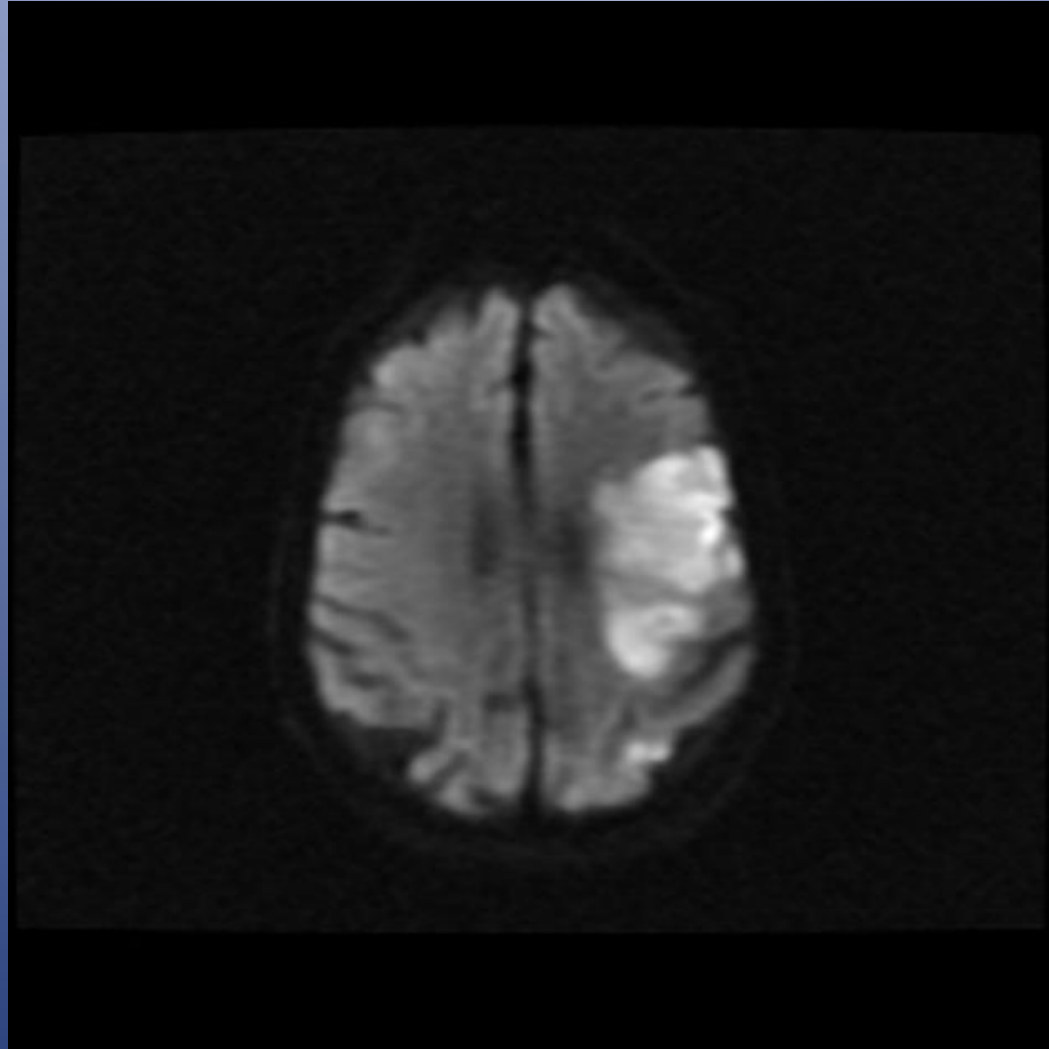
History and Physical

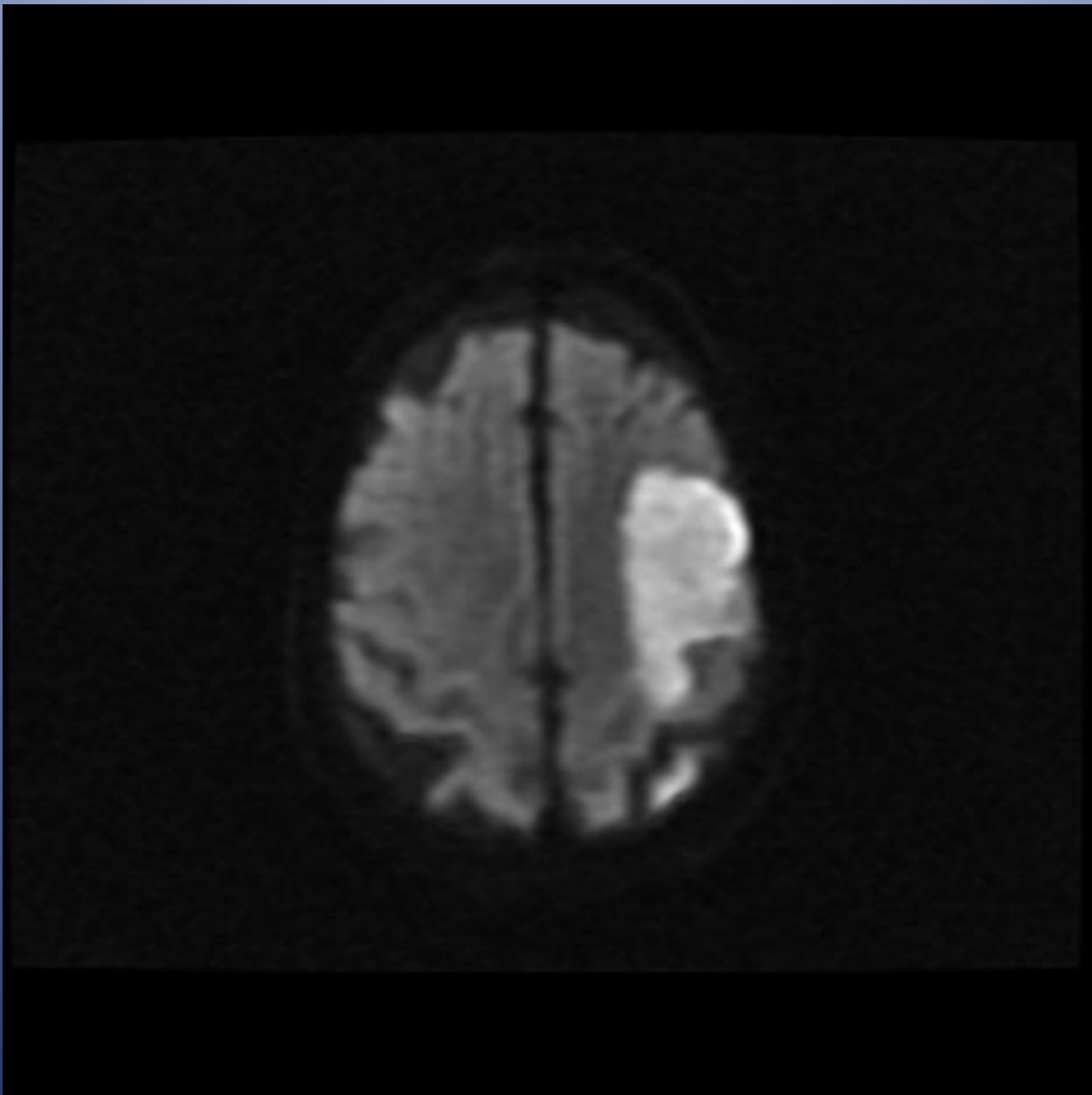
- PMH: None
- Past gynecological history: Delivered healthy baby girl 2 years ago by c-section. Previous pregnancy complicated by preeclampsia
- Medications: Pre-natal vitamin
- Family history: No family history of strokes, seizures, or other neurological conditions
- Social history: Does not smoke, drink alcohol or use recreational drugs
- Allergies: No known drug allergies

