DEFYFOUNDATION

# 4th Scientific Meeting on Vascular Ehlers-Danlos Syndrome

## PROGRAM AGENDA

### Virtual Meeting: Friday, April 9, 2021
### 10:00 am – 4:30 pm Eastern

| | | | | |
|---|---|---|---|---|
| | **10:00** | **Welcome - Anthony Yasick, Peter Byers, Hal Dietz and Xavier Juenemaitre** | | |
| | | **Patient Perspective - Why I Got Involved in Research, Zachery Burger** | | |
| **SESSION 1 — Investigation of VEDS Therapuetics and Interventions Using Mouse Models \| Moderator - Hal Dietz** | | | | |
| 1 | 10:15 | Juzwiak | Emily | Spironolactone Monotherapy Provides Overt Protection in Post-Pubertal Vascular Ehlers-Danlos Syndrome Mice |
| 2 | 10:30 | Bowen | Caitlin | A gene, variant and mechanism for a potent protective modifier of vascular Ehlers-Danlos syndrome |
| 3 | 10:45 | Dubacher | Nicolo | Drug Repositioning: Added Value of Celiprolol and Pravastatin in Vascular EDS |
| 4 | 11:00 | Sorber | Rebecca | High dose vitamin C demonstrates a sexually dimorphic survival benefit in a mouse model of severe vascular Ehlers-Danlos syndrome |
| 5 | 11:15 | Burger | Zachary | Assessing the effects of aerobic and isometric exercise in vascular Ehlers Danlos syndrome |
| | **11:30** | **10 minute Panel Discussion - Session 1 speakers & All Moderators** | | |
| | **11:40** | **5 minute Break** | | |
| **SESSION 2 — Phenotypic Characteristics in the VEDS Population \| Moderator - Shaine Morris** | | | | |
| 6 | 11:45 | Stephens | Sara | Cardiovascular Characteristics Among Children with Vascular Ehlers-Danlos Syndrome |
| 7 | 12:00 | Stephens | Sara | Vertebral Artery Tortuosity Is a Biomarker For Arterial Events in Children and Adults with Vascular Ehlers-Danlos Syndrome |
| 8 | 12:15 | Adham | Salma | Spontaneous cervical artery dissection in vascular Ehlers-Danlos syndrome: a cohort study |
| 9 | 12:30 | Frank | Michael | Lung Disease in Patients with Ehlers-Danlos Syndrome (vEDS): Frequency and CT Findings |
| | **12:45-1:15** | **30 minute Break** | | |
| **SESSION 3 — Genotype/Phenotype Correlations \| Moderator - Peter Byers** | | | | |
| 10 | 1:15 | Doherty | Elizabeth | Extracellular Matrix Variability in Vascular Ehlers-Danlos Syndrome |
| 11 | 1:30 | Lui | Madeline | Genotype-first investigation of vEDS phenotypes and penetrance among *COL3A1* mutations carriers in an ethnically diverse biobank |
| 12 | 1:45 | Yap | Norah | Clinical presentation of Vascular Ehlers-Danlos Syndrome in Children |
| **SESSION 4 — Understanding Clinical Outcomes for Better Management Care \| Moderator - Xavier Juenemaitre** | | | | |
| 13 | 2:00 | Barrett | Leanne | A Qualitative Study Exploring the Psychosocial Issues in Patients with Vascular Ehlers Danlos Syndrome |
| 14 | 2:15 | Stephens | Sara | Perinatal and Neonatal Outcomes Among Children with Vascular Ehlers-Danlos Syndrome |
| P-15 | 2:30 | Rumyantseva | Victoria | New rare genetic variant in the *COL3A1* gene found in a patient with a clinical phenotype of Ehlers-Danlos Syndrome |
| | **2:35** | **15 minute Panel Discussion - Session 2, 3, 4 Speakers & All Moderators** | | |
| | **2:50-3:00** | **10 minute Break** | | |
| **SESSION 5 — Learnings from Natural History Cohort Studies \| Moderator - Sherene Shalhub** | | | | |
| 16 | 3:00 | Barbadora | Jennifer | Bone Density Screening in Vascular Ehlers-Danlos syndrome |
| 17 | 3:15 | Bos | Jessica | Vascular Ehlers-Danlos syndrome – A comprehensive natural history study in the Dutch patient cohort, preliminary results |
| 18 | 3:30 | Legrand | Anne | Aortic involvement in vascular Ehlers-Danlos syndrome: a retrospective multicentric cohort |
| 19 | 3:45 | Shalhub | Sherene | VEDS Collaborative Research Study: Year One progress in a comprehensive natural history study |
| P-20 | 3:50 | Harris | Juliette | Stoma reversal in a cohort of individuals with vascular EDS: a description of four cases |
| | **3:55** | **10 minute Panel Discussion - Session 5 speakers & All Moderators** | | |
| | **4:05** | **5 minute Break** | | |
| | **4:10** | **Forging Continued Collaborations - Wrap-Up - Anthony Yasick, Peter Byers, Hal Dietz, Xavier Jeunemaitre** | | |
| | | LeMaire | Scott | Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan Mice |
| | | Jeunemaitre | Xavier | GWAS regions associated with colon perforation in vascular EDS |
| | 4:30 | Adjorn | | |

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***In collaboration with Fight VEDS, The Ehlers-Danlos Society, VEDS Collaborative, and Annabelle's Challenge***

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Spontaneous cervical artery dissection in vascular Ehlers-Danlos syndrome: a cohort study

Salma Adham[1,2], Clarisse Billon[1,2], Anne Legrand[1,2], Valérie Domigo[3,4], Nicolas Denarié[1], Etienne Charpentier[5], Tristan Mirault[1,2], Xavier Jeunemaitre[1,2] Michael Frank[1,2]

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**Introduction.** Vascular Ehlers-Danlos syndrome (vEDS) is a rare inherited connective tissue disorder due to pathogenic variants in the *COL3A1* gene. Arterial complications affect all anatomical areas and about 25% involve supra-aortic trunks (SAT) but no systematic assessment of cervical artery lesions has been made.
**Objectives.** Our primary objective was to determine an accurate prevalence of spontaneous SAT lesions in vEDS patients at diagnosis and during follow up. Our secondary objective was to study their neurological consequences (transient ischemic attack TIA or stroke) and the possible relationships with sex, genotype, and ascertainment status.
**Methods.** A retrospective review of a monocentric cohort with molecularly-proven vEDS patients followed in a tertiary referral centre from 2000 to 2017. SAT lesions were assessed through systematical computed tomography angiography and Doppler ultrasound performed during initial arterial assessment and yearly follow-up.
**Results.** 144 patients were analyzed, 56.9% (n=82) had SAT lesions: 64.6% females, 74.4% index-case patients. Most lesions were identified in early arterial assessment (48% at first work-up, mean age of 35.7 ± 13.0 years). Cumulative incidence of a first identification of a SAT lesion was 41.7% at 40 years old. On the complete period of survey, 183 SAT lesions (with 132 dissections and 33 aneurysms) were identified, mainly in internal carotid arteries (ICA, 56.3%) and vertebral arteries (VA, 28.9%), more rarely in patients with *COL3A1* null mutations (p=0.008). TIA or stroke were reported in n=16 (19.5%) of the 82 patients with SAT lesions without relation with age, sex, treatment or hypertension.
**Conclusion.** Cervical artery lesions are frequent and mostly asymptomatic in vEDS patients. Local dissections and aneurysms are the most frequent type of lesions, but TIA or stroke seem rare.

Word count: 272/300

Back to Program Agenda

# BONE DENSITY SCREENING IN VASCULAR EHLERS-DANLOS SYNDROME

Barbadora, Jennifer L[1]; Stephens, Sara[1]; Tays, Rachel[2]; Morris, Shaine A[1]

1. Baylor College of Medicine and Texas Children's Hospital
2. Patient advocate, Vascular Ehlers-Danlos Collaborative

**INTRODUCTION**: Multiple connective tissue disorders are associated with low bone density. Preliminary studies examining bone density in Vascular Ehlers-Danlos syndrome (VEDS) have not focused on children and young adults.

