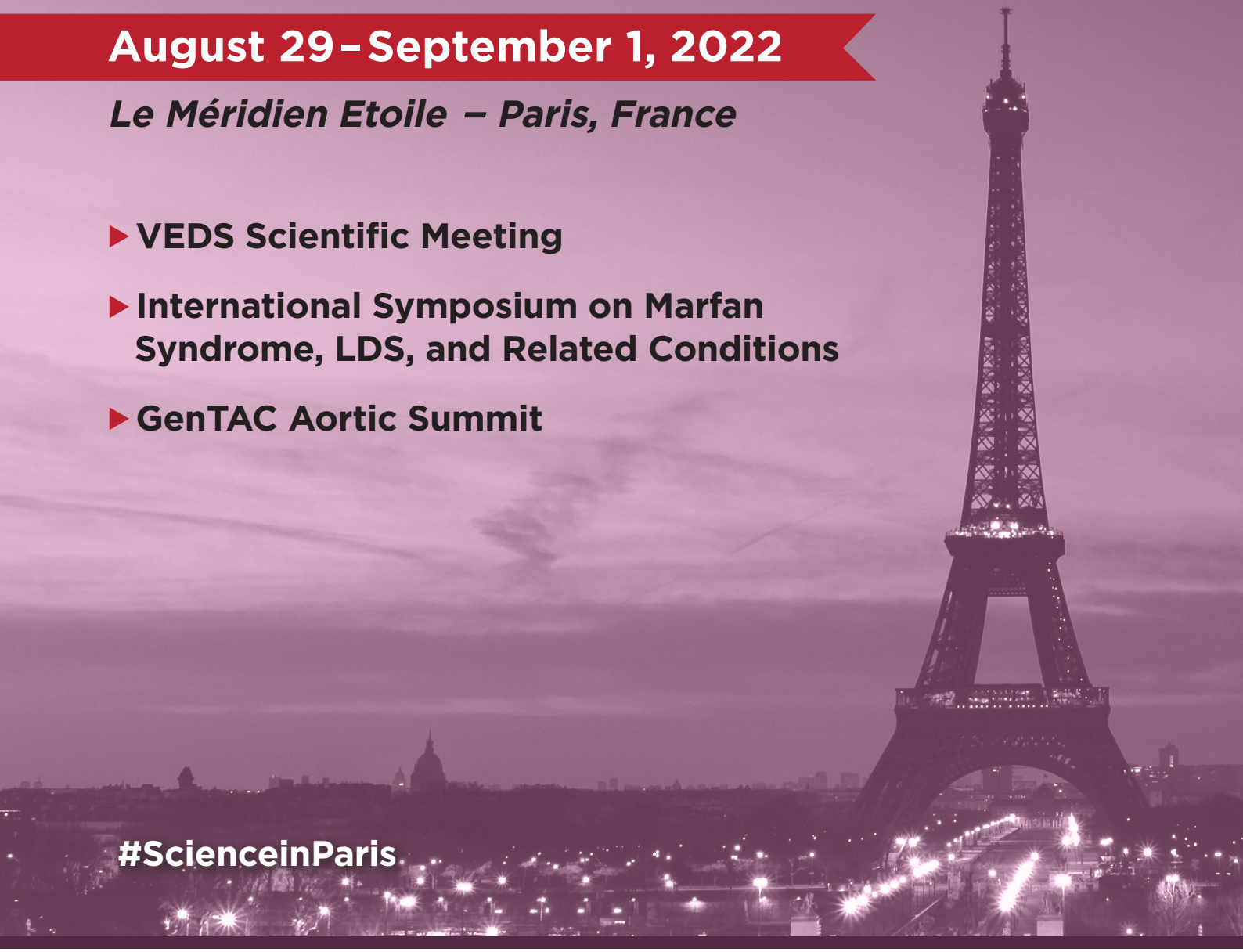
THE MARFAN FOUNDATION PRESENTS

SCIENCE IN *Paris*

August 29 – September 1, 2022

Le Méridien Etoile – Paris, France

- **VEDS Scientific Meeting**
- **International Symposium on Marfan Syndrome, LDS, and Related Conditions**
- **GenTAC Aortic Summit**



#ScienceinParis

THE MARFAN FOUNDATION

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WELCOME

The Marfan Foundation is delighted to welcome you to Science in Paris featuring the DEFY VEDS Scientific Meeting; International Marfan, Loeys-Dietz, and Related Conditions Meeting; and the 2022 GenTAC Aortic Summit. After two years of virtual get-togethers, we appreciate everyone coming together here in Paris to share and discuss great science.

We congratulate all the speakers and presenters on their incredible work to significantly advance the field of genetic aortic and vascular conditions. Your innovative thinking and breakthrough research highlights the impressive talent dedicated to this patient community. We know that the work you do every day will immensely improve patient care. We could not be more grateful.

We also want to take this opportunity to recognize the hard work of the program committee for each of these meetings (see page 4). These four days bring together many of the greatest minds in genetic aortic and vascular research, resulting in valuable discourse and collaboration that is only possible in an in-person gathering such as this.

The Marfan Foundation has long been committed to the international collaboration of scientists who are focused on Marfan, Loeys-Dietz, VEDS, and related genetic aortic and vascular conditions. Our first International Research Symposium was held in Baltimore in 1988, and we have prioritized this commitment to science throughout our 41 years.

In the past two years, we have added divisions to our organization to better serve the related conditions community. We established The VEDS Movement in 2020 and then welcomed the Loeys-Dietz Syndrome Foundation under our umbrellas the following year. In the Fall of 2020, the GenTAC Alliance became a division of the Foundation. We are also grateful to our partners around the world — Asso Marfans (French Marfan Association), Marfan Europe Network, the DEFY Foundation, Ehlers-Danlos Society, Annabelle's Challenge, Fight VEDS, the VEDS Collaborative and VASCERN, the National Heart, Lung and Blood Institute, Aytu BioPharma, and Acer Therapeutics — for their collaboration.

This coalescence demonstrates our commitment to research, as well as education and support, for these conditions. Most important, it provides the structure and unity that will lead to a patient community that lives longer and better.

We are grateful to the sponsors of Science in Paris — The National Heart, Lung and Blood Institute, and Aytu BioPharma — for their support. And to all of you for being here. Together, we can enjoy a wonderful city, appreciate exquisite wine, and bring great scientific and clinical minds together to achieve our common goal.

Warmly,

Michael Weamer
President & CEO

Cory Eaves
Chair, Board of Directors

Josephine Grima, PhD
Chief Science Officer

ORGANIZING COMMITTEE

Science In Paris Planning Committee

- Kim Eagle, MD, University of Michigan
- Marion Hofmann-Bowman, MD, University of Michigan
- Sherene Shalhub, MD, University of Washington
- Bart Loeys, MD, PhD, University of Antwerp
- Josephine Grima, PhD, The Marfan Foundation

Organizing Committee

- Josephine Grima, PhD, The Marfan Foundation
- Catherine Boileau, PhD, Hôpital Bichat
- Lauren May, MPH, The Marfan Foundation

VEDS Scientific Meeting Planning Committee

- Anthony Yasick, MD, DEFY Foundation
- Hal Dietz, MD, Johns Hopkins Hospital
- Peter Byers, MD, University of Washington
- Sherene Shalhub, MD, University of Washington
- Shaine Morris, MD, Texas Children's Hospital
- Xavier Jeunemaitre, MD, University Paris Cite

International Symposium on Marfan, LDS, and Related Conditions Planning Committee

- Catherine Boileau, PhD, Hôpital Bichat
- Alan Braverman, MD, Washington University
- Julie De Backer, MD, Ghent University
- Hal Dietz, MD, Johns Hopkins University
- Josephine Grima, PhD, The Marfan Foundation
- Guillaume Jondeau, Hôpital Bichat
- Bart Loeys, MD, PhD, University of Antwerp
- Shaine Morris, MD, Texas Children's Hospital
- Daniel Rifkin, PhD, NYU Langone Health
- Sherene Shalhub, University of Washington

GenTAC Aortic Summit Committee

- Kim Eagle, MD University of Michigan
- Marion Hofmann-Bowman, University of Michigan
- Sherene Shalhub, Washington University
- Bart Loeys, MD, University of Antwerp
- Josephine Grima, PhD, The Marfan Foundation

SCHOLARSHIP AWARD WINNERS

We are happy to announce the scholarship awards for trainee and underrepresented communities. We received a total of 9 abstracts for the VEDS meeting, 53 abstracts for the International Symposium, and 10 abstracts for the GenTAC Aortic Summit to be reviewed for the competition. The following are the award winners. Congratulations!

DEFY VEDS Scientific Meeting (Provided by the DEFY Foundation)

- Caitlin Bowen, Johns Hopkins University – A Gene, Variant and Mechanism for a Potent Protective Modifier of Vascular Ehlers-Danlos Syndrome

International Symposium on Marfan-NIH Supported

- Lauriane Sedes, Icahn School of Medicine at Mount Sinai – Loss of TGFβ Signaling in the Outer Perichondrium Causes Longitudinal Bone Overgrowth in Marfan Syndrome
- Anna Cantalupo, Icahn School of Medicine at Mount Sinai – Combination Therapy Targeting the Major Angiotensin II Receptors Prevents Thoracic Aortic Aneurysm Formation in Marfan Syndrome Mice by Reversing eNOS Uncoupling
- Marc Schoenholzer, Swiss Foundation for People with Rare Diseases – Insights into the Biomechanical Integrity of the Aorta in Mice Modelling Hereditary Aortic Diseases
- Anna Huguenard, Washington University in St. Louis – Intracranial Aneurysms in Patients with Loeys-Dietz Syndrome
- Palcah Shibale, University of Washington – Presentation and Management of Arteriopathy in Marfan Syndrome.
- Tala Curry, University of Arizona College of Medicine-Phoenix – Marfan Syndrome Accelerates Cerebrovascular Aging and Blood-Brain Barrier Permeability
- Rodrigo Barbosa De Souza, University of São Paulo – Compensatory Mechanisms in the Tunica Media of Aortic and Mesenteric Arteries of the mgΔlpn Dominant-negative Mouse Model of Marfan Syndrome.

GenTAC Aortic Summit: NIH Supported

- Tahla Niaz, Texas Children's Hospital – Role and Yield of Clinical Genetic Testing Among Patients with Bicuspid Aortic Valve and Aortic Dilation Referred to the Cardiovascular Genetics Clinic
- Laura Munio Mosquera, Ghent University Hospital – Clinical and Genetic Correlates of Mitral Valve Pathology in Patients with Heritable Thoracic Aortic Disease: Results from the Montalcino Aortic Consortium
- Robert Pena, George Washington University Hospital – Revisiting the Combination Aortic Dissection Detection Risk Score (ADD-RS) and D-Dimer Algorithm for Acute Aortic Syndrome (AAS) Rule-Out in the Emergency Department

PROGRAM

MONDAY, **AUGUST 29**, 2022

VEDS Scientific Meeting

8:00 AM WELCOME AND OPENING REMARKS
Tony Yasick, DEFY Foundation; Michael Weamer, President and CEO, The Marfan Foundation; Xavier Jeunemaitre, University Paris Cite

8:15–10:00 AM SESSION #1
PATHOGENIC MECHANISMS, GENES, AND MODIFIERS USING MOUSE MODELS

Moderator: Hal Dietz, Johns Hopkins Hospital

8:15 AM V1: **A Gene, Variant and Mechanism for a Potent Protective Modifier of Vascular Ehlers-Danlos Syndrome**
Caitlin Bowen, Johns Hopkins University School of Medicine, United States

8:30 AM V2: **Endothelin-1 Contributes to Vascular Rupture in Vascular Ehlers-Danlos Syndrome Mice**
Caitlin Bowen, Johns Hopkins University School of Medicine, United States

8:45 AM V3: **Interrogation of the Role of Androgens and Their Antagonists in the Pathogenesis and Treatment of Vascular Ehlers-Danlos Syndrome (VEDS)**
Emily Juzwiak, Johns Hopkins University, United States

9:00 AM V4: **Castration of Males Prevents Arterial Rupture in a Mouse Model of Vascular Ehlers-Danlos Syndrome**
Xavier Jeunemaitre, Universite Paris Cite, France

9:15 AM V5: **Administration of Ciprofloxacine Does Not Worsen the Vascular Prognosis in a Mouse Model of Vascular Ehlers-Danlos Syndrome**
Xavier Jeunemaitre, Universite Paris Cite, France

9:30 AM V6: **Novel Assay to Assess the Aortic Rupture of Mice Modeling Aortic Diseases**
Roland Stengl, Swiss Foundation for People with Rare Diseases, Switzerland

9:45 AM **Discussion**

10:00–10:30 AM BREAK

10:30–11:00 AM SESSION #2
THERAPEUTIC STRATEGIES

Moderator: Xavier Jeunemaitre, University Paris Cite

10:30 AM V7: **A Decentralized Study Design: A Phase 3 Clinical Study in Patients with COL3A1-Positive Vascular Ehlers-Danlos Syndrome to Determine Whether Celiprolol Delays the Onset of vEDS-related Clinical Events Compared to Placebo**
M. Björck, Acer Therapeutics, Inc, United States

10:45 AM V8: **Added Value of Statins in Vascular Ehlers-Danlos Syndrome**
Marc Schönholzer, Swiss Foundation for People with Rare Diseases, Switzerland

11:00 AM **Discussion**

11:15–12:00 NOON SESSION #3
SURGICAL MANAGEMENT OF CLINICAL OUTCOMES

Moderator: Sherene Shalhub, University of Washington

11:15 AM V9: **Iliac Artery Pathology Presentation and Management in Vascular Ehlers-Danlos Syndrome**
Asmaa El-Ghazali, University of Washington, United States

11:30 AM V10: **Presentation and Management of Splenic Arteriopathy in Patients with Vascular Ehlers-Danlos Syndrome**
Asmaa El-Ghazali, University of Washington, United States

11:45 AM V11: **Abdominal Aortic Dissection is the Predominant form of Abdominal Aortic Pathology in Vascular Ehlers-Danlos Syndrome**
Veda Gadiraju, University of Washington, United States

12:00 NOON **Discussion**

12:15-1:30 PM LUNCH Latitude Restaurant, Lobby Level

1:30-2:00 PM SESSION #4
PREGNANCY STUDIES

Moderators: Shaine Morris, Texas Children's Hospital
Peter Byers, University of Washington

1:30 PM V12: **Breastfeeding Practices and Vascular Complications Among Pregnant Women with VEDS**
Sara Stephens, Baylor College of Medicine, United States

1:45 PM V13: **Gestational Age as a Proxy for Arterial Fragility in Vascular Ehlers-Danlos Syndrome**
Sara Stephens, Baylor College of Medicine, United States

2:00–3:05 PM SESSION #5
NATURAL HISTORY STUDIES

Moderators: Shaine Morris, Texas Children's Hospital
Peter Byers, University of Washington

2:00 PM V14: **Vascular Ehlers-Danlos Syndrome – A Comprehensive Natural History Study in the Dutch Patient Cohort**
Lisa Van Den Bersselaar, Erasmus MC, Netherlands

2:15 PM V16: **A Case Series of Spontaneous Coronary Artery Dissection in Vascular Ehlers-Danlos Syndrome**
Neeti Ghali, EDS Service London, United Kingdom

2:30 PM V17: **A Diagnosis of Vascular Ehlers-Danlos Syndrome in Childhood: Clinical and Molecular Features of 60 Individuals**
Niamh R Wilkinson, MSc, National EDS Service, London North West University Healthcare NHS Trust, London, UK

2:45 PM V18: **Vascular EDS in Adulthood: An Overview of Clinical and Molecular Features of 151 Individuals**
Niamh R Wilkinson, MSc, National EDS Service, London North West University Healthcare NHS Trust, London, UK

POSTER HIGHLIGHTS

3:00 PM V19: **Self-Reported Quality of Life Issues in Adults with VEDS**
Daphne Fulton, Sam Houston State University, United States

3:05 PM V20: **Improved Physical Functioning in a VEDS Patient**
Thy Thy Vanem, Oslo University Hospital, Norway

3:15-3:30 PM MEETING CLOSING AND SUMMARY
Peter Byers, University of Washington

3:30-5:30 PM POSTER SESSION, COFFEE BREAK, AND COCKTAILS

TUESDAY, **AUGUST 30**, 2022

International Symposium on Marfan Syndrome, LDS, and Related Conditions

8:00 AM WELCOME AND OPENING REMARKS
Josephine Grima, Chief Scientific Officer, The Marfan Foundation;
Michael Weamer, President and CEO, The Marfan Foundation;
Sherene Shalhub, University of Washington; Bart Loeys, University of Antwerp

8:15-9:30 AM SESSION #1
MOLECULAR PATHOGENESIS AND MODIFIERS

Moderator: Bart Loeys, University of Antwerp

8:15 AM **Mechanistic Dissection of a Gene-by-Environment Interaction Informs Regional Vulnerability to Aortic Aneurysm and Therapeutic Opportunities in Marfan Syndrome and Related Disorders**
Nicole Anderson, Johns Hopkins Medical Institutions, United States

8:30 AM **Fibrillin Microfibril Structure Identifies Long-Range Effects of Inherited Pathogenic Mutations Affecting a Key Regulatory Binding Site for Latent TGFβ**
Clair Baldock, University of Manchester, United Kingdom

8:45 AM **BMP Driven Mechanisms in Aortic Aneurysm Formation in a Mouse Model of Marfan Syndrome**
Gerhard Sengle, University of Cologne, Germany

POSTER HIGHLIGHTS

9:00 AM **Local TGF-beta Sequestration By Fibrillin-1 Regulates Vascular Wall Homeostasis in the Thoracic Aorta**
Violette Deleeuw, Ghent University, Belgium

9:05 AM **Smooth Muscle Cell Specific Klf4 Deletion is Insufficient to Prevent Phenotypic Modulation in Marfan Syndrome Mice**
Albert Pedroza, Stanford University, United States

9:10 AM **Incomplete Penetrance and Variable Clinical Expression of a Belgian TGFB3 Founder Variant Suggests the Presence of a Genetic Modifier**
Melanie Perik, Centrum Medische Genetica, Belgium

9:15 AM **Elastin Denudation Underlies Early Aortic Degeneration in Loeys-Dietz Syndrome 3**
Geoffrey Pickering, London Health Sciences Centre, Canada

9:20 AM **Fibrillin-1-regulated miR-122 Has a Critical Role in Thoracic Aortic Aneurysm Formation**
Dieter Reinhardt, McGill University, Canada

9:25 AM **Versican Accumulation Causes Aortic Disease in Marfan Syndrome**
María Jesús Ruiz-Rodríguez, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Spain

9:30 AM **In Search of Genetic Modifiers that Explain the Phenotypic Variability in SMAD3-related Aortopathy**
Joe Davis Velchev, University of Antwerp, Belgium

9:35-10:00 AM BREAK

10:00-11:00 AM SESSION #2

ADVANCES IN IMAGING, BIOMARKERS, AND CARDIOVASCULAR RESEARCH

Moderator: Guillaume Jondeau, Hospital Bichat

10:00 AM **Mitral Annular Disjunction and Arrhythmias in Marfan Syndrome**
Fatima Ezzeddine, Mayo Clinic, United States

10:15 AM **Circulating Fibrillin Fragments as Biomarkers for Thoracic Aortic Dissection**
Lynn Sakai, Oregon Health & Science University, United States

10:30 AM **Label-free Imaging for Acute Aortic Dissection by Using Marfan Syndrome Model Mouse**
Kaori Sugiyama, Waseda University, Japan

10:45 AM **Aortic Flow Patterns by 4D Flow CMR in Marfan and Loeys-Dietz Patients Before and After Valve Sparing Aortic Root Replacement: A Comparison with Healthy Volunteers**
Gisela Teixido Tura, Hospital Universitari Vall d'Hebron, Spain

POSTER HIGHLIGHTS

11:00 AM **Vascular and Ventricular Responses to Exercise in Pediatric Marfan and Loeys-Dietz Syndrome**
Nairy Khodabakhshian, The Hospital for Sick Children (SickKids), Canada

11:05AM-12:10PM SESSION #3

NATURAL HISTORY AND CLINICAL OUTCOME STUDIES

Moderator: Julie De Backer, University of Ghent

11:05 AM **Intracranial Aneurysms in Patients with Loeys-Dietz Syndrome**
Anna Huguenard, Washington University in St. Louis, United States

11:20 AM **Family History of Aortic Dissection in Patients with a FBN1 Pathogenic Variant**
Guillaume Jondeau, APHP, France

11:35 AM **Presentation and Management of Arteriopathy in Marfan Syndrome**
Palcah Shibale, University of Washington, United States

POSTER HIGHLIGHTS

11:50 AM **Impact of Obesity on Clinical Outcomes in Marfan Syndrome**
Alan Braverman, Washington University School of Medicine, United States

11:55 AM **Individualized Aortic Root Prediction in Pediatric Marfan Syndrome**
Julia Lovin, Baylor College of Medicine, United States

12:00 NOON **Loeys-Dietz Syndrome: Natural History, Clinical Spectrum, and Assessment of Outcomes—The Mayo Clinic Experience**
Jasraj Marjara, Mayo Clinic, United States

12:05 PM **Risk of Type B Dissection in Marfan Syndrome: The Cornell Aortic Aneurysm Registry**
Nupoor Narula, Weill Cornell Medical College, United States

12:10 PM **Clinical History and Outcomes of Patients Carrying TGFB2 Gene Variants**
Talha Niaz, Texas Children's Hospital, United States

12:15-1:30 PM LUNCH Latitude Restaurant, Lobby Level

1:30-2:00 PM SESSION #4
QUALITY OF LIFE RESEARCH

Moderator: Catherine Boileau, Hôpital Bichat

1:30 PM **Quality of Life and VO2 in Children and Young Adults with Marfan and Related Conditions**
Thomas Edouard, CHU de Toulouse, France

1:45 PM **An Online Tool to Define Which School Physical Activities are Safe for Each Child with Marfan Syndrome Based on Age And Gender**
Olivier Milleron, CNMR Marfan APHP Hopital Bichat Paris, France

2:00 PM **Can 10,000 Healthy Steps a Day Slow Aortic Root Dilation in Pediatric Marfan Patients?**
Seda Tierney, Stanford University, United States

POSTER HIGHLIGHTS

2:15 PM **Pilot Study of the Effects of Moderate Intensity Exercise on Children and Young Adults with Marfan Syndrome**
Jennifer Bogardus, Texas Woman's University, United States

2:20 PM **Physical Capacity and Physical Activity in Children with Heritable Connective Tissue Disorders (HCTD)**
Raoul Engelbert, University of Applied Sciences Amsterdam, Netherlands

2:25 PM **Heritable Connective Tissue Disorders in Childhood: Increased Fatigue, Pain, Disability and Decreased General Health**
Jessica Warnink-Kavelaars, Amsterdam University Medical Centers, Netherlands

2:30-3:00 PM BREAK

3:00-5:00 PM POSTER SESSION A

6:00 PM LE PARIS SEINE RIVER BOAT CRUISE
Departs from 2 Port DeBilly, Paris. For those who pre-purchased tickets.