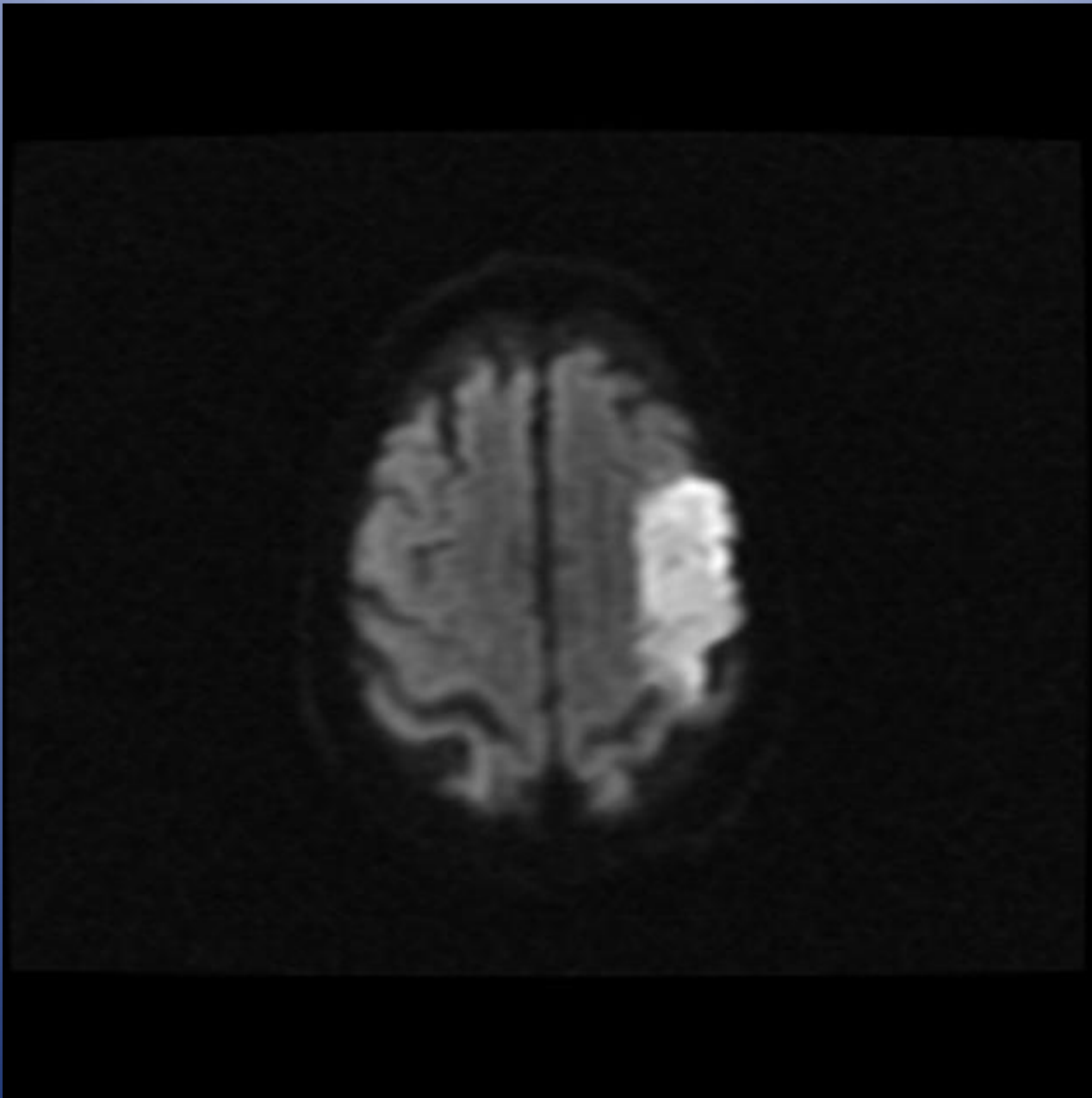
Examination

- Vitals: T: 98.6 BP: 170/90 HR: 80 RR: 18
- General: Confused, but no acute distress
- Cardiovascular: RRR, no murmurs appreciated
- Lungs: Clear to auscultation bilaterally
- OB: Normal fetal heart tones
- Neurological:
 - HIF: Drowsy but arousable. Severe expressive aphasia with severe dysarthria.
Able to follow two simple commands.
 - CN: Notable for right upper motor neuron weakness
 - Motor: Right hemiparesis of arm and leg
 - Reflexes: 3+ right biceps, BR, triceps, and patellar reflexes, 2+ on the left. Toes are up on the right, down on the left
 - Sensation: Numbness to light touch on the right face, arm, and leg
 - Cerebellar: Unable to perform finger to nose, heel to shin on right, intact on left
 - Gait: Unable to walk secondary to weakness
- **NIH stroke scale: 14**

