



# VCU Department of Neurology PGY-3 Case Presentations

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## HPI:

- KW is a 15 yo RHAAM who at 6pm 12/26/05 initially noted an unusual sensation in his R arm
- later that evening upon awakening, KW attempted to get out of bed and fell to his R onto the floor and was unable to talk per parents

## HPI cont:

- 12pm 12/26- arrived to outside ER where he was found to have dense R hemiplegia and global aphasia. After a negative HCT he was initiated on ASA 325mg, continued on 81mg qd and transferred to the PICU
- 12/27- MRI with DWI noted a large L MCA ischemic infarct, with occlusion of L MCA on MRA.

## HPI cont:

- Examination of KW revealed him to be somnolent, nonverbal but following a few simple commands.
- TTE with bubble study was normal. Repeat HCT later that evening noted L MCA hypodensity with a 1 cm shift, subfalcine/uncal herniation and questionable small hemorrhagic transformation.
- Subsequently he was given 25gms of mannitol, electively intubated and hyperventilated. On 12/28 he was transferred to VCU for neurosurgery evaluation.

## PMHx, Meds, SocHx and FamHx:

- ADHD, on no medications. NKDA
- Healthy, athletic teenager with no history of tobacco, alcohol or drugs use. He participated in football at school, though not in the 2005 season due to arm fractures during the early summer.
- one sibling with +SS trait and older (>65 yrs) aunts, uncles and grandparents with HTN, stroke and MI. There was no family history of people < 50 who had DVT, PE, stroke or MI, and he had 4 siblings, ages 13-24 that were healthy.

## Hospital course:

- The majority of KW's stay at VCU consisted of ICU care to control his increased intracranial pressure (ICP). Upon arrival he was given a R frontal ventriculostomy for accurate ICP monitoring.
- Initiated on the increased ICP protocol, consisting of mannitol prn elevated ICP, hyperventilation, hypothermia to 35 degrees Celsius, HOB at 30 degrees, as well as paralytics and sedatives.

Sensation 64  
Ex: 31012  
ThinSliceSeq 4.8 H42s  
Se: 2/2  
Im: 18/2  
Ax: 1105.2 (COI)  
JN/JW-1829558  
NO CONTRAST  
512 x 512  
H42s

A

W

Acq T

R

120.0 kV  
200.0 mA  
4.8 mm/0.0:1  
Tilt: -4.5  
1.0 s  
W:100 L:50

P

DFOV: 23.0 x 23.0cm



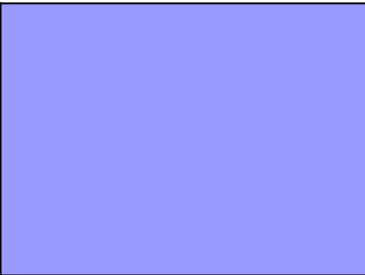
## Hospital course cont.

- The family consented for craniotomy, however after a week of the above medical interventions including 2-5 doses of 100gm of mannitol/day, the clinical exam and HCTs improved and craniotomy was not necessary.
- Dilantin was started for seizure prophylaxis and then switched to phenobarbital because of its dual use in decreasing ICP and seizure prophylaxis. Previously, an EEG was done 12/28 at CJW which noted slowing on L without epileptiform activity. This was repeated on 12/30 and 1/5 at VCU with similar results.

Sensation 16  
Ex: 31012  
ThinSliceSeq 4.5 H45s  
Se: 2/2  
Im: 19/2  
Ax: 16.9 (COI)  
DWN/1841380  
NO CONTRAST  
512 x 512  
H45s

A

Medica  
W



Acq T...

R

L



120.0 kV  
450.0 mA  
4.5 mm/0.0:1  
Tilt: -8.5  
1.0 s  
W:80 L:35

P

DFOV: 23.0 x 23.0cm

## Hospital course cont.

- By 1/12 the HCT showed almost complete resolution of the midline shift with no evidence of herniation. The ICP monitor was removed on 1/13 and ASA 325 was re-started. The etiology of KW's stroke remained unclear.
- The only abnormality in his extensive hypercoagulable work-up was an elevated lipoprotein a (Lp(a)) level of 143 (normal <30).