WEDNESDAY, **AUGUST 31**, 2022

International Symposium on Marfan Syndrome, LDS, and Related Conditions

8:00-9:40 AM SESSION #5

NEW MODEL SYSTEMS, TECHNOLOGY, AND THERAPEUTICS

Moderator: Hal Dietz, Johns Hopkins Hospital

8:00 AM **Combination Therapy Targeting the Major Angiotensin II Receptors Prevents Thoracic Aortic Aneurysm Formation in Marfan Syndrome Mice by Reversing eNOS Uncoupling**
Anna Cantalupo, Icahn School of Medicine at Mount Sinai, United States

8:15 AM **Towards Personalised Medicine – An iPSC Model of Marfan Syndrome Identifies Differential Responses to Drugs**
Hongorzul Davaapil, Wellcome-MRC Stem Cell Institute, United Kingdom

8:30 AM **Allopurinol Blocks the Formation and Progression of Aortic Aneurysm in a Mouse Model of Marfan Syndrome**
Isaac Rodríguez-Rovira, University of Barcelona School of Medicine and Health Sciences, Spain

8:45 AM **Single-cell RNA Sequencing Identifies a Disease-Associated, Losartan-Sensitive Sub-Population of Cells in the Thoracic Aorta of Marfan Syndrome Mice**
Yifei Sun, Icahn School of Medicine at Mount Sinai, United States

9:00 AM **A Novel Mouse Model of Aortic Dissection Caused by a Point Mutation in the Hybrid Domain of the Fibrillin-1 Gene**
Hiromi Yanagisawa, University of Tsukuba, Japan

POSTER HIGHLIGHTS

9:15 AM **iPSC-derived Smooth Muscle Cells Modelling Loeys-Dietz Syndrome Show Abnormal Phenotype in Response To TGF-β**
Franklin Lo, Wellcome-MRC Cambridge Stem Cell Institute, United Kingdom

9:20 AM **Development of a Web-Based Marfan Syndrome Mouse Aortic Root Cell Atlas to Enable Rapid Gene Expression Analysis**
Albert Pedroza, Stanford University, United States

9:25 AM **In Vivo Rabbit Aneurysmal Model by Using Tubular Engineering Vessels Derived from Aortic Smooth Muscle Cells from Marfan Syndrome (MFS) Patients**
Ping Qiu, University of Michigan, United States

9:30 AM **Pentagalloyl Glucose (PGG) Prevents and Restores Mechanical Changes Caused by Elastic Fiber Fragmentation in the Mouse Ascending Aorta**
Jessica Wagenseil, Washington University, United States

9:35 AM **Angiotensin II Receptor Blockers Demonstrate Wide Heterogeneity at Activating Endothelial Function in the Vasculature: Selecting the Right ARB - Telmisartan – For the Marfan Job**
Arash Tehrani, University of British Columbia, Canada

9:40 AM **Losartan in Marfan Syndrome: A Dose and Prodrug Issue?**
Elodie Sauge, University of British Columbia, Canada

9:45-10:15 AM BREAK

10:15-11:10 AM SESSION #6
MECHANOBIOLOGY

Moderator: Dan Rifkin, New York University

10:15 AM **Delineating Mechanisms of Thoracic Aortic Aneurysm and Dissection – Roles of Medial Vulnerability and Adventitial Integrity**
Jay Humphrey, Yale University, United States

10:30 AM **Computational Modeling for the Quantification of Biomechanics Indexes Associated with Adverse Remodeling in Valve Sparing Root Replacement Surgery: The Impact of Graft Stiffness**
Guido Nannini, Politecnico di Milano, Italy

10:45 AM **Insights Into the Biomechanical Integrity of the Aorta in Mice Modelling Hereditary Aortic Diseases**
Janine Meienberg, Swiss Foundation for People with Rare Diseases, Switzerland

POSTER HIGHLIGHTS

11:00 AM **In Vitro Modelling of Marfan Related Cardiomyopathy Points to Abnormalities in Mechanobiology of the Heart Muscle Cells**
Jeffrey Aalders, Ghent University, Belgium

11:05 AM **GATA4 As A Modulator of Aortic Root Sensitivity To Mechanochemical Disruptions in A Murine Model of Loeys-Dietz Syndrome**
Emily Bramel, Johns Hopkins School of Medicine, United States

11:10 AM **Abnormal Contractility And Mechanosensing in Hypertensive Patient iPSC-Derived Vascular Smooth Muscle Cells Bearing A Novel Heterozygous Mutation in the PPP1R12A (Myosin Phosphatase Target Subunit 1) Gene**
Deeti Shetty, Cambridge Stem Cell Institute, United Kingdom

11:15AM-12:10PM SESSION #7
GENOTYPE/PHENOTYPE CORRELATION

11:15 AM **Pathogenic Variants in PLEKHO2 Predispose to Heritable Thoracic Aortic Disease**
Dongchuan Guo, University of Texas Health Science Center at Houston, United States

11:30 AM **Aortic and Vascular Involvement In Loeys-Dietz Syndrome. Results from the REPAG Registry (Spanish Network of Genetic Aortic Diseases)**
Gisela Teixido Tura, Hospital Vall d'Hebron, Spain

POSTER HIGHLIGHTS

11:45 AM **Pathogenic Variants Affecting the TB5 Domain of Fibrillin-1 Protein In Marfan Syndrome and Geleophysic/Acromicric Dysplasia Patients: From Tall to Short**
Pauline Arnaud, APHP / Inserm U1148, France

11:55 AM **Aortic Dissection in TGF-β Related Vasculopathies: Results from the Montalcino Aortic Consortium (MAC)**
Maral Ouzounian, UHN - Toronto General Hospital, Canada

12:00 NOON **Aortic Versus Arterial Events in Individuals with Pathogenic Variants in Genes Encoding Proteins in the TGFβ Signaling Pathway: Findings from the Montalcino Aortic Consortium (MAC)**
Walter Velasco Torrez, University of Texas Health Science Center, United States

12:05 PM **Variable Genetic Uptake Rates in Loeys-Dietz Syndrome Genes Between Spontaneous Coronary Artery Dissection Patient Cohorts**
Aline Verstraeten, University of Antwerp, Belgium

12:10 PM **Clinical Variability in Patients with SMAD3 Aneurysm Osteoarthritis Syndrome**
Anji Yetman, University of Nebraska Medical Center, United States

12:15-1:30 PM LUNCH Latitude Restaurant, Lobby Level

1:30-2:15 PM SESSION #8
SURGICAL MANAGEMENT

Moderator: Sherene Shalhub, University of Washington

1:30 PM **27-Year Odyssey with David Valve-Sparing Aortic Root Replacement in 577 Patients**
Craig Miller, Stanford University, United States

1:45 PM **Utilization and Complications of Thoracic Endovascular Repair In Patients with Genetic Aortopathy**
Reggie Nkansah, University of Washington, United States

2:00 PM **Prophylactic Aortic Arch Replacement in Patients with Loeys-Dietz Syndrome: Surgical Outcomes and Molecular Rationale**
Albert Pedroza, Stanford University, United States

2:15 PM **Endovascular and Hybrid Repair in Patients with Heritable Thoracic Aortic Disease**
J. Westley Ohman, Washington University School of Medicine

2:30-3:00 PM SESSION #9
NON-CARDIOVASCULAR RESEARCH

Moderator: Shaine Morris, Texas Children's Hospital

2:30 PM **Fibrillin-1 Regulates White Adipose Tissue Development, Homeostasis, and Function**
Dieter Reinhardt, McGill University, Canada

POSTER HIGHLIGHTS

2:45 PM **Marfan Syndrome Accelerates Cerebrovascular Aging and Blood-Brain Barrier Permeability**
Tala Curry, University of Arizona College of Medicine-Phoenix, United States

2:50 PM **Obstetric and Neonatal Outcomes in Women with Marfan, Loeys-Dietz and Vascular Ehlers-Danlos Syndromes: Results from PROWGAD (Pregnancy and Reproductive Outcomes in Women with Genetic-Predisposition for Aortic Dissection)**
Melissa Russo, Women & Infants Hospital, Brown Alpert School of Medicine, United States

2:55 PM **Musculoskeletal Manifestations of Marfan Syndrome Including Long Bone Length and Kyphosis are Rescued by Losartan Treatment During Adolescent Growth In Mice**
Urszula Sleczka, University of Oxford, United Kingdom

3:00 PM **Altered Metabolism in Marfan Syndrome Mice Fed on High Fat Diet**
Carmen Yap, Amsterdam Medical Centre (AMC), Netherlands

3:05-3:15 PM BREAK

3:15-5:15 PM POSTER SESSION B

THURSDAY, **SEPTEMBER 1,** 2022

GenTAC Aortic Summit

8:00 AM WELCOME
Kim Eagle, University of Michigan

8:20-9:20 AM SESSION #1
FAMILIAL AORTOPATHY

Moderators: Kim Eagle, University of Michigan
Bart Loeys, University of Antwerp

8:20 AM **The Current Genetic Library & Likely Prospects**
Dianna Milewicz, University of Texas, Houston

8:40 AM **Gene-specific Decision-making Using Imaging**
Jonathan Weinsaft, Weill-Cornell Medicine

9:00 AM **Gene-specific Decision-making Using Surgical Cut Points**
Scott LeMaire, Baylor College of Medicine

9:20 AM **Gene-specific Management in Pregnancy**
Jolien Roos Hesselink, Erasmus MC

9:45-10:45 AM SESSION #2
BICUSPID AORTIC VALVE

Moderators: Simon Body, Boston University
Mary Roman, Weill-Cornell Medicine

9:45 AM **The Search for Genetic Underpinnings**
Siddharth Prakash, University of Texas, Houston

10:05 AM **Phenotypic Variations - The Valve**
Hector Michelena, Mayo Clinic

10:25 AM **Phenotypic Variations - The Aorta**
Arturo Evangelista, Vall d´Hebron Research Institute

10:45 AM **Pediatric Controversies, Including Exercise and Sports**
Shaine Morris, Texas Children's Hospital

11:05 AM BREAK

11:35-11:55 AM SESSION #3
SHOULD THE SURGICAL CUT POINT FOR BAV BE THE SAME OR DIFFERENT AS NON-GENETIC AORTOPATHIES?

Moderators: Alan Braverman, Washington University
Maral Ouzounian, University of Toronto

11:35 AM **Pro Opinion**
Chris Lau, Weill-Cornell Medicine

11:45 AM **Con Opinion**
Alessandro Della Corte, Second University of Naples

11:55 AM **Debate and Discussion**
Moderators & Panelists

12:15-1:45 PM LUNCH Latitude Restaurant, Lobby Level

1:50-2:10 PM SESSION #4
TURNER SYNDROME

Moderator: Michael Silberbach, Oregon Health & Science University

1:50 PM **Advances in Genetic Understanding**
Cheryl Maslen, Oregon Health & Science University

2:10 PM **Pearls in Managing Patients**
Emilio Quezada Liuti, University of California San Francisco

2:35-2:55 PM SESSION #5
ACUTE AORTIC SYNDROMES

Moderator: Marion Hofmann-Bowman, University of Michigan

2:35 PM **Current Classification Schemes**
Sherene Shalhub, University of Washington

2:55 PM **How to Use Biomarkers Acutely & Chronically**
Toru Suzuki, University of Leicester

3:05-3:25 PM SESSION #6
SHOULD WE OPERATE ON ASCENDING INTRAMURAL HEMATOMA?

Moderators: Scott LeMaire, Baylor College of Medicine
Jonathan Weinsaft, Weill-Cornell Medicine

3:05 PM **Pro Opinion**
Maral Ouzounian, University of Toronto

3:15 PM **Con Opinion**
Chris Lau, Weill-Cornell Medicine

3:25 PM **Debate and Discussion**
Moderator & Panelists

3:45 PM COFFEE BREAK

4:15-5:05 PM SESSION #7
SHOULD WE STENT STABLE TYPE B?

Moderator: Sherene Shalhub, University of Washington

4:15 PM **Pro Opinion**
Firas Mussa, Imperial College Healthcare NHS Trust

4:35 PM **Con Opinion**
Arturo Evangelista, Vall d´Hebron Research Institute

4:55 PM **Debate and Discussion**
Moderator and Panelists

5:05 PM **Conclusion**
Kim Eagle, University of Michigan

5:15-7:00 PM POSTER SESSION AND COCKTAILS

ABSTRACTS OF ORAL PRESENTATIONS

VEDS Scientific Meeting

Listed in Order of Presentation

A GENE, VARIANT AND MECHANISM FOR A POTENT PROTECTIVE MODIFIER OF VASCULAR EHLERS- DANLOS SYNDROME

Bowen, Caitlin MD, PhD[1,2], Sorber, Rebecca MD[3], Doyle, Jefferson J MD, PhD[4], Rykiel, Graham BS[1], Giadrosic, Juan Francisco Calderon PhD[1], Burger, Zachary BS[1], Zhang, Xiaoyan BS[1], Dietz, Harry C MD[1,2]

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Introduction

The onset and severity of disease is highly variable in vascular Ehlers-Danlos syndrome (vEDS), even within a given family, suggesting modifiers that remain to be defined.

Objectives

Identify genes that modify the vascular phenotype 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 despite no difference in biomechanical or hemodynamic parameters. This suggested that a nonproductive cellular response to an altered extracellular matrix, rather than the matrix deficiency per se, is the dominant determinant of arterial risk. Intercross F1 male and female vEDS mice show modest or near complete protection, respectively; a second cross to 129 resulted essentially complete protection in both sexes suggesting the presence of a genetic modifier that acts in an additive manner, with a sex-influenced effect. 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 consequent activation of PP1, a phosphatase that dephosphorylates pPKC and pERK. Genetic or pharmacological inhibition of this protective axis accelerated vascular rupture in a PKC/ERK-dependent manner. Survival of 129 vEDS mice haploinsufficient for *Map2k6* paralleled the sexual dimorphism seen in F1 and mixed background vEDS mice. 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 that is amenable to pharmacologic mimicry.

ENDOTHELIN-1 CONTRIBUTES TO VASCULAR RUPTURE IN VASCULAR EHLERS-DANLOS SYNDROME MICE

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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 mechanism by which this intracellular signaling cascade is activated secondary to mutations in *COL3A1* remains unknown.

Objectives

Define early and targetable pathogenic events in vEDS mice.

Materials and Methods

Using *Col3a1*$^{G938D/+}$ vEDS mice, we employed treatment trials, mechanistic analyses, and cell type-specific gene targeting to elucidate the pathogenic sequence in vEDS mice.

Results and Conclusion

Endothelin-1 (ET1), a small molecule secreted by endothelial cells that activates the endothelin receptor, a Gαq receptor, was found to be increased in *Col3a1*$^{G938D/+}$ (vEDS) aortas compared to controls. Informatively, vEDS mice on the 129S6/SvEvTac (129) background that are overtly protected from vascular rupture, show normal expression of ET1. vEDS mice treated with bosentan, an inhibitor of the ET1 receptor, showed improved long-term survival (70% vs 46% survival in untreated mice). Improved survival correlated with normalization activated PKC. Furthermore, mice treated with either a PKC or MEK inhibitor, which also have improved survival, show a significant reduction in ET1 levels, suggesting the presence of a positive feedback loop that contributes to vascular rupture risk. To specifically test the role of ET1, we utilized the Cre-Lox system to selectively inhibit *Edn1* expression in endothelial or vascular smooth muscle cells (ECs or VSMCs). Targeting *Edn1* in VSMCs had no effect on survival, but haploinsufficiency for *Edn1* in ECs dramatically improved survival to 70% (vs 10%) at 6 months, unveiling an unanticipated role for ECs in arterial rupture. These results provide evidence that vascular risk in vEDS is mediated by excessive ET1/PKC/ERK activation, perpetuated by a positive feedback loop initiated by ECs in the arterial wall, and modifiable by pharmacologic agents that antagonize this axis. Further studies focused on endothelial cell biology in vEDS will inform disease mechanisms and therapeutic strategies.

INTERROGATION OF THE ROLE OF ANDROGENS AND THEIR ANTAGONISTS IN THE PATHOGENESIS AND TREATMENT OF VASCULAR EHLERS-DANLOS SYNDROME (VEDS)

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Introduction

Males with VEDS are at an increased risk for arterial rupture during puberty compared to females. Our VEDS mouse model (*Col3a1*$^{G938D/+}$) recapitulates this sexual dimorphism, with 44% vs. 69% survival of males vs. females at 60 days of age, respectively. We hypothesized that androgens contribute to the pathogenesis of vascular rupture in VEDS through modulation of the PKC/ERK signaling axis. We had added incentive to understand the potential mechanisms by which androgen antagonists might contribute to protection from arterial events.

Objective

Understand the role of androgen receptor signaling in VEDS.

Materials and Methods

We crossed an AR conditional (floxed) allele to *Col3a1*$^{G938D/+}$ mice that globally express Cre recombinase. We treated *Col3a1*$^{G938D/+}$ mice with the selective AR antagonist (ARa) bicalutamide, the dual ARa and mineralocorticoid receptor antagonist (MRa) spironolactone, or the selective MRa eplerenone from the time of weaning until 60 days of age. Kaplan-Meier survival analysis was performed.

Results and Conclusions

Male *Col3a1*$^{G938D/+}$ AR null mice have improved survival compared to untreated *Col3a1*$^{G938D/+}$ mice at 60 days (68% vs. 44%), a protective performance mimicked by treatment with bicalutamide (65% survival). Immunoblot analysis of descending aortic lysates shows that AR blockade, either chemical or genetic, normalizes activation of the PKC/ERK axis. Taken together, these data suggest that AR signaling contributes to vascular disease in VEDS mice. Notably, male *Col3a1*$^{G938D/+}$ mice treated with the dual ARa/MRa spironolactone showed the best performance (87% survival at 60 days). Use of the selective MRa eplerenone afforded intermediate protection, approaching that of Spironolactone (81% male survival at 60 days) in selected contexts. Identical trends were observed in female *Col3a1*$^{G938D/+}$ mice. These data document that both AR and MR signaling are determinants of outcome in VEDS mice and highlight the therapeutic potential of isolated MR antagonism that should maintain normal sexual development.

CASTRATION OF MALES PREVENTS ARTERIAL RUPTURE IN A MOUSE MODEL OF VASCULAR EHLERS- DANLOS SYNDROME

Anne Legrand[1,2], Charline Guery[1], Irmine Loisel-Ferreira[1], Coralie Fontaine[3], Frank Giton[4], Salma Adham[1,2], Tristan Mirault[1,2,5], Eric Clauser[1], Xavier Jeunemaitre[1,2]

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Background

Vascular Ehlers-Danlos syndrome (vEDS) is a rare autosomal dominant inherited disorder characterized by spontaneous severe complications, usually occurring in young adulthood. A higher mortality rate is suspected in young affected men, suggesting the influence of sex hormones. Several *Col3a1* knock-in mouse models have shown a lower survival rate in males caused by aortic rupture.

Objectives

To investigate the effect of castration or the addition of sex hormones on the incidence of aortic rupture in a mouse vEDS model.

Material and Methods

Before sexual maturity, 5-week-old mice were castrated or sham-operated to avoid any endogenous sex hormones exposure. After one week of recovery, mice were evaluated daily and the survival was assessed for a 16-week period. Several sets of experiments were conducted in heterozygous Col3a1$^{+/G182R}$ mice : orchidectomy (orx) in male mice and ovariectomy (ovx) in female mice; 4-weeks administration of testosterone (T) with subcutaneous pellets; subcutaneous administration of Ang II (0.5 µg/Kg/min) to better test the protective effect of castration.

Results

Early orx in 5-weeks male mice improved the survival rate at 16 weeks compared to sham-operated controls (89% vs 67%, p=0.08) whereas early ovx in female did not modify it (96% vs 89%, ns). This sex-difference was not due to a significant difference in systolic blood pressure (SBP) change following orx or ovx. Ang II considerably worsened the survival rate in *Col3a1*$^{+/G182R}$ sham-operated male (0% survival rate at 10 days) but mortality was delayed and less severe in orx male mice (80% survival at 10 days) with a similar trend for SBP. Ovariectomy did not influence the Ang II-induced mortality rate, suggesting a specific effect of testosterone. Indeed, subcutaneous administration of testosterone in *Col3a1*$^{+/G182R}$ ovx female mice significantly worsened the survival at 16 weeks (52% vs 96%, p=0.0006). Whereas aortic diameter of female mice was smaller than those of male mice, their collagen content was similar and not influenced by ovx on this short term period.

Conclusion

This study suggests the direct implication of testosterone in causing arterial fragility in vEDS.

ADMINISTRATION OF CIPROFLOXACINE DOES NOT WORSEN THE VASCULAR PROGNOSIS IN A MOUSE MODEL OF VASCULAR EHLERS-DANLOS SYNDROME

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Background

Fluoroquinolones are a widely prescribed class of antibiotics but have been suspected as increasing the risk of aortic aneurysm and dissection (AAD) in the general population by favoring extracellular matrix degradation. They have been also shown to accelerate aortic root enlargement and the risk of aortic rupture in Marfan mice (Lemaire et al., PMID 34586071), suggesting that they should be avoided not only in patients at risk for sporadic AAD but also in patients with Marfan disease. A similar or even worse deleterious effect could occur in vascular Ehlers-Danlos syndrome (vEDS), a rare autosomal dominant disease with collagen type III deficiency.

Objectives

To test the effects of ciprofloxacin on aortic rupture in a mouse vEDS model

Methods

Since a strong sexual difference was observed in the spontaneous mortality caused by aortic rupture of our heterozygous (htz) Col3a1$^{+/G182R}$ model (Legrand et al., PMID: 35245290) (11% at 24 weeks in females vs 55% in males), we first designed a pilot study in female mice expecting a drug-induced increased mortality, whereas the second set of experiments was conducted in males. Mice were given ciprofloxacin (100 mg/kg/d) for 6 weeks and were monitored for up to 16 weeks. After sacrifice, aortic structure was examined by using histopathologic and immunostaining analyses and plasma ciprofloxacin was measured by high performance liquid chromatography.

Results

The pilot study was conducted in n=10 heterozygous 8-week old female *Col3a1*$^{+/G182R}$ mice which were given ciprofloxacin (100 mg/kg/d) for 6 weeks and were monitored for 16 weeks. At the end of the treatment period, we observed only 1 death, a proportion very similar or even lower to that observed in our previous series of female *Col3a1*$^{+/G182R}$ mice. We then conducted a second set of experiments in 10 weeks old wild-type *Col3a1*$^{+/+}$ male mice (n=10) or htz *Col3a1*$^{+/G182R}$ male mice (n=9) which were given ciprofloxacin (300 mg/kg/d) for 6 weeks and monitored for the same period. No death was observed either in the control or mutated mice. At sacrifice, plasma ciprofloxacin concentration was 0.4 ±0.1 mg/L and 0.5 ±0.2 mg/L in control and mutant mice, respectively, in the order of magnitude of the drug concentration observed when ciprofloxacin is prescribed for infections in humans. No notable structural modification of the aorta was observed. Whereas the proportion of tunel-positive cells in aorta was not significantly modified by ciprofloxacin in control mice, a marked increase was observed in treated htz *Col3a1*$^{+/G182R}$ (28 ±5% vs 3 ±1%, $p<0.01$), a witness of cell DNA damage in aortic medium.

Conclusion

Despite inducing a significant cell damage in the aortic medium of mutant mice, 6-weeks administration of ciprofloxacin does not induce an increased incidence of aortic rupture in this vEDS mouse model. Our findings do not substantiate a toxic effect of fluoroquinolones on a short mid-term duration in patients with vascular Ehlers-Danlos syndrome.

NOVEL ASSAY TO ASSESS THE AORTIC RUPTURE OF MICE MODELING AORTIC DISEASES

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Introduction: Thoracic aortic aneurysms and dissections (TAAD) characterized by a weakened aortic wall are a common cause of premature death. TAAD can be divided into syndromic and non-syndromic forms. An example for a syndromic TAAD is vascular Ehlers-Danlos syndrome (vEDS), which is a rare systemic connective tissue disorder, caused by mutations in the *COL3A1* gene, leading to weakened connective tissue, including the aorta.

Objectives: Previously, we have established an objective read-out system to measure the tensile force by stretching short murine thoracic aortic segments until rupture, with the aim of evaluating the effect of various medications on the biomechanical integrity of the aorta. Here, to gain deeper insight into the biomechanical integrity of the aorta, we present an additional, more physiological read-out system of the aortic rupture force.

Materials and Methods: Our novel assay assesses the burst pressure of the murine aorta by creating a fluid-induced load/stress on the aortic wall, thereby enabling the identification of the weakest (rupturing) site in the aortic wall by investigating the entire thoracic aorta. For this, we create a closed *in situ* system in euthanized mice and increase the intraluminal pressure with liquid until aortic rupture. The burst pressure at which the aortic rupture occurs is recorded (in mmHg).

Results: The application of our novel assay to wild-type and untreated heterozygous mice modeling vEDS (*Col3a1*$^{+/m1Lsmi}$) showed that wild-type mice had significantly higher burst pressure than heterozygous mice. The comparison with our previously established method for measuring aortic rupture force will be presented.

Conclusion: Our novel assay of burst pressure measurement can be used as an objective read-out system for assessing the biomechanical integrity of the entire thoracic aorta, enabling the evaluation of drugs to strengthen the weakened aortic wall in mice modeling aortic diseases.

A DECENTRALIZED STUDY DESIGN: A PHASE 3 CLINICAL STUDY IN PATIENTS WITH COL3A1- POSITIVE VASCULAR EHLERS-DANLOS SYNDROME TO DETERMINE WHETHER CELIPROLOL DELAYS THE ONSET OF VEDS-RELATED CLINICAL EVENTS COMPARED TO PLACEBO

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Introduction: Acer Therapeutics Inc. is developing ACER-002 (celiprolol) tablets for the treatment of patients with vEDS to reduce the risk of arterial and other hollow organ clinical events. In a previously conducted investigator-initiated clinical study in patients with vEDS, celiprolol treatment showed clinically and statistically significant improvements in time to occurrence of an arterial event, either fatal or not fatal.

Methods: This study is a prospective, Phase 3, randomized, double-blind, placebo-controlled efficacy study to evaluate celiprolol in patients with vEDS using a decentralized clinical trial design in the US. The double-blind portion of the study will continue until a sufficient number of vEDS-related events has occurred and will include a pre-specified interim analysis, which will be conducted when approximately 60% of the estimated total events have occurred.

A total of approximately 150 patients will be randomized 2:1 to receive either celiprolol or placebo, respectively. Randomization will be stratified by age group (≤32 years vs >32 years) and prior clinical events associated with vEDS. Patients will initiate treatment with 100 mg celiprolol tablets daily and up-titrate by 100 mg monthly until reaching the maximum dose of 400 mg daily, based on tolerability.

Results: The primary objective of the study is the determine whether celiprolol delays the onset of vEDS-related clinical events requiring medical attention (fatal/nonfatal cardiac or arterial events [including dissection or rupture], uterine rupture, intestinal rupture, and/or unexplained sudden death), relative to placebo as measured by time to event. Events will be assessed by an adjudication committee comprised of experts in the treatment of vEDS.

Conclusions: This study is designed as a decentralized study with the interactions of mobile nurses in participants' homes, remote clinical research coordinators, and telemedicine-based investigators to provide oversight as a method of assessing efficacy and safety in a manner that allows for greater study access.

ADDED VALUE OF STATINS IN VASCULAR EHLERS-DANLOS SYNDROME

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Introduction/Objectives: Patients with vascular Ehlers-Danlos syndrome (vEDS) are at an increased risk for fatal aortic ruptures. Aortic rupture force measurements in mice modelling vEDS have recently demonstrated that the β-blocker celiprolol can strengthen the weakened aortic wall and thus reduce the risk for arterial events as observed in clinical and retrospective studies. Similarly, we asked whether statins, which can reduce thoracic aortic aneurysm growth in mice modeling the vEDS-related Marfan syndrome, have a beneficial effect on the weakened aorta in vEDS. Thus, we have assessed the impact of two statins on the biomechanical integrity of the thoracic aorta in a mouse model of vEDS.

Materials/Methods: Four-week-old heterozygous *Col3a1*^{m1Lsmi} mice were treated for four weeks with one of two hydrophilic statins (pravastatin or rosuvastatin). Untreated wild-type and heterozygous littermates served as controls. As read-out of the biomechanical integrity of the aorta, 1.5-mm-long sections of the ascending and descending murine thoracic aorta were mounted on a tissue puller and uniaxially stretched until rupture, while the force was recorded (in mN).

Results: The aortic rupture force was significantly lower in untreated heterozygous mice compared to age- and sex-matched wild-type mice. Treatment with pravastatin or rosuvastatin significantly increased the rupture force of the ascending thoracic aorta in heterozygous mice.

Conclusion: Our data demonstrate that pravastatin/rosuvastatin can have an added value in the drug therapy of vEDS. Furthermore, our results exemplify that drug repurposing can be a powerful source to identify old drugs with added value for potential new therapeutic applications in aortic diseases, such as statins in vEDS. Further studies are needed to clarify whether or not this added value of pravastatin/rosuvastatin also applies for human use and whether or not our results can be extrapolated to other statins.

ILIAC ARTERY PATHOLOGY PRESENTATION AND MANAGEMENT IN VASCULAR EHLERS-DANLOS SYNDROME

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Introduction

Iliac arteries pathology is frequently encountered in patients with vascular Ehlers-Danlos Syndrome (VEDS).

