Differential Edema of The Legs

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Relevant Disclosure

Under the Oklahoma State Medical Association CME guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

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I have no relevant financial relationships or affiliations with commercial interests to disclose.
Topics

- Historical Perspectives
- Clinical Presentation
- Anatomy and Physiology
- Diagnosis
- Treatments
- Guidelines
- Follow up
- Case Presentations
- Befores and Afters
Historical Perspectives

- Historically, DVT reported to be more common on left side\(^1\).
- First described by McMurrich in 1908\(^2\)
  - Presence of strictures in the **left common iliac vein**
  - Thought to be congenital
- Described anatomically by R. May and J. Thurner in 1956\(^3\).
- Clinically defined by Cockett and Thomas in 1965\(^4\)
  - Defined as an acquired condition – fibrotic changes
  - Notably absent in fetal autopsy specimens
- Became known as May Thurner Syndrome (MTS).

\(^1\) Virchow R, Arch Path Anat. 1851.
\(^3\) May R, Angiology. 1957.

Anatomy
Normal Iliac Venous Anatomy
Clinical Presentation

- Female predominance 3:1*
  - *More like 5:1 in my practice*

- Classic presentation
  - Woman in 3rd or 4th decades
  - Acute DVT, recurrent, provoked or “unprovoked”
  - S/S of **Venous Claudication**

- **Risk factors for thrombosis**: malignancy, pregnancy, OC use, immobility, inherited clotting disorders, **venous obstructive disease** (provoked causes).

*Cockett FB, Br J Surg*
Clinical Presentation

○ Yet, many patients with MTS remain asymptomatic.

○ Kibbe et al\(^1\) reported series of 50 consecutive patients with abdominal CT for reasons unrelated to thrombosis.
  - 24% had greater than 50% compression of LCIV
  - 66% had greater than 25% compression of LCIV
  - No patients in series had symptoms of venous obstruction

○ The true prevalence remains debatable.
  - About 5% prevalence of May Thurner anatomy found in general population\(^2\).
  - Up to 80% of patients with DVT had iliac vein compression\(^3\).

1 Kibbe MR, J Vasc Surg 2004
2 Juhan C, Ann Vasc Surg 1987
3 Chung JW, J Vasc Interv Radiol 2004
CT Can Miss Compressions
Why do CT in the first place?

Making The Diagnosis

Patient's history, telltale signs, unusual presentations.

• Recurrent DVT of the same leg, esp. unprovoked
• “Mysterious” Pulmonary Embolism
• Unusual presentation – cryptogenic strokes
• "Venous claudication"
• Vague Pain Achiness
• Swelling Itching
• Heaviness Restlessness

Physical examination – Differentiate other causes.

Venous Ultrasound will not suffice.

Intravascular Ultrasound (IVUS) – Gold standard.

Other Causes of Edema

**Unilateral**
- Iliac vein compression
- Venous insufficiency
- Post Thrombotic Syndrome
- Deep venous thrombosis
- Lymphedema
- Angiodysplasias
- Baker cysts
- Cellulitis, arthritis

**Bilateral**
- Iliac vein compression
- Heart/liver/renal failure
- Cyclic idiopathic
- Hypoproteinemia
- Obesity
- Pregnancy
- Drugs
- Lipedema

Drugs that cause edema

A. Antihypertensives
   - Hydralazine
   - Diazoxide (Hyperstat)
   - Minoxidil
   - Methyldopa
   - Calcium Channel Blockers (e.g., Amlodipine)
   - Beta Blockers
   - Clonidine (Catapres)

B. Nonsteroidal Antinflammatory Drugs (NSAIDs)
   - Ibuprofen
   - Celecoxib (Celebrex)

C. Endocrine agents
   - Corticosteroids
   - Estrogen
   - Progesterone
   - Testosterone
   - Insulin
   - Thiazolidinediones (e.g., Actos, Avandia)

D. Antidepressants
   - Monoamine Oxidase Inhibitors
   - Trazodone

E. Chemotherapy
   - Interleukin-2 (increased vascular permeability)
   - Interleukin-4
   - Interferon alfa
   - Docetaxel (Taxotere)
   - Cyclophosphamide
   - Cisplatin
   - Mithramycin
   - Cytosine Arabinoside
   - Granulocyte colony-stimulating factor
   - Granulocyte-Macrophage colony stimulating factor

F. Antipsychotics: Phenothiazine
   - Thoridazine (Mellaril)
   - Chlorpromazine (Thorazine)
   - Trifluoperazine (Stelazine)
   - Thiothixene (Navane)

G. Diuretic Abuse or Laxative Abuse
   - Increases renin and aldosterone levels
   - Reboad salt retention on stopping medication

H. Miscellaneous agents
   - Acyclovir (Zovirax)
   - Pramipexole (Mirapex)
Hypercoagulopathies

- Evaluation of extremity DVT requires workup for hypercoagulability.
- Common risk factors or acquired hypercoagulable states*:
  - Trauma conditions
  - Inflammatory conditions
  - Surgery conditions (APLS)
  - Autoimmune
  - Immobility
  - Myeloproliferative disorders
  - Hormonal changes
  - Cancer

*Dieter, R. Venous and Lymphatic Diseases,
Inherited Hypercoagulable States*

<table>
<thead>
<tr>
<th>Inherited Conditions</th>
<th>Prevalence</th>
<th>VTE Risk</th>
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<tbody>
<tr>
<td><em>Factor V Leiden</em></td>
<td>4.8%</td>
<td>18.8%</td>
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<tr>
<td>Prothrombin G20210A</td>
<td>2.7%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>0.02%</td>
<td>1.9%</td>
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<tr>
<td>Protein C deficiency</td>
<td>0.4%</td>
<td>3.7%</td>
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<tr>
<td>Protein S deficiency</td>
<td>0.003%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>0.01%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hyperhomocysteinemia (debatable)</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Dieter, R. Venous and Lymphatic Diseases, 2011.

