Differential Edema of The Legs

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Disclosures

I having nothing to disclose.
Objectives

- Historical Perspectives
- Clinical Presentation
- Anatomy and Physiology
- Diagnosis
- Treatments
- Guidelines
- Follow up
- Case Presentations
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).

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

Figure 5. Left common iliac vein compression by the right common iliac artery. Chronic changes in the left common iliac vein secondary to endothelial damage with (a) intraluminal spurs, (b) webs and (c) channels are depicted.
**Clinical Presentation**

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

- Classic presentation – females in 3rd or 4th decades, acute DVT, provoked or unprovoked.

- Without definitive treatment patients developed pain, edema, recurrent DVT, and **venous claudication**.

- Thrombosis more likely in the presence of other risk factors: malignancy, pregnancy, OC use, immobility, inherited prothrombotic disease (provoked causes).

* Cockett FB, Br J Surg

**Clinical Presentation**

- Many patients with MTS remain asymptomatic.

- **Kibbe et al.** 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.
  - Up to 62% prevalence of May Thurner anatomy found in patients with deep venous thrombosis.²
  - Up to 80% of patients with DVT had iliac vein compression (reasons for “unprovoked causes”).³

1 Kibbe MR, J Vasc Surg 1996
2 Juhan C, Ann Vasc Surg 1987
3 Chung JW, J Vasc Interv Radiol 2004
Anatomy and Physiology

- Left common iliac vein courses between the right common iliac artery and L5 vertebral body.
- Compression can vary in severity.
- Chronic fibrotic changes = “Web and Septae”
- Leads to chronic obstruction, venous hypertension, venous insufficiency, and venous thrombosis.
- Collateralization leads to edema of the contralateral leg.

Normal Iliac Venous Anatomy
Figure 1. Normal Iliac Venous Anatomy

Figure 2. Computed tomographic scan demonstrating compression of the left common iliac vein.
CT Venography

Figure 2. Computed tomographic scan demonstrating compression of the left common iliac vein.

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
  - Young patients with non-cardiac CP
  - Unusual presentation – cryptogenic strokes
- “Venous claudication” – Constant
  - Pain Achiness
  - Swelling Itching
  - Heaviness Restlessness
- Physical examination – Differentiate other causes.
- Intravascular Ultrasound – Requires expertise.

## Other Causes of Edema

### Unilateral
- Iliac vein compression
- CVI
- PTS
- DVT
- 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

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| A. Antihypertensives | 1. Hydralazine  
2. Diazoxide (Hyperstat)  
3. Minoxidil  
4. Methyldopa  
5. Calcium Channel Blockers (e.g. Amlodipine)  
6. Beta Blockers  
7. Clonidine (Catapres) |
| B. Nonsteroidal Antiinflammatory Drugs (NSAIDs) | 1. Ibuprofen  
2. Celecoxib (Celebrex) |
| C. Endocrine agents | 1. Corticosteroids  
2. Estrogen  
3. Progesterone  
4. Testosterone  
5. Insulin  
6. Thiazolidinedione (e.g. Actos, Avandia) |
| D. Antidepressants | 1. Monoamine Oxidase Inhibitors  
2. Trazodone |
| E. Chemotherapy | 1. Interleukin-2 (Increased Vascular permeability)  
2. Interleukin-4  
3. Interferon alfa  
4. Docetaxel (Taxotere)  
5. Cyclophosphamide  
6. Cyclosporine  
7. Mitomycin  
8. Cytosine Arabinoside  
9. Granulocyte colony-stimulating factor  
10. Granulocyte-Macrophage colony stimulating factor |
| F. Antipsychotics: Phenothiazines | 1. Thoridazine (Mellaril)  
2. Chlorpromazine (Thorazine)  
3. Trifluoperazine (Stelazine)  
4. Thiothixene (Navane) |
| G. Diuretic Abuse or Laxative abuse | 1. Increases renin and aldosterone levels  
2. Rebound salt retention on stopping medication |
| H. Miscellaneous agents | 1. Acyclovir (Zovirax)  
2. Pramipexole (Mirapex) |
Hypercoagulopathy