Objective

We describe the presentation, management, and surgical outcomes of iliac arteriopathies among individuals with VEDS.

Materials and Methods

A cross sectional analysis of individuals with pathogenic/likely pathogenic variants in *COL3A1* enrolled in the VEDS Collaborative Research Study from 7/2019 to 7/2021. Patients with common, external, and internal iliac artery (CIA, EIA, IIA) aneurysms and/or dissections were selected for descriptive analysis.

Results

Among 321 enrolled individuals, 78 (24%) had iliac arteries pathology (50% male, 88.6% White). Mean age at VEDS diagnosis was 35.1±13.9 years and 39.2±11.7 years at iliac artery pathology diagnosis (no sex differences). Variant type was missense (61.5%), exon skip (15.4%), Null/haploinsufficiency (17.9%), and other (5.2%). History and exam findings included: 44.9% family history, 42.3% easy bruising, 24.4% hypertension, 7.7% smoking, 26.9% characteristic facial features, 25.6% joint hypermobility, 10.3% tendon rupture, and 3.7% club foot. Associated carotid, visceral, and aortic pathology was present in 38.5%, 44.9%, and 41% respectively. CIA pathology frequently presented with a bell-bottom configuration with sparing of the origin of the CIA. CIA and EIA pathology was symptomatic in 12 and 14 cases respectively. Operative repairs were performed in 17 (21.8%) cases: 11 open (3 aortobiiliac, 1 aortobifemoral, 3 iliac-iliac, 2 iliac-femoral, 1 femoral-femoral and 1 hematoma evacuation only) and 6 endovascular (1 endovascular aortic aneurysm repair (EVAR), 1 EVAR with branched iliac device, and 4 iliac artery stent grafts). None had a postoperative mortality. Among the entire cohort, 10 (12.8%) died due to iliac artery rupture (n=2), aortic related (n=4), spontaneous coronary artery dissection (n=1), and 3 unknown etiology.

Conclusions

Iliac artery pathology frequently affects individuals with genetically confirmed VEDS thus surveillance is warranted. While the arterial tissues are known to be fragile, surgical outcomes acceptable and lifesaving.

PRESENTATION AND MANAGEMENT OF SPLENIC ARTERIOPATHY IN PATIENTS WITH VASCULAR EHLERS-DANLOS SYNDROME

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Introduction

Vascular Ehlers-Danlos Syndrome (VEDS) is rare and associated with visceral arteriopathies.

Objective

We investigate the presentation and management of splenic artery aneurysms in this population.

Materials and Methods

Cross-sectional analysis of 1547 individuals with VEDS assembled by harmonizing data from VEDS Collaborative, UW Collagen Diagnostic Lab, and single center cohort. Patients were selected if they had splenic artery aneurysm, pseudoaneurysm, dissection, thrombosis, or rupture. Demographics, genetic *v*ariants, management, and outcomes were analyzed. Comparisons by rupture were made.

Results

A total of 88 patients presented between 1992 and 2021 with splenic arteriopathy (Mean age at diagnosis 37±11.1 years, 50% male). One third were diagnosed with VEDS prior to the splenic arteriopathy diagnosis and 17% were diagnosed post-mortem. Most had a positive family history (61%). Most had *COL3A1* variants associated with minimal normal collagen production (75%), most commonly large amino-acid substitutions. Median follow up was 8.5 (IQR 0.9-14.7) years. Initial presentation was rupture in 47% and rupture overall was 51% (N=45). No differences in VEDS related manifestations or genotype by rupture status. A total of 34 patients underwent 40 splenic artery interventions: 18 embolization, 21 open surgical, 10 splenectomies, 1 unknown procedure, and 5 more than one intervention. Open repair complications included arteriovenous fistula (n=1), intestinal or pancreatic injury (1 each), and four intraoperative deaths. Four (23.5%) developed new splenic artery aneurysm in the remaining splenic artery post embolization. All-cause mortality was 35% (n=31) including 22 related to ruptured splenic arteries.

Conclusions

Splenic arteriopathy in VEDS is associated with variants that markedly disrupted type III collagen folding and frequently present and frequently present with rupture. Rupture and open repair is associated with high morbidity and mortality while embolization is associated with favorable outcomes. Long term follow up is indicated as secondary splenic arteriopathy can occur.

ABDOMINAL AORTIC DISSECTION IS THE PREDOMINANT FORM OF ABDOMINAL AORTIC PATHOLOGY IN VASCULAR EHLERS-DANLOS SYNDROME

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Introduction

Vascular Ehlers-Danlos Syndrome (VEDS) is a known risk factor for heritable aortic pathology. However, there is a paucity of data on the characteristics of abdominal aortic pathology in this population.

Objective

We investigate the presentation, management, and outcomes of abdominal aortic pathology in patients with VEDS.

Materials and Methods

A cross sectional study of individuals enrolled in the VEDS Collaborative Research study between 6/24/2019 and 12/31/2021. Available medical records were reviewed for individuals with pathogenic/likely pathogenic *COL3A1* variants. Demographics, aortic pathology, surgical repairs, and survival were abstracted and analyzed.

Results

A total of 345 individuals met inclusion criteria (40.5% male, mean age 39±16 years). Among this cohort, 33 (9.5%) had abdominal aortic pathology (54.5% male) at a median age of diagnosis of 40.5 (IQR 32-52) years with no sex-differences in age of diagnosis. Nearly half (48.5%) were symptomatic while the rest were diagnosed incidentally or on surveillance imaging. Aortic dissection was present in 79% of the cases including 13 isolated abdominal aortic dissection. The median diameter was 30 (25.3-43.2) cm and abdominal aortic aneurysm (>3.5 cm) was present in 13 cases. The morphology of the aneurysm involved sparing of the proximal infrarenral abdominal aorta with aneurysm formation immediately proximal to the iliac bifurcation. Surgical repair was performed in 24.2% of the cases (open repair in 7 cases, endovascular repair in 1 case). For open surgical repair, estimated blood loss varied between 2000-5000 ml. There was one intraoperative mortality during attempted rupture repair. The endovascular repair case was complicated by femoral artery dissection. Aortic rupture occurred in 10 cases, 4 were associated with mortality.

Conclusions

Abdominal aortic dissection is the predominant form of abdominal aortic pathology in VEDS and can be associated with aneurysmal degeneration, frequently limited to the distal aspect of the infrarenal abdominal aorta. Open surgical repair appears to be tolerated.

BREASTFEEDING PRACTICES AND VASCULAR COMPLICATIONS AMONG PREGNANT WOMEN WITH VEDS

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Introduction

Among reproductive age women with Vascular EDS (VEDS), arterial dissection related to pregnancy is the most common cause of death. Mouse models of vEDS suggest that breastfeeding and associated hormone oxytocin are responsible for aortic dissection in pregnancy. However, literature describing breastfeeding practices among women with VEDS and associated complications are limited.

Objective

To describe the duration and method of infant feeding practices in a cohort of mother-child dyads with VEDS.

Materials and Methods

Semi-structured phone interviews were conducted with mother-child dyads, with both the mother and child having a pathogenic or likely pathogenic *COL3A1* variant. Data regarding maternal obstetric and cardiovascular complications related to pregnancy, method and duration of infant feeding were collected with descriptive statistics employed.

Results

Five affected mothers with 11 pregnancies are described, with median age at conception of 27y (IQR 26y-32y). Seventy percent of all neonates (23/33) were breastfed, including affected mothers (70%). None of the mothers with VEDS knew of their diagnosis at time of their pregnancy. Among the 7 breastfed neonates with affected mothers, the majority were fed 3-6 months (2/7, 29%) and 6-12 months (2/7, 29%).

Although none of these women had arterial dissection related to pregnancy, 4/5 (80%) had a maternal complication in at least one pregnancy including perineal tear that required transfusion, iliac arterial tear with subsequent death, uterine rupture, and placental abruption with placenta previa.

Conclusion

Pregnant women with VEDS are at high risk of complications, consistent with prior literature. A majority of women in our cohort (70%) breastfed their infants with no complications. Larger studies are needed to investigate the association between breastfeeding and vascular dissection in this population.

GESTATIONAL AGE AS A PROXY FOR ARTERIAL FRAGILITY IN VASCULAR EHLERS-DANLOS SYNDROME

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Introduction

Vascular EDS (VEDS) is associated with high risk of spontaneous vascular dissection and rupture. Affected neonates are more likely to be born premature, which is suspected to be secondary to increased amniotic sac fragility.

Objective

To evaluate the association between degree of sac fragility, measured by gestational age (GA) at birth, and the occurrence of vascular events in a cohort of children with VEDS

Materials and Methods

Patients with a pathogenic or likely pathogenic *COL3A1* variant were included. Preterm birth was defined as GA at birth <37 weeks. The primary outcome was major event before age 30y, defined as arterial dissection, rupture, and hollow organ rupture or collapse. To control for potential confounding by genotype, analysis was performed by risk-stratified genotype, classifying missense/splice site as high-risk, and null/deletion as low-risk. Survival analysis was used to examine the association between preterm birth and event.

Results

Forty-seven patients were included (70% male), of which 49% were born preterm (53% of high-risk, 33% of low-risk). Eighty-one percent (38/47) had a high-risk variant. Twelve (26%) had an event. In the high-risk cohort, 35% (7/20) of those born preterm had an event compared to 22% (4/18) of those born full-term (HR 5.3, 95% 1.1-26.7, p=0.04). Among the low-risk cohort, 33% of patients born preterm (1/3) had an event, while no one born at term (0/6) had an event (0%) (log-rank p=0.16). Among those with high-risk variants, when limiting the outcome to aortic/arterial events, 20% (4/20) of those born preterm had an event, compared to 11% (2/18) of those born at term (log-rank p=0.02).

Conclusion

Children with a high-risk *COL3A1* genotype and born preterm demonstrated higher risk for a major event. Although this study's statistical power was limited, these findings suggest preterm birth may aid in risk stratification. Additional studies with improved sample size are warranted.

VASCULAR EHLERS-DANLOS SYNDROME – A COMPREHENSIVE NATURAL HISTORY STUDY IN THE DUTCH PATIENT COHORT

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Introduction: Vascular Ehlers-Danlos Syndrome (vEDS) 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 (major events).

Objectives: To perform a national vEDS multi-center cohort study and provide further insights into the natural history of the disease and illustrate genotype-phenotype correlations. This knowledge will allow to further optimize patient care and raise awareness of the disease.

Materials and Methods: All Dutch patients carrying a (likely) pathogenic variant in the *COL3A1* gene were invited to participate. The phenotype was systematically charted by retrospect and assessment of molecular and clinical data was combined with a one-time visit to the outpatient genetics clinic for physical examination.

Results: 142 individuals participated, including 47 index patients (33%). Overall median age at genetic diagnosis was 41.0 years [IQR 28.0, 59.5]. Over half (73/142) of the individuals were heterozygous for a glycine substitution. Major events occurred at younger age in individuals with a glycine substitution, compared to heterozygotes of a haploinsufficient variant (p=0.044). Main reason to refer index patients was arterial aneurysm or dissection (65%). In almost 15% of all individuals, the diagnosis vEDS was highly suspected based on solely characteristic facial or skin features. Major events were more frequent (P=0.028) and occurred at younger age (P=<0.001) in these individuals. In total, 68 individuals (48%) had an arterial aneurysm and/ or dissection, including 55 involving the aorta and 34 outside the aorta. Seven individuals (5%) suffered from perforation or rupture of the colon and uterine rupture occurred once. Over half of the index patients met the 2017 vEDS criteria.

Conclusion: This national multi-center natural history study of Dutch vEDS patients provides a valuable basis for improving guidelines for diagnosing, follow-up and treatment of vEDS patients worldwide.

A CASE SERIES OF SPONTANEOUS CORONARY ARTERY DISSECTION IN VASCULAR EHLERS-DANLOS SYNDROME

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Introduction

Spontaneous coronary artery dissection (SCAD) is a potentially fatal, uncommon cause of acute myocardial infarction. It is diagnosed by coronary angiography. Inherited connective tissue disorders can predispose to SCAD. Vascular Ehlers-Danlos Syndrome (vEDS), a rare inherited connective tissue disorder is characterized by generalised tissue fragility, including vascular fragility often in medium-sized vessels. Spontaneous coronary artery dissection (SCAD) has previously been reported in vEDS. These have been either individual case reports, from vEDS cohorts or SCAD cohorts that have subsequently undergone genetic analysis.

Objectives

We report on 10 cases of molecularly confirmed vEDS where patients have had a SCAD.

Materials and Methods

Patients with a diagnosis of SCAD and molecularly confirmed vascular EDS (likely pathogenic or pathogenic *COL3A1* variant) have been identified through the EDS services (London and Sheffield) in the UK. With expert Cardiology review, a blinded study of the angiographic findings was carried out with age and sex-matched SCAD controls with no apparent underlying genetic diagnosis.

Results

As many of the patients with vEDS in the UK are known to either of the EDS services in London and Sheffield, we are able to propose a prevalence for SCAD in vEDS. We describe the phenotypic presentation of individuals with vEDS and SCAD including extra-cardiac findings as well as identifying any distinguishing features present in this specific cohort of patients compared to individuals with SCAD without a diagnosis of vEDS.

Conclusion

This research demonstrates that SCAD is a feature of vascular EDS and aims to increase awareness of this amongst specialists seeing patients with SCAD in the acute setting. It describes the extra-cardiac findings, which aims to improve opportunity for genetic testing for patients who have had SCAD, especially if there are other clinical features or a family history suggestive of vEDS or an alternative connective tissue disorder.

A DIAGNOSIS OF VASCULAR EHLERS-DANLOS SYNDROME IN CHILDHOOD: CLINICAL AND MOLECULAR FEATURES OF 60 INDIVIDUALS

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Introduction

The majority of Vascular Ehlers-Danlos syndrome (vEDS) diagnoses made in childhood are driven by positive family history but may also occur due to a major arterial or intestinal event. Little, however, has been reported on additional clinical characteristics in this young population group, especially in those where testing was initiated due to presence of minor diagnostic criteria.

Objectives

This research aims to capture comprehensive descriptions of clinical and molecular features of this cohort, including major clinical events, and identify drivers of vEDS diagnosis in childhood.

Materials & Methods

Individuals diagnosed with vEDS in childhood (<18 years), confirmed by identification of a (likely) pathogenic *COL3A1* variant, were identified through the National EDS Service in London. DNA analysis was completed prior to study commencement, between the years of 2004 and 2021.

Results

A total of 60 individuals (n=30 female, n=22 index) with a clinical and molecular diagnosis of vEDS in childhood were identified. Median age at diagnosis was 7 years (IQR 3-12 years). Diagnosis was predominantly driven by family history of vEDS (63%), A total of 10 major clinical events in childhood (4 vascular, 6 gastrointestinal) were recorded in 9 individuals, with one individual experiencing two gastrointestinal events. First event occurred at a median age of 9 years (IQR 0-12). In individuals who did not have a positive family history or major event, easy or excessive bruising was the most commonly identified cause for testing (82%)

Conclusion

This cohort provides further details of the clinical and molecular characteristics of individuals with vEDS and contributes new insight into drivers of diagnosis in individuals diagnosed in childhood, a population which has yet to be comprehensively described. This data also seeks to establish the foundation for future (inter) national collaborations which will be vital in allowing for improvement in diagnosis and management.

VASCULAR EDS IN ADULTHOOD: AN OVERVIEW OF CLINICAL AND MOLECULAR FEATURES OF 151 INDIVIDUALS

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Introduction: Vascular Ehlers-Danlos syndrome (vEDS) is a rare condition characterized by generalised tissue fragility and caused by pathogenic heterozygous *COL3A1* variants. The prevalence of vEDS is estimated to be 1:50,000-1:200,000. As such, descriptions of clinical and molecular characteristics of vEDS cohorts are critical in facilitating improvements to diagnosis and management.

Objectives: This research aims to provide descriptions of clinical and molecular features of this cohort, including major clinical events, and identify and interrogate phenotype- genotype relationships.

Material and Methods: Adults with a clinical and molecular diagnosis of vEDS were identified through the London EDS Service. Major clinical events were defined as a symptomatic clinical event that required specialist management or intervention that occurred spontaneously or would not have occurred to the same degree in an unaffected individual.

Results: A total of 151 adults (female = 90, index cases = 86) with a clinical and molecular diagnosis of vEDS were identified. Median age at diagnosis was 33 years (IQR 24 - 49). We identified 86 different *COL3A1* variants in this population and formed six distinct classifications. Missense substitutions and splice site variants accounted for 80% of all variants, the majority being triple-helical glycine substitutions (56%). Major clinical events were observed in 46% of individuals; vascular events were predominant (39%) followed by gastrointestinal events (15%), with first events occurring at a median age of 33 years (IQR 26-41). Analysis of this cohort also allowed identification and description of 31 family groups.

Conclusion: This cohort provides unique insight into clinical and molecular characteristics of vEDS in adults and aids more informed diagnosis, counselling, and management of the condition by furthering investigations into established genotype-phenotype associations. Through identification of family groups, the data also generate questions about intrafamilial variability and highlight the important insights future (inter)national collaborations may bring.

SELF-REPORTED HEALTH RELATED QUALITY OF LIFE IN ADULTS WITH VEDS

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Background

There have been few studies on the health-related quality of life (HRQOL) of adults with *vascular* Ehlers-Danlos syndrome (vEDS).

Methods

Using a validated instrument with questions selected especially for this population, researchers posted a HRQOL survey online via Qualtrics from May of 2021 to August of 2021 with a N = 89 people over the age of 18.

Findings

Twenty-five participants experienced a de novo mutation. Using a five-point scale of Poor, Fair, Good, Very Good, Excellent, four of the participants reported their health as excellent with the mean reporting their health as fair. Four participants reported their quality of life as excellent with the mean reporting their quality of life as good. Two participants reported their physical health as excellent and the mean was Fair. Eight participants reported having excellent mental health while the mean reported their mental health as fair. The majority of adults reported having fatigue and pain in the last seven days and forty-nine of the participants traveled over fifty miles to receive vEDS related care. The survey also assessed sleep quality, financial issues due to vEDS, the impact of the COVID-19 pandemic, hospital care, emergency department access, quality of sleep, social activities, activities of daily living, and other mental health issues. Conclusions: People living with vEDS report poorer overall quality of life than the population at whole. Further studies need to be conducted that explore genetic variant and HRQOL, dental health, and the impact of research on the HRQOL of adults vEDS as well as HRQOL in children with vEDS and the HRQOL of caregivers, spouses, and family members of people with vEDS.

IMPROVED PHYSICAL FUNCTIONING IN A VEDS PATIENT: A CASE REPORT

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Introduction

Chronic pain and disability are often associated with hypermobile Ehlers-Danlos syndrome (hEDS). There is less attention on similar symptoms in vascular EDS (vEDS) patients.

Objectives

To raise awareness and report how follow-up has improved the physical functioning of a vEDS patient with pain.

Case Description

This is a case report of a 28-year-old vEDS patient, followed up from February-September 2021 at the Department of Pain Management, Oslo University Hospital, Norway. Biallelic *COL3A1* sequence variants have previously been uncovered: c.1786C>T (pARG596Ter) and c.3851G>A (p.Gly1284Glu). The patient has a family history of vEDS with two sudden deaths. She has characteristic features of vEDS and multiple dissections/dilatations of medium-sized arteries. She suffered from chronic pain with acute exacerbations, requiring hospitalization 10 times per year for medical pain management. Her pain was treated with opioids every time she was hospitalized. She was physically inactive due to pain. At the Department of Pain Management her pain was mapped through: 1) a self-reported questionnaire on pain, general function and health-related quality of life; 2) the clinical history and 3) a pain drawing to assess pain location. The pain mapping identified which pain that needed further investigation, and which pain that was chronic benign pain. The patient reported chronic generalized pain and used three different pain medications daily. She wanted treatment with medicinal cannabis, but this was not indicated according to the Norwegian guidelines for medicinal cannabis. She was followed up weekly by a psychomotor physiotherapist and twice a month by a physician with focus on coping strategies and a low-dose physical activity plan. Psychomotor physiotherapy, pain coping strategies and physical activity plan improved her physical functioning from minimal physical activity to daily activities.

Conclusion

vEDS patients may suffer from chronic pain and disability, where they will need close follow-up to improve their physical functioning.

POSTER PRESENTATION LIST

International Symposium on Marfan Syndrome, LDS, and Related Conditions

Poster Presentation Sessions 1-4 (Posters 1-59)
Tuesday, August 30, 2022

Poster Presentation Sessions 5-9 (Posters 60-123)
Wednesday, August 31, 2022

SESSION 1: MOLECULAR PATHOGENESIS AND MODIFIERS

P1 **Mechanistic Dissection of a Gene-by-Environment Interaction Informs Regional Vulnerability to Aortic Aneurysm and Therapeutic Opportunities in Marfan Syndrome and Related Disorders**
Nicole Anderson, Johns Hopkins Medical Institutions

P2 **Fibrillin Microfibril Structure Identifies Long-Range Effects of Inherited Pathogenic Mutations Affecting a Key Regulatory Binding Site for Latent TGFβ**
Clair Baldock, University of Manchester

P3 **Striking Phenotypical Differences Between Ipo8 Knock-Out Mouse Models on Different Genetic Backgrounds**
Lucia Buccioli, University of Antwerp

P4 **EMILIN1 Deficiency Causes Arterial Tortuosity with Osteopenia and Connects Impaired Elastogenesis with Defective Collagen Fibrillogenesis**
Bert Callewaert, Ghent University Hospital

P5 **Marfan Syndrome Aortopathy is Caused by Overactivation of sGC- PRKG1 Signaling by NO**
Andrea De La Fuente-Alonso, Centro Nacional de Investigaciones Cardiovasculares (CNIC)

P6 **Defects in the First Hybrid Domain of Fibrillin-1 Affect Vascular Wall Homeostasis in the Thoracic Aorta**
Violette Deleeuw, Ghent University

P7 **Pathomechanistic Study of Biglycan Mutations in Aortopathy Development**
Josephina Meester, Universiteit Antwerpen

P8 **Smooth Muscle Cell Specific Klf4 Deletion is Insufficient to Prevent Phenotypic Modulation in Marfan Syndrome Mice**
Albert Pedroza, Stanford University

P9 **Incomplete Penetrance and Variable Clinical Expression of a Belgian TGFB3 Founder Variant Suggests the Presence of a Genetic Modifier**
Melanie Perik, Centrum Medische Genetica

P10 **Fibrillin-1-Regulated miR-122 has a Critical Role in Thoracic Aortic Aneurysm Formation**
Dieter Reinhardt, McGill University

P11 **Versican Accumulation Causes Aortic Disease in Marfan Syndrome**
María Jesús Ruiz-Rodríguez, Centro Nacional de Investigaciones Cardiovasculares (CNIC)

P12 **Proteomics of FBN1 Mutant Mouse Models of Aneurysm and Dissection**
Lynn Sakai, Oregon Health & Science University

P13 **BMP Driven Mechanisms in Aortic Aneurysm Formation in a Mouse Model of Marfan Syndrome**
Gerhard Sengle, University of Cologne

P14 **In Search of Genetic Modifiers That Explain the Phenotypic Variability in Smad3-Related Aortopathy**
Joe Davis Velchev, University of Antwerp

SESSION 2: ADVANCES IN IMAGING, BIOMARKERS, AND CARDIOVASCULAR RESEARCH

P15 **Unique Patterns of Three-dimensional Aortic Growth in Genetic Aortopathy**
Nicholas Burris, University of Michigan

P16 **Mitral Valve Prolapse, Mitral Annular Disjunction, Left Ventricular Basal Hypertrophy and Ventricular Repolarization Abnormalities in Marfan Patients**
Clemence Delhomme, Bichat-Claude Bernard

P17 **Mitral Annular Disjunction and Arrhythmias in Marfan Syndrome**
Fatima Ezzeddine, Mayo Clinic

P18 **Metabolism Role in Marfan Syndrome**
Jorge Oller, CBMSO-CSIC

P19 **D-dimer in Marfan Syndrome: Effect of Obstructive Sleep Apnea Induced Blood Pressure Surges**
Mudiaga Sowho, Johns Hopkins University

P20 **Circulating Fibrillin Fragments as Biomarkers for Thoracic Aortic Dissection**
Lynn Sakai, Oregon Health & Science University

P21 **Label-free Imaging for Acute Aortic Dissection by Using Marfan Syndrome Model Mouse**
Kaori Sugiyama, Waseda University

P22 **Aortic Flow Patterns by 4D Flow CMR in Marfan and Loeys-Dietz Patients Before and After Valve Sparing Aortic Root Replacement: A Comparison with Healthy Volunteers**
Gisela Teixido Tura, Hospital Universitari Vall d'Hebron

SESSION 3: NATURAL HISTORY AND CLINICAL OUTCOMES

P23 **Increased Incidence of TGFB2 Mutations in Manitoban Paediatric Mennonite Population**
Kayla Edison, University of Manitoba

P24 **Mosaic Monozygotic Twins for De Novo Loeys-Dietz Syndrome (LDS) 5 TGFB3 Variant**
Rajani Aatre, University of Michigan

P26 **Case Report: Longest Reported Survival for Autosomal Recessive Cutis Laxa Type 1B in 31-year-old Patient with Severe Aortopathy and Extensive Arterial Tortuosity**
Taylor Beecroft, Texas Children's Hospital and Baylor College of Medicine

P27 **Cardiovascular Outcomes and Survival in Patients with Early-Onset Marfan Syndrome**
Taylor Beecroft, Texas Children's Hospital and Baylor College of Medicine

P28 **Impact of Obesity on Clinical Outcomes in Marfan Syndrome**
Alan Braverman, Washington University School of Medicine

P29 **A Case Series of Loeys-Dietz Syndrome: How Can We Improve the Practical Utility of DNA Diagnostics for Surgical Purposes?**
Victoria Rumyantseva, Petrovsky National Research Centre of Surgery

P30 **Family History of Aortic Dissection in Patients with a FBN1 Pathogenic Variant**
Guillaume Jondeau, APHP

P31 **Individualized Aortic Root Prediction in Pediatric Marfan Syndrome**
Julia Lovin, Baylor College of Medicine

P32 **Loeys-Dietz Syndrome: Natural History, Clinical Spectrum, and Assessment of Outcomes—The Mayo Clinic Experience**
Jasraj Marjara, Mayo Clinic

P33 **Risk of Type B Dissection in Marfan Syndrome: The Cornell Aortic Aneurysm Registry**
Nupoor Narula, Weill Cornell Medical College

P34 **Clinical History and Outcomes of Patients Carrying TGFB2 Gene Variants**
Talha Niaz, Texas Children's Hospital

P35 **Aortic Dissection in TGF-β Related Vasculopathies: Results from the Montalcino Aortic Consortium (MAC)**
Maral Ouzounian, UHN - Toronto General Hospital

P36 **Organization of HTAAD Patient Care in Norway**
Nina Riise, Sunnaas Hospital HF

P37 **Arterial Tortuosity Syndrome: A Longitudinal Assessment of Cardiovascular Features**
Bita Salamat, Texas Children's Hospital / Baylor College of Medicine

P38 **Presentation and Management of Arteriopathy in Marfan Syndrome**
Palcah Shibale, University of Washington

P39 **Research Priorities Among Patients with Syndromic Heritable Aortopathies with and at Risk for Aortic Dissection**
Sherene Shalhub, University of Washington

P40 **Evaluating the Association Between Sex, Race, and Aortic Outcomes in Marfan Syndrome**
Palcah Shibale, University of Washington

P41 **Distal Aortic Repair Post Aortic Dissection in Heritable Thoracic Aortic Disease Patients with ACTA2 Pathogenic Variants: Results from the Montalcino Aortic Consortium (MAC)**
Sherene Shalhub, University of Washington

P42 **Population Management for Aortic Disease and Improving Care with Artificial Intelligence**
Matthew Solomon, Kaiser Permanente

P43 **Fatal and Non-Fatal Aortic Dissections Documented in Three Children with ACTA2 Variants**
Sara Stephens, Baylor College of Medicine

SESSION 4: PAIN/EXERCISE/QUALITY OF LIFE

P44 **Pilot Study of the Effects of Moderate Intensity Exercise on Children and Young Adults with Marfan Syndrome**
Jennifer Bogardus, Texas Woman's University

P45 **Quality of Life and VO2 in Children and Young Adults with Marfan and Related Conditions**
Thomas Edouard, CHU de Toulouse

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ABSTRACTS OF POSTER PRESENTATIONS

International Symposium on Marfan Syndrome, LDS, and Related Conditions

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MECHANISTIC DISSECTION OF A GENE-BY-ENVIRONMENT INTERACTION INFORMS REGIONAL VULNERABILITY TO AORTIC ANEURYSM AND THERAPEUTIC OPPORTUNITIES IN MARFAN SYNDROME AND RELATED DISORDERS

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Introduction

The mechanism for regional predisposition to aortic aneurysm is poorly understood. In Marfan syndrome (MFS) or Loeys-Dietz syndrome (LDS) there is predominant aortic root aneurysm (AoRA) whereas in bicuspid aortic valve with distal ascending aortic aneurysm (BAV/DAscAA), the most common inherited aneurysm condition, aneurysms involve the more distal ascending aorta. MFS and LDS relate to dysregulated TGF signaling while the BAV/DAscAA mechanism remains undefined, with rare cases attributable to haploinsufficiency for *NOTCH1* encoding a positive effector of Notch signaling. We showed that mouse models of MFS show a transition from AoRA to DAscAA and tear when treated with calcium channel blockers (CCBs) that is preventable upon concomitant treatment with PKC or ERK inhibitors (ERKi).

