Vascular Ehlers Danlos Syndrom
When Do Cardiologists need to think about?

Emmanuel Messas M.D., Ph.D., F.E.S.C

The reference center of rare vascular diseases

Munich, August 28th 2012
European Society of Cardiology
Clinical Case

• Patient of 35 yrs. old came for acute dyspnea, chest pain and cardiogenic choc at Day 2 post partum after a first pregnancy.

• After hemodynamic stabilization, auscultation found a severe systolic murmur, a transoesophageal echocardiography is performed under general anesthesia.
Posterior papillary muscle rupture with no Wall motion abnormalities associated
Follow up 4 years after
Medical history and clinical feature

- No Cardiovascular risk factors, No family history.
- No history of murmur or of Mitral valve prolapse.
- Pneumothorax at birth,
- After minim trauma she got spontaneous rupture of the cruciate ligament.
- At physical exam, she has acrogeria, hypermobility of the joint, multiple dystrophic scar and a characteristic facial appearance with face of madone and a tendency of alopecia. She is not tall, no bifid uvula and no pectus excavatum and the aortic root at echocardiography is normal.
- After consent was obtained, we performed genetic testing, we found point mutation in the gene COL3A1 and
- She was diagnosed for Vascular Ehlers Danlos Syndrome.
Clinical Case 2

• Patient of 40 yrs old came to ER for abdominal pain and dizziness
• No CV risk factors
• History of Carotid Cavernous fistula discover during pregnancy 7 years ago which motivated early interruption and Percutaneous closure of the fistula with coil. This intervention was complicated by bilateral iliac dissection
• She got also spontaneous rupture of sigmoid colon five years ago
Angio CT scanner
3D reconstruction

Aorto iliac Dissecting Aneurysm
Clinical Case 2

- At the physical exam she presented all the characteristics with acrogeria, face of Madone and bruising.
- She got genetic testing and was positive for mutation in the COL3A1 gene.
- The Abdominal aortic dissected aneurysm was treated medically with Celiprolol and ACE inhibitor.
- The patient was followed by Angio CT.
Ehlers Danlos syndrom

- Heterogeneous group of multiple genetic disease of conjunctive tissues which have in common:
  - Skin Hyperextensibility
  - Joint hypermobility
  - Easy Bruising and tissular fragility

- The clinical diagnosis of Ehlers–Danlos syndrome type IV, the vascular type, is made on the basis of four clinical criteria:
  - easy bruising,
  - thin skin with visible veins,
  - characteristic facial features,
  and rupture of arteries, uterus, or intestines
Ehlers Danlos Syndromes
Villefranche Classification

<table>
<thead>
<tr>
<th>New Type</th>
<th>Former Type</th>
<th>OMIM</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical type</td>
<td>Gravis (EDS type I)</td>
<td>130000</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Mitis (EDS type II)</td>
<td>130010</td>
<td>AD</td>
</tr>
<tr>
<td>Hypermobility type</td>
<td>Hypermobile (EDS type III)</td>
<td>130020</td>
<td>AD</td>
</tr>
<tr>
<td>Vascular type</td>
<td>Arterial-ecchymotic (EDS type IV)</td>
<td>130050 (225350)</td>
<td>AD</td>
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<tr>
<td>Kyphoscoliosis type</td>
<td>Ocular-Scoliotic (EDS type VI)</td>
<td>225400 (229200)</td>
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<td>Arthrogryposis type</td>
<td>Arthrochalasis multiplex congenita (EDS types VIIA and VIIB)</td>
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<td>AD</td>
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<tr>
<td>Dermatosparaxis type</td>
<td>Human dermatosparaxis (EDS type VIIC)</td>
<td>225410</td>
<td>AR</td>
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<td>Other forms</td>
<td>X-linked EDS (EDS type V)</td>
<td>305200</td>
<td>XL</td>
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<td></td>
<td>Periodontitis type (EDS type VIII)</td>
<td>130080</td>
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<tr>
<td></td>
<td>Fibronectin-deficient EDS (EDS type X)</td>
<td>225310</td>
<td>?</td>
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<td></td>
<td>Familial hypermobility syndrome (EDS type XI)</td>
<td>147900</td>
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<td></td>
<td>Progeroid EDS</td>
<td>130070</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Unspecified forms</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

The presence of any two or more of the major criteria is highly indicative of the diagnosis, and laboratory testing is strongly recommended.