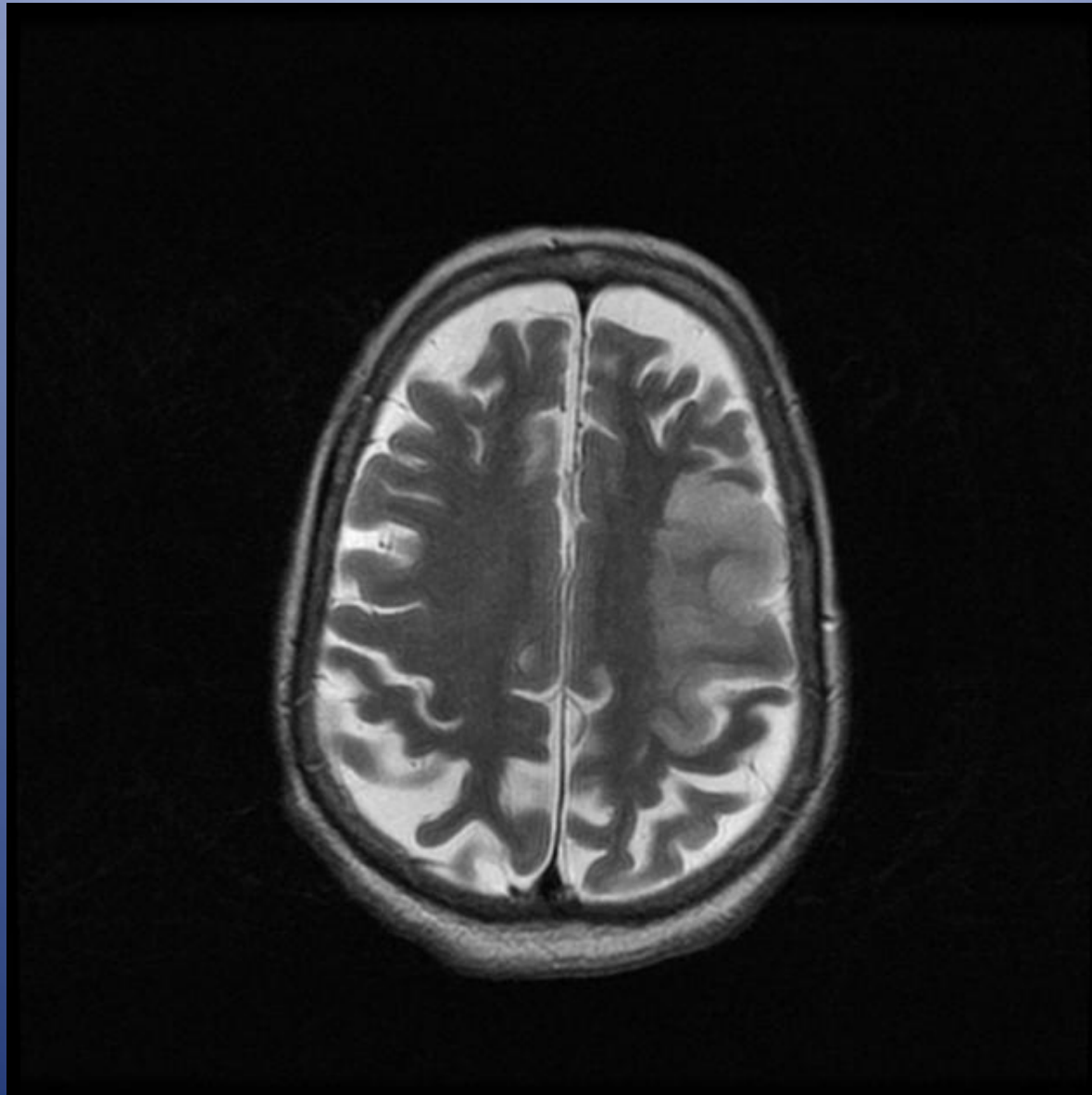
MRI Images—DWI

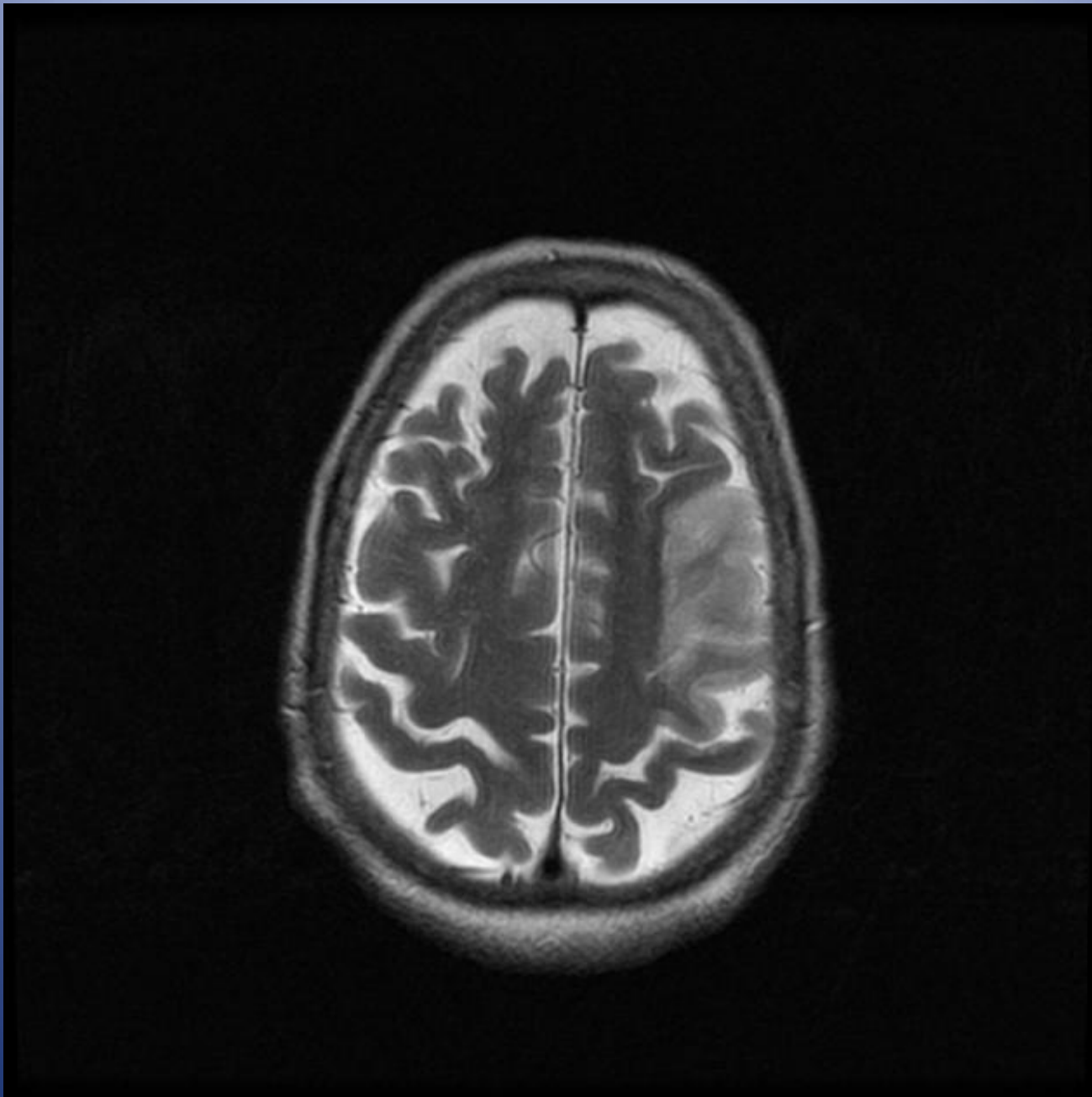






MRI Images—T2/FLAIR





Additional Data

- EKG: Normal Sinus Rhythm
- Labs: Stroke labs were negative
- Did not qualify for tPA as she is pregnant
- Echo: normal left ventricular size, an ejection fraction $>65\%$, and normal left ventricular diastolic filling. No evidence of patent foramen ovale with agitated saline
- Lower extremity dopplers: Negative for blood clot

Stroke Risk Factors and Management

Our patient's risk factors for stroke

- Pregnancy
- Prior history of pre-eclampsia
- Age (35 years old)
- Ethnicity (African- American)

Pregnancy and Stroke

- Stroke is **UNCOMMON** in pregnancy (34 strokes/100,000 deliveries) but risk of stroke is **HIGHER** in pregnant vs. non-pregnant women (21 per 100,000)
- Stroke risk **HIGHEST** in 3rd trimester and post-partum period up to 6 weeks
- Pregnancy related HTN is **LEADING** cause of both hemorrhagic stroke and ischemic stroke



Risk factors for pregnancy-related stroke

- Preeclampsia, eclampsia, or pregnancy induced hypertension
- Pregnancy physiological changes: activated protein C resistance, lower levels of protein S, increased fibrinogen
- Complications of pregnancy and labor and delivery: hyperemesis gravidarum, anemia, thrombocytopenia, postpartum hemorrhage, transfusion, fluid, electrolyte and acid-base disorders, infection, pre-term birth, small for gestational age baby, first-trimester bleeding
- Age >35 years old
- African-American ethnicity
- C-section → controversial