**OBJECTIVES:** We aimed to describe bone density in a cohort of children and young adults with genetically confirmed VEDS.

**MATERIALS AND METHODS**: We performed a retrospective review of a cohort of patients <35 years old evaluated at our center with VEDS. Bone density evaluation using dual energy x-ray absorptiometry (DEXA) became standard of care for baseline evaluation at our institution in 2019 for patients with VEDS. Clinically performed studies were collected and z-scores were calculated based on age, sex, and race-matched controls. Z-scores were compared against the expected population value of "0" for each region (femoral head, lumbar spine, and total body excluding head) using one-sample Wilcoxon signed-rank analysis.

**RESULTS**: Eighteen patients underwent DEXA (median age at testing 9.5 years, range 5.0-33.4 years; 89% male). One study was performed for frequent fractures; the remainder were surveillance. Variant types were: 10 splice site (56%), 6 glycine missense (33%), 1 nonsense (6%), and 1 multigene deletion (6%). Four (22%) had a history of fractures, all with z-scores <0, one with z-score <-2. Four (22%) had a z-score <-2 for at least one region. The patient with a multigene deletion had z-scores far outside the expected range (femur: -8.7, lumbar -6.5, body -6.6), and was excluded from other analyses. Remaining median z-scores for each region were <0, but did not meet statistical significance (Figure). When stratifying by genotype, similar patterns were noted.

**CONCLUSION:** Low bone density was observed more frequently in this cohort than seen in the general population. These findings may have long-term implications for therapeutic strategies. Integrating bone density evaluation into this population's clinical care should be considered.

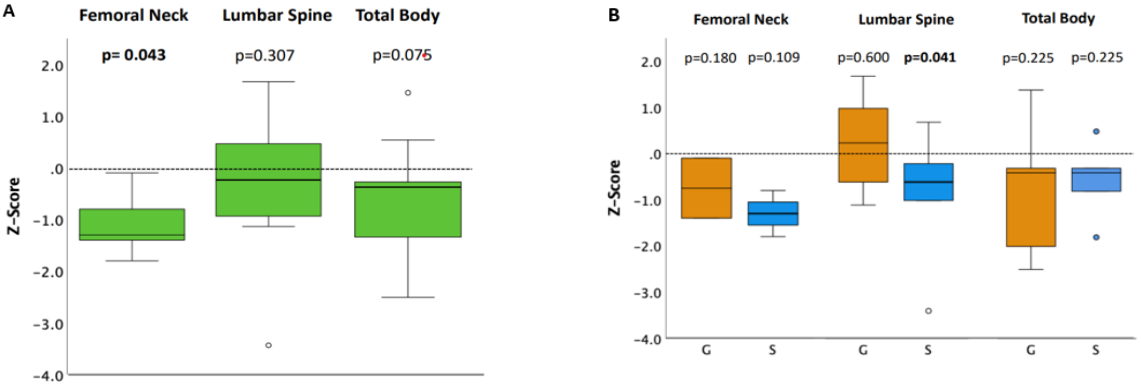


Figure B: G: Glycine missense; S: Splice site

Back to Program Agenda

# A Qualitative Study Exploring the Psychosocial Issues in Patients with Vascular Ehlers Danlos Syndrome.

Leanne Barrett[1], Claire Green[2], Marion McAllister[3], Jared Griffin[4].

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3. Centre for Medical Education, School of Medicine, Cardiff University, Cardiff, UK
4. Annabelle's Challenge Vascular EDS Charity, Bury, UK

## Introduction

Vascular Ehlers Danlos (vEDS) is characterised by thin translucent skin, easy bruising and an increased risk of sudden death, due to vascular rupture. There is little published evidence reporting psychosocial issues faced by people living with vEDS. This exploratory qualitative study was the first in the UK to address the psychological and social implications of living with the condition.

## Objectives

The study aimed to explore the day-to-day experiences of people living with vEDS and the impact of the condition on work/study, social life and activities, relationships, and mental health.

## Materials and methods

Participants were recruited through the UK vEDS support group Annabelle's Challenge, following ethics approval from Cardiff University School of Medicine. In-depth one-to-one semi-structured telephone interviews were conducted with participants, transcribed in full and analysed using thematic analysis.

## Results

In total, 21 participants were recruited, aged 19-61 years (response rate = 61%). Six dominant themes were identified in participants' accounts. Physical limitations to daily life was identified as an area that significantly affected participants' daily lives. A further five themes also emerged from data analysis: risk perception and existential thoughts, communication and support, responsibility, loss, and resilience and coping mechanisms. Mental health issues were reported by some participants, with the majority commenting on frustration and lack of knowledge amongst healthcare professionals, along with concern for future generations.

## Conclusion

Findings suggest that vEDS patients are faced with some significant psychosocial challenges that are not always addressed by their healthcare providers. Care for vEDS patients could be improved by upskilling healthcare professionals to address the psychosocial aspects of vEDS using psychotherapeutic approaches. There is scope for future psychosocial research with vEDS patients, including further exploration of the significance of age at diagnosis, quality of life, coping mechanisms and relationships.

Back to Program Agenda

**Vascular Ehlers-Danlos syndrome – A comprehensive natural history study in the Dutch patient cohort, preliminary results**

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**Introduction:** Vascular Ehlers Danlos Syndrome (vEDS; OMIM 130050; ORPHA 286) is a rare connective tissue disorder, caused by heterozygous pathogenic variants in the *COL3A1* gene. The phenotype is highly variable. vEDS patients are at risk for arterial, bowel and uterine rupture. **Objectives:** To perform a national multi-center cohort study in all known Dutch vEDS patients, to provide further insights into the natural history of the disease. This knowledge will allow us to optimize patient care. **Materials and methods:** After METC approval, all known Dutch patients carrying a (likely) pathogenic variant in the *COL3A1* gene were invited to participate in the study (n=~130). The phenotype was systematically charted by retrospective and cross-sectional assessment of molecular and clinical data. **Preliminary results:** Eighty-seven patients have been included thus far (44 males, mean age 48 years (4-94 years)). Thirty-one of 85 (36%) were index patients (2 missing data). Of the 87 patients, 52 (60%) had a symptomatic history. The main reasons for referral were: family member with (likely) pathogenic variant (60%), arterial dissection (13%) and aneurysm (9%). In total, 30 patients (34%) had aneurysm(s), 29 (33%) dissection(s), 28 (32%) varicose veins and 8 (9%) cardiac valve insufficiency. Six (7%) suffered from (iatrogenic) perforation of the colon. Twenty-two of 62 (34%) did not meet the 2017 criteria suggestive for vEDS. **Conclusion:** This national multi-center natural history study of Dutch vEDS patients provides a basis for improving guidelines for diagnosing, follow-up and treatment of vEDS patients worldwide.

