Background

- Primarily observed in children with severe dehydration
  - Incidence in neonates 0.26% to 0.7%
- In adults with nephrotic syndrome, renal tumors, hypercoagulable states, and after surgery or trauma to the renal vessels
- May also involve the ureteric, gonadal, adrenal, and phrenic branches on the left
- More extensive network on venous vessels on left protects against infarction by allowing collaterals to form
Clinical Features

- Unilateral vs Bilateral; may extend into the inferior vena cava
- Chronic:
  - Insidious onset
  - Associated with extensive venous collaterals
  - Often asymptomatic
- Acute:
  - Presents with symptoms of renal infarction, including flank pain, hematuria (microscopic or gross), low grade fevers
  - Elevation in LDH
  - Renal enlargement
  - Bilateral disease, solitary kidney, or transplant may present with acute renal failure
  - Increase in proteinuria from increased pressure
  - Glycosuria from renal tubular dysfunction
  - In severe cases, rupture leading to retroperitoneal hemorrhage
Prevalence

- Risk of both arterial and venous thrombosis is higher in patients with nephrotic syndrome compared to the general population

- Prevalence of RVT varies in studies: 5% to 60%

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Membranous GN</th>
<th>MPGN</th>
<th>MCD</th>
<th>FSGS</th>
<th>Other</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llach, et al. [7]</td>
<td>29.0 (69)</td>
<td>22.2 (27)</td>
<td>20.0 (10)</td>
<td>25.0 (4)</td>
<td>9.8 (41)</td>
<td>21.9 (151)</td>
</tr>
<tr>
<td>Chugh, et al. [8]</td>
<td>42.9 (7)</td>
<td>20.0 (5)</td>
<td>26.3 (19)</td>
<td>0 (5)</td>
<td>25.0 (8)</td>
<td>25.0 (44)</td>
</tr>
<tr>
<td>Velasquez, et al. [9]</td>
<td>60.0 (5)</td>
<td>40.0 (10)</td>
<td>0 (0)</td>
<td>28.6 (7)</td>
<td>50.0 (4)</td>
<td>42.3 (26)</td>
</tr>
<tr>
<td>Wagoner, et al. [10]</td>
<td>51.9 (27)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>51.9 (27)</td>
</tr>
<tr>
<td>Overall</td>
<td>37.0 (108)</td>
<td>26.2 (42)</td>
<td>24.1 (29)</td>
<td>18.8 (16)</td>
<td>15.1 (53)</td>
<td>27.9 (269)</td>
</tr>
</tbody>
</table>

GN: glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis.

<table>
<thead>
<tr>
<th>Renal diagnosis</th>
<th>With renal vein thrombosis</th>
<th>Without renal vein thrombosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous nephropathy</td>
<td>20</td>
<td>49</td>
<td>69</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>6</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Lipoid nephrosis</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Rapidly progressive glomerulonephritis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Focal sclerosis</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Renal sarcoidosis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>1</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>0</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Focal glomerulonephritis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Acute post-streptococcal glomerulonephritis</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>33</td>
<td>118</td>
<td>151</td>
</tr>
</tbody>
</table>
Risk Factors: Mahmoodi, et al

• Retrospective, single center study of 298 patients with nephrotic syndrome
• Mean follow-up of 10 +/- 9 years
• Primary outcome: Objectively verified symptomatic thromboembolic events (both arterial and venous)
• Annual incidences of VTE and ATE were 1.02% and 1.48%, respectively (8x > general population)
• Over the first 6 months of follow-up, rates were 9.85% and 5.42%, respectively

Figure 3. Proportional-hazards analysis of association with the time to the first VTE and ATE among the total cohort. Solid squares denote the hazard ratios of VTE (black) and ATE (red), with the corresponding 95% CIs represented by the horizontal bars. HR indicates hazard ratio; MSD, multisystem disease; NE, not estimable; and P/A ratio, ratio of proteinuria to serum albumin.