Causes of ischemic stroke during pregnancy

Table 2

Published causes of ischemic stroke during pregnancy.

Etiologies of ischemic stroke	Preeclampsia/eclampsia (%)	CNS vasculopathy (%)	Arterial dissection (%)	TTP/DIC (%)	Thrombophilia (%)	Amniotic fluid embolism (%)	Cardioembolic (%)	Atherosclerosis (lacune) (%)	Ref.
Kittner <i>et al.</i> , n (%) (total n = 17)	4 (24)	3 (18)	1 (6)	1 (6)	–	–	–	–	[1]
Sharshar <i>et al.</i> , n (%) (total n = 15)	7 (47)	1 (7)	1 (7)	–	1 (7)	1 (7)	–	–	[8]
Jaigobin <i>et al.</i> , n (%) (total n = 21)	6 (29)	–	1 (5)	–	5 (24)	–	4 (19)	–	[11]
Jeng <i>et al.</i> , n (%) (total = 27)	1 (4)	–	–	–	10 (37)	–	9 (33)	–	[20]
Liang <i>et al.</i> , n (%) (total n = 11)	2 (18)	–	–	–	–	1 (9)	4 (36)	1 (9)	[12]

DIC: Disseminated intravascular coagulation; TIP: Thrombotic thrombocytopenic purpura.

Causes of pregnancy-related intracerebral hemorrhage

Table 3

Published causes of pregnancy-related intracerebral hemorrhage.

Etiologies of ICH	Preeclampsia/eclampsia (%)	Vascular anomaly (%)	Cocaine (%)	CNS vasculopathy (%)	DIC/coagulopathy (%)	Ref.
Kittner <i>et al.</i> , n (%) (total n = 14)	2 (14)	3 (21)	2 (14)	2 (14)	–	[1]
Bateman <i>et al.</i> , n (%) (total n = 425)	129 (31)	30 (7)	–	–	36 (9)	[7]
Sharshar <i>et al.</i> , n (%) (total n = 16)	7 (44)	6 (38)	–	–	–	[8]
Jaigobin <i>et al.</i> , n (%) (total n = 13)	1 (8)	8 (62)	–	–	2 (15)	[11]
Jeng <i>et al.</i> , n (%) (total = 22)	7 (32)	8 (36)	–	–	1 (5)	[20]
Liang <i>et al.</i> , n (%) (total n = 21)	5 (24)	6 (29)	–	–	4 (19)	[12]

DIC: Disseminated intravascular coagulation; ICH: Intracerebral hemorrhage.