- Evaluation of extremity DVT requires workup for hypercoagulability.
- Common risk factors or acquired hypercoagulable states*:
  - Trauma
  - Inflammatory conditions
  - Surgery
    - Autoimmune conditions (APLS)
  - 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>Factor V Leiden</td>
<td>4.8%</td>
<td></td>
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<tr>
<td>Prothrombin G20210A</td>
<td>2.7%</td>
<td>7.1%</td>
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<tr>
<td>Antiphospholipid Syndrome</td>
<td>2 – 5%</td>
<td>12%</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>0.02%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.4%</td>
<td>3.7%</td>
</tr>
<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.
- The development of severe chronic venous insufficiency following deep venous thrombosis (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 – Most definitive.
A Multidisciplinary Team

- **Primary Providers** – Diagnosis starts
- Imaging expertise – CT, US, 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.
- Costs more than generic socks but well worth it.
- Sigvaris, Medi, Jobst, inelastic wraps, ACE wraps, etc.
- 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
- Strictly iliac vein compression intervention:
  - 3 months of anticoagulation.
- Some venous experts use aspirin and clopidogrel.
- Warfarin – Only as a last resort.
Mechanical Intervention

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

Endovascular therapies – excellent results.
- Mainly 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

Management of Obstruction of the Femorocaval Venous System

Introduction:
The ACP Guidelines Committee was developed to assess medical literature and make recommendations to help physicians make evidence-based decisions for the benefit of patients with venous disorders. The Committee’s goals are to create documents reviewing specific medical conditions, and then, using expert opinion, to make recommendations for or against certain methods of evaluation and treatment.

We Recommend:

- **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 femoroiliacal 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

Mr. EK – 67 yo man referred for cardiac care.
- Chest pain – better with medical therapy.
- Left leg bothered him more than chest pain.

Symptoms included:
- Swelling
- Discoloration
- Pain at rest
- No DVT

Venogram, angioplasty, and successful Wallstent placement.
Case Presentation 3

NM – 38 yo accountant in Norman referred by PCP for management of anticoagulation.
- Symptoms of recurrent DVT of the left leg for 10 years.
- Diagnosed with Heterozygous Factor V Leiden Mutation remotely in Wisconsin.
- Had 2 pregnancies, each required C-Section and Lovenox injections.
- Had DVT on Xarelto and was changed to Warfarin.
- Saw a hematologist in OKC and was placed on Lovenox injections for life due to lack of response to Warfarin.
- Classic symptoms of May Thurner in left leg.
“Before’s and After’s”
Take Home Points

- Iliac Vein Compression is not a benign condition.
- May Thurner Syndrome is 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. “Venous Claudication”
- Treatments requires expertise in venous disease.
- Response to treatment = improved quality of
Differential Edema of The Legs

Awareness

This is a disease of the pelvic deep venous system mainly involving iliac veins. The patient often experience pain, swelling, heaviness, etc. at night, venous claudication, and deep venous thrombosis of the affected leg. This is one of the main causes of pulmonary embolism without apparent deep venous thrombosis in the extremities. The left leg is more commonly involved since the left common iliac vein crosses the space between the right common iliac artery and the L5 vertebrae to drain into the inferior vena cava and is often compressed. Compression can occur in the right leg as well. This disease is also referred to as May-Thurner Syndrome or Iliac Vein Compression Syndrome.

Diagnosis for this disease can be performed by any provider with Computed Tomography (CT) of the abdomen and pelvis without contrast (ICD-10 code is I81.1) and proper documentation of the patient's signs and symptoms.

This condition can often be completely cured if diagnosed and treated properly with expeditious therapy. The treatments include patient education, compression therapy, Iliac vein stenting followed by a short period of anticoagulation.

The response to treatment is dramatic and life-changing. The patient's quality of life can be significantly improved with resolution of pain and even cessation of long-term anticoagulation in the case of unprovoked deep venous thrombosis.

Please don’t ignore the signs and symptoms of this commonly occurring disease.
Thank You !!!