Objectives and Methods

To interrogate the pathogenesis of DAscAA, we applied rigorous *a priori* filters to transcriptomics data derived from the ascending aorta of MFS mice in tight temporal sequence with exposure to CCBs with or without ERKi. Candidate pathways were scrutinized with genetic and/or pharmacologic provocations.

Results

Unbiased methods identified the Notch signaling pathway as the predominant determinant of AscAA in CCB-treated MFS mice; this predisposition was recapitulated upon concomitant administration of DBZ, a pharmacologic Notch antagonist. AscAA was preventable using inhibitors of AT1R – directly implicating involvement of Gaq-mediated G-protein coupled receptor (GPCR) signaling. Expression studies demonstrated that the diagnosis (MFS), the vulnerable aortic segment (DAscAo), and environment (CCB/DBZ use) all associated with reduced expression of regulators of G-protein signaling molecules RGS4/5. Genetic targeting of *Rgs4* was sufficient to induce AscAA in otherwise resistant MFS mice. Concordant observations were observed in LDS mouse models.

Conclusion

These data document that genetic/environmental factors that oppose Notch signaling or inhibit RGS protein expression predispose to disease of the distal ascending aorta in MFS or LDS. Notch or RGS protein agonists emerge as viable therapeutic strategies.

FIBRILLIN MICROFIBRIL STRUCTURE IDENTIFIES LONG-RANGE EFFECTS OF INHERITED PATHOGENIC MUTATIONS AFFECTING A KEY REGULATORY BINDING SITE FOR LATENT TGFβ

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Introduction

Mutations in fibrillin microfibrils cause a range of serious inherited diseases such as Marfan syndrome and Weill-Marchesani syndrome (WMS). These diseases typically show major dysregulation of tissue development and growth, but links between the structural impact of mutations and disease mechanism is lacking, hampered by the absence of a high-resolution structure of fibrillin microfibrils.

Objectives

The aim of this study was to determine the high-resolution structure of native fibrillin microfibrils and map the locations of important functional regions such as the site of latent TGFβ-binding.

Materials and Methods

We have analysed the structure of native fibrillin microfibrils purified from mammalian tissue by cryo-electron microscopy, the first such analysis of any extracellular matrix fibrillar assembly. Fibrillin microfibrils purified from two mouse models with domain deletions that either cause WMS or perturb the latent TGFβ-binding site were also imaged.

Results

The cryo-EM structure of native fibrillin microfibrils reveals the molecular ultrastructure of the microfibril at high resolution. The bead region has pseudo 8-fold symmetry and a buried protease resistant N-terminal core. Microfibrils with the WMS-causing deletion induces a rearrangement with long-range effects blocking interaction with latent TGFβ-binding protein (LTBP)-1 at a remote site. Separate deletion of the LTBP1-binding domain resulted in the assembly of shorter fibrillin microfibrils with structural alterations.

Conclusion

These results establish that in complex extracellular protein assemblies, such as in fibrillin, mutations may have long-range structural consequences to disrupt growth factor signalling and cause disease.

STRIKING PHENOTYPICAL DIFFERENCES BETWEEN *IPO8* KNOCK-OUT MOUSE MODELS ON DIFFERENT GENETIC BACKGROUNDS

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Introduction

IPO8 encodes importin-8, a ubiquitously expressed nuclear transport receptor of the importin-β family. Importin-8 translocates cargoes such as proteins, RNAs and ribonucleoproteins from the cytosol to the nucleus in a Ran-GTP dependent manner. We recently found bi-allelic loss-of-function variants in *IPO8* causing a syndromic form of thoracic aortic aneurysm. Also, an *Ipo8* knock-out (*Ipo8*$^{-/-}$) mouse on a C57Bl/6N genetic background displayed root and ascending aortic aneurysms from 8 weeks of age onwards as well as an aortic expression signature compatible with dysregulation of the TGFβ signaling pathway. Embryonic lethality of 50% of the homozygous animals was also observed.

Objectives

This study was conducted to examine the influence of backcrossing C57Bl/6N *Ipo8*$^{-/-}$ to a Sv129 background.

Materials and Methods

Echocardiographic screening and embryonic lethality studies were conducted. The latter data are complemented with histological characterization, pSmad2 immunohistochemistry and aortic wall RNA-sequencing (currently ongoing). Additionally, timed matings (dissection at E13.5) are being done to investigate the cause of embryonic lethality in C57Bl/6N *Ipo8*$^{-/-}$ mice.

Results

Echocardiographic screening of *Ipo8*$^{-/-}$ mice on a Sv129 genetic background did not reveal aortic aneurysms, which is in sharp contrast to the pronounced aortic phenotype of the C57Bl/6N *Ipo8*$^{-/-}$ mice. 33% of C57Bl/6N *Ipo8*$^{-/-}$ male mice died from thoracic aortic rupture around 36 weeks, a finding never observed in the Sv129 *Ipo8*$^{-/-}$ mice up to 52 weeks. In contrast to C57Bl/6N *Ipo8*$^{-/-}$ mice, no embryonic lethality was observed in Sv129 *Ipo8*$^{-/-}$ mice. Based on the striking divergent cardiovascular phenotype of the C57Bl/6N and Sv129 *Ipo8*$^{-/-}$ strains and the embryonic lethality only observed in the C57Bl/6N mice, we hypothesize that aberrant cardiovascular development might be involved.

Conclusion

We describe striking differences in the phenotype of Sv129 versus C57Bl/6N *Ipo8*$^{-/-}$ mice, emphasizing the importance of mouse genetic backgrounds in disease modelling.

EMILIN1 DEFICIENCY CAUSES ARTERIAL TORTUOSITY WITH OSTEOPENIA AND CONNECTS IMPAIRED ELASTOGENESIS WITH DEFECTIVE COLLAGEN FIBRILLOGENESIS

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Introduction

EMILIN-1 (Elastin-Microfibril-Interface-Located-proteIN-1) is a structural component of elastic fibers and localizes to the interface between the fibrillin microfibril scaffold and the elastin core. How EMILIN-1 contributes to connective tissue integrity is not fully understood.

Objectives

To characterize a novel clinical phenotype associated with EMILIN-1 deficiency and to dissect the mechanism how EMILIN1 deficiency results both in defective elastin and collagen fiber synthesis.

Materials and Methods

We performed exome sequencing in four families presenting with a phenotype compatible with autosomal recessive cutis laxa type 1B and normal *FBLN4* sequencing. We applied transmission (immuno)electron microscopy on human and murine skin and skin-derived fibroblasts to evaluate the morphology of elastin and collagen fibers in control, EMILIN-1 deficient, or FIBULIN-4 deficient states. In these skin fibroblasts, we further investigated elastin and collagen fibril formation and lysyl oxidase (LOX) activity with qPCR analysis, western blotting, immunocytochemistry, liquid chromatography mass spectrometry, and a lysyloxidase activity and collagen crosslinking and morphometry assay. We evaluated transforming growth factor β (TGFβ) signaling on skin fibroblasts and vascular tissue. We analyzed bone strength with a three-point bending assay and histology with microcomputed tomography in *EMILIN-1* deficient mice.

Results

We identified biallelic loss-of-function variants in *EMILIN1* underlying a novel clinical entity characterized by cutis laxa, arterial tortuosity, aneurysm formation and bone fragility. Absence of EMILIN-1 impedes FIBULIN-4 deposition in the extracellular matrix. Absence of EMILIN-1 or FIBULIN-4 impairs LOX activity causing defective elastogenesis and reduced collagen crosslinking. Collagen fiber ultrastructure in EMILIN-1 or FIBULIN-4 deficient skin corroborate these findings. Murine *EMILIN-1* deficient femora show abnormal trabecular bone formation and strength. EMILIN-1 deficiency does not alter TGFβ secretion, but increases downstream TGFβ signaling.

Conclusion

Altogether, EMILIN-1 is a molecular link between elastic fiber and collagen fibril formation, and is required for proper LOX functioning in skin, bone and vascular tissue homeostasis.

MARFAN SYNDROME AORTOPATHY IS CAUSED BY OVERACTIVATION OF SGC-PRKG1 SIGNALING BY NO

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[5] MRC and JMR jointly directed this work.

Introduction

Despite advances in the genetics of thoracic aortic aneurysm and dissection (TAAD), current pharmacological treatments neither effectively retard aortic expansion nor prevent catastrophic failure in these diseases, including Marfan syndrome (MFS). We have described Nos2 as a critical mediator in the development of aneurysms, whose expression is induced in MFS. However, the mechanisms by which NOS2 contributes to TAAD in MFS remain unclear.

Objectives

We aim to investigate if NO-sGC-PRKG1 signaling is implicated in MFS aortopathy and identify novel targets that could improve diagnosis, treatment and/or prognosis of this disease.

Materials and Methods

MFS disease was studied in a genetic MFS mouse model and NO-donors were administered to assess their capacity to induce aortopathy in wild-type mice. Pharmacological inhibitors and lentivirus encoding shRNA specific of sGC-PRKG pathway components were administered to study TAAD reversion in MFS mice. Additionally, blood and aortic tissue samples from healthy donors, Marfan patients, and mouse models were examined by high throughput proteomics analysis.

Results

We show that increased NOS2-derived NO levels stimulate sGC– PRKG1 pathway in Marfan patients and mice, as evidenced by increased plasma cGMP and aortic staining of pVASP-S239. Our data also show that inhibitors of either sGC or PRKG1, or lentiviral-mediated silencing of *Prkg1* in the aorta, regress MFS mice aortopathy. Nitrated protein levels are higher in plasma from MFS patients and mice and in aortic tissue from MFS mice, indicating elevated circulating and tissue NO and suggesting that NO also mediates pathophysiological processes in a cGMP-independent fashion through mechanisms involving protein nitration.

Conclusions

These results show that NO-sGC-PRKG1 signaling mediates aortopathy in MFS mice and is activated in MFS mice and patients. Our findings also identify potential therapeutic targets for intervention in human MFS as well as circulating biomarkers for monitoring and clinical follow up of MFS disease.

DEFECTS IN THE FIRST HYBRID DOMAIN OF FIBRILLIN-1 AFFECT VASCULAR WALL HOMEOSTASIS IN THE THORACIC AORTA

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Introduction

Aortic dissection and rupture is the main cause of early cardiovascular mortality in patients with Marfan syndrome (MFS). MFS is caused by a defect in fibrillin-1, which binds transforming growth factor beta (TGF-beta) via interaction with latent TGF-beta binding proteins (LTBPs). The role of TGF-beta in MFS is controversial, with earlier studies suggesting that excess release of TGF-beta leads to aortic dilation and vascular damage, while other studies showed an important protective effect.

Objectives

We aim to use dedicated mouse models for MFS, with defects interfering with TGF-beta binding and -function, to gain insights into the role of TGF-beta signaling in aneurysm formation and dissection.

Material and Methods

Mice lacking the fibrillin-1 binding site for LTBPs (*Fbn1*$^{H1\Delta/+}$ and *Fbn1*$^{H1\Delta/H1\Delta}$), mice with a truncated fibrillin-1 (*Fbn1*$^{GT\text{-}8/+}$), and mice with a combination of both alleles (*Fbn1*$^{GT\text{-}8/H1\Delta}$) were subjected to cardiac ultrasound and ex vivo synchrotron X-ray imaging.

Results

Only *Fbn1*$^{GT\text{-}8/H1\Delta}$ mice showed increased mortality due to aortic rupture starting at 4-5 months of age, whereas all other mice had a normal life span. Aortic root dilatation occurred both in *Fbn1*$^{GT\text{-}8/+}$ and *Fbn1*$^{GT\text{-}8/H1\Delta}$ mice at 6 months of age, but not in *Fbn1*$^{H1D/+}$ or *Fbn1*$^{H1\Delta/H1\Delta}$ mice. Significant elastin fragmentation was observed in the thoracic aortic wall of Fbn1$^{GT\text{-}8/+}$ mice, and to a larger extent in *Fbn1*$^{GT\text{-}8/H1\Delta}$ mice. Surprisingly, localized elastin fragmentation was also found in the ascending aorta of *Fbn1*$^{H1\Delta/+}$ and *Fbn1*$^{H1\Delta/H1\Delta}$ mice, despite a lack of aortic aneurysm formation. Moreover, *Fbn1*$^{H1\Delta/H1\Delta}$ mice displayed more severe aortic wall damage.

Conclusion

Our data suggest that loss of LTBP binding to fibrillin-1 leads to the development of localized microdissections in the aorta in the absence of aortic aneurysm, and exacerbates the aortic wall morphology abnormalities in mice with truncated fibrillin-1. We therefore hypothesize that local TGF-beta sequestration is required to maintain aortic homeostasis.

PATHOMECHANISTIC STUDY OF BIGLYCAN MUTATIONS IN AORTOPATHY DEVELOPMENT

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Introduction

Mutations in the X-linked gene *BGN* lead to syndromic thoracic aortic aneurysms and dissections. Aortic dissection/rupture in BALB/c Bgn$^{-/0}$ mice was previously reported in literature. After breeding this mouse model for pathomechanistic studies, we observed that in our facility these mice rarely develop spontaneous aortic dissections/ruptures. It is hypothesized that the mice from the original publication were living under more stressful conditions.

Objectives

The objective of this study was to provoke aortic dissection/rupture in the Bgn$^{-/0}$ mouse model, which was attempted by the infusion of Angiotensin II (AngII). The mice are subsequently used to study the pathomechanism of biglycan-related aortopathy.

Materials and Methods

Alzet minipumps (filled with either AngII or vehicle) were implanted at the age of 8 weeks and infusion lasted for 4 weeks. For the pathomechanistic experiments, the animals were sacrificed 5 days after implantation of the minipump.

Results

Infusion of both low and high dose of AngII (100 to 1000 ng/kg/min) provoked aortic dissection/rupture in mutant mice within days (2 to 33 days). In contrast, WT AngII-treated animals did not die. Bulk RNA-sequencing on descending aortic tissue (the predilection site for dissection) revealed an important role for the immune system in aortopathy development. The expression of multiple Toll-like receptors (Tlr2, 7-9 and 13), key regulators of immune responses and known BGN binding partners, was significantly increased. Furthermore, a significant enrichment in genes involved in neutrophil chemotaxis was observed, a process previously linked to the development of abdominal aortic aneurysms. Western Blotting and histological/immunohistochemical stainings are ongoing and will uncover structural and functional effects of genotype and AngII-treatment on Bgn$^{-/0}$ mice.

Conclusion

Our data shows that even a low dose of AngII is successful in provoking aortic dissection/rupture in Bgn$^{-/0}$ mice. RNA-sequencing data analysis showed a strong involvement of the immune system in aortopathy development and additional experiments will shed light on the pathomechanisms of Bgn-related aortic disease.

SMOOTH MUSCLE CELL SPECIFIC *KLF4* DELETION IS INSUFFICIENT TO PREVENT PHENOTYPICMODULATION IN MARFAN SYNDROME MICE

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Introduction

Smooth muscle cell (SMC) phenotypic reprogramming toward a mixed synthetic-proteolytic state is a core feature of aortic root aneurysm progression in Marfan syndrome (MFS). Previous work identified *Klf4* as a potential mediator of SMC plasticity in MFS.

Objectives

To determine whether targeted *Klf4* deletion in SMCs prevents progressive phenotype derangement during MFS aortic aneurysm progression.

Materials and Methods

We developed MFS ($Fbn1^{C1041G/+}$) mouse strains with an inducible vascular SMC fluorescent reporter ($Fbn1^{SMC}$) with or without SMC-specific deletion of *Klf4* exons 2-3 ($Fbn1^{SMC\text{-}Klf411}$). We induced permanent SMC tracing and simultaneous *Klf4* loss-of-function in *Klf411* mice at 6 weeks old and measured aneurysm growth via echocardiography (4-24 weeks), followed by aortic single cell RNA sequencing (scRNAseq) at 24 weeks.

Results

MFS mice demonstrated progressive aortic root dilatation compared to control (WT^{SMC}) mice regardless of *Klf4* genotype ($p<0.001$ via mixed models analysis for repeated measures). We found no difference in aortic root growth in $Fbn1^{SMC\text{-}Klf411}$ *vs.* $Fbn1^{SMC}$ ($p=0.884$). Efficient *Klf4* deletion was confirmed via tissue *in situ* hybridization. Analysis of traced SMCs by scRNAseq revealed a highly similar pattern of phenotype modulation marked by loss of contractile markers (*e.g., Myh11, Cnn1*) and heightened expression of matrix genes (*e.g., Col1a1, Fn1*) between *Klf4* genotypes. Quantitative, scoring of SMC dedifferentiation along this phenotypic spectrum confirmed that *Klf4* deletion did not alter the global extent of phenotype modulation, but reduced expression of 23 genes during this phenotype transition in $Fbn1^{SMC\text{-}Klf411}$ mice, including multiple chondrogenic genes expressed by only the most severely dedifferentiated SMCs (*e.g., Cytl1, Tnfrsf11b*).

Conclusion

Despite activated *Klf4* expression by SMCs in MFS aortic aneurysm, *Klf4*-mediated transcriptional regulation is not required to initiate SMC phenotype modulation. Mechanistically, *Klf4* may exert regulatory control over chondrogenic genes in a small subset of highly dedifferentiated SMCs, limiting its applicability as a target to block wholesale SMC modulation.

INCOMPLETE PENETRANCE AND VARIABLE CLINICAL EXPRESSION OF A BELGIAN *TGFB3* FOUNDER VARIANT SUGGESTS THE PRESENCE OF A GENETIC MODIFIER

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Background

Pathogenic *TGFB3* variants cause Loeys-Dietz syndrome type 5, an aortic aneurysm-presenting connective tissue disorder.

Methodology

We provide the results of an haplotype analysis as well as a medical record review of clinical features of 29 individuals from five families segregating an identical pathogenic *TGFB3* variant, p.Asp263His, which affects a critical integrin-recognizing RGD motif.

Results

In five families with the p.Asp263His variant, we identified a shared haplotype (min 1.92Mb-max 4.14Mb), suggesting the presence of a founder originating ±400 years ago. Remarkably, only 4/29 patients presented with aortic aneurysms/dissections. One 31-years old male presented with a type A dissection, while another 66-years old male underwent a Bentall procedure because of severe insufficiency of a bicuspid aortic valve and a sinus of Valsalva aneurysm (50mm, z-score=5.2). Two other male mutation carriers presented with a pathologically enlarged ascending aorta or aortic root aneurysm at older age (75 and 80 years). None of the 25 other *TGFB3* founder mutation carriers (10-84 years, 14 males/11 females) had aortic aneurysms.

Additional cardiovascular observations are ventricular septal defect, valve insufficiency and variable conduction abnormalities. We also observed minor systemic involvement such as easy bruising, inguinal hernia and ruptured ligaments and tendons.

Conclusion

The low penetrance for aortic involvement suggests that the pathogenic *TGFB3* variant is not sufficient to cause the aneurysm phenotype. No aggravating cardiovascular risk factors were documented in the aneurysm-presenting patients. Comparative whole genome- and RNA-sequencing of iPSC-vascular smooth muscle cells of affected and unaffected variant carriers is currently being performed to pinpoint genetic modifiers.

FIBRILLIN-1-REGULATED MIR-122 HAS A CRITICAL ROLE IN THORACIC AORTIC ANEURYSM FORMATION

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Introduction and Objective

Thoracic aortic aneurysms (TAA) in Marfan syndrome, caused by fibrillin-1 mutations, are characterized by elevated cytokines and fragmentated elastic laminae in the aortic wall. This study explored whether and how specific fibrillin-1-regulated miRNAs mediate inflammatory cytokine expression and elastic laminae degradation in TAA.

Methods and Results

Large scale miRNA expression profiling at early and late TAA stages using a severe Marfan mouse model (*Fbn1*$^{mgR/mgR}$) revealed a spectrum of differentially regulated miRNAs. Bioinformatic analyses predicted the involvement of these miRNAs in inflammatory and extracellular matrix related pathways. We demonstrate that upregulation of pro-inflammatory cytokines and matrix metalloproteases is a common characteristic of mouse and human TAA tissues. miR-122, the most downregulated miRNA in the aortae of 10-week old *Fbn1*$^{mgR/mgR}$ mice, post-transcriptionally upregulated CCL2, IL-1β and MMP12. Similar data were obtained at 70 weeks of age using *Fbn1*$^{C1041G/+}$ mice. Deficient fibrillin-1-smooth muscle cell interaction suppressed miR-122 levels. The marker for tissue hypoxia HIF-1α was upregulated in the aortic wall of *Fbn1*$^{mgR/mgR}$ mice, and miR-122 was reduced under hypoxic conditions in cell and organ cultures. Reduced miR-122 was partially rescued by HIF-1α inhibitors, digoxin and 2-methoxyestradiol in aortic smooth muscle cells. Digoxin-treated *Fbn1*$^{mgR/mgR}$ mice demonstrated elevated miR-122 and suppressed CCL2 and MMP12 levels in the ascending aortae, with reduced elastin fragmentation and aortic dilation.

Conclusion

This study demonstrates that miR-122 in the aortic wall inhibits inflammatory responses and matrix remodeling, which is suppressed by deficient fibrillin-1-cell interaction and hypoxia in TAA. Digoxin treatment improves TAA pathology.

VERSICAN ACCUMULATION CAUSES AORTIC DISEASE IN MARFAN SYNDROME

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Introduction

Thoracic aortic aneurysm and dissection (TAAD) is a life-threatening condition associated with Marfan syndrome (MFS). The metalloproteinase Adamts1 is a major mediator of vascular homeostasis, as its genetic deficiency in mice induces an aortic phenotype similar to MFS. Of note, reduced ADAMTS1 levels and enhanced levels of NOS2 have been found in mice and patients with MFS. However, the functional role of Adamts1 substrates in MFS remains unknown.

Objective

To assess the specific role of Adamts1 substrates Versican (Vcan) and Aggrecan (Acan) in MFS aortic disease.

Materials and Methods

The contribution of Adamts1 substrates to MFS aortopathy was addressed knocking down aortic *Vcan* and *Acan* expression in a mouse model of MFS (*Fbn1*$^{C1039G/+}$) with high-titer lentiviral vectors encoding a *Vcan*- or *Acan*-specific shRNA. Additionally, we also used *Vcan* or *Acan* haploinsufficient MFS mice (MFS;*Vcan*$^{hdf/+}$ or MFS;*Acan*$^{cmd/+}$, respectively).

Results

Vcan accumulates in the aortic medial layer of MFS mice, whereas Acan protein levels remain unaltered relative to WT aortas. Moreover, Vcan plays a key functional role in MFS aortopathy, as its lentivirus-mediated knockdown in the aorta reverts aortic dilation, medial degeneration and Nos2 upregulation in MFS mice. Furthermore, *Vcan* haploinsufficiency partially protects MFS mice from aortic dilation. In contrast, *Acan* deficiency fails to improve MFS aortic enlargement and medial degeneration, suggesting that Acan does not play a substantial role in this mouse model of MFS.