Preeclampsia, eclampsia, and pregnancy-induced hypertension



- Women with HTN during pregnancy are **6-9 times** more likely to have a stroke
- Increases risk of both ischemic and hemorrhagic stroke
- Preeclampsia and eclampsia causes reversible posterior leukoencephalopathy syndrome and intracerebral hemorrhage
- Preeclampsia and gestational hypertension → associated with higher risk of stroke beyond childbearing years

2014 AHA/ASA Stroke Guidelines re: Preeclampsia and Pregnancy Outcomes

Prevention of Preeclampsia

- Women with chronic primary or secondary HTN or previous pregnancy related-hypertension should take **low-dose aspirin from 12th week of gestation until delivery**
- Calcium supplementation (1g/day) should be considered in women with low dietary intake of calcium (<600 mg/d)



2014 AHA/ASA Stroke Guidelines re: Preeclampsia and Pregnancy Outcomes

Treatment of HTN in Pregnancy and Post-partum

- Severe HTN (>160/110) should be treated with safe and effective medications (labetalol, methyldopa, and nifedipine)
- Moderate HTN (150-159/100-109): consider treating hypertension with safe and effective medications
- Atenolol, ARBPs, and direct renin inhibitors are **CONTRAINDICATED** in pregnancy
- After giving birth, women with chronic HTN should be continued on anti-HTN medications with dose adjustments. Also women should be monitored carefully for development of postpartum preeclampsia

2014 AHA/ASA Stroke Guidelines re: Preeclampsia and Pregnancy Outcomes

Prevention of Stroke in Women with a History of Preeclampsia

- Consider evaluating all women 6-12 months postpartum as well as those who are past childbearing age, for a history of preeclampsia/eclampsia and document this history as a risk factor
- Evaluate and treat for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidemia

In our patient....

- Etiology of stroke: Preeclampsia causing reversible cerebral vasoconstriction syndrome
- Started on low dose aspirin
- Given labetalol IV for better control of her BP and discharged on labetalol PO
- Discharged to acute inpatient rehabilitation for physical and speech therapy

Case #3

- 25 y/o woman with history of migraine with aura and asthma presented with a 2 day history of headache, blurred vision, and vomiting. She describes a throbbing pain on the left side of her headache. States it is very different from her typical migraine headache. Tried taking Excedrin migraine which did not help.