Facial Morphotype
« Face of madone »

- Thin nose, horizontal lip mildly ourled
- Hollow Cheek, tight firm lobeless ears
- Prominent staring eyes because of a paucity Adipose tissue
Dermal Sign
Translucent skin

- Pale skin sometimes velvety to the touch
- Subcutaneous veinous pattern particularly apparent on the anterior part of the chest
Cutaneous signs
Skin fragility

- Spontaneous bruising,
- Sometimes delayed healing with scar having a thin atrophic papyraceous appearance on friction points.
Cutaneous signs
Skin Hyperextensibility

Extensor surface of the elbows
Signs skin

Acrogeria

Skin thin and retracted ends of the tendons giving hands and feet look emaciated, prematurely aged.
Articular signs

- Large joints hypermobile rare in vEDS
- **Moderate joint laxity affecting the small joints** of the fingers and toes.
- The notion of congenital dislocation of the hip, a talipes equinovarus or simply in a cavus have the value of minor sign
- **Repeated sprains or dislocations of the shoulders, joints and ankles** are sometimes in the foreground.
- Early osteoarthritis linked to hypermobility is a source of pain and joint stiffness.
Articular signs

Hypermobility of the small joints

Figure 1. Beighton's modification of the Carter and Wilkinson scoring system. Give yourself 1 point for each of the manoeuvres you can do, up to a maximum of 9 points.
Genetic feature and Epidemiology

• vEDS is uncommon (the precise incidence and prevalence are not known about about 1/150,000), and in part because of its rarity, the diagnosis is often made only after a catastrophic complication or at postmortem examination.

• Autosomal dominant disorder with high level of neomutation (50%).

• The diagnosis is confirmed by the demonstration that
  - cultured dermal fibroblasts synthesize abnormal type III procollagen molecules or
  - by the identification of a mutation in the gene for type III pro-collagen (COL3A1) an essential constituent of arterial wall, skin, articular capsules, uterine and gastrointestinal wall specially sigmoid colon

• The high arterial and tissular fragility are responsible of the extrem gravity of the disease.
Type 3 Procollagene

- Fibrillar Collagene formed by homotrimer of proa1(III) chains with triple-helical domain and C and N terminal globular
- **Triple helical stability** linked to the conservation of its primary repetitive structure: **Amino acid triplet starting with Glycine**
- In each instance, the effect of an abnormal allele product is amplified, since type III procollagen is a homotrimer.
- **As a consequence, an abnormal product from one allele is expected to result in seven of eight molecules being abnormal.**
vEDS autosomal dominant
- with dominant negative effect
- with haplo - insufficiency
- Private mutation (and more than 50% of neo-mutation)

Approximately **two-thirds of the mutations are single-nucleotide substitutions** that result in **substitutions for glycine** residues in the triple-helical domain of the proa1(III) chain. **Most of the rest are splice-site mutations that result in exon skipping**, and a small number are larger genomic deletions (Kuivaniemi et al. 1997).

Ongoing trial on genotype/phenotype analysis
The reference center of rare vascular diseases

Vascular Medicine – HTA

Pr Emmanuel Messas
Dr Tristan Mirault
Pr Jean-Noël Fiessinger
Pr Joseph Emmerich
Pr Pierre-François Plouin
Dr Nicolas Denarié
Assistants of department

Genetic

Pr Xavier Jeunemaitre
Dr Michaël Frank
Dr Anne-Laure Fauret
Diane Molière

Lymphology Department

Dr Stéphane Vignes

Psychiatry

Dr Khadija Lahlou-Laforêt

www.maladiesvasculairesrares.com
11 CENTRES OF EXPERTISE
Patient population

• 160 families with molecularly proven vEDS, one of the largest active cohorts of patients

• Standardized vascular diagnostic work-up and long-term follow-up available for 95 patients totalling 365 hospital stays

• Unique insights in the epidemiology and natural course of the disease:
  - Redefinition of clinical phenotype
  - Genotype-phenotype correlations
  - Evolutivity of vascular lesions
  - Development of treatment strategies for arterial, digestive and respiratory events
  - Management of pregnancy
Clinical phenotype and diagnosis of vEDS

• Redefining oral involvement: (Ferré et al. BMJ Open 2012)
  • invalidation of gingival recession as a diagnostic criterion
  • description of oral involvement and design of a novel diagnostic score

• Definition of an arterial phenotype of vEDS: (Boutouyrie et al. Circulation 2004)
  • Increase of circumferential carotid wall stress
  • Decrease of carotid intima-media thickness
  • Ultrafastecho (Poster session Tuesday August 28 (village 10))