Conclusion

Our findings show that Vcan accumulation, but not Acan, is a causal driver of MFS-related aortic disease.

PROTEOMICS OF *FBN1* MUTANT MOUSE MODELS OF ANEURYSM AND DISSECTION

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Introduction

Aortic dissection is the main driver of early cardiovascular death as well as of long-term complications in people with Marfan syndrome (MFS). Surgical replacement of the diseased aortic segment is the main treatment for the prevention of early death. Aortic disease in patients with MFS is not limited to the aortic root—with a risk for type B dissection that is independent of the aortic root size—and can also occur after previous root replacement, resulting in the need for surgical intervention in more distal segments.

Objectives

We aim to use mouse models of various stages of aortic aneurysm and dissection in order to better understand the underlying pathophysiology and sequence of aortic disease. This strategy allows us to uncover molecular pathways associated with both early and late events and to focus on early events that are required for the progression of aortic disease.

Materials and Methods

The ascending aorta of 4 months old *Fbn1* mutant mouse models which develop (i) aortic aneurysm without dissection ($Fbn1^{GT\text{-}8/+}$), (ii) microdissections without aortic aneurysm ($Fbn1^{H1\Delta/+}$), and (iii) aortic aneurysm and rupture ($Fbn1^{GT\text{-}8/H1\Delta}$) were analyzed using mass spectrometry. Relative abundance of peptides was determined using TMT labeled reporter ions.

Results

Proteomics analyses showed marked differences between genotypes and sexes. 2610 proteins were quantifiable in both males and females. Statistically significant proteins were identified in all mutant genotypes compared to wildtype and when mutants were compared to each other (e.g., when mice about to rupture were compared to mice with aneurysm).

Conclusion

Significantly different molecules associated with early events in the development of aneurysm and dissection have been identified in these proteomics analyses. Later time points will chart these molecules as aortic disease progresses. This approach may allow key early molecular pathways for dissection to emerge.

BMP DRIVEN MECHANISMS IN AORTIC ANEURYSM FORMATION IN A MOUSE MODEL OF MARFAN SYNDROME

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Introduction

Fibrillin microfibrils target and sequester growth factors of the TGF-β superfamily within the extracellular microenvironment of aortic resident cells. Bone morphogenetic proteins (BMPs) interact with microfibrils via their prodomains which induces a conformational change that renders them latent. Recently, we demonstrated that prodomain degradation by matrix metalloproteinases (MMPs) leads to activation of BMPs (PMID: 33629769). To assure tissue homeostasis, a fine-tuned balance between BMP and MMP activity is crucial. In disease situations characterized by ECM degradation, such as Marfan syndrome, that is caused by fibrillin-1 deficiency, small amounts of active BMP or MMP may initiate a vicious feed-forward cycle where MMP-mediated BMP release from ECM-targeted pools further promotes MMP production, ultimately resulting in severe ECM destruction.

Objectives

To uncover early ECM derived detrimental events in the pathology of aortic aneurysm formation in Marfan syndrome. Targeting dysregulated ECM remodeling events in the aorta may open up new treatment options for patients.

Materials and Methods

Aortas from GT8 *Fbn1* knock-in Marfan mice expressing a fibrillin-1 C-terminal truncation mutation were analyzed by echocardiography and microscopy. Cell culture and genetic breeding experiments were conducted. A preclinical trial with a specific MMP13 inhibitor was conducted.

Results

GT8 *Fbn1* mice showed significant aortic root enlargement already at P10 which correlated with the onset of aberrantly increased BMP signaling and MMP-13 expression levels. BMPs upregulated MMP-13 expression in VSMCs. Breeding of the *Fbn1* GT8 Marfan allele onto a *Mmp13* null background prevented aortic root enlargement implicating the relevance of this mechanism in aortic aneurysm formation in Marfan syndrome. Pharmacological inhibition of MMP-13 effectively blunted postnatal aortic root growth in GT8 mice.

Conclusion

Here we identified a new activation mechanism of BMPs from ECM-bound pools and MMP-13 as a new potential therapeutic target relevant for aortic disease progression in MFS.

IN SEARCH OF GENETIC MODIFIERS THAT EXPLAIN THE PHENOTYPIC VARIABILITY IN *SMAD3*-RELATED AORTOPATHY

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Introduction

Loeys-Dietz Syndrome (LDS) is an autosomal dominant connective tissue disorder presenting with thoracic aortic aneurysm and dissection (TAAD). Remarkably, some LDS patients remain cardiovascularly unaffected throughout life, while others carrying the exact same genetic variant die early because of an aortic dissection. We hypothesize that genetic modifiers are the basis of this observation.

Objectives

1. Identify genetic modifiers that explain the variability in LDS-related aortopathy.
2. Generate a patient-specific iPSC-vascular smooth muscle cell (VSMC) model to allow functional validation of genetic modifiers.

Material and Methods

We have access to a large LDS family segregating a pathogenic *SMAD3* (p.Arg287Gln) variant. Identification of candidate modifiers in this family encompasses genome-wide SNP-based linkage analysis (n=19, available mutation carriers) and WGS (3 affected (AMC) and 4 unaffected mutation carriers (UMC)). Subsequent functional validation involves CRISPR/Cas-based modifier correction in iPSC-VSMCs of an affected variant carrier, which are created using the CytoTune iPS 2.0 Kit and the Granata et al. VSMC differentiation protocols.

Results

Linkage analysis suggests the presence of an aggravating modifier at chr2 (LOD: 2.68). The region of 14 Mb contains 19 protein coding genes of which the *TNFAIP6* gene was ToppGene prioritized. There were no exonic variants in any of the genes that segregate with affection status. However, 472 non-coding variants are only present in AMC. We are currently investigating their potential as modifiers.

iPSCs of an AMC and its isogenic control were created. They express core pluripotency markers and possess trilineage differentiation potential in the absence of the Sendai vectors. SNP array confirmed the genomic stability and identity of the cells.

Conclusion and Future Work

The obtained data suggest the presence of an aggravating modifier at chr2. Further analyses are ongoing to pinpoint the exact modifier variant explaining the linkage signal. Subsequently, the identified modifier(s) will be modelled in an in-vitro created iPSC-VSMC model.

UNIQUE PATTERNS OF THREE-DIMENSIONAL AORTIC GROWTH IN GENETIC AORTOPATHY

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Introduction

Patients with genetically-mediated thoracic aortic aneurysm (TAA) are at high risk of progressive aortic growth, although growth is variable and often difficult to accurately define using conventional diameter measurements. An emerging imaging technique, vascular deformation mapping (VDM), provides accurate, three-dimensional (3D) mapping of aortic growth.

Objective

To investigate 3D patterns of aortic growth among patients with genetically mediated TAA using VDM.

Material and Methods

We included adult patients at our center with genetically-mediated TAA and at least 2 CT angiograms >1 year apart. 3D aortic growth was measured by VDM. The longest interval with acceptable image quality was used for analysis. Patients were excluded if image artifacts prevented accurate VDM analysis.

Results

61 patients (average follow-up 5.4 ± 3.6 years, cumulative 331 years) were included, with TAA etiologies: Marfan (n=41), Loeys-Dietz (n=2), vascular Ehlers-Danlos (n=5), and familial/non-syndromic genetic (n=13). Average age was 54.8 ± 16.6 years and 42.6% were female (n=26). The majority (n=38, 62%) had a history of open aortic repair (n=38 root/ascending, n=4 descending). Among post-surgical patients, three patterns emerged from VDM growth maps: 1) “One and done”– prior root/ascending repair with disease limited to the repaired segment with no further growth during surveillance (n=14); 2) “Adjacent segment”– growth limited to native aorta just immediately adjunct to surgically repaired segment (n=9); 3) “Diffuse growth”– significant growth involving all unrepaired aortic segments (n=15). Among non-surgical patients (n=23, 38%) there were similarly three growth patterns by VDM: 1) “Stable” – no growth (n=9); 2) “Heterogeneous growth” – multi-focal growth with intervening regions without growth (n=7); 3) “Diffuse growth” – contiguous growth involving all segments (n=7).

Conclusion

Growth in genetic aortopathy is highly variable in extent and degree in both the pre- and post-operative settings. Unique patterns of 3D growth identified by VDM may have important implications for risk stratification and surgical planning.

MITRAL VALVE PROLAPSE, MITRAL ANNULAR DISJUNCTION, LEFT VENTRICULAR BASAL HYPERTROPHY AND VENTRICULAR REPOLARIZATION ABNORMALITIES IN MARFAN PATIENTS

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Introduction

Mitral valve prolapse (MVP) has been associated with ventricular arrhythmia, originating from inferolateral left ventricle (LV) wall. However, its mecanism remains unclear.

Objectives

To take advantage of the high prevalence of MVP in Marfan syndrome (MFS) to study the relationship of MVP, mitral annular disjunction (MAD), LV basal hypertrophy and ECG abnormalities.

Materials and Methods

We included all MFS patients (≥14 yo) without a history of thoracic surgery seen in our center between 2015 and 2017. MVP was identified on echocardiography according to Levine definition and the other cases of abnormal systolic mitral leaflet displacement were defined as billowing. Basal inferolateral hypertrophy (BILH) was defined as basal inferolateral thickness ≥12mm and basal to mild wall thickness ratio ≥1.5. QTc was measured on rest 12-lead ECG.

Results

250 MFS patients were included. Billowing or MVP (BMVP) was present in 187 (74.80%) patients. MAD was present in 52/235 (22.13%) and was associated with BMVP in all cases. End-systole mitral annular diameter was larger when BMVP was present (mean: 34.82mm vs. 30.53mm, $p<0.0001$) and in MAD+ than in MAD- (mean: 37.14mm vs. 32.46mm, $p<0.0001$) with a correlation between MAD length and end-systole mitral annular diameter ($r=0.395$ $p<0.0001$). Whereas mitral annular diameter decreased in systole in MAD-, it increased in MAD+ (mean mitral annular diameter (diastolic – systolic): 3.69mm vs. -0.87mm, $p<0.0001$). BILH was present in 18/175 (10.29%) patients with BMVP vs. in 1/59 (1.69%) without ($p=0.0367$) and in 9/50 (18%) MAD+ vs. 10/174 (5.75%) MAD- ($p=0.006$). No electric abnormality on ECGs was associated with MAD or BMVP. In contrast, patients with BILH had a longer QTc than patients without HBIL (mean: 426ms vs. 411.4ms, $p=0.0220$).

Conclusion

In MFS population, MAD is associated with BMVP, systolic mitral annular dilatation, and BILH but not with ECG abnormalities. Only patients with BILH present a QTc prolongation.

MITRAL ANNULAR DISJUNCTION AND ARRHYTHMIAS IN MARFAN SYNDROME

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Background

Mitral annular disjunction (MAD) has recently been recognized as an arrhythmogenic entity. There is limited data about the prevalence of MAD and arrhythmias in patients with Marfan syndrome (MFS).

Objective

To assess the prevalence of MAD and arrhythmias in patients with MFS.

Methods

We performed a retrospective review of patients with MFS and fibrillin-1 (FBN1) gene mutation who were evaluated at Mayo Clinic, Rochester, MN from 1992 to 2020. Demographic, echocardiographic, electrocardiographic, and clinical data were collected.

Results

213 patients were included in this study. Mean age was 37±18 years, and 53% were male. Transthoracic echocardiography was performed in 203 (95%) patients. Mean left ventricular ejection fraction was 57±8%. MAD was present in 40 (20%) patients (mean length: 8.1±1.9 mm). Among the 213 patients with MFS, atrial arrhythmias occurred in 35 (16%) patients while ventricular arrhythmias occurred in 10 (5%) patients. Among the 35 patients with atrial arrhythmias, 32 (91%) patients had atrial fibrillation (paroxysmal n=23 (72%), persistent n=4 (13%), and permanent n=5 (16%)), 2 (6%) patients had atrial flutter, and 1 (3%) patient had typical atrioventricular nodal reentry. Mean age at the time of diagnosis of atrial fibrillation was 45±13 years.

MAD was present in 5 (14%) patients with atrial arrhythmias. Among the 10 (5%) patients with ventricular arrhythmias, 7 (70%) patients had ventricular tachycardia, 2 (20%) patients had frequent ventricular ectopy, and 1 (10%) patient had both ventricular tachycardia and frequent ventricular ectopy. MAD was present in 1 (10%) patient with ventricular arrhythmias.

Conclusion

In our cohort of patients with MFS, the overall prevalence of MAD was 20%. The majority of patients with arrhythmias did not have MAD. Further studies are needed to investigate the predictors of arrhythmias in patients with MFS.

MITOCHONDRIAL ROLE IN AORTIC ANEURYSM

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Abstract

Marfan syndrome (MFS) is an autosomal dominant disorder of the connective tissue caused by mutations in the *FBN1* (fibrillin-1) gene encoding a large glycoprotein in the extracellular matrix called fibrillin-1. The major complication of this connective disorder is the risk to develop thoracic aortic aneurysm. To date, no effective pharmacologic therapies have been identified for the management of thoracic aortic disease and the only options capable of preventing aneurysm rupture are endovascular repair or open surgery. We have studied the role of mitochondrial dysfunction and metabolism in the progression of thoracic aortic aneurysm and mitochondrial boosting strategies as a potential treatment to managing syndromic aortic aneurysms

D-DIMER IN MARFAN SYNDROME: EFFECT OF OBSTRUCTIVE SLEEP APNEA INDUCED BLOOD PRESSURE SURGES

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Introduction

Aortic dissection and rupture are the major causes of premature death in persons with Marfan Syndrome (MFS), a rare genetic disorder featuring cardiovascular, skeletal and ocular impairments. We and others have found that obstructive sleep apnea (OSA) confers significant vascular stress in this population and may accelerate aortic disease progression.

Objectives

Our goal in this study was to determine the effect of OSA induced hemodynamic fluctuations on D-dimer levels in MFS patients without overt aortic dissection. We hypothesized that D-dimer, a diagnostic biomarker for several types of vascular injury that is also elevated in MFS persons with aortic enlargement, may be sensitive to cardiovascular stresses caused by OSA.

Materials and Methods

To test this concept, we recruited 16 MFS persons without aortic dissection and randomized them to two nights of polysomnography, without (baseline) and with OSA treatment: continuous positive airway pressure (CPAP). In addition to scoring OSA by the apnea-hypopnea-index (AHI), beat-by-beat systolic-BP (SBP) and pulse-pressure (PP) fluctuations were quantified. Morning blood samples were also assayed for D-dimer levels.

Results

In this cohort (M|F:10|6, Age: 35.6±13.4 years, Aortic diameter; 4.0±0.6 cm), CPAP eliminated OSA (AHI:19.5±16.7 vs 3.2±1.9 events/hr, p=0.001), and decreased fluctuations in SBP (13.3±4.3 vs 9.4±3.2 mmHg, p=0.011) and PP (7.0±2.2 vs 5.1±1.6 mmHg, p=0.013). CPAP also reduced D-dimer levels from 1108.1±655.7 to 882.2±532.1 ng/ml (p=0.023). Linear regression revealed a positive association between the maximum PP during OSA and D-dimer (r=0.523, p=0.038), and the association improved (r=0.733, p=0.028) after adjusting for contemporaneous aortic root diameter.

Conclusion

Our study revealed that overnight CPAP reduces D-dimer levels commensurate with elimination of OSA and concomitant hemodynamic fluctuations. Morning D-dimer measurements together with OSA screening might serve as predictors of vascular injury in MFS.

CIRCULATING FIBRILLIN FRAGMENTS AS BIOMARKERS FOR THORACIC AORTIC DISSECTION

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Introduction

Patients with acute aortic dissections and other acute thoracic aortic pathology often present with chest pain. Currently, there are no reliable biomarkers that can detect or exclude aortic pathology in patients presenting with chest pain. Plasma fibrillin-1 and fibrillin-2 fragment levels (PFFLs) are elevated in patients with thoracic aortic aneurysms and dissections compared to control patients without aortic pathology.

Objectives

We sought to determine if PFFLs differ between patients with thoracic aortic pathology and those presenting with non-aortic chest pain.

Materials and Methods

PFFLs were measured in patients with thoracic aortic aneurysm (n=27) or dissection (n=28). For comparison, patients without aortic pathology, presenting to the emergency department with acute chest pain (n=281), were categorized into groups based on the cause of chest pain: group 1, ischemic cardiac chest pain; group 2, non-ischemic cardiac chest pain; group 3, noncardiac chest pain. PFFLs were measured using sandwich enzyme-linked immunosorbent assays (ELISAs).

Results

Fibrillin-1 PFFLs were detectable in all patients and concentrations were lowest in the ischemic cardiac chest pain group. Age, gender and hypertension were associated with differences in fibrillin-1 fragment levels. Fibrillin-2 fragments were more commonly detectable in the thoracic aneurysm and dissection groups compared to the ED chest pain group ($P<0.0001$). Patients with aortic dissection demonstrated increased detectability ($p=0.05$) and concentration ($p=0.06$) of fibrillin-2 fragments compared to patients with aortic aneurysms.

Conclusion

Patients with thoracic aortic dissections demonstrate elevated plasma fibrillin-2 fragment levels compared to patients presenting with non-aortic chest pain and increased fibrillin-1 levels compared to patients with ischemic cardiac chest pain. The use of fibrillin-1 and 2 as potential biomarkers of thoracic aortic dissection warrants further investigation.

LABEL-FREE IMAGING FOR ACUTE AORTIC DISSECTION BY USING MARFAN SYNDROME MODEL MOUSE

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Background

Marfan syndrome (MFS) is a genetic disorder caused by mutations in the gene encoding the extracellular matrix Fibrillin-1 (FBN1), resulting in systemic connective tissue abnormalities. The most common life-threatening conditions are aortic rupture and/or dissection. Aortic dissections show a high mortality rate, but the details of molecular triggers are unknown, particularly in acute aortic dissection (AAD). Raman spectroscopy is a technique for analyzing molecular structures from Raman spectra. It has recently attracted attention in the biology field because it can non-invasively distinguish between disease and non-disease areas.

Objectives

This study aimed to identify the signals that induce changes in the aortic wall prior to acute aortic dissection using genetic analysis and Raman spectroscopy with preservation of positional information.

Methods

An acute aortic dissection model was created by using MFS model mice ($Fbn1^{mgR/mgR}$) by administration of angiotensin II (AngII) via osmotic pump ($Fbn1^{mgR/mgR}$-AAD). Aortas from wild-type (WT), $Fbn1^{mgR/mgR}$ and $Fbn1^{mgR/mgR}$-AAD mice were harvested, and frozen sections were prepared. The vascular wall of each mouse was assessed histologically, followed by spatial RNAseq and Raman microscopy measurements. Multivariate data analysis was performed on the obtained Raman spectra

Results

Label-free imaging of extracellular substrates (collagen fibres, elastic fibres, versican, and aggrecan), lipids, and cells was produced in WT, $Fbn1^{mgR/mgR}$ and $Fbn1^{mgR/mgR}$-AAD aortic tissue. Spatial RNAseq identified differentially expressed genes among these aortas.

AORTIC FLOW PATTERNS BY 4D FLOW CMR IN MARFAN AND LOEYS-DIETZ PATIENTS BEFORE AND AFTER VALVE SPARING AORTIC ROOT REPLACEMENT: A COMPARISON WITH HEALTHY VOLUNTEERS

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Introduction

Abnormal aortic blood flow patterns in patients with Marfan (MFS) or Loeys-Dietz syndrome (LDS) may contribute to aortic root dilation (1,2). Valve sparing aortic root replacement (VSARR), which is effective in reducing the risk of aortic dissection in case of severe dilation, may also normalize flow patterns beyond the replaced aorta and potentially slow its progressive aortic dilation.

Objectives

To assess aortic flow dynamics in patients with a MFS/LDS by 4D flow cardiovascular magnetic resonance (CMR) before and after VSARR (David surgery), and to compare the results with those of healthy volunteers (HV).

Methods

Patients with MFS or LDS underwent two non-contrast enhanced 4D flow CMR, one before and another after undergoing David surgery. HV matched for age, sex and BSA, were also included for comparison. Maximum velocity, in-plane rotational flow (IRF), systolic flow reversal ratio (SFRR) and wall shear stress (WSS) magnitude and its axial and circumferential components were obtained at

24 planes covering the thoracic aorta from the sinotubular junction to the descending aorta at the diaphragmatic level (3-5).

Results

Sixteen patients and 21 healthy volunteers were included. Demographic and clinical data is presented in Table. Mean time between CMR prior and after surgery was 15 months. Compared to HV, patients with MFS/LDS before intervention presented lower maximum velocity at the proximal ascending aorta (Fig.1A), lower IRF and circumferential WSS at the arch and the proximal descending aorta (Fig 1B and F), lower magnitude and axial WSS at the proximal ascending and descending aorta (Fig 1E and D), and increased SFRR at the proximal descending aorta (Fig 1C). The intervention completely restored maximum velocity and partially-restored physiological helical flow and circumferential WSS, but barely improved axial WSS and SFRR.

Conclusion

Valve sparing aortic root replacement in patients with Marfan or Loeys-Dietz syndrome partially restore to physiological level both in-plane rotational flow and circumferential wall shear stress in the descending aorta. This flow normalization may contribute to prevent progressive dilation after the surgery.

INCREASED INCIDENCE OF TGFB2 MUTATIONS IN MANITOBAN PAEDIATRIC MENNONITE POPULATION

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Introduction

Loeys Dietz syndrome (LDS) is a heterogenous connective tissue disorder that is characterized by aggressive progression of aortic aneurysms that can result in early rupture at smaller diameters compared to more common connective tissue disorders. (Loeys Et al, 2005). There are six distinct categories of LDS, based on genetic and clinical findings TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3 and SMAD2.

Objective

To date, there have been no findings to suggest an association between the above gene mutations and any particular ethnic or racial group. In this study, we report on increased incidence of LDS among specific communities in our specific paediatric Manitoban population.

Methods

Retrospective review Manitoban database for LDS diagnosis in paediatric population.

Results

In our population we have a total of 12 subjects diagnosed with LDS. The incidence of LDS amongst Mennonite children in the Province of Manitoba, Canada, appears to be higher than any other racial/ethnic group. Of interest there are 6 Mennonite children of our cohort with a TBFB2 mutation. Interestingly, two of these children are siblings with a deletion of the TGFB2 1q41 gene associated with a syndrome associated with mild developmental delay and minimal cardiac involvement.

Conclusion

We observed a relationship between ethnic background and genetic mutations associated with LDS previously unreported in the literature. Due to the high population of children of Mennonite background living in Manitoba, we are cautious of children with this background with possible connective tissue disorders. These findings suggest a higher index of suspicion of these genetic mutations among patients with connective tissue disorders of Mennonite background.

References:

1. Loeys, B. L., Chen, J., Neptune, E. R., Judge, D. P., Podowski, M., Holm, T., et al. (2005). A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nature Genetics, 37(3), 275–281. https://doi.org/10.1038/ng1511.

MOSAIC MONOZYGOTIC TWINS FOR DE NOVO LOEYS-DIETZ SYNDROME (LDS) 5 TGFB3 VARIANT

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We present a family with a mosaic TGFB3 variant, discordant in identical twins. E (age 18) presented to pediatric cardiogenetics with a history of heart-racing, pectus excavatum, bifid uvula, diaphragmatic hernia s/p repair in infancy, hiatal hernia, loose joints, aortic root dilatation and scoliosis. Genetic testing revealed a pathogenic variant in TGFB3 (c.898C>T; p.Arg300Trp), consistent with a diagnosis of LDS. Her brother (A, 16) also tested positive for the variant with congenital forefoot supination and acquired mild inferior pectus carinatum. Their mother (M, 44) was found to be mosaic for the TGFB3 variant with 14-24% presence of the variant in her saliva sample. On clinical evaluation she was found to have a pectus deformation, easy bruising and bleeding, prior hernia repair, varicose veins and allergies with normal neck, thoracic and abdominal CT. Her identical twin sister (A, confirmed by zygosity studies) was negative for the variant on a buccal swab and not clinically evaluated. One-time CTA was recommended in A for herself since mosacism could not be ruled out and consideration to have her children evaluated. Their mother (76, grandmother of proband) had a reported family history of LDS-like features in a 2nd degree relative but did not carry the variant.

This case raises interesting questions on not only post-zygotic division origin of the TGFB3 variant but also implications of mosaicism. M's clinical presentation suggests a higher proportion of the variant in different tissue types and gonadal presence leading to 2 non-mosaic positive children. The implications for her twin (and children) is less clear. The absence of the TGFB3 variant in her buccal sample has made them less motivated to pursue clinical evaluation but concern still exists for a possible LDS phenotype in case she is also mosaic and the risk to her children if she had gonadal mosaicism.

CASE REPORT: LONGEST REPORTED SURVIVAL FOR AUTOSOMAL RECESSIVE CUTIS LAXA TYPE 1B IN 31-YEAR-OLD PATIENT WITH SEVERE AORTOPATHY AND EXTENSIVE ARTERIAL TORTUOSITY

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Abstract

Homozygous and compound heterozygous variants in the *EFEMP2* (alias *FBLN4)* gene are associated with autosomal recessive cutis laxa type 1B (ARCL1B). This is a rare connective tissue disorder characterized by cutis laxa, dysmorphic features, joint laxity, and severe cardiovascular manifestations, including arterial stenosis, arterial tortuosity, and aortic aneurysm. The cardiovascular disease results in high lethality in early childhood, with ~90% mortality by age 4. Herein, we present the oldest reported case of ARCL1B in a 31-year-old male with a homozygous variant in *EFEMP2*. This patient was postnatally diagnosed with severe aortic coarctation (CoA) and bilateral branch pulmonary artery stenosis. In infancy, he was clinically diagnosed with arterial tortuosity syndrome due to profound tortuosity of the intracranial arteries, common carotid arteries, right innominate artery, vertebral arteries, and thoracic aorta. He underwent end-to-end CoA repair at age 29 days, followed by repeat repair with left subclavian flap at 9 weeks. By age 8, he developed severe ascending aortic dilation, for which he underwent ascending aortic replacement with a 20 mm Dacron graft, composite graft augmentation of the transverse arch, resection of descending aortic arch aneurysm, and aortic arch advancement. His only other intervention was a left pulmonary artery balloon dilation and stent placement at age 20. He has no history of arterial dissection or rupture. At age 30, he presented to our cardiovascular genetics clinic, where his physical exam revealed enophthalmos, sagging cheeks, long beaked nose, long philtrum, and microretrognathia. Genetic testing revealed the homozygous variant in *EFEMP2* (c.835C>T, p.Arg279Cys). This report broadens the clinical presentation of ARCL1B to include a patient with the longest survival reported in the literature to date.