Pathophysiology

• Multiple proteins of the coagulation cascade have altered levels in nephrotic syndrome
  • Levels of Factors V and VIII (cofactors in the coagulation cascade) have found to be increased in nephrotic syndrome
  • Hypoalbuminemia and/or low oncotic pressure thought to stimulate the liver to synthesize them
  • Factors V and VIII not found in the urine (too large)
  • Increased synthesis of Factors IX, X, XII as well urinary loss leads to decreased levels overall
  • Still not good explanation of hypercoagulable state
• Increased level of fibrinogen
  • Synthesis by the liver also stimulated by hypoalbuminemia
  • Levels inversely correlate to amount of albumin
• Alterations in fibrinolysis
  • Plasma plasminogen concentrations are decreased – thought to be 2/2 urinary loss
  • Increased levels of alpha-2 antiplasmin, which inhibits plasmin
Pathophysiology, cont’d

• Antithrombin-III
  • Alpha-2 globulin that is the main inhibitor of thrombin; also inhibits activated Factors VII, IX, X, XI
  • Rate of inhibition of these enzymes is markedly increased by Heparin
  • Studies have found increased urinary excretion of AT-III in nephrotic patients – classically thought that decreased AT-III was the etiology of the hypercoagulable state
  • Correlation between urine protein excretion and AT-III serum concentration is variable – may be because of increased hepatic synthesis
    • Could explain why risk of thrombosis is highest early on – when renal losses of AT-III have occurred but before increased hepatic synthesis
Chen, et al

- Study of 21 patients with nephrotic syndrome; 16 normal controls matched for age and sex
- Measured levels of TAT and FPA:
  - TAT = thrombin-antithrombin III complex, the irreversible, inactive complex formed by AT-III
  - FPA = fibrinopeptide A, one of the by-products of thrombin’s action on fibrinogen in the final process of blood coagulation (released when fibrinogen → fibrin)
- Found levels of both were significantly higher in the patients with nephrotic syndrome compared to controls
- Suggests that low grade intravascular coagulation is occurring in patients with nephrotic syndrome
- Argue that even though AT-III excretion in the urine is elevated, increased production by the liver provides enough to maintain inhibition of thrombin in vivo
- Low serum levels are explained by combination of urinary excretion and consumption in TAT complexes
- They suggest that hypercoagulability in nephrotic syndrome may be due more to an increased in vivo activation of coagulation than to urinary loss of antithrombin III
- Of note, none of the 21 pts developed thromboembolic complications (1 yr follow-up period)

Pathophysiology, cont’d

- Platelet aggregation is enhanced
  - Hypoalbuminemia
    - Leads to increased availability of normally albumin-bound arachidonic acid → increased formation of thromboxane A2, which stimulates platelet activation and aggregation
  - Hyperfibrinogenemia
    - Essential cofactor at the GPIIb/IIIa receptor
Fig. 1. Schematic representation of pathogenetic factors leading to hypercoagulability, thromboembolic phenomena, and renal vein thrombosis in nephrotic syndrome.
Diagnosis

• Renal venography = gold standard
  • Invasive and associated with complications (PE from clot dislodgement, IVC perforation, contrast-induced nephropathy)
• Intravenous pyelogram: 34.1 % sensitive, 87.2% specific
  • Becoming obsolete
• Doppler ultrasound: 85% sensitive and 56% specific
  • Variable; operator-dependent
• Computed tomography (CT): 92% sensitive and 100% specific
  • With contrast
• MRI: only a few small studies evaluating its use
Treatment

• Anti-coagulation (Heparin, Coumadin)
• Fibrinolytic therapy
  • Systemic
  • Localized
• Catheter embolectomy
Prospective study of 151 patients with nephrotic syndrome looking at the incidence of RVT, the modes of presentation (acute vs chronic), the pathologic course, and response to A/C therapy

33/151 patients with RVT
- 4 with acute disease: flank pain, CVA tenderness, hematuria
- 29 with chronic disease: asymptomatic, negative IVPs, collaterals