# Differential Dx:

## Large Vessel stroke in an adolescent

**Embolic vs. Thrombotic** → History, Neuroimaging and Echocardiogram

### **Hypercoagulable States**

#### **Acquired**

Drugs  
Surgery, trauma, burns, central lines  
Pregnancy  
Infections  
Malignancies  
SLE  
Smoking  
Vasculitis  
Dehydration  
Carotid Dissection

#### **Inherited**

Factor V Leiden  
PT 20210  
Homocysteine / MTHFR  
Anti-thrombin III mutation  
Prot C and S deficiencies  
Fibrinogen/Plasminogen abn  
Elevated Lp(a)  
Sickle cell disease  
Severe Dyslipidemia  
Polycythemia

## DDx cont.

- Other etiologies to consider- congenital heart malformations, vascular abnormalities, connective tissue diseases, organic acid disorders, ornithine transcarbamylase deficiency, alpha-galactosidase A defect, CADASIL, mitochondrial disorders (MELAS).

**TABLE 1.** Incidence of Genetic Risk Factors for Thrombophilia in Children With Arterial or Venous Thromboembolism

	Arterial Thrombosis (n = 36)	Venous Thrombosis (n = 36)
Genetic risk factors	21/36 (58 %)	29/36 (80 %)
Lipoprotein (a)	8/36 (22 %)	5/36 (14 %)
Factor V Leiden	11/36 (30 %)	14/36 (38 %)
Protein C deficiency type I	2/36 (5.5%)	8/36 (22 %)
Antithrombin deficiency type I	0/36	2/36 (5.5%)


## Final Diagnosis:


### **L MCA ischemic infarct secondary to elevated Lp(a)**

- Diagnosis of exclusion.
- Thrombosis was felt to be more likely than embolic due to normal echo and MRA of the neck as well as the slow onset of symptoms.
- Extensive lab work-up of the above acquired and inherited risk factors were found to be wnl except the Lp(a) level which was 143 mg/dL.
- Since elevated Lp(a) is now an established prothrombotic factor that can contribute to spontaneous ischemic stroke in children and young adults,<sup>1</sup> this was felt to be the cause of this otherwise cryptogenic stroke.

## **How does Lp(a) cause a prothrombotic state and should we routinely assess for it in all pts <55 years old with stroke?**

- Lp(a) is a cholesterol rich plasma lipoprotein with a lipid composition similar to LDL.
- Different from LDL in that it is made of 2 apolipoproteins (a) and (b) that are bound by a disulfide bridge.
- The apo (a) chain has five domains called “kringles.”
- The fourth kringle can fit into the fibrin-binding site of plasminogen, blocking its activation and the clot lysis that the activation would accomplish.
- Lp(a) competes with plasminogen binding and interferes with fibrinolysis.<sup>2,3</sup>
- Lp(a) promotes the deposition of cholesterol in atherosclerotic plaques by binding to macrophages that promote foam cell formation.<sup>3</sup>

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- The majority of evidence to date supports the role of elevated Lp(a) as a risk factor for atherosclerosis and its complications.
  - Significant associations have been found in both sexes and in different ethnic groups with the level of Lp(a) and the presence and severity of CAD, MI, restenosis after angioplasty and cerebrovascular disease.<sup>2</sup>
  - Review of the literature indicates that Lp(a) levels should be added to the basic hypercoagulable work-up done on stroke patients < 55 yo.

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- Per evidence based articles the initial lab work for a young person with ischemic stroke are the following:
    - CBC, BMP, ESR, fasting glucose, PT,PTT, lipid profile, RPR, tox screen, anticardiolipin antibodies, pregnancy screen, hgb electrophoresis, homocystine and L(a).
  - Then if the dx is still elusive the additional blood work should consist of:
    - antithrombin III, protein C and S antigen and activity, DD, FSP, fibrinogen, other antiphospholipid antibodies, factor V Leiden mutation, prothrombin 20210 mutation, Russell viper venom time and HIV

# Therapeutic Options

## Aspirin

- A small study by Akaike et al in 2002 found that in pts with elevated Lp(a) levels and known CAD or cerebral infarction ASA 81mg significantly lowered Lp(a) levels to 80-85% of baseline levels after three months. Patients with the high molecular weight isoform benefited the most. They proposed that ASA lowers Lp(a) levels by reducing the apo(a) gene transcription.<sup>5</sup>

# Therapeutic Options cont.

## Nicotinic Acid

- A dose of 3-4 g/d can lower Lp(a) levels by as much as 38%.<sup>3,6</sup>

## Hormones

- Conjugated estrogens have been reported to reduce Lp(a) levels by 15-50% in postmenopausal women and by 50% in men with prostate cancer.<sup>2,3</sup> One review article also states that androgens, progestins have similar effects.<sup>2</sup>

\*\*\*Statins and bile acid sequestrates do NOT reduce Lp(a) levels.<sup>2,3</sup>



# **Patient/Family Resources**

## 1. Pediatric Stroke Network

<http://www.pediatricstrokenetwork.com/>

## 2. American Stroke Association web site

-Life after Stroke

-Recovery; Pediatric Stroke; For Family Caregivers; etc.