• Design of an ultrastructural diagnostic score for skin biopsies: (Ong et al. Wirchows Arch. 2012)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>Status</th>
<th>Status</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=134</td>
<td>N=93</td>
<td>N=41</td>
<td>IC vs R</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>128/132 (97%)</td>
<td>88/92</td>
<td>40/40</td>
<td>1.00</td>
</tr>
<tr>
<td>Male gender</td>
<td>54/134 (41%)</td>
<td>35/93</td>
<td>19/41</td>
<td>0.343</td>
</tr>
<tr>
<td>Age at last follow-up visit</td>
<td>35[24-45]</td>
<td>34[26-44]</td>
<td>42[20-53]</td>
<td>0.590</td>
</tr>
<tr>
<td>Familial sudden death</td>
<td>46/124 (37%)</td>
<td>25/83</td>
<td>21/41</td>
<td>0.022</td>
</tr>
<tr>
<td>Madone’s Face</td>
<td>93/119 (78%)</td>
<td>75/86</td>
<td>18/33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thin skin</td>
<td>98/118 (83%)</td>
<td>75/84</td>
<td>23/33</td>
<td>0.010</td>
</tr>
<tr>
<td>Acrogeria</td>
<td>84/116 (72%)</td>
<td>65/82</td>
<td>19/34</td>
<td>0.010</td>
</tr>
<tr>
<td>Bruises</td>
<td>94/121 (77%)</td>
<td>73/87</td>
<td>21/34</td>
<td>0.008</td>
</tr>
<tr>
<td>&gt;1 major complication</td>
<td>107/129 (83%)</td>
<td>85/93</td>
<td>22/36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>median age of the 1st one</td>
<td>26[22-35]</td>
<td>25[21-33]</td>
<td>28[23-38]</td>
<td>0.227</td>
</tr>
<tr>
<td>&gt;1 vascular complication</td>
<td>95/124 (76%)</td>
<td>73/90</td>
<td>22/34</td>
<td>0.054</td>
</tr>
<tr>
<td>median age of the 1st one</td>
<td>31[24-38]</td>
<td>30[23-38]</td>
<td>36[27-40]</td>
<td>0.276</td>
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<tr>
<td>&gt;1 digestive complication</td>
<td>48/127 (37%)</td>
<td>39/90</td>
<td>9/37</td>
<td>0.045</td>
</tr>
<tr>
<td>&gt;1 obstetrical complication *</td>
<td>19/79 (24%)</td>
<td>13/57</td>
<td>6/22</td>
<td>0.677</td>
</tr>
<tr>
<td>median age of the 1st one</td>
<td>28[26-33]</td>
<td>28[25-33]</td>
<td>26[26-32]</td>
<td>0.725</td>
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<td>Median nb of major criteria</td>
<td>3[2-4]</td>
<td>3[3-4]</td>
<td>2[1-3]</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* females only, quantitative variables are given in medians [interquartile range]
Onset of clinical events in respect of mutation type

Number of subjects at risk

<table>
<thead>
<tr>
<th>age</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>gly mutations:</td>
<td>73</td>
<td>70</td>
<td>61</td>
<td>30</td>
<td>13</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>splice/del/ins/dup:</td>
<td>34</td>
<td>34</td>
<td>20</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>nonGly/Cterm/Nterm:</td>
<td>21</td>
<td>20</td>
<td>20</td>
<td>16</td>
<td>10</td>
<td>6</td>
<td>5</td>
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</tbody>
</table>
MV abnormalities in Ehlers Danlos Syndrom?
Mitral Valve and EDS
Literature analysis

- 78 references (2011-1966)
- 31 are relevant (about MVP)
- Most are review or case report (n=15 corresponding to 20 patients)
- Very few cohort analysis (n=8)
- Cohort analysis involved all type of EDS with very few Vascular EDS
- One Vascular EDS study: 10 patients from the same family !!!
To evaluate whether abnormal production of type III collagen, the characteristic biochemical feature of patients with the type IV Ehlers-Danlos syndrome, consistently predisposes to mitral valve prolapse, we evaluated the family of a proband with classic type IV Ehlers-Danlos syndrome. Production of type III collagen was assessed with the use of cultured skin fibroblasts. Mitral valve prolapse was detected by M-mode and two-dimensional echocardiography. Biochemical abnormalities in the production of type III collagen and echocardiographic findings of mitral valve prolapse were completely concordant. All patients with abnormal production of type III collagen had mitral valve prolapse and all subjects with normal production of type III collagen had entirely normal echocardiograms. Six of the eight patients with abnormal production of type III collagen had subtle cutaneous abnormalities. The consistent association of abnormal production of type III collagen and mitral valve prolapse in this family suggests that this abnormality of collagen may give rise to mitral valve prolapse.
Mitral Valve and Vascular EDS

M mode or by 2D
PSLA or Apical 4 Chview
8 over 10 have mvp
Mitral Valve and Collagene type 3
William G et al. Biochem 1984

Normal Human mitral valve:  
74% type I collagen  
24% type III collagen  
2% type V collagen

Myxomatous mitral valve:  
67% type I collagen  
31% type III collagen  
2% type V collagen

Increase by 53% amount of collagene mostly on type 3  
possibly linked to repair process with  
Primary defect malformation of Valve  
which led  
as a result of cyclical loading to  
disruption of the collagen fibers
**Human study**

**Method**

<table>
<thead>
<tr>
<th>Vascular EDS</th>
<th>Vascular Sdr</th>
<th>Normal matched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Col 3A1 +</td>
<td>Col 3A1 –</td>
<td>sexe and age</td>
</tr>
<tr>
<td>N= 50</td>
<td>N= 50</td>
<td>N= 50</td>
</tr>
</tbody>
</table>