Moreover, it offers insight to consider ARCL1B in patients with concomitant arterial stenosis, aneurysm, and tortuosity, and highlights the importance of genetic testing to provide molecular confirmation of the diagnosis.

CARDIOVASCULAR OUTCOMES AND SURVIVAL IN PATIENTS WITH EARLY-ONSET MARFAN SYNDROME

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Introduction

Little is known about contemporary outcomes in early-onset (neonatal) Marfan syndrome.

Objectives

Describe cardiovascular outcomes and survival in early-onset Marfan syndrome.

Methods

Patients included from MAC and CLARITY with the diagnosis of early-onset Marfan syndrome, defined as severe manifestations at early age, an *FBN1* variant, and an early-onset score >16. Cardiovascular manifestations, interventions, and survival is described.

Results

Of 13 included patients, 9 were male (69.2%). Median age at diagnosis was 8 months (range 0, 2.5 years) and median age at follow-up was 6.5 years (IQR 0.67, 10.4). Genetic testing confirmed 69.2% (N=9) with variants in the high risk region of *FBN1*. The remaining 4 patients harbored variants in exons 24 and 34, an intronic splice site variant, and a deletion encompassing exons 7-30. Median aortic root z-score at diagnosis was +7.4 (range +3.6, +21.6). Five subjects (38.5%) underwent aortic root replacement at a median age of 2.9 years (range 1.8, 6 years). Eleven (85%) had moderate-to-severe mitral valve disease, for which eight (61.5%) underwent repair/replacement at a median age of 1.5 years (range 0.2, 15.8 years), and 23.1% (N=3) died before intervention. At last follow-up, 38.5% (N=5) were deceased, in three patients due to cardiorespiratory failure at ages 10 days, 18 days, and 8 months (All unoperated), one due to complications of a staph infection at age 6 months, and one due to complications after a type B aortic dissection at age 10 years. The remaining 61.5% (N=8) were living at a median age of 9.0 years (range: 4.0, 21.0).

Conclusion:

In our cohort, the median age of patients with early-onset Marfan syndrome is higher than previously reported ages of death, suggesting patients are living longer. The high rate of successful mitral and aortic surgery may be contributing to this increased lifespan.

IMPACT OF OBESITY ON CLINICAL OUTCOMES IN MARFAN SYNDROME

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Introduction

Patients with Marfan syndrome (MFS) are described as tall and thin with a recognizable phenotype. However, individuals with MFS are not immune to the global obesity epidemic. Thus, obesity may be an underappreciated factor in cardiovascular health in this population.

Objectives

We sought to characterize the frequency of obesity in a Marfan population and to examine its clinical impact in this population.

Materials and Methods

We performed a retrospective cross-sectional study of individuals with MFS evaluated at Washington University School of Medicine from 2015 to present. Clinical features and aortic outcomes were compiled from chart review and patient interviews. BMI categories were: 1) underweight and normal weight; 2) overweight; 3) obese and morbidly obese. Significance testing utilized Cochran-Armitage testing for categorical variables.

Results

313 individuals (mean age 43.2 $\pm$14.8 years) were included, with 157 men (50.2%). Mean BMI was 26.4 $\pm$ 6.5 kg/m^2 with 54% of the cohort overweight or heavier. Hypertension (HTN) was more frequent in overweight or obese compared to underweight/normal individuals, but did not reach statistical significance. Angiotensin- receptor blocker use was significantly associated with higher BMI categories ($p = 0.003$). Aortic surgery occurred in 45.1% of the entire cohort and rates were similar across BMI groups. Aortic dissection (AoD) was more common in the obese/morbidly obese (30%) and overweight (28.1%) cohorts compared to the normal/underweight group (18.7%, $p = 0.04$). Type B AoD occurred in 9% of normal/underweight patients, 15.7% of overweight patients, and 21.3% of obese patients ($p = 0.01$).

Conclusion

Obesity is common in individuals with MFS and has important implications for disease outcomes as increasing BMI associates with a higher frequency of HTN and history of AoD. Alternatively, the Marfan diagnosis and its aortic disease may lead to adoption of an unhealthy sedentary lifestyle that associates with increasing BMI.

A CASE SERIES OF LOEYS-DIETZ SYNDROME: HOW CAN WE IMPROVE THE PRACTICAL UTILITY OF DNA DIAGNOSTICS FOR SURGICAL PURPOSES?

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Introduction

Loeys-Dietz syndrome (LDS) is characterized by more severe thoracic aortic disease (TAD) than other connective tissue disorders (CTDs). The definite diagnosis of LDS can be established exclusively by genetic testing. This, along with strong overlapping of LDS symptoms with those of other CTDs, leads to significant underdiagnosis of LDS in patients with aortic aneurysms.

Objectives

To present the first LDS case series from Russia, to discuss the genotype-phenotype correlations and practical utility of these results.

Materials and Methods

In 10 years of genetic counseling for patients with TAD, we have found 6 genetically confirmed cases of LDS. Genetic testing was performed by next generation sequencing (NGS) followed by Sanger validation of detected variants.

Results

All 6 probands presented with remarkable symptoms of TAD, while extracardiac manifestations were significantly diverse. None had symptoms reported to be unique for LDS (hypertelorism, bifid uvula, cleft palate). Prevalent genetic findings were in the *TGFB2* and *TGFBR2* genes (2 and 2 of 6 probands, respectively). One proband had a *TGFBR1* variant and one had a *TGFB3* variant. One of *TGFB2*-positive patients was compound heterozygote, and one proband with *TGFBR2* variant had an additional finding of uncertain significance in the *COL3A1* gene. The rest probands were heterozygous. In all cases, except one, the diagnosis of LDS was established retrospectively after aortic surgery. The operated patients demonstrated poor tolerance to surgery, increased blood loss and severe postoperative complications with tendency to further vessel dissection.

Conclusions

The LDS patients demonstrate higher risk of aneurysm progression and early rupture and are more prone to postoperative complications in comparison with other CTDs. Meanwhile, our results indicate a common underestimation of surgical risks in LDS. We believe that low recognition of LDS in routine surgery may be partially overcome by accumulating the data on genotype-phenotype correlations and informing the surgeons.

FAMILY HISTORY OF AORTIC DISSECTION IN PATIENTS WITH A *FBN1* PATHOGENIC VARIANT

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Introduction

Guidelines recommend to lower the surgical prophylactic threshold diameter in patients with Marfan Syndrome when a family history of aortic dissection (AD) is present.

Objectives

To evaluate whether an AD in the family is a risk marker for AD in patients with a *FBN1* pathogenic variant.

Material and Methods

Retrospective study of patients coming to the French reference centre carrying a *FBN1* pathogenic variant. Patients with an AD within the family were compared with patients without.

Results

The personal risk for AD was similar in patients with and without an AD within the family. This was true when all 1700 patients with a *FBN1* pathogenic variant were included : 38 AD in 481 patients with AD in the family (7.9%) versus 107 AD in 1219 patients without AD in the family (8.8%). This was also true when only the 1250 patients with familial forms were included : 38 AD in 481 patients with AD in the family (7.9%) versus 62 AD in 767 patients without AD in the family (8.0%).

The personal risk for aortic prophylactic surgery was also similar in patients with and without an AD within the family : 18% vs 19% when the 1700 patients are considered; 18% vs 16.8% when the only patients with familial forms are considered. Ages at the time of AD or surgery were also similar.

75% of families with AD presented only one occurrence of dissection. Presence of AD within families was related to the number of affected members in the family.

Conclusion

In patients with *FBN1* pathogenic variants, the personal risk for aortic dissection was similar in patients with and without a family history of aortic dissection. Family history of aortic dissection is therefore not a risk marker for aortic dissection in this population.

INDIVIDUALIZED AORTIC ROOT PREDICTION IN PEDIATRIC MARFAN SYNDROME

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Introduction:

Marfan syndrome is associated with progressive aortic root dilation, although rates of change vary during different periods of growth in a child. While multiple population indexed means have been published for children, data predicting an individual child's aortic root trajectory have been limited.

Objectives

To create a validated prediction model for aortic root growth in children with Marfan Syndrome.

Materials and Methods

Patients in the test cohort were identified from an institutional database from 6/1996-1/2022 containing 1456 transthoracic echocardiograms (TTE) in 178 subjects. The validation cohort was from the Pediatric Heart Network (PHN) Marfan study (2932 TTEs in 599 subjects), Inclusion criteria were 1) Marfan Syndrome meeting Ghent 2010 criteria and 2) >1 TTE performed at age <25 years. TTEs after aortic surgery were excluded. Mixed linear regression models were used to create a prediction model based on prior aortic root size, age, and sex. Predicted root sizes were then compared to observed values in the test and validation cohorts using Pearson correlation accounting for correlation of subject means.

Results

The test model suggested slope changes throughout childhood and puberty. In the test cohort the correlation coefficient (R) was 0.993 between observed and predicted root size at the first follow-up (FU) TTE, with mean difference +0.1 mm (95%CI 0.0,0.2). In the validation cohort, R= 0.988 and mean difference was -0.2 mm (95%CI -0.1,-0.3) for the first FU, and R=0.988 with a larger mean difference of -1.4 mm (95%CI -1.4, -1.5) at second FU.

Conclusions

We have created a validated prediction model for estimation of aortic root growth in children with Marfan Syndrome. The slightly more negative values in the validation cohort from a clinical trial suggest the next step should be to add medication effects to the model.

The NIH/NHLBI Pediatric Heart Network Marfan Study dataset was used in preparation of this work. Data were downloaded from http://pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets.aspx on 05/10/2022

LOEYS-DIETZ SYNDROME: NATURAL HISTORY, CLINICAL SPECTRUM, AND ASSESSMENT OF OUTCOMES—THE MAYO CLINIC EXPERIENCE

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Introduction: Loeys-Dietz syndrome (LDS) is a rare, autosomal dominant disease characterized by distinct physical and circulatory manifestations.[1,2,3] Each genetic subgroup within the disease spectrum has been associated with specific features and unique progression.[4,5] Given the rarity of LDS, there have been few published large and descriptive cohorts.

Objectives: We aim to describe the characteristics and outcomes of LDS patients evaluated at Mayo Clinic.

Materials/Methods: All Mayo Clinic patients with a genetically confirmed diagnosis of LDS were identified by database inquiry. Clinical findings, patient outcomes, and genetic mutations were abstracted and reviewed. Left-truncated survival analysis was conducted for outcomes age at death and age at first dissection (aortic or other artery). Patients were considered to have entered the risk set at the date of their first Mayo Clinic visit. Left-truncated Cox regression was used to test for differences in outcomes by genetic subgroup (TGFBR1/TGFBR2 [n=69], TGFB2/TGFB3 [n=17], SMAD [n=34]) and by sex.

Results: We identified 120 (61 female, 51.3%) LDS patients with confirmed genetic testing. Mean age at diagnosis (36.2-42.5 years), prevalence of aortic root aneurysm (52.9-72.5%), and other aortic aneurysms (ascending 31.3-50.0%; descending 11.6-17.6%) were similar across genetic subgroups. Common medical co-morbidities were migraine headache, asthma, and other allergic syndromes (i.e. seasonal rhinitis, drug allergy). Patients with SMAD3 mutation were significantly more likely to have a family history of sudden cardiac death (44.1% p=0.007).

Overall survival (60.2-79.4 years) and age at first dissection (49.4-51.9 years) were similar across genetic subgroups and between sexes. While aortic dissection rates were also similar across subgroups (12.5-24.2%), patients with SMAD3 mutations were significantly more likely to develop dissection of other arteries (38.5% p=0.015).

Conclusion: In our retrospective study, we show prevalence of several clinical features and outcomes frequently observed in various genetic subtypes of LDS.

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RISK OF TYPE B DISSECTION IN MARFAN SYNDROME: THE CORNELL AORTIC ANEURYSM REGISTRY

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Introduction

Life expectancy in patients with Marfan syndrome (MFS) has improved due to advances in detection and care, resulting in a decrease in type A dissections. As a corollary, rates of type B dissections, the risk factors for which remain largely uncertain, appear to be increasing.

Objectives

We explore the phenotypic, clinical, imaging, and genetic-based determinants of type B dissection risk in patients with MFS enrolled in our large single-center Cornell Aortic Aneurysm Registry.

Materials and Methods

Relevant demographic, anthropometric, cardiovascular disease, surgical history factors, pregnancy history, and aortic dimensions were compared between MFS patients with and without type B dissection.

Results

Of 329 MFS patients (150 men and 179 women), 47 (14%) experienced a type B dissection (versus type A dissection in 10.9%). After exclusion of those with type 1 dissection, patients with versus without type B dissection were older (mean 51±12 versus 42±16 years, $p<0.001$), and more likely to have undergone elective root replacement (83 versus 43%, $p<0.001$), 55% of whom had elective surgery a mean of 14 years before the type B dissection and 21% of whom had elective surgery afterward. Valve replacement was more common than valve-sparing repair in those with type B dissection (62% versus 22%, $p<0.001$). 39 (83%) patients were aware of their MFS diagnosis prior to type B dissection. Patients with type B dissection were also more likely to have undergone mitral valve surgery (31 versus 11%, $p=0.003$).

Conclusion

In our contemporary cohort, type B dissections are more common than type A. The association of type B dissection with increased likelihood of elective root replacement and mitral surgery suggests a more severe phenotype. Altered flow dynamics, especially following valve replacement rather than sparing, may be an additional factor. Genetic-based determinants of dissection risk are currently being studied in this patient cohort.

CLINICAL HISTORY AND OUTCOMES OF PATIENTS CARRYING *TGFB2* GENE VARIANTS

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Introduction: Rare heterozygous variants in *TGFB2* gene, encoding transforming growth factor β2, are associated with heritable thoracic aortic disease (HTAD).

Objectives: To determine the clinical phenotype and longitudinal outcomes among patients harboring *TGFB2* mutations.

Materials and Methods: The Montalcino Aortic Consortium (MAC), a multicenter international registry from centers specializing in HTAD, was utilized to identify 84 patients from 36 families with documented pathogenic/likely pathogenic variants in the *TGFB2* gene and their obligate carriers.

Results: Among 84 patients, 36% (30/84) were probands with slight male predominance (61%,51/84). The most common phenotypic features were joint hypermobility (57%,28/49), doughy skin texture (54%,22/41), pes-planus (53%,30/56), high-arched palate (44%,25/57), retrognathia (43%,24/56) and prominent skin striae (43%,25/58). Aortic root dilation was reported in 81% (65/80) patients and was more commonly present among males (OR versus females 6.6, 95%CI 1.9-23.5, p=0.0025). Arterial tortuosity was reported in 36%(24/67), mitral valve prolapse in 14%(11/76) and bicuspid aortic valve in 7%(5/71) patients. At a median follow-up age of 33 years (IQR 15-44) and a cumulative follow-up of 2550 years, 36% (29/80) patients had an aortic dissection or preventative/elective repair; and 6% (5/80) had an extra-aortic arterial event. Composite aortic event-free survival was 96% at 25 years and 46% at 50 years. Type-A dissection occurred at a rate of 3.4/1000 person-years with a greater risk among males versus females (4.48 vs 1.9/1000 person-years, p=0.038) and those harboring missense variants outside of RKKR-motif (8/1000 person-years, p <0.001) in comparison to within RKKR-motif and variants leading to premature-termination-codon (PTC). A pregnancy was reported among 69% (22/32) females with 37 completed pregnancies and no known aortic or extra-vascular events.

Conclusions: Patients with *TGFB2* variants causing HTAD seem to exhibit a milder phenotype then seen in those with *TGFBR1/TGFBR2* variants. Type-A dissections occur more frequently among males and those harboring missense variants outside RKKR-motif.

AORTIC DISSECTION IN TGF-β RELATED VASCULOPATHIES: RESULTS FROM THE MONTALCINO AORTIC CONSORTIUM (MAC)

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Introduction: The management and outcomes of acute aortic dissection in patients with TGF-β vasculopathies are poorly understood.

Objectives: To examine the clinical outcomes of patients with TGF-β vasculopathies after acute Type A or B aortic dissection.

Materials/Methods: Patients with TGF-β vasculopathies enrolled in the Montalcino Aortic Consortium (MAC) who suffered an aortic dissection were included. Clinical features and surgical management were examined. Long-term outcomes of interest were survival and need for aortic reintervention following dissection.

Results: Of the 532 patients with TGF-β vasculopathies enrolled in MAC, 105 (19.7%) experienced an aortic dissection (Type A: n=75 (71.4%) vs. Type B: n=25 (23.8%); unknown Stanford classification: n=5 (4.7%). Pathogenic variants in the following genes were observed in patients with dissection: *TGFBR2* (n=35, 33.3%), *TGFBR1* (n=13, 12.3%), *SMAD3* (n=36, 34.3%), *TGFB2* (n=18, 17.1%), and *TGFB3* (n=3, 2.8%). Mean age at the time of dissection was 42.2±14 years and 46.6% were female. All patients with Type A dissection underwent immediate proximal aortic repair, whereas the majority (84%) of Type B dissections were treated medically, with a small proportion (n=4, 16%) receiving endovascular repair at the time of dissection. Median follow-up duration for the cohort was 5.8 (IQR 1.2-8.5) years. Survival at 10 years was 64.1% for those with Type A dissection vs. 86.3% after Type B dissection (log rank p=0.134). Following both Type A and Type B dissection, patients with TGF-β vasculopathies experienced high rates of aortic reoperation or reintervention (Kaplan-Meier at 10 years for Type A 68.0% vs. Type B 38.3% (log rank p=0.536).

Conclusions: In patients with TGF-β vasculopathies, survival after acute Type A or Type B dissection was poor, and patients experienced high rates of aortic reinterventions during follow-up. These observations confirm the need for lifelong surveillance imaging in these patients.

ORGANIZATION OF HTAAD PATIENT CARE IN NORWAY

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Introduction

In 2017 Oslo University Hospital started a multidisciplinary clinic for HTAAD patients in collaboration with TRS National Resource Centre. According to a prior study, patients indicated a high degree of satisfaction with this clinic, whereas controls who received regular follow-up reported poor coordination of medical follow-up.

Objectives

Expansion of the clinic for a broader approach to the patients' complaints and establishing a national and international network.

Materials and Methods

The clinic is led by a vascular surgeon and coordinated by a nurse, both working at the Department of Cardiothoracic Surgery. On the first consultation a surgeon, clinical geneticist, physiatrist, cardiologist / pediatric cardiologist and the nurse are present. Other affiliated members (ophthalmologist, radiologist or obstetrician) are included according to demand. The clinic was recently expanded with an additional day for selected patients who require other health care professionals: physiotherapist, special teacher in physical education, psychologist, occupational therapist and social worker. After evaluation, patients are referred to a group-based 4-week rehabilitation program when needed. All Norwegian patients have digital access to their medical records. The clinic has been a VASCERN member since January 2022, with an established national network. Consenting patients are included in a register with demographic and clinical variables as a foundation for future research and quality control.

Results

We have seen 241 patients by May 2022, and 238 are included in the register. Five patients have been to the recently expanded consultation since January 2022, and the first four HTAAD patients have been at the cardiovascular rehabilitation clinic in May 2022.

Conclusion

We intend to start a study similar to the evaluation of the original multidisciplinary clinic in the near future.

ARTERIAL TORTUOSITY SYNDROME: A LONGITUDINAL ASSESSMENT OF CARDIOVASCULAR FEATURES

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Introduction

Arterial tortuosity syndrome (ATS) is an ultrarare arteriopathy caused by pathogenic biallelic variants in *SLC2A10* leading to tortuosity, elongation, and dilation of vessels, and pulmonary artery (PA) stenosis. No studies to date have evaluated the progression of cardiovascular features, including aortic root (AR) and ascending aorta (AA) dilation.

Objective

To evaluate trends of cardiovascular features of those with ATS, particularly the rate of dilation of AR and AA over time.

Methods

We conducted a retrospective cohort study of patients followed either clinically or through a prospective research study with ATS, defined by homozygous or compound heterozygous *SLC2A10* variants with consistent phenotypes, from 2000-2022.

Cardiovascular imaging, medications, and interventions were reviewed. AR and AA measurements were collected from echocardiographic reports and z-scores were calculated. Dilation was defined as z-score > +2. Slopes were calculated using mixed linear regression.

Results

Nine subjects (7 males) aged ~1 month-16 years at diagnosis were included. AR dilation was noted in 89% of patients (maximum AR z-score range -2.28 to +13.29). From available data, 3 of 8 had AA dilation (maximum AA z-score range -3.14 to

+22.71), and 3 of 6 had main or branch PA stenosis at a given point. AR mean annual change was 1.09 mm/year, with z-score change 0.00/year (95%CI -0.08, 0.08). AA mean annual change was 1.01 mm/year, with z-score change +0.09/year (95%CI -0.05, 0.22). Three patients had cardiovascular interventions, of which 2 underwent multiple bilateral PA angioplasties and stenting for PA stenosis, and 1 had an aortopexy. Five patients were prescribed beta-blockers, losartan, or both. One patient was prescribed amlodipine for hypertension. None had aortic dissection.

Conclusions

In conclusion, AR and AA dilations are common and persist in ATS but with stable z-scores similar to other aortopathies. Larger sample size investigations may further elucidate the role of medications in ATS.

PRESENTATION AND MANAGEMENT OF ARTERIOPATHY IN MARFAN SYNDROME

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Introduction

Marfan syndrome (MFS) is a known cause of genetic aortopathy, however, there is a paucity of data regarding non-aortic arteriopathy associated with MFS.

Objective

We aim to evaluate the prevalence, presentation, and management of arteriopathy in MFS.

Materials and Methods

Retrospective single system study of patients with clinical or genetic diagnosis MFS presenting between 1992 and 2022. All patients with arteriopathy not related to aortic dissection were selected for analysis. Arteriopathy included arterial (non-aortic) aneurysms, pseudoaneurysms, dissections, and rupture. Data abstracted included demographics, method of MFS diagnosis, associated aortic pathology, arteriopathy anatomic location, surgical repairs, and outcomes.

Results

Of the 394 patients with MFS, 39 (10%) had involvement in 104 arteries (64.1% male, 20.5% non-White, mean age at diagnosis 41.6±12.8 years). Genetic testing confirming *FBN1* pathogenic variants was performed in 19 patients (48.7%), the rest were diagnosed clinically. Arteriopathy included aneurysm (N=80, 76.9%), dissection (N=13, 12.5%), pseudoaneurysm (N=6, 5.8%), and rupture (N=2, 1.9%). The most common site was iliac artery aneurysms (N=22, 21.6%), followed by subclavian artery aneurysms (SCAA, N=18, 17.3%). Operative repair was performed for 20 arteries in 12 patients. The most common operative repair was open iliac repair (N=4, 20%), open repair of SCAAs (N=3, 15%), and open repair of internal carotid aneurysms (N=3, 15%). There was no arterial related operative mortality. All-cause mortality was 43.5%: 8 were aortic related and one arterial related mortality due to a ruptured gastro- duodenal artery aneurysm.

Conclusions

Among patients with MFS, one in ten have involvement outside the aorta. Most commonly, aneurysms occur in the subclavian or iliac arteries. Surveillance of these arteries is warranted in MFS. Operative repair can be undertaken safely in this population.

RESEARCH PRIORITIES AMONG PATIENTS WITH SYNDROMIC HERITABLE AORTOPATHIES WITH AND AT RISK FOR AORTIC DISSECTION

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Introduction

The AD Collaborative built a research infrastructure to facilitate patient centered outcomes research (PCOR) and identify priorities for aortic dissection (AD) research. Little is known about what patients with syndromic heritable aortopathies find most important from a research perspective.

Objectives

We report the PCOR priorities identified by patients with syndromic heritable aortopathies including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Vascular Ehlers-Danlos syndrome (VEDS).

Materials and Methods

The foundational engagement work identified 7 PCOR topic: Education, Genetics, Pregnancy, Medications, Mental health, Surgery, and Telemedicine. Evidence gaps were identified and 8 PCOR research questions were designed. An anonymous research prioritization survey was disseminated from 11/22/2021 to 2/28/2022 globally to the virtual research network of patients to rank the research questions. Responses by patients with syndromic heritable aortopathies were selected for analysis. The percentage of respondents ranking each question among their top three priorities was analyzed to derive the final ranked order of research questions.

Results

A total of 239 respondents met inclusion criteria: 139 with MFS, 61 with LDs, and 39 with VEDS (mean age 47.4±12.7 years, 66.9% in the United States). Educational resources for doctors was the highest ranked research priority (61.1%). Other highly ranked topics were genetic testing for underlying AD risk factors (51.9%), educational resources for patients (48.5%). The timing of surgery, impact of exercise, and mediations ranked lower (45.2%, 38.9%, and 38.5% respectively). Mental health and telehealth research ranked last (12.6% and 3.3%).

These research priorities were no different when compared to patients with aortic dissection who did not have a genetic diagnosis.

Conclusions

Through stakeholder engagement, we identified the PCOR priorities of the AD community and found that research priorities of patients with syndromic heritable aortopati3es closely align with patients without such diagnosis. Educating physicians on AD was ranked highest among all research priorities.

EVALUATING THE ASSOCIATION BETWEEN SEX, RACE, AND AORTIC OUTCOMES IN MARFAN SYNDROME

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Introduction

Marfan syndrome (MFS) is associated with aortic root aneurysms and aortic dissection (AD). Cross-sectional analysis of the GenTAC Registry suggested males are more likely to undergo prophylactic root repair (though adjustment for body surface area [BSA] eliminated this association) and found no significant difference in AD prevalence.

Objective

We aim to characterize sex and race mediated differences in aortic pathology attributable to MFS.