<http://www.strokeassociation.org>

# Outcomes

- **With treatment Lp(a) levels can be significantly reduced which should decrease risk of further thrombotic events.**
- In KW's case, after 2 weeks of ASA 325mg and 3 weeks of Niacin 100mg TID his Lp(a) level came down to 58mg/dL.
- With the help of speech therapy, PT and OT, by the time of discharge on 1/30 to an in-patient rehab facility he was alert with full strength on L, taking a pureed and honey-thickened diet, following 1-step commands and vocalizing a few small words. His residual deficits included a severe R hemiparesis, R VF cut and significant aphasia.

## Question #1:

At present, screening and treatment for Lp(a) excess levels should only be considered for which of the following:


- a. patients with coronary heart disease and no other identifiable dyslipidemia
- b. patients with a strong family history of coronary heart disease and no other dyslipidemia
- c. patients with HTN and early premature target organ damage
- d. patients with hypercholesterolemia refractory to therapy with statins and bile acid sequestrants
- e. patients less than age 55 with ischemic stroke and no obvious etiology

- A. a, c and e
- B. all except b
- C. a and e only
- D. all of the above
- E. none of the above



Answer: D all of the above<sup>3</sup>

- Currently there is much more evidence available in the literature regarding elevated Lp(a) levels associated with CAD than with cerebral artery disease.
- Due to the genetic nature of the dyslipidemias it is recommended that even patients who simply have a strong family history of CAD without abnormalities in their standard lipid profile should be tested for elevations in their Lp(a) levels.

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- This could be extrapolated to 1st degree relatives of patients with any thrombotic event of unclear etiology at a young age (<55).
  - Multiple studies have found an association with elevated Lp(a) levels and ischemic stroke, and the consensus is to evaluate for this in patients who have an uncertain cause for the stroke or who have a family history significant for DVT, PE, CAD, venous sinus thrombosis or ischemic stroke at a younger age.<sup>1,4,6,8,9</sup>



Question #2:

Which of the choices listed, has the highest incidence of stroke in children (ages 1yr-18 yrs)?


- A. Small vessel disease
- B. Moyamoya
- C. Dissection
- D. Prothrombotic state
- E. Vasculitis



Answer: D-

Prothrombotic state is the most common  
(of the choices given)

- When using the TOAST criteria to categorize childhood stroke, most fall into cardioembolic (CE), other, or unknown.
- The proportion of children with large-vessel atherothromboembolic or small vessel disease has been found to be extremely low, as one would expect.


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- Studies from the Mayo Clinic and Case Western Reserve found that CE accounted for the highest proportion of childhood strokes, and most of these children had cyanotic heart disease.
  - Other series found the “other determined cause” category to have the highest percentage.
  - The “other” category can be further broken down, with prothrombotic state almost always occupying the majority of cases. That is if sickle cell disease is not separated out, as it makes up the preponderance of prothrombotic cases.<sup>10</sup>



Question #3:

Which of the following has the highest incidence of stroke in young adults (ages 19-45yrs)?

- A. Small vessel disease
- B. Moyamoya
- C. Dissection
- D. Prothrombotic state
- E. Vasculitis



**Answer: C-** dissection is the most common (of the choices given).

- Cervicocephalic dissection, Antiphospholipid antibodies and atherothromboembolic disease are common causes of stroke in young adults.

- A review by Williams, L.S. et al, published in Neurology found that of the 116 ischemic stroke patients between the ages of 18-45yrs studied,
  - 16% were large vessel disease related,
  - 14% were CE,
  - 3% were from small vessel disease,
  - 44% were other identified cause,
    - 15% were due to dissection,
    - 14% were from pro thrombotic state,
    - 6% were due to vasculitis
    - 5% were related to moyamoya
  - 23% had unknown etiologies

## Other Comments:

- Incidence of stroke in children is ~1-2 per 100,000 and half of these are ischemic.
- Most studies suggest that approximately 30% of the ischemic stroke cases in children are deemed to be due to an undetermined etiology
- Since early reoccurrence occurs in an estimated 10% of patients presenting with their first stroke in childhood, the search for modifiable risk factors should be a priority.<sup>7</sup>
- LP(a) elevation has established its place as a RF for cardiac disease and though the literature is more controversial regarding its association with stroke, it appears clear that it should not be overlooked when attempting to put an etiology on a stroke that would otherwise be called cryptogenic or undetermined, especially in someone <55.

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*Thanks for  
listening!*

*Any  
questions?*