**Transthoracic Echo (Philips IU33)**
- MV analysis: Function, Leaflet length and thickness and distensibility
- Aortic Root dimension

**Supersonic Imagine (Aixplorer)**
- MV leaflet stiffness
- Variation of stiffness over cardiac cycle
- Arterial stiffness
LEAFLET STIFFNESS
Elastography

IN PROCESS...
Animal Mice Model of vSED

Homozygot Col3A1-/-

Only 2 mice of 49 and 205 days

High mortality

Heterozygot Col3A1+/-

116 with 39 older than 300 days

No abnormal Vascular and Valvular aspect

Knock in in Process
Mice Model
Endpoint

• Valve Analysis by imaging:
  - Vevo: Function, length and thickness
  - UFecho: stiffness

• Valve plasticity analysis:
  - Histopathology with collagen and TGF beta signaling study
PROGNOSIS
• **220 index cases** (diagnosed by dermal fibroblast culture after major complication: 154, because of family history and physical finding: 32 and because of physical finding only: 34)

• **199 relative affected** diagnoses by Dermal fibroblast culture or because of clinical course

• Included from 1976 to 1998, 13 families in Seattle and 3 families from Zurich
**TABLE 1. CHARACTERISTICS OF 220 INDEX PATIENTS AND 199 RELATIVES WITH EHlers–DANLOS SYNDROME TYPE IV.*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>ALL SUBJECTS (N=419)</th>
<th>MALE SUBJECTS (N=215)</th>
<th>FEMALE SUBJECTS (N=204)</th>
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</thead>
<tbody>
<tr>
<td>Index patients — no. (%)</td>
<td>220</td>
<td>120 (54.5)</td>
<td>100 (45.5)</td>
</tr>
<tr>
<td>Relatives — no. (%)</td>
<td>199</td>
<td>95 (47.7)</td>
<td>104 (52.3)</td>
</tr>
<tr>
<td>Mean age at ascertainment — yr†</td>
<td>28.7±14.8</td>
<td>28.0±15.0</td>
<td>29.3±14.5</td>
</tr>
<tr>
<td>Index patients</td>
<td>24.9±13.0</td>
<td>25.1±13.5</td>
<td>24.7±12.4</td>
</tr>
<tr>
<td>Relatives</td>
<td>33.3±15.6‡</td>
<td>32.4±17.0‡</td>
<td>35.0±15.2‡</td>
</tr>
<tr>
<td>Family history of the disease in the index patients — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84 (38.2)</td>
<td>39</td>
<td>45</td>
</tr>
<tr>
<td>No</td>
<td>91 (41.4)</td>
<td>54</td>
<td>37</td>
</tr>
<tr>
<td>Unknown</td>
<td>45 (20.5)</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Age at first complication in index patients — yr</td>
<td>23.5±11.1</td>
<td>23.9±10.9</td>
<td>22.8±11.4</td>
</tr>
<tr>
<td>No. of patients with data available</td>
<td>136</td>
<td>84</td>
<td>52</td>
</tr>
<tr>
<td>Type of first complication in index patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial dissection or rupture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>24.6±11.0</td>
<td>24.8±11.4</td>
<td>24.7±10.1</td>
</tr>
<tr>
<td>No. of patients with data available</td>
<td>89</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>Gastrointestinal rupture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>20.6±11.0$</td>
<td>21.3±9.3</td>
<td>19.8±12.9</td>
</tr>
<tr>
<td>No. of patients with data available</td>
<td>41</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Organ rupture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>28.0±7.5</td>
<td>28.5±8.2</td>
<td>27.0±8.5</td>
</tr>
<tr>
<td>No. of patients with data available</td>
<td>6</td>
<td>4</td>
<td>2</td>
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</table>

*Plus–minus values are means ±SD.
†The analysis included 207 index patients and 167 relatives.
‡P<0.001 for the comparison with index patients.
§P<0.03 for the comparison with index patients with arterial complications.

Age at the Time of a First Complication among 207 Index Patients.


- 25% of patients before the age of 20
- 80% before 40
<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Total</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>131</td>
<td>77</td>
<td>54</td>
</tr>
<tr>
<td>Arterial rupture</td>
<td>103</td>
<td>62</td>
<td>41</td>
</tr>
<tr>
<td>Organ rupture</td>
<td>13</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Uterus</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Heart*</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Liver or spleen</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal rupture</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Other causes†</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

*The cause of death was left ventricular rupture.

†Two relatives died of other causes: an adolescent boy died in a motor vehicle accident at the age of 17 years, and a 70-year-old woman died of an apparent heart attack.
Clinical and genetic features of EDS type IV, the vascular type.

*Pepin M et al. N Engl J Med 2000;342;673-80*

Type of first complication

- Arterial (46%)
- Gastro-intestinal (19%)
- Organ (5%)
- None (30%)

38% of patients who survived a first complication have a second major episode, fatal in 12% of cases.
Clinical and genetic features of EDS type IV, the vascular type.