All patients found to have RVT (even asymptomatic) were anti-coagulated with Warfarin

Acute RVT pts were followed for four to ten months after diagnosis
Chronic RVT pts were followed for 6 to 34 months

Significant inc in Cr Cl in acute grp after tx
Pts with chronic RVT and without RVT had slight decrease in renal fxn over study period
No new thromboembolic events in Chr grp on A/C; 4 pts in control grp developed pulmonary emboli
### Systemic Thrombolytics

#### Table 1. Renal Vein Thrombosis Treated With Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Case No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Etiology</th>
<th>UREA Protein Level</th>
<th>MEASURES of Renal Biopsy</th>
<th>Pain</th>
<th>Thrombolytic Agent</th>
<th>DIVISION of Thrombolytic Therapy (ml)</th>
<th>Extent of RVThrombo-emboli</th>
<th>Follow-up</th>
<th>Renal Function Grant</th>
<th>Renal Function Follow-up</th>
<th>Repeat study of RVThrombo-emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lalvani et al., 1988</td>
<td>1</td>
<td>62</td>
<td>M</td>
<td>PAN</td>
<td>NR</td>
<td>PAN</td>
<td>Yes</td>
<td>Bilateral</td>
<td>None</td>
<td>Died at 2 mo from CNS hemorrhage</td>
<td>Not done</td>
<td>ARF</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>21</td>
<td>M</td>
<td>Minimal change</td>
<td>NR</td>
<td>Minimal change</td>
<td>No</td>
<td>Bilateral</td>
<td>DVT, PE</td>
<td>Died at 5 d from mesenteric hemorrhage</td>
<td>Not done</td>
<td>ARF</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>61</td>
<td>M</td>
<td>MGN</td>
<td>NR</td>
<td>MGN</td>
<td>No</td>
<td>Bilateral</td>
<td>RV, PE</td>
<td>Normal, Normal</td>
<td>Not done</td>
<td>ARF</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>22</td>
<td>F</td>
<td>MGN</td>
<td>NR</td>
<td>MGN</td>
<td>No</td>
<td>Bilateral</td>
<td>RV, PE</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>60</td>
<td>M</td>
<td>Unknown</td>
<td>NR</td>
<td>Not done</td>
<td>No</td>
<td>Bilateral</td>
<td>RV, PE</td>
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<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>60</td>
<td>F</td>
<td>Unknown</td>
<td>NR</td>
<td>Not done</td>
<td>No</td>
<td>Bilateral</td>
<td>RV, PE</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
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<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>42</td>
<td>M</td>
<td>MGN</td>
<td>NR</td>
<td>MGN</td>
<td>No</td>
<td>Bilateral</td>
<td>RV, PE</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>51</td>
<td>M</td>
<td>Unknown</td>
<td>NR</td>
<td>MGN</td>
<td>No</td>
<td>Bilateral</td>
<td>RV, PE</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>50</td>
<td>M</td>
<td>MGN</td>
<td>NR</td>
<td>MGN</td>
<td>Yes</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Mostly recovered</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>34</td>
<td>M</td>
<td>Unknown</td>
<td>NR</td>
<td>Unknown</td>
<td>No</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Mostly recovered</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>54</td>
<td>M</td>
<td>MGN</td>
<td>NR</td>
<td>MGN</td>
<td>Yes</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Normal</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>10</td>
<td>F</td>
<td>Chronic pyelonephritis</td>
<td>NR</td>
<td>Normal</td>
<td>No</td>
<td>Right, direct</td>
<td>administration</td>
<td>Normal, Normal</td>
<td>Normal</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>33</td>
<td>M</td>
<td>Unknown</td>
<td>NR</td>
<td>MGN</td>
<td>No</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Normal</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
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</tr>
<tr>
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<td>14</td>
<td>20</td>
<td>F</td>
<td>SLE-MGN</td>
<td>NR</td>
<td>SLE</td>
<td>No</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Normal</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>50</td>
<td>F</td>
<td>Oral MGN</td>
<td>Unknown</td>
<td>Unknown</td>
<td>No</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Partially recovered</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>50</td>
<td>F</td>
<td>Oral MGN</td>
<td>Unknown</td>
<td>Unknown</td>
<td>No</td>
<td>Right, RA</td>
<td>None</td>
<td>Normal, Normal</td>
<td>Normal</td>
<td>RVThrombo-emboli cleared</td>
<td>RVThrombo-emboli cleared</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- 3 patients died 2/2 complications from bleeding
- In the other 18 pts, renal fxn remained the same or improved
- In 14 of 18 cases (78%) where repeat studies were performed, the renal veins had cleared