Back to Program Agenda

**A gene, variant and mechanism for a potent protective modifier of vascular Ehlers-Danlos syndrome**

Caitlin J Bowen[1,2], Zachary Burger[1,2], Rebecca Sorber[3], Juan Francisco Calderón Giadrosic[1], Jefferson Doyle[1], Graham Rykiel[1], Xiaoyan Zhang[1,2], Elena Gallo MacFarlane[1], Harry C Dietz[1,2]

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**Introduction:** Attenuation of PKC/ERK pathway activation affords protection from vascular rupture in mouse models of vascular Ehlers Danlos syndrome (vEDS). The onset and severity of disease is highly variable, even within a given family, suggesting potential genetic or environmental modifiers that remain to be defined.
**Objectives:** Identify modifier genes in vEDS.
**Materials and Methods:** Using *Col3a1*$^{G938D/+}$ vEDS mice, we employed an unbiased mapping approach and mechanistic analyses to elucidate genetic modifiers of vascular disease.
**Results and Conclusion:** Compared to the C57BL/6J (BL6) background, vEDS mice on the 129S6/SvEvTac (129) background show near-complete life-long protection from death due to vascular rupture. This was not associated with improved aortic wall biomechanical strength, histologic architecture, or changes in blood pressure, but rather with decreased PKC/ERK signaling. This unanticipated dissociation between structural tissue integrity and phenotypic outcome provided evidence that a nonproductive cellular response to altered extracellular matrix, rather than the matrix deficiency per se, is the dominant determinant of vascular disease in vEDS. Genome-wide genotyping of intercrossed BL6/129 vEDS mice stratified by survival identified a single significant protective locus on mouse chromosome 11 (OR=0.2293). *Map2k6*, encoding a p38-activating kinase, emerged as the only candidate gene based on expression data and strain-specific sequence variation (p.G76E). Protected 129 vEDS mice showed higher expression of *Map2k6* in the aorta and increased phosphorylation of p38 with increased activation of its substrate PP1 in the aortic wall, a phosphatase that dephosphorylates pPKC and pERK. Genetic or pharmacological inhibition of this protective axis accelerated vascular rupture in a PKC/ERK-dependent manner. These results both validate and extend our understanding of cellular signaling events that culminate in vascular rupture in vEDS and define a pathway of natural potent protective disease modification. We anticipate that pharmacologic interventions that mimic nature's successful modification strategy will afford substantial protection to patients with vEDS.

Back to Program Agenda

**Assessing the effects of aerobic and isometric exercise in vascular Ehlers Danlos syndrome**

Zachary Burger[1], Rebecca A. Sorber[1,2], Caitlin J. Bowen[1], Emily Juzwiak[1], Graham Rykiel[1], Juan Francisco Calderon Giadrosic[1], & Harry C Dietz[1]
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**Introduction**: Vascular Ehlers-Danlos (vEDS), caused by type III collagen deficiency is characterized by spontaneous arterial rupture. Patients are routinely advised to avoid strenuous or isometric exercise, but direct evidence to support or refute this restriction is lacking.

**Objectives**: This work investigates the effects of isometric and aerobic exercise in a knock-in mouse model of severe vEDS (*Col3a1*$^{G938D/+}$).

**Materials and methods**: *Col3a1*$^{G938D/+}$ mice show 50% mortality from aortic rupture by 50 days of age. Aerobic exercise was simulated with treadmill running for 30 min/day, 5 days/week for 5 weeks. Isometric exercise was imposed by requiring sustained support of body weight against gravity for 10 min/day for the same time period.

**Results**: Overall, 47% of unexercised vEDS mice survived, compared with 51% in the aerobic exercise group and 67% in the isometric exercise group ($p>0.05$ for all comparisons). Sex-specific survival curves demonstrated 100% survival among female vEDS mice in the isometric exercise arm, which was significantly greater than that observed in female vEDS mice in the cardiovascular exercise or the no exercise groups ($p<0.05$). Histologic examination of exercised aortas versus unexercised controls demonstrated no significant increases in elastin breaks or aortic wall thickness for vEDS mice in the aerobic exercise group. Notably the aortas from vEDS mice in the isometric exercise group demonstrated an increased frequency of chronic dissections and elastic fiber breaks compared with unexercised controls ($p=0.0018$). It remains unclear if this manifests subclinical vascular events in mice that otherwise would have died of aortic rupture in the absence of isometric exercise or isometric exercise-induced deterioration of wall integrity.

**Conclusions**: Overall, these data suggest that neither moderate aerobic nor isometric exercise increase overall mortality in vEDS mice. The mechanistic basis for the observed sexual dimorphism in the protection afforded by isometric exercise against vascular rupture warrants further investigation.

Back to Program Agenda

**Extracellular Matrix Variability in Vascular Ehlers-Danlos Syndrome**

Elizabeth L. Doherty[1,2], Wen Yih Aw[2], Stefanie Howell[2], Anthony J. Hickey[1,2], and William J. Polacheck[1]

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**Introduction:** Vascular Ehlers-Danlos Syndrome (vEDS) is a rare disease characterized by *COL3A1* mutations causing procollagen III malformations, which result in weakened connective tissues, including arterial walls.[1,2] *COL3A1* mutations alter extracellular matrix (ECM) composition, yet the effects on ECM mechanics and cellular behavior are unclear.

**Objectives:** We characterized changes in ECM properties produced by vEDS patient-derived cells and determined the effect of these properties on endothelial cells. This study provides a comprehensive set of cellular and mechanical phenotypes to expand upon the mechanisms by which ECM mechanics impact vEDS disease phenotype.

**Materials and Methods:** Human dermal fibroblasts (HDFs) were obtained from one healthy (WT) donor and three vEDS patients with heterozygous null (*COL3A1*$^{+/-}$), or glycine substitution (*COL3A1*$^{G939D/+}$) *COL3A1* mutations. To generate cell-derived matrix (CDM), HDFs were plated at confluence and cultured with 50 µg/mL ascorbic acid supplemented media for six days, after which samples were decellularized. Decellularization was confirmed by staining for filamentous actin and DNA. CDMs were analyzed in terms of composition, structure and thickness (confocal reflectance microscopy), and mechanical properties (nanoindentation). To assess endothelial cell response to CDM, human umbilical vein endothelial cells (HUVECs) were characterized after plating on CDM.

**Results and Conclusion:** All cell lines produced fibrous CDM that was effectively decellularized. *COL3A1*$^{+/-}$ HDFs demonstrated decreased *COL3A1* expression, while *COL3A1*$^{G939D/+}$ HDFs had increased expression compared to WT HDFs. Interestingly, our data suggest that the type of *COL3A1* mutation has an impact on CDM production and stiffness. *COL3A1*$^{+/-}$ CDM grows slower and is stiffer than WT and *COL3A1*$^{G939D/+}$ CDM. Further, HUVEC focal adhesion expression differs when plated on CDM from different genotypes. These results indicate that the specific *COL3A1* mutation impacts ECM synthesis and mechanics, which translates to differences in HUVEC response.

**References:** [1]Pepin, MN. Engl. J. Med. 2000. 342:673–680. [2]Germain, DP. Orphanet J. Rare Dis. 2007. 2:32.

Back to Program Agenda

## Drug Repositioning: Added Value of Celiprolol and Pravastatin in Vascular EDS

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**Introduction:** Patients affected by the rare connective tissue disorder vascular Ehlers-Danlos syndrome (vEDS) are at increased risk for fatal aortic ruptures. To date, no targeted therapy is available.

**Objectives:** Recently, we have established an objective read-out system for measuring the biomechanical integrity of the murine thoracic aorta. This system allowed us to identify market-approved drugs (cheap with high level of knowledge) with a potential added value of strengthening the weakened aorta in the medical therapy of vEDS.

**Materials and Methods:** Mice modelling vEDS were treated with the beta-blockers celiprolol or bisoprolol, the angiotensin-II-type-1-receptor-blocker losartan, or the HMG-CoA-reductase-inhibitor pravastatin for 4 weeks. 1.5-mm-long sections of the ascending and descending murine thoracic aorta were mounted on a tissue puller and uniaxially stretched until rupture. For the tested drugs, we considered pharmacogenetic information from the PharmGKB website as well as from the guidelines of the Dutch Pharmacogenetics Working Group and the Clinical Pharmacogenetics Implementation Consortium.

**Results:** The rupture forces (mN) were significantly lower in untreated heterozygous compared to wild-type mice, while celiprolol and pravastatin but neither bisoprolol nor losartan increased the thoracic aortic rupture force in heterozygous mice. While losartan and bisoprolol undergo cytochrome-P450-mediated metabolism and the plasma concentration of pravastatin may be affected by *SLCO1B1*, celiprolol is secreted unmetabolized.

**Conclusions:** Unlike losartan and bisoprolol, celiprolol and pravastatin have added value regarding the strengthening of the weakened murine vEDS aorta. Despite this potential added value of pravastatin, celiprolol prevails due to its favourable pharmacokinetic profile and, hence, should currently be the medical therapy of choice for vEDS, until further evidence emerges. Our results exemplify that drug repositioning/repurposing can be a powerful source to identify old drugs for potential new therapeutic approaches in aortic diseases.