Type of second complication (after a 1st arterial complication)

- Arterial (30%)
- Gastro-intestinal (9%)
- None (30%)

n= 54
n=27 (2 deaths)
n= 8

Type of second complication (after a 1\textsuperscript{st} gastrointestinal complication)

- Arterial (27%)
- Gastro-intestinal (6%)
- None (59%)

n= 24
- n= 11 (4 deaths)
- n= 6
Arterial complications

- Dissecting aneurysms and dissections
- Arterial rupture
- Arterial-venous fistulas (carotid-cavernous sinus)
- Occur in arteries of normal caliber
- Medium caliber arteries preferentially with Digestive collateral of aorta
Spectrum and distribution of vascular findings in Ehlers-Danlos syndrome: total of 83 abnormal vascular findings including ectasia, aneurysm, dissection, and occlusion

Angiographic aspects of Spontaneous Complications during vSED
Aspect of dissecting aneurysm by Echo Doppler
Endovascular treatment. An arteriovenous fistula
ARTERIAL PHENOTYPE IN vEDS
Increased Carotid Wall Stress in Vascular Ehlers-Danlos Syndrome

Pierre Boutouyrie, MD, PhD; Dominique P. Germain, MD, PhD; Jean-Noël Fiessinger, MD; Brigitte Laloux, PhD; Jérôme Perdu, MD; Stéphane Laurent, MD, PhD

Background—Vascular Ehlers-Danlos syndrome (vEDS), also known as EDS type IV, an inherited disorder of connective tissue, results from mutations in the gene encoding type III procollagen (COL3A1). Affected patients are at risk for arterial dissection or rupture, the main cause of death. To understand the pathogenesis of the vascular lesions, we used a biomechanical approach and determined steady and pulsatile wall stress.

Methods and Results—Sixteen patients with vEDS and 16 age-, gender-, and blood pressure–matched control subjects were included in this cross-sectional noninvasive study. Circumferential wall stress was determined under steady and pulsatile conditions at the site of an elastic (common carotid) and a muscular (radial) artery from the measurements of intima-media thickness and internal diameter with high-resolution echo-tracking systems and either mean blood pressure or pulse pressure, respectively. At the site of the carotid artery, steady circumferential wall stress was 43% higher in vEDS patients than in control subjects (68.9 ± 14.3 versus 48.2 ± 12.1 kPa, P < 0.001), and pulsatile circumferential wall stress was 22% higher (28.2 ± 7.7 versus 23.1 ± 5.7 kPa, P < 0.001). Carotid intima-media thickness was 32% lower (408 ± 56 versus 598 ± 171 μm, P < 0.001) in vEDS patients, and internal diameter was not different between groups. Radial artery parameters were not significantly different between groups.

Conclusions—In vEDS patients, an abnormally low intima-media thickness generates a higher wall stress than in control subjects at the site of an elastic artery, which may increase the risk of arterial dissection and rupture. (Circulation. 2004; 109:1530-1535.)

Key Words: arteries ■ carotid arteries ■ collagen ■ elasticity ■ ultrasonics
## TABLE 2. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>vEDS</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=16)</td>
<td>(n=16)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>30±11</td>
<td>31±10</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>3/13</td>
<td>3/13</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>160±7</td>
<td>166±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>51±8</td>
<td>60±11</td>
<td>0.01</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.49±0.16</td>
<td>1.66±0.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>108±7</td>
<td>110±12</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>65±7</td>
<td>66±9</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial MBP, mm Hg</td>
<td>79±7</td>
<td>81±9</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±12</td>
<td>70±14</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid PP, mm Hg</td>
<td>31±7</td>
<td>38±12</td>
<td>NS</td>
</tr>
<tr>
<td>Radial PP, mm Hg</td>
<td>37±9</td>
<td>39±11</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>9.3±2.0</td>
<td>9.9±2.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates BP measured at the brachial artery level with a mercury sphygmomanometer; SBP, systolic BP; DBP, diastolic BP; MBP, mean BP; and PP, pulse pressure. Values are mean±SD (minimum–maximum).
<table>
<thead>
<tr>
<th>Parameters</th>
<th>vEDS (n=16)</th>
<th>Control Subjects (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal diastolic diameter, mm</strong></td>
<td>5.25 ± 0.45 (4.70–6.11)</td>
<td>5.09 ± 0.48 (4.41–6.22)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Stroke change in diameter, mm x 10^-3</strong></td>
<td>578 ± 205 (177–929)</td>
<td>543 ± 194 (230–726)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>IMT, mm x 10^-3</strong></td>
<td>408 ± 56 (257–513)</td>
<td>598 ± 171 (417–968)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>WCSA, mm²</strong></td>
<td>7.3 ± 1.2 (4.0–9.0)</td>
<td>10.7 ± 3.6 (7.0–19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Wall-to-lumen ratio</strong></td>
<td>0.16 ± 0.03 (0.11–0.20)</td>
<td>0.24 ± 0.07 (0.13–0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DC, kPa⁻¹ x 10⁻³</strong></td>
<td>61 ± 30 (16–122)</td>
<td>48 ± 20 (15–92)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Young’s elastic modulus, kPa x 10³</strong></td>
<td>0.27 ± 0.22 (0.08–1.02)</td>
<td>0.23 ± 0.11 (0.08–0.43)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Steady standard circumferential wall stress, kPa</strong></td>
<td>68.9 ± 14.3 (53.6–110.7)</td>
<td>48.2 ± 12.1 (29.5–78.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Steady midwall circumferential wall stress, kPa</strong></td>
<td>74.4 ± 14.5 (58.9–116.8)</td>
<td>53.5 ± 12.2 (33.8–83.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pulsatile wall stress, kPa</strong></td>
<td>28.2 ± 7.7 (13.6–45.2)</td>
<td>23.1 ± 5.7 (14.1–33.0)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