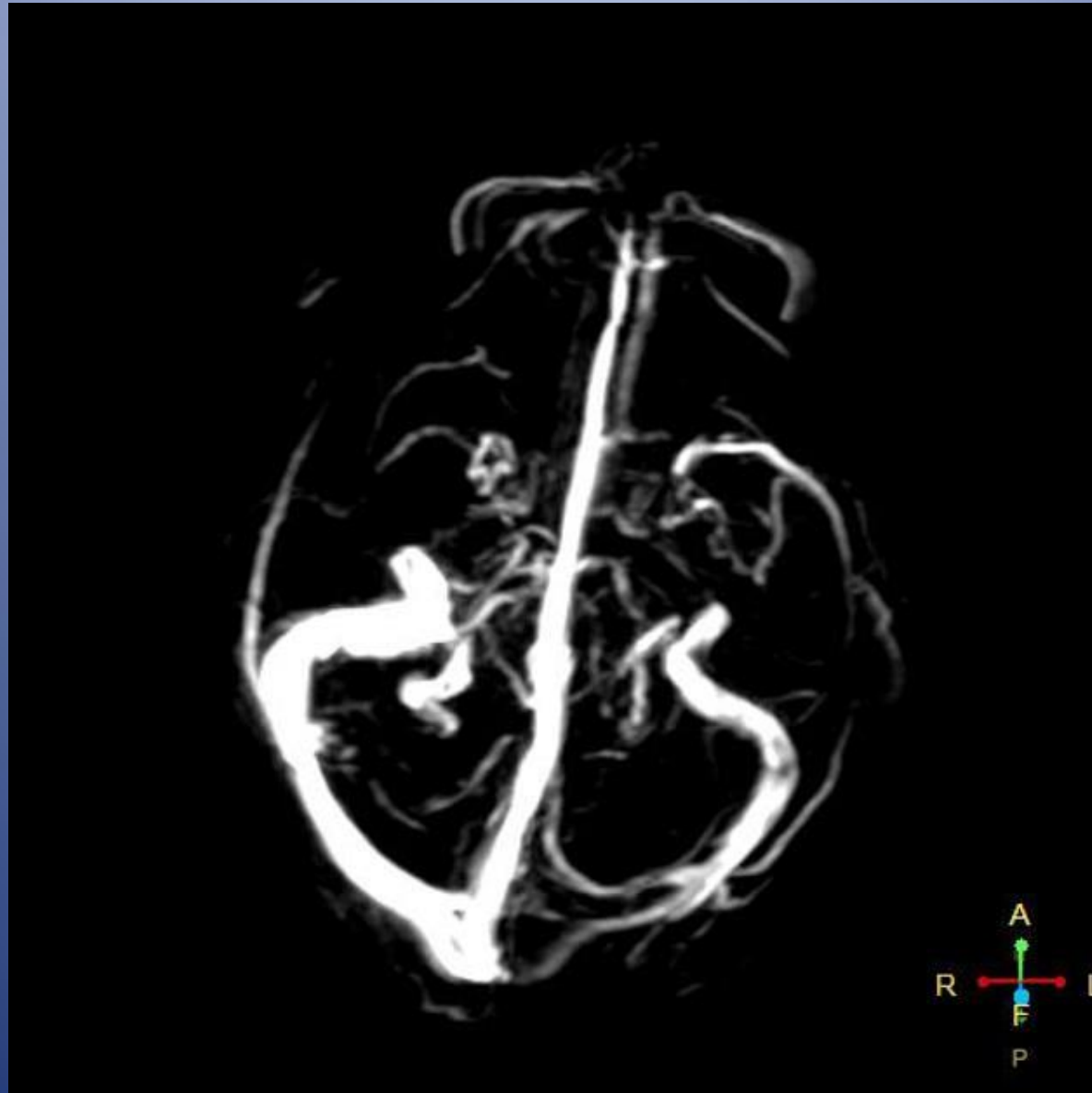
History and Physical

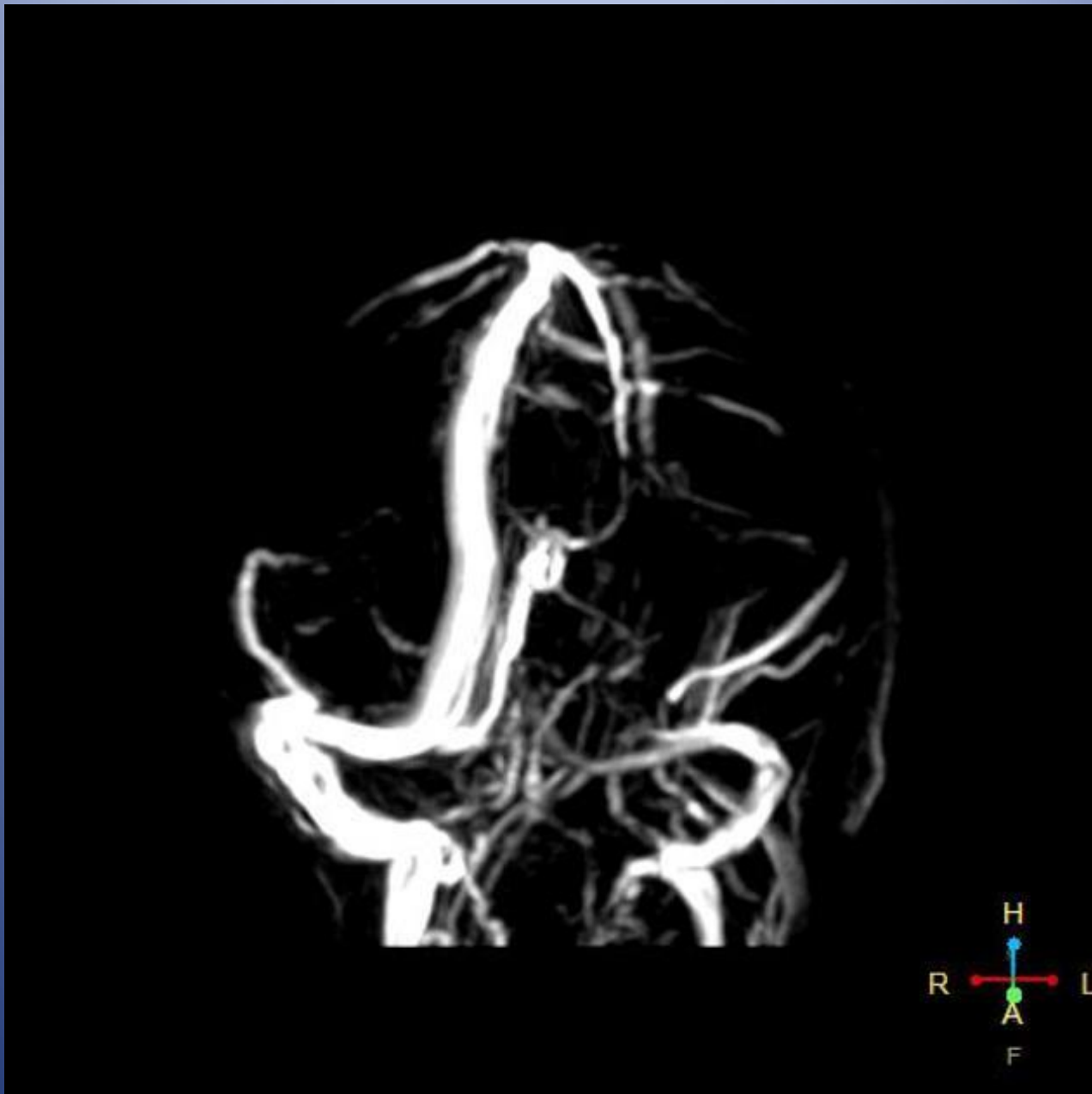
- **PMH:** Migraine with aura, asthma
- **FH:** Migraine in mother and brother
- **SH:** Does not smoke, drink alcohol, or use illicit drugs. Masters student in Neuroscience
- **Medications:** Excedrin Migraine prn headache, Loestrin
- **Allergies:** None