Back to Program Agenda

**Lung-Disease in Patients with Ehlers–Danlos Syndrome (vEDS): Frequency and CT Findings.**

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[9] Department of Cardiovascular Imaging, Hôpital Européen Georges Pompidou, AP-HP Centre Université de Paris, Paris, France.

**OBJECTIVES:** To describe clinical characteristics and CT features of lung involvement in patients with Vascular Ehlers–Danlos syndrome (vEDS), a rare genetic condition caused by pathogenic variants within the *COL3A1* gene, characterized by recurrent arterial, digestive and pulmonary events. The most common respiratory events are hemo-/pneumothoraces and pulmonary bleeding, but any association with a specific lung disease is unknown.

**MATERIAL AND METHODS:** All consecutive vEDS patients referred to the national tertiary referral center for vEDS, between 2004 and 2016, were included. Chest CT scans obtained during the initial vascular work-up were reviewed retrospectively by two chest radiologists for lung involvement. Five surgical samples underwent histologic examination.

**RESULTS:** Among 136 enrolled patients (83 women, 53 men; mean age 37 years) with molecularly confirmed vEDS. 24 (17.6%) had a history of respiratory events: 17 with pneumothorax, 4 with hemothorax and 3 with hemoptysis that necessitated thoracic surgery in 11. CT scans detected lung abnormalities in 78 (57.3%) patients: emphysema (mostly centrilobular and paraseptal) in 44 (32.3%), comparable for smokers and nonsmokers; clusters of calcified small pulmonary nodules in 9 (6.6%); and cavitated nodules in 4 (2.9%). Histologic examination of surgical samples found emphysema, with alveolar ruptures in 3, accompanied by diffuse hemorrhage-increased hemosiderin resorption.

**CONCLUSION:** The most frequently observed CT finding in vEDS patients, even those asymptomatic, was emphysema suggesting alveolar-wall rupture. Identification of this pattern by radiologists might facilitate diagnostic screening of undiagnosed probands. The prognostic value and evolution of these parenchymal abnormalities remain to be evaluated.

Back to Program Agenda

## Stoma reversal in a cohort of individuals with vascular EDS: a description of four cases

Harris Juliette M[1], Angwin Chloe[1,2], Ghali Neeti[1,2], van Dijk Fleur S[1,2]

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### Introduction

By the age of 40 years, 80% of individuals with vascular Ehlers Danlos Syndrome (vEDS) have had a complication. Bowel rupture often involving the sigmoid colon accounts for a quarter of complications and half of patients undergo a Hartmann procedure with the creation of a stoma. The impact that stoma can have on quality of life means that vEDS patients do request stoma reversal, however it is generally advised against due to tissue friability and chance of re-perforation.

### Objectives

To identify individuals with vEDS, who underwent stoma reversal, and to document outcome and follow-up data.

### Materials & Methods

Out of 153 individuals with a diagnosis of vEDS, four were found to have had a stoma reversal. Reviews of their medical documentation and interviews were performed.

### Results

All individuals had a molecularly confirmed diagnosis of vEDS (splice site variant(n=2), triple helix glycine substitutions(n=2). Age at bowel perforation ranged from 6 days to 31 years. Bowel perforations were spontaneous(n=3) and after colonoscopy(n=1). All had a (modified) Hartmann's procedure and a stoma reversal 6 months later, with intraoperative complications in one individual due to adhesions and fragility. Post-operative complications were MRSA infection and delayed wound healing (n=1). Three individuals were diagnosed with vEDS after stoma reversal. Time since reversal varies from 10 to 28 years. Long-term outcomes vary from no complications(n=1) to incisional hernias(n=1), occasional rectal bleeding of unknown origin(n=1), and complaints of occasional abdominal pain, constipation and diarrhoea(n=1).

### Conclusion

It has been demonstrated that for several individuals with vEDS, stoma reversal did not lead to major or life threatening complications during and after surgery and no re-perforation has occurred. However, from this limited case series no conclusions can be drawn with regard to factors influencing successful outcome of reversal. Further data from more individuals with vEDS and stoma reversal are necessary.

Back to Program Agenda

**GWAS regions associated with colon perforation in vascular EDS**

Anne Legrand[1,2], Barthélémy Caron[3], Michael Frank[1], Salma Adham[1,2], Clarisse Billon[1,2], Jean Michael Mazzella[1], Anne Boland[4], Jean-François Deleuze[4], Tristan Mirault[1,2], Antonio Rausell[3], Xavier Jeunemaitre[1,2], on behalf of the French RaDiCo SEDVASC registry.

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**Introduction:** Vascular Ehlers-Danlos syndrome (vEDS) is a rare inherited connective tissue disorder due to pathogenic variants in the *COL3A1* gene. The large phenotypic heterogeneity is only partly explained by the type of genetic variant (dominant negative DN vs haplo-insufficient HI).
**Objectives:** To identify modifier genes explaining the phenotypic heterogeneity of vEDS.
**Methods:** Genome-wide association study (GWAS) of a French cohort of molecularly-proven vEDS patients was performed using the Illumina HumanOmniExpressExome array. Several qualitative and quantitative traits (acrogeria, age at the first severe complication, digestive complication, vascular complication, number of affected arteries, number of acute arterial complications) were assessed through a generalized linear mixed model, after adjusting for age, sex, array, the 2 first principal components (PC) of the genetic data and interindividual relatedness. The search for modifier genes associated with colon perforation was restricted to patients with DN *COL3A1* variants (glycine or splice variants), as this complication is rare in patients with HI variants.
**Results:** After quality controls and exclusion of outliers based on ancestry, 290 vEDS patients belonging to 185 families were kept, including 54 patients (41% males) with colon perforation (mean age of onset 24.1 ±1.7 years). We identified one modifier locus significantly associated with an increased risk of colon perforation (OR=7.5, IC: 3.2 – 17.1) on chromosome 4 (p-value = $2.3 \times 10^{-8}$). When further correcting for false-discovery rate (FDR), we identified five additional loci that associate with colon perforation (FDR <= 0.05). Further experiments will be performed to confirm their relevance in the occurrence of colon perforation.
**Conclusion:** Six candidate risk loci for colon perforation in vEDS patients were identified and require replication in other vEDS cohorts. These results support the existence of modifier genes involved in one of the most severe complication of vEDS. The identification of such factors is critical to understand the mechanisms causing colon perforation and for the development of a personalized care of vEDS patients.

Word count: 311/300

Back to Program Agenda

Title: Spironolactone Monotherapy Provides Overt Protection in Post-Pubertal Vascular Ehlers-Danlos Syndrome Mice

Authors: Juzwiak, E.[1,2], Bowen, C.[1,2], Sorber, R.[3], Dietz, H.[1,2]

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Introduction: Currently, there are no therapeutic treatments to prevent arterial rupture and premature death in Vascular Ehlers-Danlos Syndrome (vEDS). Male vEDS patients are at an increased risk for vascular catastrophe after puberty; this vulnerability is not observed in female patients, suggesting that androgens contribute to vascular demise. Our vEDS mouse model (*Col3a1*$^{G938D/+}$) recapitulates this pubertal sexual dimorphism, as female - but not male - *Col3a1*$^{G938D/+}$ mice are protected by the antihypertensive drug hydralazine through puberty (60% female vs. 25% male survival at 100 days). Furthermore, treatment with hydralazine and spironolactone, an androgen receptor antagonist, provides complete protection when administered at weaning ($p<0.0001$). However, it remains unknown if spironolactone efficacy depends on co-treatment with hydralazine or age of treatment initiation.

Objective: To test if spironolactone monotherapy provides vascular protection when initiated either at or after puberty.

Materials and Methods: Spironolactone treatment was initiated at weaning until 70 days of age or post puberty (60 days of age) until 100 days of age. Kaplan-Meier survival analysis was performed.