DC indicates cross-sectional distensibility. Values are mean ± SD (minimum–maximum).

Boutouyrie et al, Circulation 2004
BIOMECHANICAL OF ARTERY WALL PROPERTY

- Marfan Syndrome
  - Mostly Aorta
  - Decreased distensibility
  - Increased stiffness index
  - Increased pulse wave velocity

- Vascular EDS
  - Mostly peripheral artery
  - No changes in Distensibility and stiffness
  - Decrease of WALL Thickness
  - Increase of wall stress

Boutouyrie et al., Circulation 2004
"We use in our center the threshold of IMT less than 400 µm as minor parameter to motivate gene testing."
ELASTOGRAPHY ULTRASOUND with conventional vascular probe

- Sending a wave train ("push") focused from the probe for vibration
- Visualization of the shear wave through ultrafast mode
- Determining the Young's modulus from the speed of the shear wave

\[ c = \sqrt{\frac{\mu}{\rho}} \]
Arterial stiffness variation during one cardiac cycle.
Arterial complications? 
When thinking about a vEDS?

• Spontaneous Carotid-cavernous sinus fistula

• Dissecting aneurysm localized at internal carotid (post bulbar) and external iliac

• Dissecting aneurysm of the digestive branches of Aorta
Arterial complications
Conservative Treatment

- **Conservative treatment with no treatment most often**
  
  Bed rest and analgesic, local compression, transfusion
  Avoid puncture

- **Indications of endovascular treatments are:**
  - Selective embolization of an artery for hemostasis goal
  - Occlusion carotid-cavernous fistula

  **Indication for surgery as a last resort:**
  - Bypass for limb salvage.
    - Difficulty for clamping, hemostasis and suturing of vessels
    - venous bypass proscribed
    - Anastomoses performed without tension point reinforced by separate horizontal "pledgets".
  - skin suture is made of separate points nonabsorbable suture left in place for an extended period.
Digestive complications

• Spontaneous rupture of the gastrointestinal tract (80% of the sigmoid)
• The episode is fatal in 2% of cases
• High risk of recurrence: 50% of colonic perforations
• Inguinal hernias, umbilical, hiatal, diaphragmatic and white line hernias are common.
• Spontaneous rupture of the spleen and liver (rare)
• Acute abdomen: abdominal CT need urgently.

Pulmonary Complications

• Pneumothorax
• Hémoptysia
• Pulmonary blebs
Obstetric complications

- Maternal mortality to 11.5% in relation to uterine rupture during labor or vascular rupture in post partum.
- Little specific data on the subject
- Current study VEDOC (Frank et al)
- Discussion on:
  - Routine Caesarean after 32 weeks
  - If vaginal delivery: forceps and strengthening perineal
  - Beta blocker prescription during labor
  - Type of anesthesia: epidural avoid
- Contraception: IUDs prevent
Because of the risk of uterine rupture, Ehlers–Danlos syndrome type IV is a contraindication for pregnancy.
ESC Guidelines on the management of cardiovascular diseases during pregnancy

The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by the European Society of Gynecology (ESG), the Association for European Paediatric Cardiology (AEPC), and the German Society for Gender Medicine (DGesGM)

Interventions. In patients with Marfan syndrome or other syndromes with high risk of dissection, such as Loeys–Dietz syndrome, Ehlers–Danlos, or Smad-3 gen mutation, pre-pregnancy surgery is recommended when the ascending aorta is ≥45 mm, depending on individual characteristics. In other patients with dilatation of the aorta, pre-pregnancy surgery should be considered when the ascending aorta is ≥50 mm. Body surface area should be calculated using the following formula:

To take this with very cautious…..
Venous complications

• Early onset varicose veins
• Stripping of the great saphenous vein to avoid.
• Deep thrombophlebitis secondary to prolonged immobility
Initial assessment of the lesions

- Duplex Doppler of aorta and lower limb and of carotid artery by experienced operator for this type of pathology
- Angio CT scanner
- Study of the mitral valve apparatus by echocardiography.
- Annual Hospitalisation and semi-annual consultation.
Prophylactic measures