Examination

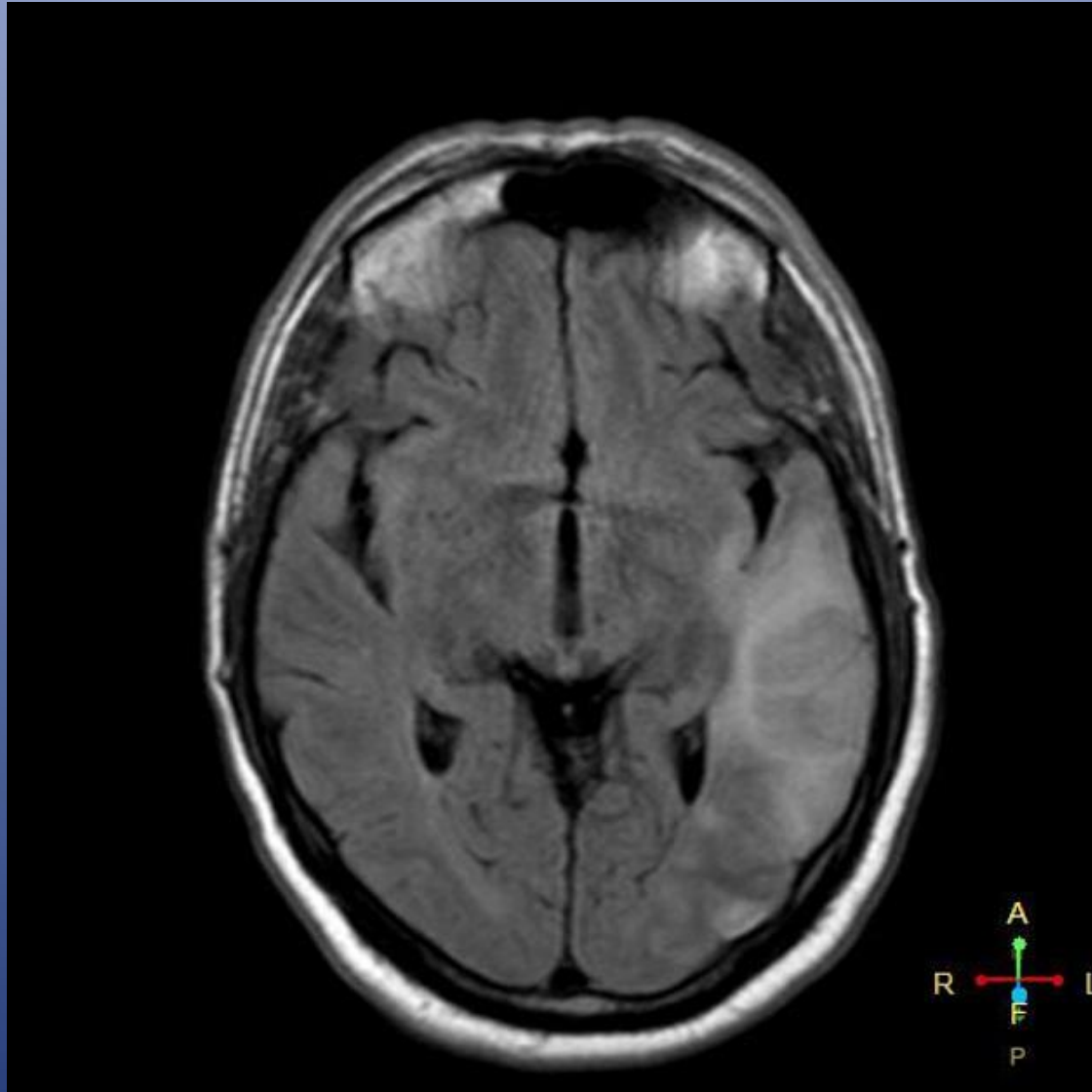
- Vitals: T: 96 BP: 120/65HR: 89 RR: 16
- General: Mildly distressed from pain
- Cardiovascular: RRR, no murmurs appreciated
- Lungs: Clear to auscultation bilaterally
- Neurological:
 - HIF: A&O x 3. Fluent speech. Able to follow two simple commands.
 - CN: Notable for bilateral papilledema and diminished visual acuity
 - Motor: 5/5 strength in upper and lower extremities bilaterally throughout
 - Reflexes: 2+ biceps, BR, triceps, and patellar reflexes. Toes were both down
 - Sensation: Intact to light touch in all extremities
 - Cerebellar: FTN was intact b/l. HTS intact
- Gait: Took a few steps; narrow based gait
- **NIH stroke scale: 0**

MRV Images





MRI Image—FLAIR



Cerebral Venous Thrombosis(CVT)

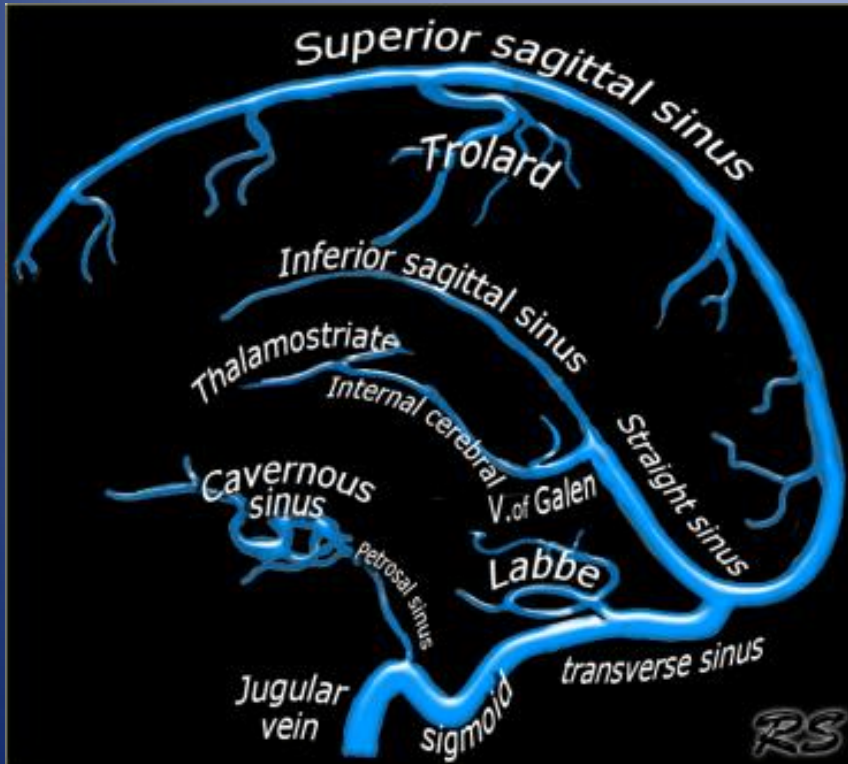
Risk Factors and Management

Our patient's risk factors for CVT

- Oral contraception

Cerebral Venous Thrombosis (CVT)

- Make up 0.5-1% of all strokes
- >70% of those affected are women
- 2 major risk factors: oral contraception and pregnancy
- Most pregnancy-related CVT occurs in 3rd trimester and first four weeks post partum
- Treatment: anticoagulation with IV unfractionated heparin or LMWH followed by oral anticoagulation