Results and Conclusions: When *Col3a1*$^{G938D/+}$ mice are given spironolactone from weaning until adulthood male mice exhibited a significant improvement in survival (from 32% to 67%, $p=0.0477$), whereas females did not (from 54% to 64%, $p=0.5347$). This did not approximate the 100% male and female survival observed with hydralazine and spironolactone combination therapy. Importantly, post-pubertal spironolactone monotherapy provided 96% survival in *Col3a1*$^{G938D/+}$ males (vs. 71% in untreated males, $p=0.0378$) and 100% in *Col3a1*$^{G938D/+}$ females (vs. 60% in untreated females, $p=0.0098$). These data suggest that hydralazine is needed to enhance survival up to puberty whereas spironolactone is sufficient for essentially-complete post-pubertal protection. Given the safety, high tolerance, and efficacy of spironolactone in the treatment of androgen-related phenotypes in both sexes, these data warrant consideration of a clinical trial of spironolactone monotherapy in adults with vEDS.

Back to Program Agenda

Genotype-first investigation of vEDS phenotypes and penetrance among *COL3A1* mutations carriers in an ethnically diverse biobank

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Icahn School of Medicine at Mount Sinai

**Introduction:** Descriptions of *COL3A1*-related phenotypes come primarily from studies of symptomatic patients diagnosed with vascular Ehlers-Danlos syndrome (vEDS).

**Objective**: Using a genotype-first approach, we ascertained vEDS-associated phenotypes in biobank participants harboring putatively deleterious *COL3A1* variants.

**Materials and Methods:** Potentially deleterious *COL3A1* variants (missense substitutions for glycine in the triple helical domain (HD), variants disrupting splice sites, frameshift insertions/deletions or those reported likely pathogenic/pathogenic in ClinVar) were identified from exome sequencing data of ~30k enrollees in the *BioMe* biobank and linked electronic health records (EHR) of carriers were reviewed for phenotypes associated with vEDS.

**Results:** Relevant *COL3A1* variants were found in 18 (61% F) individuals (15 glycine substitutions in the HD; 2 splicing variants; 1 frameshift deletion of glycine in the HD). None carried an EHR diagnosis of vEDS or genetic arteriopathy. Median age at last EHR encounter for living subjects was 54 years (range 34-74) and 61 years for deceased subjects (range 50-64); none died of vascular, obstetric, or gastrointestinal causes. One participant, with a splicing variant, had a history of numerous aneurysms, a major vEDS criteria. Four participants harboring glycine substitutions met minor vEDS criteria for non-arterial manifestations; aspartate and valine substitutions, previously found to be more destabilizing and associated with poorer survival, were present in two of these individuals. Interestingly, 89% of subjects had a history of invasive procedures or surgery, including colonoscopy, spine surgery, and invasive angiography, which would typically be contraindicated after vEDS diagnoses. The subject who met major criteria for vEDS underwent an uncomplicated lumbar laminectomy and partial diskectomy and robotic renal cyst decortication. Female subjects with obstetric histories (n = 5) survived pregnancies (average parity: 3).

**Conclusion:** A genotype-first approach to identifying individuals with putatively pathogenic *COL3A1* variants reveals heterogeneous and milder phenotypes, and lower penetrance than predicted based on prior vEDS cohort studies.

Back to Program Agenda

Aortic involvement in vascular Ehlers-Danlos syndrome: a retrospective multicentric cohort

Salma Adham[1,2], Anne Legrand[1,2], Rosa Maria Bruno[2,3], Violaine Dalens[4], Clarisse Billon[1,2], Jean-Michael Mazzella[1], Pierre Boutouyrie[2,3], Michael Frank[1], French vEDS group, Tristan Mirault[1,2], Xavier Jeunemaitre[1,2]

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**Introduction:** Vascular Ehlers-Danlos syndrome (vEDS) is a rare inherited connective tissue disorder due to pathogenic variants in the *COL3A1* gene, leading to medium-size artery dissection, aneurysm and rupture with a poor prognosis. Aortic damage is rarer and classically associated with haploinsufficient (HI) *COL3A1* variants.
**Objectives:** To describe the association between the distribution of medium-size artery and aortic lesions and the type of *COL3A1* variants in a multicentric cohort of vEDS patients.
**Methods:** *COL3A1* variants were identified using NGS sequencing and/or Sanger sequencing and classified according to their functional consequences. Computed tomography angiography (CTA) was systematically performed during the initial work-up of patients. Carotid arterial wall parameters were also assessed by ultrafast echotracking in a subset group.
**Results:** Among 341 vEDS adult patients (61% females, 41 years (IQR: 28-51)), 59% had glycine-missense variants, 22% splice-site variants and 19% HI variants. Medium-size artery or aortic lesions were reported in 242 (71%) patients and distributed as follows: 198/242 (82%) had medium-size artery lesions alone, 9 (4%) had aortic lesions alone and 35 (14%) had both. The genotype did not influence the presence of arterial lesions or not ($P$=0.064). However dominant negative (DN) variants (glycine-missense and splice-site variants) were associated with more medium-size artery lesions than HI ($P$=0.008), and particularly on supra-aortic trunks ($P$ <0.001). Stiffness assessment in 139 (41%) patients found a lower Young's modulus in DN variants than HI ($P$=0.007). Finally, patients with HI variant had a higher frequency of aortic lesions than patients with DN variant (33% vs 15%), a statistical significance that disappeared when adjusted for age.
**Conclusion:** Whereas the prevalence of aortic lesions is not influenced by the *COL3A1* genotype when adjusted for age, patients with DN variants have a higher frequency of supra-aortic lesions which is associated with a lower stiffness of these arteries.

Word count: 296/300.

Back to Program Agenda

# New rare genetic variant in the *COL3A1* gene found in a patient with a clinical phenotype of Ehlers-Danlos Syndrome

***Rusinova V.S., Rumyantseva V.A., Zaklyazminskaya E.V.***

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**Introduction.**

Hypermobile joints, easy bruising and fragile skin are the well-known features of Ehlers-Danlos (EDS). Classical EDS can be painful and disabling. It affects skin, wound healing and joints. Vascular EDS is considered the most serious form of EDS due to the high risk of arterial or organ rupture, and shortened lifespan. Genetic testing helps to predict and manage possible complications, especially during pregnancy and childbirth in women with this disease.

**Materials and methods.**

We have observed a Russian female patient 26 y.o. complaining on frequent hematomas either spontaneously or after minor trauma. Once she was treated with emergency surgical drainage. Routine blood coagulation tests were normal. She has typical classic EDS phenotype: smooth, velvety hyper-extensibility skin, multiple widened atrophic scarring, joint hypermobility, permanent joints dislocations, and subcutaneous spheroids of the legs. Her family history is compromised with sudden deaths due to dissection aneurysm of father's grandmother at the age of 50, and her father has aneurysm now. Patient underwent genetic testing via whole exome sequencing (WES) on Illumina platform followed by capillary Sanger re-sequencing.

**Results.**

Genetic testing revealed rare heterozygote variant NM_000090: c.1297G>A (p.Glu433Lys, chr2:188994544 G/A) in the exon 19 of the *COL3A1* gene in the proband's DNA. The described variant was not found in a public databases such as gnomAD. Bioinformatic tools (SIFT, Provean, Mutation Taster, and Polyphen2.0) predict ambiguous effect on protein function. In connection with the available data, we interpreted this variant as an uncertain significance (Class III), with assignment of PM2 and PP2 criteria (ACMG2015). Cascade familial screening revealed, this variant also in affected father. This variant is registered in ClinVar Database as an uncertain significance twice in unrelated probands with consistent phenotype.

**Conclusion:**

Further functional study is necessary to elucidate exact functional effect of this variant. But we hypothesize it might have a clinical significance in EDS phenotype.

This work was supported by Russian Science Foundation Grant № 18-78-10132.

Back to Program Agenda

# Surgeon's uneasy unfortunate regular patient.

**Rumyantseva V.A.[1],Kurlenkova A.[2], Bazarov D.V.[1], Abramyan A.V[1]. Zaklyazminskaya E.V[1].**

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**Introduction**

Vascular Ehlers-Danlos (vEDS) is a rare connective tissue disorder. A poor prognosis can lead to possible potentially life-threatening of arterial or organ rupture due to the typical features of the syndrome. Surgical treatment of the clinical symptoms may often be associated with a high risk of the recurrence and postoperative. Patients should establish an ongoing relationship with medical team (cardiologist, vascular surgeon, general surgeon and geneticist) before a major medical event occurs.