- Document "passport AFSED" or care card issued by the CRMVR
- Safe puncture
- Intramuscular and central KT subclavian to avoid
- Anti hypertension (preferred beta blocker Celiprolol)
- Sports with flexion contraindicated (cycling, skiing)
- Transit with regular laxative.
- Rectal temperature and colonoscopy to avoid.
- IUD not recommended
Medication

• Since Bbest study all vEDS under Celiprolol 200mg x 2 / d
• AT2 Inhibitor in case of need to control blood pressure
• No etiological treatment
• Experimental studies on the benefit of doxycycline or cell therapy.
Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial

Kim-Thanh Ong, Jérôme Perdu, Julie De Backer, Erwan Bozec, Patrick Collignon, Joseph Emmerich, Anne-Laure Fauret, Jean-Noël Fiessinger, Dominique P Germain, Gabriella Georgesco, Jean-Sebastien Hulot, Anne De Paepe, Henri Plauchu, Xavier Jeunemaître, Stéphane Laurent, Pierre Boutouryrie

Summary
Background Vascular Ehlers-Danlos syndrome is a rare severe disease that causes arterial dissections and ruptures that can lead to early death. No preventive treatment has yet been validated. Our aim was to assess the ability of celiprolol, a β1-adrenoeceptor antagonist with a β2-adrenoeceptor agonist action, to prevent arterial dissections and ruptures in vascular Ehlers-Danlos syndrome.

Methods Our study was a multicentre, randomised, open trial with blinded assessment of clinical events in eight centres in France and one in Belgium. Patients with clinical vascular Ehlers-Danlos syndrome were randomly assigned to 5 years of treatment with celiprolol or to no treatment. Randomisation was done from a centralised, previously established list of sealed envelopes with stratification by patients’ age (≤32 years or >32 years). 33 patients were positive for mutation of collagen 3A1 (COL3A1). Celiprolol was uptitrated every 6 months by steps of 100 mg to a maximum of 400 mg twice daily. The primary endpoints were arterial events (rupture or dissection, fatal or not). This study is registered with ClinicalTrials.gov, number NCT00190411.

Findings 53 patients were randomly assigned to celiprolol (25 patients) or control groups (28). Mean duration of follow-up was 47 (SD 5) months, with the trial stopped early for treatment benefit. The primary endpoints were reached by five (20%) in the celiprolol group and by 14 (50%) controls (hazard ratio [HR] 0.36; 95% CI 0.15–0.88; p=0.040). Adverse events were severe fatigue in one patient after starting 100 mg celiprolol and mild fatigue in two patients related to dose uptitration.

Interpretation We suggest that celiprolol might be the treatment of choice for physicians aiming to prevent major complications in patients with vascular Ehlers-Danlos syndrome. Whether patients with similar clinical presentations and no mutation are also protected remains to be established.

Fifty three patients with clinical presentation of vEDS (33 are positive for mutation collagen 3A1) were randomized to a 5-year treatment with either celiprolol (n=25) or no treatment (n=28).

Celiprolol was up-titrated from 100 to 400 mg twice a day by 100 mg steps every 6 months.

The primary endpoints were arterial events (rupture or dissection, fatal or not).

Secondary endpoints were intestinal or uterine rupture or major clinical events, related to vEDS.
Mean duration of follow-up was 47 (± 15) months.

The primary endpoint was reached by 5 patients (20%) in the celiprolol group and by 14 patients (50%) in the control group (hazard ratio, 0.36; 95% CI, 0.15 to 0.88; P=0.04).

Primary plus secondary endpoints occurred in 6 patients (24%) in the celiprolol group and in 17 patients (61%) in the control group (hazard ratio, 0.31; 95% CI, 0.14 to 0.71; P=0.0097).

Twenty-nine patients carrying mutation for COL3A1 gene were also protected since 1/10 presented a primary event under celiprolol versus 11/19 in the control group (p=0.025).
Kaplan-Meier curves of event-free survival of all patients in PROBE design
Conclusions

• Ehlers Danlos syndrome consist of a heterogeneous group of inherited connective tissue disorders.
• The vascular type is most severe because of its potential vascular, and hollow organ dissection or rupture.
• Cardiologist should think about this rare vascular disease in case of early severe vascular or, cardiac event in young patient without cardiovascular risk.
• Atypical arterial site of the dissection its association to digestive and or uterine complication should also make think of this disease.
• Interest of Genetic testing and familial tree.
• The rule is less invasive treatment.
• Interest of Celiprolol for all suspected vEDS patient.
Perspective

- **Ultrafast**: Three real-time information:
  - longitudinal shear modulus: mode push
  - circumferential shear modulus: Pulse wave velocity
  - Variation of shear modulus during a cardiac cycle
- **Type knock in and knock out** (Prs. Emmerich et Jeunemaitre)
- **Benefit ARA2 ou IEC** in this indication
- **Benefit** of doxycycline
The Loeys–Dietz syndrome is a recently described autosomal dominant aortic-aneurysm syndrome with widespread systemic involvement. The disease is characterized by the triad of

- arterial tortuosity and aneurysms,
- hypertelorism,
- and bifid uvulaor cleft palate

and is caused by heterozygous mutations in the genes encoding trans-forming growth factor β receptors 1 and 2 (TGFBR1 and TGFBR2, respectively).
They found a mutation in TGFBR1 or TGFBR2 in all probands with typical Loeys–Dietz syndrome (type I) and in 12 probands (out of 40) presenting with vascular EDS (Loeys–Dietz syndrome type II).

