Cryptogenic Strokes in a Middle-Aged Man

**unknowns**
- vascular risks
- associated systemic features
- tox screen
- stroke treatment

**knowns**
- nonsmoker
- maternal grandmother: recurrent strokes in her 40s
- daughter: AML, age 16
- swimming, running marathons, traveling to Spain

**Cryptogenic Strokes in a Middle-Aged Man**

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**Ischemic Stroke in the Young Adult**

- the usual suspects*: hypertension, diabetes, hyperlipidemia, smoking
- arterial dissection*
  - trauma, arteriopathy
- drugs
  - cocaine, methamphetamine <OCPs>...
- infection
  - syphilis, HIV, VZV, TB & fungal meningitis, neurocysticercosis, endocarditis...
- bad blood
  - hypercoagulability: hereditary (factor V Leiden, prothrombin), acquired (APLA, cancer, HIT), both (protein S/C, AT3)...
  - cells: sickle, p vera, essential thrombocytosis...
- broken heart
  - R-L shunt, myxoma <Chagas>
- busted pipes
  - systemic or primary CNS vasculitides
- genetic syndromes
  - CADASIL, Fabry's, mitochondrial (MELAS, POLG1?)...
- other systemic disorders
  - malignant atrophic papulosis, microangiopathic hemolytic anemias, connective tissue disorders, post-radiation...

Not So Uncommon After All?

<table>
<thead>
<tr>
<th>Fabry’s Disease</th>
<th>Mitochondrial Encephalomyopathy Lactic Acidosis &amp; Stroke-Like Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>inheritance</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>systemic</td>
<td>angiokeratomata, eye, renal, cardiac</td>
</tr>
<tr>
<td>neurologic</td>
<td>painful neuropathy, ischemic stroke (small vessel)</td>
</tr>
<tr>
<td>mechanism</td>
<td>α-galactosidase A deficiency</td>
</tr>
<tr>
<td>diagnosis</td>
<td>genetic testing</td>
</tr>
</tbody>
</table>
| treatment        | enzyme replacement                                                     

α-galactosidase A deficiency


January – March 2012 (age 55): Left Leg Swelling & Erythema

calf → foot: progressive, with pain studies

LE Doppler: no DVT
leukopenic with low ANC
muscle biopsy: focal mild endomysial inflammation in 1 fascicle, with histiocytes (necrotic fibers or vessel walls?)

rx: better with prednisone?

Atraumatic Painful, Swollen Leg: Differential Diagnosis

non-neurologic

DVT
cellulitis
diabetics

muscle infarction
pyomyositis
“focal myositis”
local inflammatory myopathy
neurogenic


May 2012 (Moffitt): Problems Spanning the Neuroaxis

general exam: chronic arterial insufficiency left leg, with erythema, tenderness, pitting edema

neurological exam

bilateral hemispheric dysfunction (old on the right)
left foot drop with painful, swollen posterior compartment muscles

• inflammatory +/- ischemic (popliteal artery branches) muscle dysfunction (compartment syndrome?)
• denervation-related muscle abnormalities, in tibial nerve distribution (microvascular?)

right ulnar (versus lower plexus) sensory loss
"The Full Moffitt"

<table>
<thead>
<tr>
<th>the usual suspects</th>
<th>nonsmoker, normal blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>arterial dissection</td>
<td></td>
</tr>
<tr>
<td>drugs</td>
<td></td>
</tr>
<tr>
<td>infection</td>
<td>negative: HIV, BC x 4 (before antibiotics), RPR; CSF VDRL, VZV PCR, AFB, Whipple PCR, CSF culture likely contaminant</td>
</tr>
<tr>
<td>bad blood</td>
<td>prothrombin G20210A heterozygote normal PT/PTT, anticardiolipin IgM slightly up, protein S slightly down</td>
</tr>
<tr>
<td>broken heart</td>
<td>TTE/TEE neg with bubble, TCD of MCAs quiet x 30&quot;</td>
</tr>
<tr>
<td>busted pipes</td>
<td>current MRA/MRV (&amp; prior angio) negative; arteritis of small &amp; medium vessels?</td>
</tr>
<tr>
<td>genetic syndromes</td>
<td>focal, not generalized neuromuscular dysfunction, with systemic disease largely hematologic (lactate slightly elevated)</td>
</tr>
<tr>
<td>other systemic disorders</td>
<td>pancytopenia, hyperferritinemia, hypofibrinogenemia, ACE slightly up</td>
</tr>
<tr>
<td>disorders</td>
<td>normal: IL-2, NK cell function, kidneys, liver, lungs, SPEP, UPEP, ESR, CRP, ANA, ANCA, C3, C4, CH50</td>
</tr>
</tbody>
</table>

CSF Glucose: How Low Is Low?

| Fishman RA: CSF in Diseases of the Nervous System, 2nd ed (1992) |

Completing the Workup

<table>
<thead>
<tr>
<th>the usual suspects</th>
<th>Hgb A1C, lipid studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>arterial dissection</td>
<td>CSF VZV antibodies, Bartonella serologies</td>
</tr>
<tr>
<td>drugs</td>
<td>hemolysis studies: LDH, indirect bilirubin, haptoglobin, reticulocyte count, blood smear (bone marrow biopsy)</td>
</tr>
<tr>
<td>infection</td>
<td>review muscle biopsy, consider ophthalmology evaluation cerebral angiogram or brain biopsy</td>
</tr>
<tr>
<td>broken heart</td>
<td>cerebral angiogram or brain biopsy</td>
</tr>
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<tr>
<td>disorders</td>
<td>revisit history &amp; exam of skin and joints assessment of other vascular beds (G3?) monitor liver &amp; renal function</td>
</tr>
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UCSF/SFGH
Recurrent Cerebral Ischemia with Focal Neuromuscular Disease

not typical for cardioembolism (& relevant workup negative)

Prothrombin mutation could potentially link the patient & his maternal grandmother but seem unlikely to be sole cause for his illness.

Kidney, lung, liver (along with heart) spared, with pancytopenia

microangiopathic hemolytic syndrome (DIC or PNH) with multiple thromboses vs systemic vasculitis with central & peripheral nervous system involvement?

Paroxysmal Nocturnal Hemoglobinuria

rare hematopoetic stem cell defect: complement-mediated intravascular hemolysis

multisystem illness: visceral (especially abdominal) usually venous, neurologic involvement typically CNS, not PNS

dx: hemoglobinurics, markers of intravascular hemolysis, flow cytometry, bone marrow biopsy

tx: eculizamab + anticoagulation?

Systemic Vasculitis 101

Polyarteritis Nodosa, Classified

Chapel Hill, 2012:  
“Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCAs).”

ACR, 1990  
weight loss > 4kg  
livedo reticularis  
testicular pain  
myalgias  
mononeuritis or polyneuritis  
hypertension  
creatinine >1.5mg/dL  
HBV or HCV  
pathologic angio histology

Polyarteritis Nodosa

rare necrotizing medium (& small) vessel vasculitis  
associated with HBV: epidemiology evolving  
multisystem illness: constitutional, renal, orchitis, neurologic (PNS>CNS), cutaneous, GI, cardiovascular (pulmonary & hematologic rare)  
dx: biopsy or angio (stenoses, microaneurysms)  
tx: corticosteroids + cyclophosphamide for severe disease

Thanks

collaborators  
Mark Burish, MD PhD  
Andy Bollen, MD DVM  
co-conspirators  
Vineeta Singh, MD  
Alisa Gean, MD