Catheter-directed Thrombectomy and Local Thrombolysis

- Retrospective study of 6 patients with acute RVT who were treated with percutaneous catheter-directed thrombectomy in one center between 2000-2004
- 4 of the patients also received local thrombolytics for residual clots
- 2 allografts and 5 native veins
  - 1 patient had IVC thrombosis thought to be the etiology; the remaining 5 patients had been diagnosed with a glomerulopathy
- Diagnosis confirmed by direct renal venography in all cases
- Decision to treat with thrombectomy +/- thrombolytics instead of anticoagulation was at the discretion of the treating physicians

Results

Table 2: Percutaneous Thrombectomy/Thrombolysis and Clinical Outcome*

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Thrombectomy Device</th>
<th>Thrombolytic Agent</th>
<th>Lytic Therapy Duration (h)</th>
<th>Lytic Agent Dose</th>
<th>Length of Hospital Stay (d)</th>
<th>Length of Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amplatz device</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>AngioJet/Amplatz device</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>AngioJet</td>
<td>tPA</td>
<td>35</td>
<td>22.75 mg</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>AngioJet</td>
<td>UK</td>
<td>45</td>
<td>6,220,000 U</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>AngioJet/Amplatz device</td>
<td>UK</td>
<td>4</td>
<td>6,220,000 U</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>AngioJet</td>
<td>tPA</td>
<td>4.5</td>
<td>500,000 U</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

* No complications were seen at 30 days.
Note.—tPA = tissue plasminogen activator, UK = urokinase, NA = not available.

Table 3: Renal Function Tests Results

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>GFR (mL/min per 1.73 m²)</th>
<th>Creatinine Level (mg/dL)</th>
<th>Time to Baseline Renal Function (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Before Treatment</td>
<td>After Treatment</td>
<td>Baseline Before Treatment</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>23</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>19</td>
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</tr>
<tr>
<td>5</td>
<td>63</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>205</td>
<td>75</td>
<td>166</td>
</tr>
</tbody>
</table>

Summary of Treatment

- Depends on clinical presentation, extent of disease, and underlying renal function
- Anticoagulation (Heparin, Coumadin)
  - Considered the mainstay of treatment
  - Successful and carries reasonable amount of risk
- Fibrinolytics (systemic vs local), Catheter embolectomy
  - Considered in patients with bilateral disease, extension of clot into the IVC, concurrent pulmonary emboli, or acute renal failure
Prophylaxis

• No randomized, controlled studies comparing the risk of anticoagulation vs the risk of developing thromboembolism

• One study in KI in 1994 used a Markov-based decision analysis considering the risks of thromboembolism vs bleeding from a/c
  • Concluded that in nephrotic patient’s with membranous nephropathy, the benefit of anticoagulation outweighs the risks

• General concensus now is to consider prophylaxis in case by case basis in patients thought to be at highest risk
  • Membranous nephropathy
  • Massive proteinuria, as evidenced by a serum albumin below 2.0 g/dL
  • Any additional risk factors for thrombosis (ie, prior event, family history)
  • No contraindications to a/c

Role of Screening for RVT

• Not current standard of care
• No proven benefit to treating occult disease
• A negative study does not help with the decision to prophylactically treat with anticoagulation
• A patient with a negative test may develop RVT at a later time, requiring sequential studies
Thank You