Materials and Methods

Retrospective review of patients with clinical or genetically confirmed MFS presenting to a single health care system between 2000 and 2020. Demographics, aortic repair and aortic dissection data were abstracted. Mann-Whitney U and chi-squared tests were used for continuous and categorical variables, respectively. Cox proportional hazards modeling was employed for time-to-event analysis.

Results

In a cohort of 393 patients meeting inclusion criteria, 44.3% were female (n=174) and 76.3% were white. In univariate analysis, aortic root repair was more common in males (HR 2.03, 95% CI 1.50-2.73, p<0.001). There was no difference in aortic dissection (HR 1.26, 0.85-1.87), though males were younger (median 34 vs 41 years; p=0.027). BSA, larger in males (2.2 vs. 1.9 m^2, p<0.001), was associated aortic root repair (HR 2.03, 1.50 - 2.73, p < 0.001) but not AD (HR 1.59, 0.81-3.13). Black race was associated with AD (HR 3.04, 1.79-5.17, p<0.001) but not aortic root repair (HR 0.98, 0.59-1.62). Multivariable models, including race and BSA, demonstrated no association between sex and AD (HR 1.04, 0.65-1.66), though Black race remained significant (HR 3.15, 95% 1.81-5.49, p<0.001). Male sex was associated with aortic root repair (HR 2.00, 1.40-2.86, p<0.001) but BSA became non-significant.

Conclusions

Contrasting with the GenTAC analysis, male sex remained associated with earlier aortic root repair after adjustment for BSA, which may represent a biological mechanism or disparity. Association between Black race and AD is concerning for disparity in care.

DISTAL AORTIC REPAIR POST AORTIC DISSECTION IN HERITABLE THORACIC AORTIC DISEASE PATIENTS WITH *ACTA2* PATHOGENIC VARIANTS: RESULTS FROM THE MONTALCINO AORTIC CONSORTIUM (MAC)

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Introduction

Outcomes of aortic dissection (AD) in ACTA2-related aortopathies are poorly understood.

Objectives

To examine the clinical outcomes of AD in patients with *ACTA2*-related aortopathies enrolled in the Montalcino Aortic Consortium.

Materials/Methods

Individuals with *ACTA2* pathogenic/likely pathogenic variants were selected for analysis. Proximal (root, ascending aorta, or arch) and distal (descending thoracic and abdominal) aortic surgical repair after ADs was examined. Distal aortic repair included thoracic endovascular repair (TEVAR). Primary outcome was timing to distal aortic repair post AD.

Results

A total of 145 individuals were enrolled (50.3% male, median age of enrollment 42 [IQR 27.5-55.5] years). AD occurred among 58 (40%) patients (63.8% male, median age of AD 36 [IQR 27.2-51.1] years). Type A (N=42) was more common that type B AD (N=15) and one AD had an unknown type. Genetic diagnosis was established in only 5 (8.6%) patients prior to AD. There were no differences in AD age between type A and B (39.2±15.9 vs 36.7±11 years, P=.576). Proximal aortic repair was performed in 85.7% of type A and 33.3% of type B cases (p<.001). Distal aortic repair was performed in 18 (31.6%) cases at a median interval of 8.3 [IQR 1.2-10] years for a median maximum aortic diameter of 57 [IQR 35.3-60.7] mm. This repair was more common among patients with type B AD compared to type A (53.3% vs 23.8%, p<.035). TEVAR was utilized in 7 repairs: 2 type A with proximal landing zone in the arch, 5 type B of which 3 had total arch repair).

Conclusions

While type A AD is more common than type B AD among patients with ACTA2 related aortopathies, those with type B AD are more likely to require distal aortic repair.

POPULATION MANAGEMENT FOR AORTIC DISEASE AND IMPROVING CARE WITH ARTIFICIAL INTELLIGENCE

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Introduction

Patients with heritable thoracic aortic diseases (HTAD), are at highest risk for thoracic aortic aneurysms (TAA) and dissections (AD). Most AD-related deaths are preventable if at-risk individuals are identified and optimally managed. Within Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system caring for 4.5 million persons, we developed a robust TAA population management program for 15,000-20,000 patients. However, because HTAD is under-recognized by most physicians, some patients may not be diagnosed or referred to specialty clinics despite having high-risk features.

Objectives

Develop novel methods to identify HTAD patients from electronic medical records (EMR) who may be undiagnosed.

Materials and Methods

We are developing and validating algorithms using a combination of administrative codes and natural language processing (NLP) techniques applied to unstructured EMR data to identify (1) all existing HTAD patients, and (2) potentially undiagnosed HTAD patients. After first developing reproducible combinations of EMR variables that are sensitive and specific for identifying known HTAD patients (i.e., diagnostic codes or NLP results for “Marfan syndrome”, “Loeys-Dietz syndrome”, and/or a constellation of phenotypic features such as “ectopia lentis”, “dural ectasia”, etc.), we will conduct manual chart review to ascertain the optimal EMR signature. The final algorithm will integrate combinations of skeletal, craniofacial, cutaneous and cardiovascular manifestations, will be tested on a sample of patients to assess positive and negative predictive value, and identified HTAD patients will enter the population management program for evaluation.

Results

This study is a concept proposal currently in preliminary stages within KPNC. Pilot results will be available by the time of Science in Paris. Would aim to present the algorithm methods and the details of the KPNC TAA population management program.

Conclusion

Utilizing a “big data” approach may lead to better identification and diagnosis for HTAD patients, leading to improved care and saving lives.

FATAL AND NON-FATAL AORTIC DISSECTIONS DOCUMENTED IN THREE CHILDREN WITH *ACTA2* VARIANTS

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Introduction

Aortic dissection (AD) in children is rare, and typically described in syndromic conditions.

Objective

Report on 3 nonsyndromic male children with a pathogenic *ACTA2* variant and AD.

Materials and Methods

Medical records, autopsy reports, and genetic testing were reviewed for all cases of dissection in children with an *ACTA2* variant.

Results

Patients A-C were ages 14-16 years at first AD. Two died following their event (A and B), neither of whom knew their diagnosis. The surviving patient (patient C) was diagnosed at 15 yo, given maternal and paternal history of AD (*ACTA2* p.R212Q variant maternally inherited, paternal etiology unknown). Patients A and B had a history of patent ductus arteriosus (PDA). Both patients that died presented to the emergency department for significant abdominal pain and emesis, were discharged home, and represented with worsened symptoms. Patient A's cause of death was bilateral hemothoraces due to late recognition of a ruptured Stanford Type B AD extending to bilateral iliac arteries. A cardiac echocardiogram for patient B revealed a Stanford type A acute AD, which he underwent aortic arch reconstruction with hemiarch replacement for but died within 24 hours. Postmortem testing for patients A and B revealed a maternally inherited pathogenic *ACTA2* variant (p.R149C and p.R258C, respectively). Patient C presented after presented with tachycardia and differential arm blood pressures, which the family knew warranted emergent evaluation given his known diagnosis. Imaging demonstrated a Type A dissection for which he received emergent root reconstruction and resection of the descending aorta.

Conclusion

Reports of children harboring *ACTA2* variants with ADs are rare and are likely underappreciated by healthcare providers due to its rare incidence of AD in children and lack of syndromic features in affected individuals. History of PDA and familial history of AD may be helpful clinical markers to identify these children.

PILOT STUDY OF THE EFFECTS OF MODERATE INTENSITY EXERCISE ON CHILDREN AND YOUNG ADULTS WITH MARFAN SYNDROME

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Introduction: Given anecdotal reports of aortic dissection, limited evidence from in-vitro studies, and theoretical concerns, the majority of patients with MFS are restricted from certain physical activities. Recent animal studies have demonstrated cardioprotective effects of a moderate intensity exercise program in mice with Marfan Syndrome.

Objectives: To determine the impact on cardiovascular function and emotional status following a supervised moderate intensity exercise program.

Materials & Methods: Patients with Marfan syndrome age 12-21 years were prospectively recruited. Participants underwent a supervised, moderate-intensity exercise protocol via virtual sessions. Baseline and post-intervention testing included exercise stress Test, cardiac MRI, endothelial function, and carotid-femoral applanation tonometry and mental health screening (DASS-21). Due to poor compliance, the intervention was modified to add virtual partnered exercise sessions and shorten the intervention to 8 weeks. Given the protocol change, the decision was made to perform a mid-study assessment. This report is for the first 10 subjects.

Results: In the first group (n=5), 1 patient was lost to follow-up, and 2 did not participate in the intervention, for a failure rate of 60%. After modification, all subjects completed the study (n=7). Five participants were female with a median age of 20.3 years. The primary outcome, Max VO2 significantly increased and systolic blood pressure at rest decreased, while aortic root dimension and z-score did not change. Stress scores also decreased. Left ventricular ejection fraction decreased although maintained in the normal range, and this appeared to be driven by a decrease in left-ventricular end-diastolic volume without a decrease in end-systolic volume.

Conclusion: These pilot data suggests that there is potential for a moderate intensity exercise intervention to improve cardiovascular fitness without accelerating aortic root growth, although a larger sample size is needed. We also noted that the addition of virtual partnered exercise sessions improved compliance in this cohort.

QUALITY OF LIFE AND VO2 IN CHILDREN AND YOUNG ADULTS WITH MARFAN AND RELATED CONDITIONS

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Introduction

Marfan syndrome (MFS) is characterized by the association of multisystem damage related to connective tissue fragility. The risk of aortic dissection has diverted attention from significant musculoskeletal damage despite its perceived impact on the patient's quality of life.

Objectives

We have analysed the impact of the disease on the quality of life (QoL) of patients from a young age until early adulthood, and investigated the correlation with the performance at a cardiopulmonary exercise test.

Materials and Methods

This study included 63 Marfan or associated syndrome patients between 5 and 21 years (average 12.4 years). Their responses to the generic health-related quality of life questionnaires PedsQL^{TM} 4.0 and KidScreen were compared with those of a healthy age-equivalent cohort. Socio-demographic parameters were also considered. VO2max, as measured by cardiopulmonary exercise test, was analysed in 28 patients of the Marfan cohort between 7 and 20 years (average 12.6 years).

Results

Preliminary results confirm the disease's significant impact on the life quality of Marfan patients from a young age. The $VO2_{max}$ values were severely impaired in this population, on average reaching 63.8% of the expected values. A correlation between the QoL and cardiopulmonary exercise test performance parameters was demonstrated.

Conclusion

The impact of the Marfan syndrome's multisystemic damage and deconditioning on the patient's QoL is evident from a young age and should not be neglected. Namely, the care provided to patients should include adapted physical activity programs from a young age.

PHYSICAL CAPACITY AND PHYSICAL ACTIVITY IN CHILDREN WITH HERITABLE CONNECTIVE TISSUE DISORDERS (HCTD)

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Background: Health problems in patients with heritable connective tissue disorders (HCTD) are diverse and complex, and might lead to decreased physical activity and physical functioning. However, it is unknown if and to what extent physical capacity and physical activity are affected in children with HCTD.

Objectives: To investigate physical capacity and physical activity in a sample of children with HCTD and subgroups.

Methods: This cross-sectional, multicentre study included 56 children (median (IQR) age: 11.6 (8.8-15.8) years; 59% male), with molecularly confirmed EDS (n=13), Marfan syndrome (MFS) (n=40) and Loeys-Dietz syndrome (LDS) (n=7) and approval from the paediatric cardiologist. Physical capacity was measured as 1) cardiovascular endurance; Fitkids Treadmill Test (FTT), 2) muscle strength; maximal hand grip strength test, and 3) motor proficiency; Bruininsk-Oseretsky Test of Motor Proficiency-2 (BOT-2). Physical activity was assessed by the 1) Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) subscale mobility, and 2) accelerometer-based activity monitor (ActivPAL). Results are shown as mean (SD) Z-scores.

Results: Compared to normative data, children with HCTD showed severely reduced cardiovascular endurance (-3.3;3.2) and a mild to moderately reduced muscle strength (-1.1;1.2). Motor proficiency was not significantly different (-.24;1.0). Physical activity was mild to moderately reduced in terms of mobility in daily functioning (-1.4;1.6) in the total HCTD group. HCTD children were active for 4.4(1.1) hours and inactive for 8.8(1.7) hours/day, and performed 8595.9(3565.1) steps a day.

Conclusion: This study is the first to demonstrate severely reduced physical capacity and physical activity in children with HCTD. A possible explanation for reduced cardiovascular endurance and muscle strength is deconditioning in combination with genetic factors.

INTENSIVE PHYSICAL TRAINING IS SAFE, FEASIBLE AND EFFECTIVE IN CHILDREN WITH HERITABLE CONNECTIVE TISSUE DISORDERS (HCTD): A PILOT STUDY.

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Introduction: Children with heritable connective tissue disorders (HCTD) show reduced physical functioning. Research on the effect of exercise training in children with HCTD is lacking.

Objective: To investigate the feasibility and preliminary effectiveness of an intensive physical training program to improve physical functioning in children 6-18 years with HCTD.

Methods: Ten children with HCTD (Marfan Syndrome n=7, Ehlers-Danlos Syndrome n=2, and Loeys Dietz syndrome n=1) participated after approval from the paediatric cardiologist. Physical functioning in terms of aerobic capacity (Fitkids Treadmill Test (FTT), anaerobic capacity (Muscle Power Sprint Test (MPST), and strength and agility (domain strength and agility of the Bruininsk-Oseretsky Test of Motor Proficiency-2 (BOT-2) were measured at baseline (T0) and after 12 weeks of training (T1). The training program consisted of an intensive tailor made physical training (High Intensity training or Power training) and was conducted 3 times a week for 45 minutes. Three multidisciplinary information meetings were organized to inform the parents. Feasibility was determined by measuring participation rates, adverse events, reached training goals, and rated feasibility on a 10-point scale by parents and children (0= not feasible, 10= very feasible). Preliminary effectiveness was determined by progression (∆) and reliable change index (RCI) in physical functioning.

Results: 9/10 children completed at least 90% of the trainings sessions, no adverse events occurred, and 8/10 children achieved their training goals. Parents and children rated the training program as very feasible (mean (SD) of 8.0(1.3) and 8.0(1.1), respectively). The scores on the FTT (∆=+1.6(1.8) minutes, p=<.001, RCI= 5/10), MPST (mean power ∆=+59,8(96.1) watt, p=.012, RCI=3/10), and BOT-2 (∆=+11(6.7) points, RCI=8/10) improved significantly.

Conclusion: This pilot study demonstrated that a high intensive training program, combined with multidisciplinary meetings, is safe, feasible and effective to improve physical functioning in children with HCTD. These results call for more extensive RCT studies to determine training effects in these children.

EVALUATION OF FITNESS CAPACITIES OF CHILDREN AND YOUNG ADULTS WITH MARFAN AND RELATED CONDITIONS

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Introduction

Early diagnosis of Marfan syndrome (MFS) leads us to a comprehensive approach to the multisystem damage related to connective tissue fragility. Impairment in exercise capacity has a great impact on quality of life (QoL) and rehabilitation programs need to address his ultimate causes.

Objectives

We have analysed fitness capacities of patients from a young age until early adulthood, and analysed the causes of limitation.

Materials and Methods

This study included 28 Marfan or associated syndrome patients between 7 and 20 years (average 12.6 years), with mild aortic dilatation for 50% (mean z-score +2,4), no major valvulopathy, no cardiac impairment and history of pneumothorax for 3 of them; most where under preventive betablocker treatment (93%). All of them performed a cardiopulmonary exercise test (CPET) on step incremental cycloergometer.

Results

All but one patients reached maximum effort. Results confirm the disease's significant impact on the exercise capacity from a young age. The VO2max values were severely impaired in this population, on average reaching 63.4% of the expected values (mean peak of 104 Watts, 72% of expected work), with a limitation occurring in 71% and resulting from peripheral muscle deconditioning beside chronotropic limitation from betablockers (mean heart rate at peak of 163 bpm, 80,7% of the theoretical maximum). No intrinsic cardiac or pulmonary limitation was observed whereas dyspnoea was a major limiting factor in our patients, over muscular fatigue (dotted 6,5/10 vs 5,8/10 respectively). These results were correlated to QoL when compared to a control population.

Conclusion

The impact of the Marfan syndrome's multisystemic damage and deconditioning on the patient's QoL is evident from a young age and should not be neglected. Namely, the care provided to patients should include adapted physical activity programs from a young age.

ADULTS WITH LOEYS-DIETZ SYNDROME AND VASCULAR EHLERS-DANLOS SYNDROME: CROSS-SECTIONAL STUDY OF LIFE SATISFACTION AND WORK PARTICIPATION

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Submitted to the theme: Physical activity and quality of life.

Introduction

There is a lack of knowledge about how potentially life-threatening diseases such as Loeys-Dietz syndrome (LDS) and vascular Ehlers-Danlos syndrome (vEDS) may affect life satisfaction and work participation.

Objective

To study self-reported life satisfaction and work participation among adults with molecularly verified LDS and vEDS.

Materials and Methods

In this cross-sectional study, 70 adults were invited through a National Resource Centre for Rare Disorders. We used validated instruments measuring work participation, life satisfaction, chronic pain, fatigue and anxiety & depression symptoms as well as a study specific questionnaire about disease burden.

Results

52 persons participated, 58% women, aged 18-68 years, (response rate 74%), of whom 34 had LDS and 18 had vEDS. vEDS participants reported higher life satisfaction on most life domains compared with LDS. In both groups, we found highest satisfaction with family life, partner relationship, activity of daily living, and lowest satisfaction with vocation, somatic health and sexual life. High global life satisfaction seemed to be associated with lower fatigue (p=0.002), and/or lower anxiety (p=0.001). Two thirds had retired early or received disability/rehabilitation benefits, and the average age for retirement was 40 years. One third used to be in sedentary work and 10 % heavy manual work. Persons still in work were younger (p=0.014), less fatigued (p=0.035), had less sleep problems (p=0.028), and higher life satisfaction (p=0.001) than those not in work.

Conclusion

Life satisfaction was significantly reduced in adults with LDS and vEDS. Work participation was positively associated with higher life satisfaction. Psychosocial support, counseling on educational choices, as well as relevant workplace adaptations can improve work participation and life satisfaction. More research is warrant.

Based on:

- Adults with Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome: A cross-sectional study of life satisfaction - PubMed (nih.gov)
- Education and employment status among adults with Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome in Norway, a questionnaire based study (planned to submit summer2022)

ADULTS WITH LOEYS-DIETZ SYNDROME AND VASCULAR EHLERS-DANLOS SYNDROME: CROSS-SECTIONAL STUDY OF DISEASE BURDEN, PAIN AND FATIGUE

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Submitted to the theme: Physical activity and quality of life.

Introduction

There is a lack of knowledge on disease burden in adults with these diagnoses.

Objective

Was to study self-reported disease burden, chronic pain and fatigue symptoms among adults with molecularly verified LDS and vEDS.

Materials and Methods

In this cross sectional study, 70 adults registered at the National Resource Centre for Rare Disorders were invited. We used the Brief Pain Inventory, Standardized Nordic Questionnaire, Fatigue Severity Scale, Hospital Anxiety & Depression Scale, and a study specific questionnaire on physical activity and disease burden.

Results

Fifty-two persons (58% women) aged 18 to 64 years participated (response rate 74%), of whom 34 had LDS, and 18 had vEDS. Median age at diagnosis was 34 years (range 18-64). The participants reported severe vascular burdens (68%), multi-organ burdens (48%), chronic pain (79%) and fatigue symptoms (58%). Half developed pain during childhood/adolescence. Sleep problems and high multi-organ burden were significantly associated with *chronic pain (*p=0.004*,* p=0.014*)* and *high fatigue symptoms (*p<0.001*,* p<0.001*).* Higher scores of *fatigue* symptoms was associated with higher cardiovascular burden (p=0.025), higher symptoms of anxiety (p=0.001) and chronic pain (p=0.002). Overall, in our study group, LDS participants reported more disease burden compared to vEDS participants.

Conclusion

In this study, symptoms of chronic pain, fatigue, sleep problems and disease burden seemed to mutually reinforce each other. Initiatives should consider interventions aimed at postponing the onset and reducing symptoms of pain, fatigue and sleep problems, and thus reduce the total disease burden at an early stage in patients with these complex conditions.

Based on:

- Adults with Loeys–Dietz syndrome and vascular Ehlers–Danlos syndrome: A cross-sectional study of health burden perspectives - Johansen - 2020 - American Journal of Medical Genetics Part A - Wiley Online Library
- Pain and fatigue in adults with Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome, a questionnaire based study (in press AJMG)

VASCULAR AND VENTRICULAR RESPONSES TO EXERCISE IN PEDIATRIC MARFAN AND LOEYS-DIETZ SYNDROME

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Introduction

Pediatric Marfan (MFS) and Loeys-Dietz (LDS) Syndrome patients with severe aortic dilatation represent aggressive phenotypes at higher risk for complications. Clinical management includes restricting exercises which promote prolonged cardiac output. However, the impact of prolonged cardiac output on aortic dilatation or MFS/LDS-associated vascular remodeling is unknown. Studying aortic and vascular responses to exercise can elucidate subclinical abnormalities which negatively influence disease progression. Proactive identification of phenotypically high-risk pediatric MFS/LDS patients may reduce long-term adverse aortic events.

Objectives

1. Study aortic and vascular properties in pediatric MFS/LDS at rest and during exercise.
2. Study the association between aortic and vascular responses to exercise and the degree and rate of aortic dilatation in pediatric MFS/LDS.

Methods

50 pediatric MFS/LDS patients (ages 10-17) and 50 age-matched controls will undergo aortic biophysical properties assessment via echocardiography at rest and during exercise. Vascular function will be assessed at rest using Flow-Mediated Dilatation (FMD) and endoPAT, and during exercise using carotid-femoral Pulse Wave Velocity (PWV). During exercise, participants pedal on a semi-supine bicycle at 60rpm against increasing resistance. Exercise concludes at 85% of maximum heart rate or fatigue.

Results

Compared to controls (n=5), MFS/LDS (n=9) have reduced aortic distensibility (**4.4±0.0x10-3mmHg vs. 4.1±0.0x10-3mmHg**, p=0.93), increased stiffness index (**4.5±1.4 vs. 4.6±3.9,** p=0.97), and reduced strain (**13.7±5.2% vs. 13.1±4.7%**, p=0.81). MFS/LDS patients have increased endothelial dysfunction (% change in vessel diameter via FMD: **6.2±3.8% vs. 5.7±2.7%,** p=0.79) and Reactive HypeRémia Index (via endoPAT: **1.8±0.1 vs. 2.0±0.6,** p=0.64). Resting PWV is higher in pediatric MFS/LDS patients **(6.5±0.8m/s vs. 6.1±0.4m/s,** p=0.29**).** Peak exercise reveals a larger increase in PWV for MFS/LDS patients **(7.4±1.2m/s vs. 6.8±0.6m/s**, p=0.39).

Conclusion

Our preliminary data suggests that when compared to healthy controls, pediatric MFS/LDS patients have impaired resting aortic biophysical properties, paradoxical reductions in resting endothelial function with increased peripheral vasodilation, and abnormal vascular response to exercise.

A WEB-BASED TOOL TO DEFINE WHICH SCHOOL PHYSICAL ACTIVITIES ARE SAFE FOR EACH CHILD WITH MARFAN SYNDROME BASED ON AGE AND GENDER

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Introduction

Marfan syndrome is associated with skeletal, ophthalmic and aortic impairments that may be worsened by the practice of certain physical activities. However, sports activity is necessary in children with Marfan syndrome.

Objective

To propose a web tool defining for each child with Marfan syndrome the physical school activities that are or are not contraindicated according to skeletal, ophthalmic and aortic characteristics, gender and school level.

Materials and Methods

Sports proposed at school were classified according to their effect on the musculoskeletal system, the risk of contact and the hemodynamic effect (increase in blood pressure, which increases with age and at a younger age in boys than girls). Patients were classified according to presence/absence of 4 skeletal features (hypermobility, clubfoot, scoliosis, and spondylolisthesis), presence of ectopia lentis (no EL, EL, aphakia, pseudophakia) and their aortic risk evaluated by aortic dilatation, presence of pathogenic variant and family history. An online tool including these parameters generates a report indicating sports to be avoided for each patient, adapted to the specific program of his/her class, and to the child characteristics.

Results

In the French Marfan clinics, this online tool is used for each child with Marfan syndrome. After physical examination and TTE, skeletal characteristics, the level of severity of ectopia lentis and the level of increased blood pressure allowed are entered in the web tool. A pdf report is generated containing the list of the physical activities for the school grade and the mention for each “allowed” or “contraindicated”. This report is printed or sent by email to the family who is free to use it or not. During the last 3 years, in our center in Paris, 165 reports have been generated.

Conclusions

Physical activity is mandatory for children with Marfan syndrome, but some activities may be harmful depending on the severity of skeletal, ophthalmic and aortic involvement. We developed an online tool to accurately and individually define safe activities based on age and gender.

COMPARE MARFAN: A LONGITUDINAL ONLINE SURVEY TO STUDY THE QUALITY OF LIFE AND THE IMPACT OF MARFAN SYNDROME ON DAILY LIFE

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Introduction

The life expectancy of patients with Marfan syndrome has increased dramatically over the past 50 years. However, the aortic, skeletal and ophthalmological impairments and their treatment have a significant impact on daily life.

Objectives

Improve the quality of life and care of patients by involving them in research.

Materials and Methods

ComPaRe is an online survey on chronic diseases. A specific ComPaRe Marfan cohort has been designed. Patients register online and indicate that they have Marfan syndrome. They are then asked to fill in a specific questionnaire about their Marfan syndrome history. Once registered, they are invited to complete a survey every month or two on a different topic: symptoms (MYMOP2), treatment burden questionnaire, quality of life (EuroQUOL)... Patients are recruited through healthcare professionals, patient associations and social networks.

Results

Since March 2020, 255 patients have registered. 59% are women and the median age is 42. 11% of the participants are not being followed at an expert center. 87% underwent genetic testing, which revealed a mutation in 9 out of 10 cases. A history of aortic dissection was reported by 29% of participants and a history of aortic surgery by 55%.

Pain was reported by 52% and fatigue by 44% of participants.