Having an operation in a controlled setting is preferable for emergency surgery. Because blood vessels and other hollow organs are fragile and subject to rupture in people with VEDS, doctors recommend surgery only when there is a substantial risk of a life-threatening event such as blood vessel rupture or abdominal infection.

**Materials, methods and results.**

We have been observing for 6 years a Russian male patient starting from the age of 12 who had two cases of spontaneous pneumothorax without a traumatic agent. During examination it's been identified following: the skin was thin and translucent with increased vein visibility; multiple widened atrophic scarring and hematomas; joint hypermobility and characteristic facial appearance (thin lips, thin nose and deep-set eyes). In addition, previously, a bilateral inguinal hernia was operated on. Patient underwent genetic testing followed by capillary Sanger sequencing: heterozygous mutation p.Gly939Asp in the *COL3A1* gene was found (de novo). Thoracoscopic left-sided sub-lobar lung resection of the upper lobe and subtotal parietal pleurectomy were performed as the first stage of the treatment. However, the patient had required further surgical treatment because of the recurrence of the spontaneous pneumothorax on the right side. At the age of 14 again he went to surgeons with a thrombosis saphenous veins of the right leg after playing football. At the age of 16 he had varicose veins of both legs and aneurysm of the saphenofemoral anastomosis up to 3 cm by ultrasound. Now he is 17, and there is negative dynamics of the small saphenous vein on his left leg and a subfascial hematoma.

**Conclusion.**

Clinicians should give more consideration to rare genetic syndromes, especially in the case of symptoms from different clinical areas. Russia does not have a self-help group or a community of people with Ehlers-Danlos, neither there is a single coordinating medical center for helping patients with this disease. In some instances, surgery to repair abnormal blood vessels may be necessary before an emergency occurs.

This work was supported by Russian Science Foundation Grant № 18-78-10132.

Back to Program Agenda

**The VEDS Collaborative Research Study: Year One progress in a comprehensive natural history study**

Stephanie E. Wallace [1], Jimmy Nguyen [1], Shaine A. Morris [2], Melissa L. Russo [3], Gretchen MacCarrick [4], Peter H. Byers [5], Sherene Shalhub [1]

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**Background:** The VEDS Collaborative is a patient-clinician driven study created as an outcome of the VEDS Collaborative engagement work and aims to detail a comprehensive natural history of Vascular Ehlers-Danlos syndrome (VEDS). We provide an overview of the currently enrolled cohort and future directions.

**Methods**: **Methods**: Adults and minors with pathogenic, likely pathogenic, or variant of unknown significance (VUS) in *COL3A1* are eligible for enrollment. Individuals were recruited globally through the VEDS collaborative virtual research network, the VEDS movement, patient and physician social media groups, and clinical visits at the University of Washington, starting July 2019. Medical records and medical images were collected through patient engagement, electronic medical records infrastructure (Epic care everywhere features), and direct communication with physicians. Abstracted data include demographics, diagnostic criteria, medications, presentation and outcomes over multiple visits and years. Vascular (aortic, arterial, venous), intestinal, pulmonary, and pregnancy complications were also abstracted.

**Results:** To date 232 individuals have been enrolled, of whom 197 had pathogenic/likely pathogenic variants. Eighteen were under the age of 18 years. The population is 64% female (n=126), with a median current age of 41 years in the 140 individuals that are currently living. The most common pathogenic/likely pathogenic variant type is substitution for glycine residues in the triple helical domain (n=122, 62%) followed by splice donor (n=33, 17%), null (n=30, 15%) and splice acceptor (n=5, 3%) mutations. Complete medical records have been collected and abstracted for two-thirds of individuals (n=133). This cohort has 250 arterial events as follows: thoracic aorta (n=20, 8%), and abdominal aorta (n=19, 10%), iliac (n=45, 23%), carotid (n=42, 21%), vertebral (n=21, 11%), celiac artery (n=21, 11%), superior mesenteric artery (n=18, 9%) and renal artery (n=21, 11%).

**Conclusion:** Engaging patients in VEDS research has allowed for successful collaboration among physicians, surgeons, researchers, and patients. The VEDS Collaborative Research Study is primed to provide detailed natural history data and address gaps in knowledge regarding VEDS care.

Back to Program Agenda

**High dose vitamin C demonstrates a sexually dimorphic survival benefit in a mouse model of severe vascular Ehlers-Danlos syndrome**

Rebecca A. Sorber[1,2], Caitlin J. Bowen[1], Zachary Burger[1], Emily Juzwiak[1], Graham Rykiel[1], Juan Francisco Calderon Giadrosic[1], & Harry C Dietz[1]
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**Introduction**: Vascular Ehlers-Danlos syndrome (vEDS) is caused by autosomal dominant mutations in *COL3A1* encoding type III collagen. Vitamin C is an essential cofactor for collagen processing and is utilized in vEDS treatment due to theoretical benefits. There is currently no direct evidence to support its use.

**Objectives**: This work investigates the efficacy of vitamin C supplementation in a mouse model of severe vEDS.

**Materials and methods**: We utilized a knock-in mouse model of vEDS (*Col3a1*$^{G938D/+}$), characterized by 50% mortality from aortic rupture by 50 days of age. Vitamin C was administered in chow. Collagen content of tissues was assessed with hydroxyproline assays and RNAseq was used to measure expression of the *Gulo* gene that allows endogenous vitamin C production in mice.

**Results**: Vitamin C supplementation at weaning did not affect survival in males but led to 100% survival in female mice at 50 days (versus 72% in untreated females). Initiation of vitamin C supplementation in utero resulted in a similar survival benefit that was limited to female vEDS mice (100% females vs 45% males alive at 45 days of age, $p<0.01$). Protection in female vEDS mice exposed to supplemental vitamin C at conception was not sustained if treatment was withdrawn postnatally. There was no increase in the aortic collagen content of protected vEDS female mice receiving vitamin C, consistent with a predominant influence on the quality (i.e. cross-linking) vs. quantity of collagen. Female mice showed significantly lower hepatic expression of *Gulo*, plausibly contributing to their greater benefit upon vitamin C supplementation ($p<0.05$).

**Conclusions**: These data highlight vitamin C as a safe therapeutic adjunct for vEDS. The mechanism for sexual dimorphism may relate to sex-limited endogenous production of vitamin C and perhaps cross-talk with pubertal androgens. These and other issues are currently being explored in *Gulo*-null vEDS mice.

Back to Program Agenda

# Perinatal and Neonatal Outcomes Among Children with Vascular Ehlers-Danlos Syndrome

Stephens, Sara, MPH[1], Russo, Melissa, MD[2], Beecroft, Taylor, MS, CGC[1], Weigand, Justin, MD[1], Milewicz, Dianna, MD, PhD[3], Morris, Shaine, MD, MPH[1]

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**Introduction:** There is little evidence to date describing the birth outcomes of patients with VEDS.

**Objective:** We aimed to examine prevalence of perinatal and neonatal complications in a cohort of children with VEDS.

**Materials and Methods:** Patients with a pathogenic variant of *COL3A1* were included. Outcomes examined included gestational age (GA), birthweight (BW), maternal complications, and congenital anomalies. BW z-score based on GA was calculated. GA at birth and BW were compared to Texas population vital statistics data, compared among those with and without an affected mother, and then by mutation type.