The natural history of both types was characterized by aggressive arterial aneurysms (mean age at death, 26.0 years) and a high incidence of pregnancy-related complications (in 6 of 12 women).

Patients with Loeys–Dietz syndrome type I, as compared with those with type II, underwent cardiovascular surgery earlier and died earlier.

There were 59 vascular surgeries in the cohort, with one death during the procedure. This low rate of intraoperative mortality distinguishes the Loeys–Dietz syndrome from vascular EDS.
Patophysiology

- **Marfan Syndrome**
  - Deficiency of fibrillin-1 and abnormal elastin synthesis
  - Increase bioavailability of TGFβ in response to the defect in its chelation with abnormal fibrillin
  - Increased stiffness index
  - Increased pulse wave velocity

- **Vascular EDS**
  - Mostly peripheral artery
  - Deficiency of synthesis secretion and structure of procollagen type III affecting entire arterial tree
  - Some report of raisedf of TGF β in patient but can be sign of healing

Boutouyrie et al, Circulation 2004
Evolution and Prognosis

• Median survival is 48 years
• Causes:
  - arterial rupture ++ (unpredictable) : 78.5%
  - gastrointestinal perforation : 7.5%
  - uterine rupture, cardiac or hepatosplenic : 10%
• Heterogeneity between and within family
• The age of death in the series of Pepin ranged from 6-73 years.
• In this study, the patient's prognosis is better than that of the related suffering.
• Maternal mortality: 11.5%
Genetic Counseling

• **Autosomal dominant**
• Two systematic reviews of genetic testing
• **Problem of detection of minor**
• Related issue of testing (COL3A1 not detected in the index case)
• Problem of **prenatal screening** (trophoblast puncture between 8 and 12 weeks) or **preimplantation genetic diagnosis** required prior identification of the causal mutation in one of the two parents.
Visceral complications

- Average age of the first occurrence of complication was 23.5 years
- 25% of patients had complications before the age of 20
- More than 80% at least 40 years old.
- Median survival is 48 years
- Arterial rupture is responsible for most deaths.

Pepin M et al, NEJM 2000
Visceral complications

- Arterial complications
- Gastrointestinal complications
- Obstetric complications
- Respiratory complications
- Venous complications
Bienvenue

Le Centre National de Référence des Maladies Vasculaires Rares a été labellisé en juillet 2006 par le ministère de la Santé afin de développer la filière de soin pour six pathologies vasculaires distinctes : le syndrome d' Ehlers-Danlos vasculaire, la dysplasie fibromusculaire artérielle, la maladie de Buerger, la maladie de Takayasu, le lymphœdème primitif et les bicuspidies familiales de la valve aortique.

Le Centre comprend deux sites, l'Hôpital Européen Georges Pompidou dédié aux maladies cardiovasculaires rares et l'Hôtel Cognacq-Jay prenant en charge plus spécifiquement le traitement des maladies lymphatiques primitives.

Que vous soyez professionnel de santé, parent d'un malade ou vous-même atteint de l'une de ces pathologies, vous trouverez sur ce site des informations médicales adaptées, la manière d'accéder aux...
Carte de soins et d’urgence

Syndrome d’Ehlers-Danlos Vasculaire
(Vasculaire Ehlers-Danlos Syndrome)
Back To History ....

Pierre Curie

Theory of Piezo-electricity

Paul Langevin - 1914

First Sonar Experiment
Precursor of Modern Medical Echography

Langevin Radiation Force

Visit www.loa.espci.fr/epom/epom_main.html
Mitral Valve and Collagene type 3

William G et al. Biochem 1984

- Collagen fibres of the mitral valve prevent the leaflet of prolapsing.

- Observation by Hammer et al (1979) that Myxomatous MV can lack type III and type V collagen.

- Bonella et al (1980) accumulation of procollagen that resembled the biomechanical abnormalities reported in the type VII form of EDS.

- Type 1 and type 3 abundant in normal MV leaflet.

- Analyze of 13 normal (autopsy) and 19 Myxomatous valve (surgery).
Human Study Endpoints

- Evaluate incidence of MVP in vEDS
- Evaluate MV abnormalities in vEDS and Vascular susceptibility patient
- Correlate MV stiffness to Carotid stiffness in vEDS.