Post-Thrombotic Syndrome*

- A common, burdensome, and costly complication of DVT.
- Development of severe chronic venous insufficiency following DVT (more than 50% patients).
- Only 20% of DVT will recanalize on anticoagulation, i.e. 80% won't.
- Reflux increases from 17% of patients on week one to 69% at one year after diagnosis of DVT.
- Undiagnosed iliac vein compression plays a major role in PTS, because Extremity Duplex alone is not adequate.
- Degree of occlusion and large/proximal veins = higher risk.
- Results: Tissue edema, SQ fibrosis, tissue hypoxemia and ulceration.

*UpToDate. February 2016
Treatments

- A multidisciplinary team approach.

- **Compression therapy**
  - Not all compression stockings are created equal
  - Properly fitted compression ensures compliance
  - Some may require life-long therapy

- **Anticoagulation** – Depending on other health issues.
  - Prevents recurrent thrombosis
  - Does nothing to correct resulting venous insufficiency due to mechanical nature of the obstruction

- **Venous intervention**
A Multidisciplinary Team

- Encounter Providers – Diagnosis starts
- Imaging expertise – CT, MRI, Interpreting Radiologists
- Wound Care Providers
- Home Health with compression expertise
- Vascular Surgery
- Interventionalists (cardiologist, radiologist, surgeon)

Compression Therapy

- Must be fitted for better compliance and tolerability.
- Degree of compression depends on disease severity.
- Sigvaris, Medi, Jobst, inelastic wraps, ACE wraps, etc.
- Cost vs. insurance coverage varies.
- Compression during daytime and off at night.
- Use of assist devices such as a donning device.
- Home Health is a good resource for elderly.
Anticoagulation

- Duration of therapy depends on other health issues and coagulopathic disorders.

- Newer agents (Novel Oral AntiCoagulants):
  - Eliquis
  - Savaysa
  - Xarelto
  - Pradaxa

- Iliac vein compression intervention:
  - 3 months of anticoagulation.

- I use NOACs and Antiplatelets.

- Warfarin – Only as a last resort.
**Mechanical Interventions**

- A variety of surgical procedures were described.
  - Venovenous bypass grafts – moderate success
  - Mobilization of the right iliac artery (RIA)
  - Vein patch angioplasty with rerouting of RIA

- Endovascular therapies – excellent results.
  - Percutaneous venoplasty and stent placement
  - Success rate 100% if vessel is patent (not occluded)
  - Stent patency rate between 95% - 100%

- Complications – low rate, variable, well tolerated.

**Follow Up**

- Venous duplex at 3 months to verify iliac vein stent patency and venous velocities.
- Can also be used to assess for venous insufficiency to determine duration of compression therapy.
- Yearly venous duplex optional.
- Long-term patency is excellent at 5 years*
  - 90-100% - nonthrombotic obstruction
  - 74-89% - postthrombotic obstruction

Grade of recommendation – Strong (1) or Weak (2) based upon risk:benefit ratio.

Quality of evidence – High (A), Medium (B), Low (C).

We Recommend:

Venous angioplasty and stenting of iliac and femoral veins in symptomatic patients to improve quality of life (QOL) (1B)
  • Pain, edema not better with compression
  • Active venous ulcers
We Recommend:

- Venous angioplasty and stenting of non-thrombotic and post thrombotic IVC obstructions (1C).
- Venous angioplasty and stenting as adjunct to catheter-directed thrombectomy for acute femoriliocaval DVT when residual obstructions are found post thrombolysis (1B).

We Recommend:

- Venous angioplasty and stenting for iliac vein obstructions in patients with:
  - Chronic pelvic pain
  - Deep dyspareunia
  - Low back pain, which severely affects QOL

When other likely causes have been excluded and The severity of iliac vein is considered sufficient to explain the symptoms (1C).
Case Presentation 1

- SK – 46 yo healthy woman referred to left leg edema.
  - No other past history.
  - Used to run 4 miles without any problems.
  - Left leg pain, swelling, restlessness at night, and varicosities.
  - Decreased run distance due to venous claudication.
- CT of pelvis without contrast confirmed May Thurner physiology.
- Fitted compression therapy and leg elevation not effective.
- Venogram, angioplasty, and Wallstent placement.
- Complete resolution of left leg symptoms.
Case Presentation 2

- NM – 38 yo accountant in Norman referred by PCP for management of anticoagulation.
  - Recurrent DVT of the left leg for 10 years.
  - Diagnosed with Heterozygous Factor V Leiden in Wisconsin.
  - Had 2 pregnancies, each required C-Section and Lovenox injections.
  - Had DVT on Xarelto and was changed to warfarin.
  - Saw a hematologist and was placed on Life-Long Lovenox injection due to high dose warfarin.
  - Classic symptoms of May Thurner.
"Befores and Afters"
Iliac vein compression is not a rare or benign condition.

Often overlooked, underdiagnosed, and undertreated due to lack of awareness and expertise.

- 80% of patients with DVT had iliac vein compression.
- Venous duplex will not be adequate to assess compression.

It carries serious health consequences if not properly diagnosed and treated.

Diagnosis requires awareness of the disease and careful history and examination.

Treatments require in-depth knowledge of venous disease.

Response to treatment = Improved quality of life.

Thank You !!!!