**Results:** Thirty children were included (83% male). Median GA at birth was 37 weeks (IQR 35-38) with 46.7% (n=14) born preterm, which was greater than noted in the population (10.8%, $p<0.001$). Median BW was also low at 2.9 kg (IQR 2.3, 3.4), although BW was appropriate after adjusting for GA (median GA-adjusted z-score 0.01 (IQR -0.63, 0.97, $p=0.26$) compared to z-score of 0.0). Comparing GA by mother's affected status, there was no difference between groups (affected median GA 35.0 weeks vs. non-affected GA 37.0 weeks, $p=0.15$). Neonates with high-risk variants had more preterm birth (14/27=51.9% vs. 0/3=0.0%, $p=0.23$), though this didn't reach significance, and lower birthweight those with null variants (2.9 vs. 3.7 kg, $p=0.03$). Serious complications were observed in 75.0% (n=3) affected mothers of affected children, including placental abruption, uterine rupture, and death secondary to cardiovascular collapse.

**Conclusion:** Prevalence of preterm birth and low birthweight among children with VEDS is higher than the general population, although birthweight was appropriate for gestational age. Preterm delivery was not associated with maternal affected status, suggesting that the risk is conferred by the fetal affected status alone. The signs of VEDS may be detected as early as birth. Additional studies are needed to further explore birth outcomes in this population.

Back to Program Agenda

# Cardiovascular Characteristics Among Children with Vascular Ehlers-Danlos Syndrome

Stephens, Sara, MPH[1], Nieuwsma, Asela, RDC[1], Doan, Tam, MD[1], Weigand, Justin, MD[1], Beecroft, Taylor, MS, CGC[1], Cecchi, Alana, MS, CGC[2], Shittu, Teniola, MS, MPH[1], LeMaire, Scott, MD[1], Krishnamurthy, Rajesh, MD[3], Keyes, Ashley[1], Lacro, Ronald, MD[4], Milewicz, Dianna, MD, PhD[2], Morris, Shaine A., MD, MPH[1]

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**Introduction:** Despite the high risk of life-threatening events, there is a paucity of data describing the phenotypic variability of cardiovascular findings in children with Vascular Ehlers-Danlos Syndrome (VEDS).

**Objective:** We aimed to describe the phenotypic manifestations and spectrum of *COL3A1* variation in individuals diagnosed with VEDS <18 years.

**Materials and Methods:** We reviewed medical records and serial cardiovascular imaging studies of patients <18 years of age with VEDS (confirmed *COL3A1* variants) followed at our institution.

**Results:** Thirty-four subjects were included (79% male). Median age at diagnosis was 5.0 years (IQR 3.0-9.0) and median age at last follow-up was 10.5 years (IQR 6.5-14.2 years). Pathogenic variants included higher-risk variants (splice site alterations [n=15, 44%] or glycine substitutions [n=13, 38%]), and lower-risk haploinsufficient variants (nonsense or *COL3A1* deletions [n=6, 18%]). Eighteen subjects (53%) had a *de novo* mutation. On exam, the most common features were hindfoot valgus (76%), easy bruising (74%), thin lips (71%) and prominent eyes (63%). Congenital heart disease was present in 6 (18%), including 1 each with subaortic stenosis, bicuspid aortic valve, myocardial bridge, and Ebstein anomaly. Four (12%, all male, all with higher-risk variants) had a major event, including 2 with internal carotid artery dissections (in monozygotic twins at ages 10 and 12 years), 1 with aortic rupture (age 9 years) as a complication of subaortic stenosis surgery followed by subclavian artery rupture (age 13 years), and 1 with a bladder rupture (age 3 years); all four survived.

**Conclusion:** Our findings suggest that the prevalence of congenital heart disease and arterial events among children with VEDS is higher than in the general population. This risk for spontaneous arterial dissection/rupture may be higher among those with higher-risk variants, and can present as early as childhood. Additional strategies for risk surveillance and prognostication are critically needed for this population.

Back to Program Agenda

# Vertebral Artery Tortuosity Is a Biomarker For Arterial Events in Children and Adults with Vascular Ehlers-Danlos Syndrome

Stephens, Sara, MPH[1], Shalhub, Sherene, MD, MPH[3], Dodd, Nicholas[2], Oda, Seitaro, MD[4], Kancherla, Kalyan, MD[7], Doan, Tam, MD[1], Weigand, Justin, MD[1], Asch, Federico, MD[7], Beecroft, Taylor, MS, CGC[1], Cecchi, Alana, MS, CGC[2], Shittu, Teniola, MS, MPH[1], Preiss, Liliana, MS[8], LeMaire, Scott A., MD[1], Devereux, Richard B., MD[9], Pyeritz, Reed E., MD, PhD[10], Holmes, Kathryn W., MD, MPH[11], Roman, Mary J., MD[9], Lacro, Ronald, V., MD[6], Shohet, Ralph V., MD[12], Krishnamurthy, Rajesh, MD[5], Eagle, Kim, MD, MACC[13], Byers, Peter H., MD[3], Milewicz, Dianna M., MD, PhD[2], Morris, Shaine A., MD, MPH[1]

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**Introduction:** Vertebral artery tortuosity has been associated with adverse events in Marfan and Loeys-Dietz syndromes, but has not been assessed in vascular Ehlers-Danlos syndrome (VEDS).

**Objective:** To assess vertebral artery tortuosity in a cohort with VEDS.

**Materials and Methods:** Subjects <55 years old with VEDS (pathogenic *COL3A1* variants) were included from our institution (n=28) and the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC; n=23). We calculated the height-adjusted vertebral artery tortuosity index (VTI-h) that indexes VTI across the age range using MRA/CTA. We evaluated associations between VTI-h (continuous and dichotomized) and the outcome of arterial dissection, rupture, or aneurysm intervention using ROC, Kaplan-Meier and Cox methods.

**Results:** For the 51 subjects, median age at last follow-up was 15.8 years (range 3.7-48.8 years, 58% male). Median VTI-h was 10 (IQR 8-15). Thirteen primary events included 2 aortic dissections, 9 arterial dissections/ruptures, 1 carotid cavernous aneurysm rupture, and 1 aneurysm requiring embolization. Higher VTI-h was associated with events at younger age (HR per 1 unit increase 1.08, 95% CI 1.01-1.15, p=0.023). ROC suggested optimal discrimination at VTI-h ≥15, with an event by age 25y in 6/12 (50.0%) with VTI-h ≥15 vs. 2/37 (5.4%) <15 (sensitivity 75%, specificity 83%; HR 3.9, 95% CI 1.2-12.4). Among missense/splice site variants (n=39), VTI-h ≥15 remained associated with the outcome, occurring in 5/10 (50.0%) with VTI-h≥15 versus 3/30 (10.0%) <15 (log rank p=0.023). VTI-h could not be evaluated among null variants, as only 2/6 had events, both in patients age 38 and 39y, with VTI-h <15.

**Conclusion:** Increased vertebral artery tortuosity is associated with earlier arterial events in patients with VEDS. Using VTI-h in a risk stratification model has potential for improving cardiovascular care, particularly prognostication, for patients with VEDS. Additional studies are needed for delineate further its utility in this population.

Back to Program Agenda

# Clinical presentation of Vascular Ehlers-Danlos Syndrome in Children

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## Introduction

Vascular Ehlers-Danlos Syndrome (vEDS) caused by pathogenic mutations within the COL3A1 gene leads to vascular fragility, life-threatening vascular events and hollow organ ruptures.

## Objectives

We describe the clinical presentation of paediatric vEDS in a tertiary inherited cardiovascular disease centre.

## Materials and methods

We performed a retrospective cohort study on our vEDS patients', follow-up until December 2020. Clinical details and findings during longitudinal monitoring were collected.

## Results

41 patients were identified; 23 males: 18 females. Median age at diagnosis was 7 years old (2 weeks-17 yo).

COL3A1 gene mutation is identified through predictive genetic testing (25, 61%), after major event (11, 26.8%) or suspicious minor features (5, 12.2%). Commonest genotypes is Glycine substitutions (27, 65%) (Figure1). 7 are de novo mutations, 31 familial and 3 unknown. 16 are the proband (39%).