2014 AHA/ASA Stroke Guidelines re: Cerebral Venous Thrombosis

Management of acute CVT

- Routine blood studies (CBC, chem, PT, aPTT) should be performed
- Screening for prothrombotic conditions that may predispose pts to CVT is recommended (OCPs, underlying infectious disease, infection)
- Testing for prothrombotic conditions (Protein S and C, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A, and factor V Leiden) can be beneficial. Test for protein S, Protein C, and antithrombin deficiency 2-4 weeks AFTER completion of anticoagulation
- Provoked CVT: Anticoagulate with vitamin K antagonist for 3-6 months
- Unprovoked CVT: Anticoagulate with vitamin K antagonist for 6-12 months

2014 AHA/ASA Stroke Guidelines re: Cerebral Venous Thrombosis

Recurrent CVT

- Patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia should be considered for indefinite anticoagulation



2014 AHA/ASA Stroke Guidelines re: Cerebral Venous Thrombosis

CVT during pregnancy

- Use LMWH in full anticoagulant doses throughout pregnancy
- LMWH or vitamin K antagonist should be continued for >6 weeks post partum (for minimum duration of therapy of six months)
- Future pregnancies is NOT contraindicated in these women.
- Reasonable to treat acute CVT with full dose LMWH rather than unfractionated heparin
- Reasonable to use LMWH prophylaxis during future pregnancies and post-partum period



Oral Contraception

- Increases risk of ischemic stroke and CVT 1.4-2.0 fold
- Factors that further increase risk: prior thromboembolic events, HTN, CIGARETTE SMOKING, hyperlipidemia, diabetes, and obesity
- Unclear whether it increases risk of hemorrhagic stroke
- Marginally increases BP and infrequently leads to hypertension

2014 AHA/ASA Guidelines re: Oral Contraception (OC)



- OC may be harmful in women with additional risk factors (cigarette smoking, prior thromboembolic events)
- Among OC users, aggressive therapy of stroke risk factors is reasonable
- Screening for pro-thrombotic conditions is NOT useful prior to starting hormonal contraception
- **Measurement of BP** is recommended before initiation of hormonal contraception

Migraine Headache with Aura

- Women → 4x more likely than men to have migraine headache
- **NO evidence** that specific treatment strategies (calcium channel blockers, beta blockers, anti-epileptic drugs) reduce risk of stroke



2014 AHA/ASA Stroke Guidelines re: Migraine with Aura

- Treatments to reduce migraine frequency might be reasonable although evidence is LACKING that this treatment reduces risk of first stroke
- Strongly recommend smoking cessation in women with migraine headaches with aura

In our patient...

- LMWH heparin was initiated with a bridge to Coumadin (target INR was 2.0-3.0). Continued on Coumadin for 6 months
- OC was discontinued. She agreed to use a Mirena IUD for contraception
- 7 months later, she was tested for prothrombotic conditions and tested negative
- Likely etiology of CVT: prothrombotic state from hormonal contraception

**Other Risk Factors for Stroke
Unique to or More Common in
Women**

Post-Menopausal Hormonal Therapy

- Menopause and risk of stroke may be related but evidence is **INCONSISTENT**
- Hormonal therapy use for primary and secondary prevention of stroke is **UNIVERSALLY NEGATIVE** (HERS, WEST, and WHI HT studies)
- Hormone therapy in all formulations does **NOT** stroke risk and may increase the risk of stroke

2014 AHA/ASA Stroke Guidelines re: Postmenopausal Hormone Therapy

- Hormone Therapy (conjugated equine estrogen with or without medroxyprogesterone) should NOT be used in the primary or secondary prevention of stroke
- Selective estrogen receptor modulators (raloxifene, tamoxifen, or tibolone) should not be used in the primary prevention of stroke



Stroke Prevention Strategies

Carotid Stenosis

- Women with symptomatic carotid stenosis may be LESS LIKELY to receive CEA than men
- CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) showed women have HIGHER percentage of peri-procedural complications compared to men
- Management of symptomatic and asymptomatic carotid stenosis is SAME in both sexes

2014 AHA/ASA Stroke Guidelines re: Carotid Stenosis Management

- Women with asymptomatic carotid stenosis should be screened for treatable risk factors for stroke
- Women undergoing CEA → ASA is recommended unless contraindicated
- Prophylactic CEA performed <3% morbidity/mortality can be useful in highly selected patients with asymptomatic carotid stenosis

2014 AHA/ASA Stroke Guidelines re: Carotid Stenosis Management

Severity of ipsilateral carotid stenosis	Recommended procedure
Severe (70-99%)	CEA if perioperative M&M <6%
Moderate (50-69%)	CEA if perioperative M&M <6%

When CEA is indicated with women with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery

Aspirin for Stroke Prevention



- No convincing evidence that a specific antiplatelet therapy or dosage is more/less beneficial in women than men
- Women's Health Study (WHS) showed 100 mg ASA did not reduce risk of MI or death from CV causes, but did reduce stroke events
- One metaanalysis of aspirin and primary prevention showed women are protected from stroke whereas men are protected from MI
- ATT trial (Antithrombotic trial) showed **NO SEX** difference of any vascular outcomes

2014 AHA/ASA Stroke Guidelines re: Aspirin for Stroke Prevention

- ASA therapy (75-325 mg/d) reasonable in women with diabetes mellitus unless contraindicated
- In high-risk (10 year predicted CVD risk >10%), women has indication of ASA but intolerant of ASA, then clopidogrel should be substituted
- ASA therapy can be useful in women >65 years old (81 mg/day or 100 mg/day every other day) if BP is controlled and benefit for IS and MI prevention outweighs the risk of GI bleeding and hemorrhagic stroke and may be reasonable in women <65 y/o for ischemic stroke prevention

Questions?



References

1. Bushnell, C, et. al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014 May;45(5):1545-88.
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3. Howard, V, et. al. Influence of Sex on the Outcomes of Stenting Versus Endarterectomy: a Subgroup Analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol*. 2011 Jun;10(6):530-7
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