29.2% (12) had major events (Figure 2), of which 72.7% had glycine substitution. All diagnosed after their event. One patient (2.4%) with pulmonary atresia with intact ventricular septum had vascular rupture causing neurological damage during neonatal intervention. This is the only patient with aortic dilatation but has a BT shunt. Two (4.9%) had fatal aortic dissection (Type A and B at age 15 and 14 yo respectively) were diagnosed on molecular autopsy. Five had (12.2%) arterial tree abnormalities including one popliteal artery rupture and one subdural haemorrhages in infancy. Four had hollow organ rupture (9.7%); two neonates and two adolescences with recurrence.

26 patients (63.4%) are on medication with 88.5% on celiprolol which is well tolerated. No events documented during treatment although average follow-up is only 4.7 years.

Back to Program Agenda

## Conclusion

vEDS is rarely diagnosed in childhood but over 25% presented with life-threatening events by 15yo. We observed high prevalence of major events with two fatalities in our cohort. Further study on role of chemoprophylaxis in paediatric vEDS is needed.

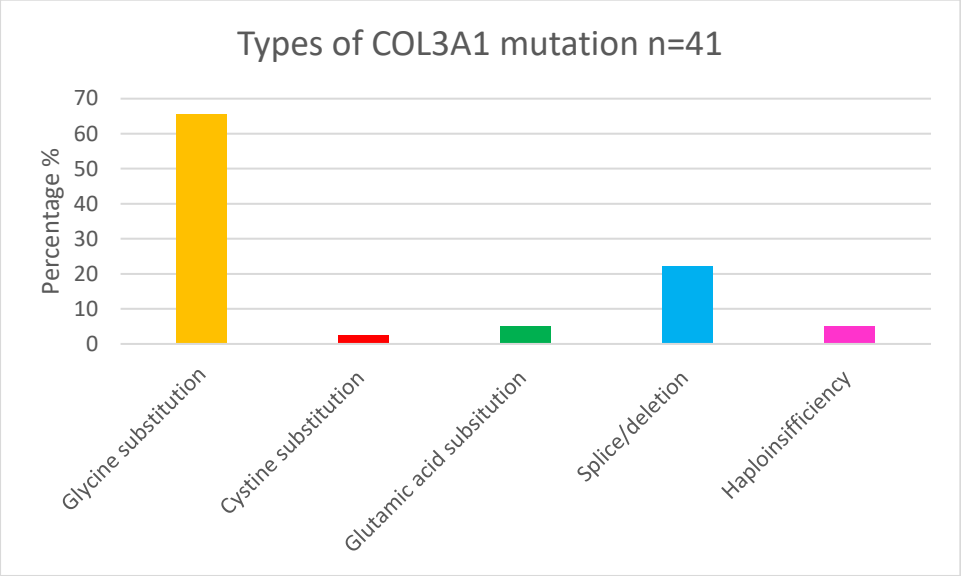



Figure 1

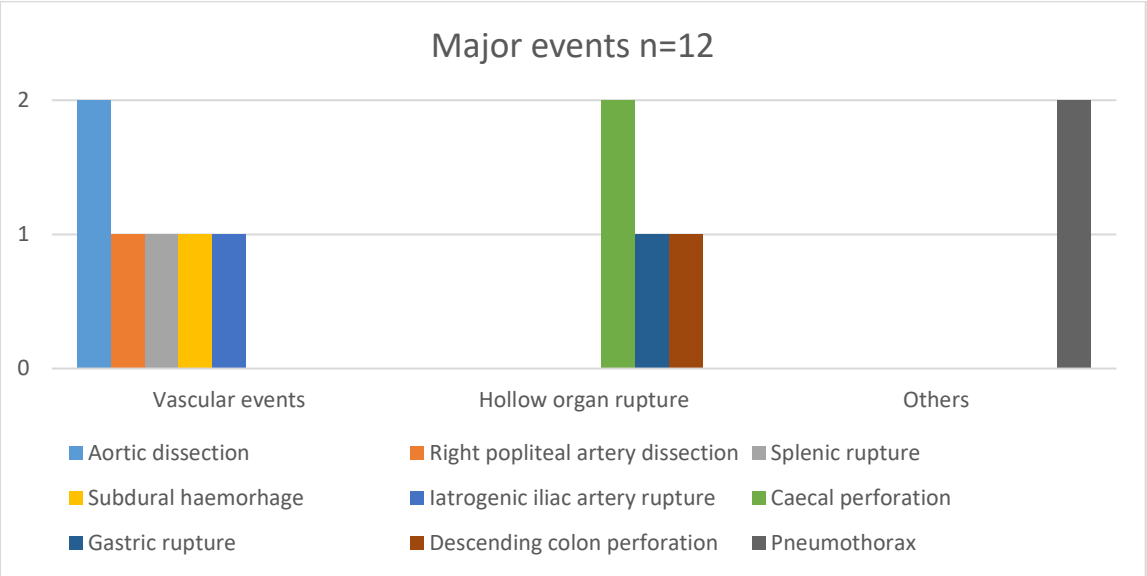
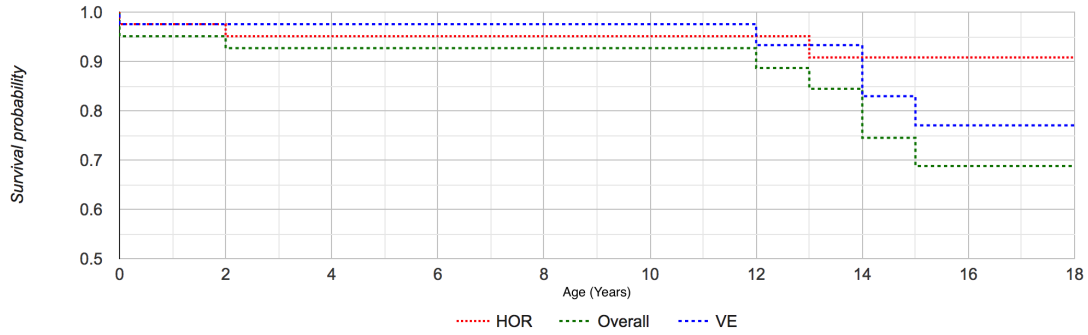



Figure 2

Back to Program Agenda




Kaplan-Meier curve showing the event free survival for paediatric patients with vEDS. Overall= combined events, HOR= hollow organ rupture, VE= vascular complications

Back to Program Agenda

# Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice

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Objective: Aortic aneurysm and dissection are major life-threatening complications of Marfan syndrome. Avoiding factors that promote aortic damage is critical in managing the care of these patients. Findings from clinical and animal studies raise concerns regarding fluoroquinolone use in patients at risk for aortic aneurysm and dissection. Therefore, we examined the effects of ciprofloxacin on aortic aneurysm and dissection development in Marfan mice.

Methods: Eight-week-old Marfan mice ($Fbn1^{C1041G/+}$) were given ciprofloxacin (100 mg/kg/d; n = 51) or vehicle (n =59) for 4 weeks. Mice were monitored for 16 weeks. Aortic diameters were measured by using ultrasonography, and aortic structure was examined by using histopathologic and immunostaining analyses.

Results: Vehicle-treated $Fbn1^{C1041G/+}$ mice showed progressive aortic enlargement, with aortic rupture occurring in 5% of these mice. Compared with vehicle-treated $Fbn1^{C1041G/+}$ mice, ciprofloxacin-treated $Fbn1^{C1041G/+}$ mice showed accelerated aortic enlargement ($P$ = .01) and increased incidences of aortic dissection (25% vs 47%, $P$= .03) and rupture (5% vs 25%, $P$=.005). Furthermore, ciprofloxacin-treated $Fbn1^{C1041G/+}$ mice had higher levels of elastic fiber fragmentation, matrix metalloproteinase expression, and apoptosis than did vehicle-treated $Fbn1^{C1041G/+}$ mice.

Conclusions: Ciprofloxacin accelerates aortic root enlargement and increases the incidence of aortic dissection and rupture in Marfan mice, partially by suppressing lysyl oxidase expression and further compromising the inherited defect in aortic elastic fibers. Our findings substantiate that ciprofloxacin should be avoided in patients with Marfan syndrome. (J Thorac Cardiovasc Surg 2020;:1-12)

Back to Program Agenda