With regard to education level and professional activity, we found a high representation of participants with a post-secondary education (67%) and the proportion of participants working or looking for a job is similar to that of the general French population (74%). The only determinant of work inactivity was the history of aortic dissection (16% inactivity without history of dissection vs 53% inactivity with history of aortic dissection, $p<0.0001$).

Conclusion

ComPaRe Marfan is an online survey allowing patients to participate in research and to better understand the impact of Marfan syndrome on daily life.

CAN 10,000 HEALTHY STEPS A DAY SLOW AORTIC ROOT DILATION IN PEDIATRIC MARFAN PATIENTS?

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Objectives

Stiffer aortas are associated with a faster rate of aortic root (AoR) dilation and higher risk of aortic dissection in patients with Marfan Syndrome. We have previously shown that mild aerobic exercise reduces aortic stiffness and rate of AoR dilation in a Marfan mouse model. In this pilot study we investigated if these results can be translated to pediatric Marfan patients.

Methods

We enrolled 24 Marfan patients 8-19 years old to participate in a 6-month exercise intervention, excluding those with ventricular dysfunction or prior history of aortic surgery. We instructed patients to take 10,000 steps/day, tracked by an activity tracker. At baseline and 6 months, we measured AoR dimension, arterial stiffness, endothelial function, physical activity indices, inflammatory biomarkers, and coping scores. Controls consisted of 15 age-matched Marfan patients.

Results

Twenty-four Marfan patients (median age=14.4 years [IQR 12.2, 16.8], 14 males) were enrolled. Baseline assessment demonstrated that the majority of these patients were sedentary and had abnormal arterial health. Twenty-two patients completed the intervention and took an average of 7,709±2,177 steps/day (median=7,627 [IQR 6,344-9,671]). Patients wore their Garmin trackers at a median of 92.8% [IQR 84-97] of their intervention days. AoR z-score in the intervention group had a significantly lower rate of change per year compared to the controls (rate of change - 0.24 vs. +0.008, p=0.01).

Conclusions

In this pilot clinical intervention in pediatric Marfan patients, we demonstrated that a simple exercise intervention was feasible in this population and has the potential to decrease the AoR dilation rate.

PHYSICAL ACTIVITY AND HEALTH LITERACY IN ADULTS WITH HEREDITARY THORACIC AORTIC ANEURYSMS AND AORTIC DISSECTIONS (HTAAD): A REVIEW IN COMBINATION WITH CROSS SECTIONAL QUANTITATIVE AND QUALITATIVE STUDIES

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Submitted to the theme: Physical activity and quality of life.

Introduction: Most people with HTAADs are recommended to limit their physical activity, but it can be challenging to deal with such recommendations in daily life.

Objectives: To achieve an overview of relevant literature and increase more in-depth knowledge of how people with HTAADs deal with physical activity and recommendations, including the significance of health-literacy.

Materials and Methods

Literature review and mixed method cross-sectional studies with triangulation of results from a quantitative questionnaire study (n = 52) including several validated instruments, and a qualitative focus groups (n = 36) of people with verified HTAADs; Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome.

Results

Only 13 articles, 3 reviews and 10 primary studies fulfilled the inclusion criteria. The studies indicate that low-to-moderate physical activity is recommended, but international evidence-based guidelines are warranted. The cross-sectional studies showed that most participants (85%) had received advices regarding physical activity, mostly emphasizing restrictions. Most had modified their physical activity and 40% were less active than recommended. Anxiety symptoms (94%), pain (79%) and fatigue (58%) were prevalent, and significantly associated with lower levels of physical activity. Many described difficulty in transforming the advices into practice, which could result in an inactive lifestyle. Finding the balance between healthy and unhealthy activity seems challenging for many. How health care providers communicate recommendations for physical activity is crucial to acquiring sufficient health literacy.

Conclusion

More knowledge about which types of activities and exercises that are healthy may help people with HTAADs to establish better coping strategies and activity habits. Improved health literacy is considered important to master the challenges associated of living with a potential life-threatening diagnosis. Therefore, it is important that health care providers counselling people with HTAADs focus on the challenges as well as the possibilities of physical activity.

Based on the following scientific articles:

- Physical exercise for people with hereditable thoracic aortic disease. A study of patient perspectives -PubMed (nih.gov)
- Adults with Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome: a cross-sectional study of patient experiences with physical activity -PubMed (nih.gov)
- Fysisk aktivitet og trening for personer med familiære thorakale aortaaneurismer og aortadisseksjoner. En oversiktsartikkel (fysioterapeuten.no)
- Fysisk aktivitet og helsekompetanse for personer med familiære torakale aortaaneurismer og -disseksjoner (sykepleien.no)

QUALITY OF LIFE IN PEOPLE WITH HEREDITARY THORACIC AORTIC ANEURYSMS AND AORTIC DISSECTIONS (HTAAD): A SYSTEMATIC REVIEW OF RELEVANT LITERATURE

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Submitted to the theme: Physical activity and quality of life.

Introduction

Living with potentially life-threatening illnesses as HTAADs may be challenging and negatively impact quality of life (QoL).

Objectives

To explore, critically appraise and synthesize the literature on QoL in patients with HTAAD; including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), vascular Ehlers-Danlos syndrome (vEDS) and other HTAAD diagnoses.

Materials and Methods

A systematic review was performed by searching (updated search 15.03.22) available medical, physical, psychological and social databases and other sources. Studies addressing QoL in people with HTAADs, published in peer-reviewed journals were assessed.

Results

Twenty-seven articles satisfied the eligibility criteria, including five on children. Twenty-three dealt with MFS, one with vEDS and LDS, and three with different HTAADs. Most studies were published the last 3 years. All were cross-sectional quantitative studies, besides one pilot quantitative intervention study and one longitudinal study. No qualitative studies were identified. Nearly all studies used generic validated QoL instruments, but none used disease specific instruments. Most studies had small sample sizes and/ or low response rates. Despite these limitations, the results indicate that HTAADs negatively impact QoL, but other factors may be confounders. Some studies found negative association between QoL and pain, fatigue, scoliosis, dural ectasia and executive dysfunctions. Nevertheless, few studies found associations between aortic problems and decreased QoL. Studies also found that QoL was significantly associated with other aspects such as demographic factors, but the results were divergent.

Conclusions

More research is needed to develop evidence-based knowledge on factors that influence QoL in order to establish appropriate interventions. Assessment of patient-reported QoL should be incorporated into clinical practice to ensure that the patient`s perspective is included in clinical decision making. We will encourage internationally collaboration to develop diagnose-specific scales for measuring QoL in patients with HTAADs to provide a more exact picture of how the diagnosis impact QoL across different cultures and context.

Based on the review article (updated version 32.04.22): Systematic review of quality of life in persons with hereditary thoracic aortic aneurysm and dissection diagnoses - PubMed (nih.gov) –

HERITABLE CONNECTIVE TISSUE DISORDERS IN CHILDHOOD: INCREASED FATIGUE, PAIN, DISABILITY AND DECREASED GENERAL HEALTH

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on behalf of the Pediatric Heritable Connective Tissue Disorders Study Group

Introduction: Heritable Connective Tissue Disorders (HCTD) show overlap in the physical features that can evolve in childhood. It is unclear to what extent children with HCTD experience burden of disease.

Objective: This study aims to quantify fatigue, pain, disability and general health with standardized validated questionnaires.

Materials and Methods: This observational, multicenter study included 107 children, aged 4–18 years, with Marfan syndrome (MFS), 58%; Loeys-Dietz syndrome (LDS), 7%; Ehlers-Danlos syndromes (EDS), 8%; and hypermobile Ehlers-Danlos syndrome (hEDS), 27%. The assessments included PROMIS Fatigue Parent–Proxy and Pediatric self-report, pain and general health Visual-Analogue-Scales (VAS) and a Childhood Health Assessment Questionnaire (CHAQ). Results. Compared to normative data, the total HCTD-group showed significantly higher parent-rated fatigue T-scores ($M = 53$ ($SD = 12$), $p = 0.004$, $d = 0.3$), pain VAS scores ($M = 2.8$ ($SD = 3.1$), $p < 0.001$, $d = 1.27$), general health VAS scores ($M = 2.5$ ($SD = 1.8$), $p < 0.001$, $d = 2.04$) and CHAQ disability index scores ($M = 0.9$ ($SD = 0.7$), $p < 0.001$, $d = 1.23$). HCTD-subgroups showed similar results. The most adverse sequels were reported in children with hEDS, whereas the least were reported in those with MFS. Disability showed significant relationships with fatigue ($p < 0.001$, $rs = 0.68$), pain ($p < 0.001$, $rs = 0.64$) and general health ($p < 0.001$, $rs = 0.59$).

Conclusions: Compared to normative data, children and adolescents with HCTD reported increased fatigue, pain, disability and decreased general health, with most differences translating into very large-sized effects. The most adverse sequels were reported in children with hEDS, whereas the least were reported in those with MFS. This new knowledge calls for systematic monitoring with standardized validated questionnaires, physical assessments and tailored interventions in clinical care.

PARENTING A CHILD WITH MARFAN SYNDROME: DISTRESS AND EVERYDAY PROBLEMS

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Introduction: Marfan syndrome (MFS) is a multisystemic, autosomal dominant connective tissue disorder that occurs de novo in 25%. In many families, parent and child(ren) are affected, which may increase distress in parents.

Objectives: The aim of this study is to assess distress and everyday problems in parents of a child with MFS.

Materials and Methods: Forty-two mothers (29% MFS) and 25 fathers (60% MFS) of 43 affected children completed the validated screening-questionnaire Distress-Thermometer for parents of a chronically ill child. This questionnaire includes questions on overall distress (score 0–10; ≥4 denoting "clinical distress") and everyday problems (score 0–36). Data were compared to 1.134 control-group parents of healthy children.

Results: Mothers reported significantly less overall distress (2, 1–4 vs. 3, 1–6; $p = .049$; $r = -.07$) and total everyday problems (3, 0–6 vs. 4, 1–8; $p = .03$; $r = -.08$) compared to control-group-mothers. Mothers without MFS reported significantly less overall distress compared to mothers with MFS, both of a child with MFS (1, 0–4 vs. 3.5, 2– 5; $p = .039$; $r = -.17$). No significant differences were found between the father-groups, nor between the group of healthy parents of an affected child living together with an affected partner compared to control-group-parents. No differences in percentages of clinical distress were reported between mothers and control-group-mothers (33 vs. 42%); fathers and control-group-fathers (28 vs. 32%); nor between the other groups. Distress was not associated with the children's MFS characteristics.

Conclusion: Parents of a child with MFS did not show more clinical distress compared to parents of healthy children. However, clinical distress was reported in approximately one-third and may increase in case of acute medical complications. We advise monitoring distress in parents of a child with MFS to provide targeted support.

HERITABLE CONNECTIVE TISSUE DISORDERS IN CHILDHOOD: DECREASED HEALTH-RELATED QUALITY OF LIFE AND MENTAL HEALTH

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on behalf of the Pediatric Heritable Connective Tissue Disorders Study Group

Introduction: The psychosocial consequences of growing up with Heritable Connective Tissue Disorders (HCTD) are largely unknown.

Objective: To assess Health Related Quality of Life (HRQoL) and mental health of children and adolescents with HCTD.

Materials and Methods: This observational multicenter study included 126 children, aged 4-18 years, with Marfan syndrome (MFS, n=74), Loeys-Dietz syndrome (LDS, n=8), molecular confirmed Ehlers-Danlos syndromes (EDS, n=15), and hypermobile Ehlers-Danlos syndrome (hEDS, n=29). HRQoL and mental health were assessed through the parent and child reported Child Health Questionnaires (CHQ-PF50 and CHQ-CF45, respectively) and the parent reported Strengths and Difficulties Questionnaire (SDQ).

Results: Compared to a representative general population sample, parent reported HRQoL of the HCTD group showed significantly decreased Physical scores ($p<.001$, $d=.9$) and Psychosocial scores ($p=.024$, $d=.2$), indicating decreased HRQoL. Both, males and females with MFS obtained significantly lower Physical scores compared to scores of the representative general population sample and no differences were found for the Psychosocial scores. Further analyses of the MFS subgroups showed significantly lower scores on subscales Physical Functioning and General Health Perceptions. On the item "Change in Health over the last year", parents of the male and female MFS subgroups, reported 9% and 25%, respectively, their children to have "somewhat worse to much worse" health in the last year compared to previous years. Similar findings were obtained for child reported HRQoL.

The parent reported mental health of the HCTD group showed significantly increased Total difficulties scores ($p=.01$, $d=.3$), indicating decreased mental health. While the male and female MFS and hEDS subgroups both reported decreased HRQoL, only the hEDS subgroup reported decreased mental health.

Conclusions: Children and adolescents with HCTD report decreased HRQoL and mental health, with most adverse outcomes reported in children with hEDS and least in those with MFS. These findings call for systematic monitoring and tailored interventions.

COMPENSATORY MECHANISMS IN THE TUNICA MEDIA OF AORTIC AND MESENTERIC ARTERIES OF THE MGΔ^{LPN} DOMINANT-NEGATIVE MOUSE MODEL OF MARFAN SYNDROME

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Elastic fiber abnormalities in MFS are frequently detected in the aortic tunica media. Losartan is reported to improve in some cases the aortic phenotype of MFS patients. While elastic fibers are present in the mesentery artery, phenotypic description and losartan efficiency have received little attention. Here we characterize the mesenteric artery in the mgΔ^{lpn} mouse model of MFS and the effects of losartan treatment.

Female mice at 4 months of age were used: mgΔ^{lpn} mice (n=10); mgΔ^{lpn} treated with losartan for 3 months (n=10); and wild-type (WT) (n=10). The aorta and mesenteric arteries were examined by histological analysis. Distribution and quantification of fibrillin-1 and α-smooth muscle actin (αSMA) were analyzed by immunofluorescence. Blood flow was monitored with an ultrasound probe.

In both thoracic aorta and mesenteric artery, we observed a significant reduction of fibrillin-1 and elastic fiber integrity (EFI) in mgΔ^{lpn} mice when compared to WT. We suggest these alterations may be associated with the loss of passive vessel mechanics. However, we did not observe a significant difference in blood flow in both vessel types, indicating a possible compensatory mechanism. αSMA in arteries regulate contractile functions. In both vessel types, we observed a significant increase of the αSMA in mgΔ^{lpn} mice compared to WT, suggesting that αSMA participates in the compensatory mechanism of vessel dynamics. Losartan therapy improved fibrillin-1 intensity and EFI and led to decreased blood flow in both vessels as expected. Alpha-SMA was reduced in the aorta and increased in the mesenteric artery of losartan treated MFS-mice.

In conclusion, we observed elastic fiber alterations in the mesenteric artery of mgΔ^{lpn} mice, coupled with an increase in αSMA intensity, which can be auxiliary to the homeostasis of blood flow. Losartan therapy improved those phenotypes but did not restore it, indicating the need for different therapeutic strategies for MFS.

COMBINATION THERAPY TARGETING THE MAJOR ANGIOTENSIN II RECEPTORS PREVENTS THORACIC AORTIC ANEURYSM FORMATION IN MARFAN SYNDROME MICE BY REVERSING ENOS UNCOUPLING

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Earlier analyses of Marfan syndrome (MFS) patients have suggested a peripheral endothelial cell (EC) abnormality associated with low nitric oxide (NO) production and thoracic aortic aneurysm (TAA) formation. Mice with early onset, progressively severe MFS (*Fbn1*$^{mgR/mgR}$ mice) were therefore examined with respect to endothelial nitric oxide synthase (eNOS) activity and vasomotor function. Addition of acetylcholine (ACh) to pre-constricted aortic rings isolated from *Fbn1*$^{mgR/mgR}$ samples and mounted in a wire myograph system revealed a significant reduction in vasorelaxation relative to the WT counterparts. Unremarkable maximal relaxation of mutant samples treated with an exogenous NO-donor excluded a smooth muscle cell defect. Impaired EC-dependent vasorelaxation was correlated to reduced eNOS activation and to eNOS uncoupling, as respectively evidenced by lower-than-normal levels of p(Ser1177)eNOS and eNOS dimer-monomer ratio, and elevated superoxide production. Vascular tone is regulated by a balance between vasoconstrictor and vasodilator signals, such as those respectively mediated by the angiotensin receptors AT1r and AT2r. Previous studies have shown that abnormally high AT1r signaling on ECs is an early contributing factor to aneurysm development in MFS mice. *Fbn1*$^{mgR/mgR}$ mice were therefore treated with the AT1r antagonist losartan or the AT2r agonist compound 21 (C21) or both drugs. Treatments spanned from P16 to P180 when all vehicle-treated *Fbn1*$^{mgR/mgR}$ mice are expected to die from TAA complications. These experiments revealed that the combination of AT1r inhibition and AT2r stimulation prevented TAA formation and death from acute aortic dissection in nearly 90% of *Fbn1*$^{mgR/mgR}$ mice. Of note, echocardiographic measurements performed at P150 showed a statistically significant enlargement of the ascending aorta only in the losartan treatment arm, thus implying that co-treatment with C21 had a longer lasting effect on preventing aneurysm formation. Additional in vivo and ex vivo findings correlated the therapeutic effect of the double treatment to normalized aortic wall architecture and restored vasomotor function.

TOWARDS PERSONALISED MEDICINE – AN IPSC MODEL OF MARFAN SYNDROME IDENTIFIES DIFFERENTIAL RESPONSES TO DRUGS

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Introduction

Marfan syndrome (MFS) is a connective tissue disorder resulting from mutations in the *FBN1* gene. The vascular complications are potentially life-threatening, where patients can develop aortic aneurysm and dissection. Evidence from animal models and human samples suggests that vascular smooth muscle cells (VSMCs) are major drivers for disease. Our group has developed an *in vitro* model of MFS which recapitulates key disease features using induced pluripotent stem cell (iPSC)-derived VSMCs. Using this system, we have previously identified two drug targets which were highly effective in reducing the disease phenotype – p38 inhibitor (losmapimod) and GSK3β inhibitor (AZD1080).

Aims

Here, we sought to determine how six additional MFS patient lines would respond to drug treatment.

Method

We tested pan-MMP inhibitor doxycycline and angiotensin receptor blocker losartan in addition to our two novel drugs, and performed phenotypic assays to look at key disease features.

Results

We demonstrate that these patient lines do not respond uniformly to drug treatment, suggesting that there are more complex disease mechanisms underlying MFS yet to be uncovered.

Conclusions

This work highlights that i) there are likely to be distinct signalling abnormalities in different patients, ii) a targeted and personalised approach would be beneficial in treating this disease and iii) these differences are important to consider when constructing future clinical trials.

ZEBRAFISH AS A TOOL TO STUDY CARDIOVASCULAR EFFECTS CAUSED BY FIBRILLIN IMPAIRMENT

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Introduction

Marfan syndrome (MFS) is the most common type of fibrillinopathy with a high predisposition to develop aneurysms and dissections of the ascending aorta. While the development of several mouse models of MFS has contributed greatly to our current knowledge, a thorough understanding of the underlying mechanisms is still lacking. There is a particular need for more flexible *in vivo* models to address this knowledge gap.

Objectives

We aimed to generate a relevant zebrafish model to gain insight into the molecular mechanisms relating fibrillin defects to the cardiovascular system.

Methods

The CRISPR/Cas9 system was used to systematically target the three different fibrillin genes (*fbn1*, *fbn2a* and *fbn2b*) in Tg(kdrl:GFP) reporter zebrafish. Time-lapse fluorescent microscopy was used to evaluate the cardiovascular phenotype.

Results

We found that zebrafish lacking *fbn1* and/or *fbn2a* do not show any cardiovascular phenotype during early-stage development. On the other hand, approximately 50% of homozygous *fbn2b* mutant (*fbn2b*$^{-/-}$) zebrafish embryo's show a severe phenotype characterized by endocardial detachment, leading to vascular embolism and premature mortality at 7-9 dpf. Interestingly, the remaining *fbn2b*$^{-/-}$ zebrafish survive until adulthood, but during larval stages already develop a dilation of the bulbus arteriosus, a structure anatomically related to the aortic root in humans. In addition, the caudal vein of all *fbn2b*$^{-/-}$ embryos develops abnormally as a cavernous structure lacking vessel integrity. This phenotype is resolved in embryos retaining normal blood flow and aggravated upon pharmacological inhibition of blood flow during development.

Conclusion

These data indicate that our new *fbn2b*$^{-/-}$ zebrafish model recapitulates cardiovascular complications observed with fibrillin deficiency, and can thus be considered as a relevant model to study the mechanisms underlying MFS pathogenesis. Our preliminary data suggest that there is an interplay between fibrillin deficiency and biomechanical signaling in the regulation of cardiovascular development.

IPSC-DERIVED SMOOTH MUSCLE CELLS MODELLING LOEYS-DIETZ SYNDROME SHOW ABNORMAL PHENOTYPE IN RESPONSE TO TGF-β

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Introduction

Loeys-Dietz syndrome (LDS) is a connective tissue disorder caused by mutations in the components of the transforming growth factor (TGF)-β pathway. Patients with LDS often suffer from a potentially fatal thoracic aortic aneurysm and dissection as early as 3 months of age. Mechanisms underlying the development and progression of aneurysms in LDS are still unknown and treatment options are limited. Interestingly, aneurysms occur frequently at the aortic root, where smooth muscle cells (SMCs) from two distinct embryonic origins – the lateral mesoderm (LM) and neural crest (NC) – intermingle. We hypothesise that the interaction between these lineage-specific SMCs plays a key role in aneurysm development and progression in LDS.

Objective

To model LDS *in vitro* using LDS patient-derived induced pluripotent stem cells (iPSCs) which have a heterozygous mutation in the kinase domain of TGF-β receptor 1 (*TGFBR1*) and its CRISPR-corrected isogenic control.

Materials and Methods

Western blots, qPCR, immunocytochemistry, and flow cytometry.

Results

Our iPSC lines can be differentiated into both LM-SMCs and NC-SMCs at over 90% efficiency. Upon exposure to varying concentrations of TGF-β, a reduction in the phosphorylation of SMAD2 was detected in LDS LM-SMCs compared with isogenic LM-SMCs. This difference was not detected between LDS and isogenic NC-SMCs. These LDS LM-SMCs have a reduced expression of *PAI-1*, a downstream target gene of the TGF-β pathway, compared to control LM-SMCs following TGF-β stimulation. Furthermore, they exhibited enhanced expression of *COL3A1* and *MMP10*.

Conclusion

In summary, we identified an abnormal phenotype in LM-SMCs caused by the *TGFBR1* mutation that might underlie the development and progression of aneurysms in LDS. For future studies, we hope to use our iPSC- derived LDS models as screening platforms to identify and validate novel therapeutic targets.

PHENOTYPIC SCREENING IN MARFAN SYNDROME PRIMARY CELLS

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Introduction: Due to the high genetic diversity within the Marfan syndrome (MFS) patient population, genotype-phenotype predictions on disease progression and response to therapy remain complex. Furthermore, current preclinical models represent only a subset of FBN1 mutations, which makes translational drug development challenging. Therefore, there is an urgent need for improved preclinical approaches to model the clinical variability in MFS.

Objectives: To develop preclinical models using primary cells of MFS patients that represent clinical variability to develop novel drug strategies.

Materials and Methods: Human primary fibroblasts were isolated from skin biopsies derived from patients (n=56) participating in the COMPARE trial. Human aortic smooth muscle cells (AoSMCs) were isolated from aortic tissue derived from prophylactic surgery (n=4). In addition, mouse $Fbn1^{+/C1041G}$ AoSMCs were cultured. Long-term cultures of these primary cells and non-MFS controls in 384-well plates were assessed for the presence of fibrillin-1 extracellular fibers, and expression of Krüppel-like factor 4 (KLF4) and alpha smooth muscle actin (ASMA)

Results: Analysis of MFS fibroblast phenotypic screening showed either a reduced or abolished fibrillin-1 matrix, indicating at least two subpopulations. MFS fibroblasts with an abolished fibrillin-1 matrix were associated with patients with rapid aortic root diameter growth (>0,4 mm/year). Exploring disease-relevant signaling pathways revealed reduced nuclear KLF4 expression in MFS fibroblasts as compared to controls, with least expression in fibroblasts without a fibrillin-1 network, whereas ASMA expression was increased in both groups. These findings were validated in AoSMC cultures, also showing these KLF4 and ASMA expression profiles. In addition, a low-throughput drug screen discovered lead targets for normalization of nuclear KLF4 signaling.

Conclusion: Phenotypic screening of patient-derived fibroblasts contributes to improved understanding of disease pathogenesis and could be a preclinical tool for risk assessment and drug development for MFS and related conditions.

A NEW *SMAD4* MOUSE MODEL TO BETTER UNDERSTAND CARDIOVASCULAR PHENOTYPES IN SMAD4PATHIES

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Introduction

Myhre syndrome, Hereditary Hemorrhagic Telangiectasia (HHT), and Thoracic Aortic Aneurysm and Dissection (TAAD) are diseases that share the presence of pathogenic variants in the *SMAD4* gene encoding the co-mediator of the TGFβ/BMP signaling pathways. Although diverse, these pathologies (SMAD4pathies) all share distinct vascular anomalies. The project is to unravel the specific pathogenic mechanisms of these distinct diseases using cellular and mouse models.

Objective

This work aims to investigate the pathomechanisms underlying MS using a newly generated *Smad4* mouse model to better understand these SMAD4pathies.

Materials and Methods

The most frequent mutation found in Myhre syndrome has been introduced in the genome of the new *Smad4* mouse model (*Smad4*$^{Ile500Val/+}$). General phenotyping has been performed to characterize this model, focusing on skeletal and cardiovascular aspects.

Results

The mouse model *Smad4*$^{Ile500Val/+}$ is viable. The *Smad4*$^{Ile500Val/+}$ mouse model presents stature retardation associated with growth plates and chondrocyte differentiation defects. The hearts of mutant mice are smaller with thicker ventricle walls. Interestingly, homozygous mice *Smad4*$^{Ile500Val/Ile500Val}$ exhibit a more severe phenotype with a perinatal lethality thought to be linked to septal defects. Furthermore, even if *Smad4* mutations induce thoracic aortic aneurysms, no aortic events have been observed. The mutated protein Smad4^{Ile500Val} exhibits higher stability than the wild-type protein, with no difference in the activation of the signaling pathways. But, establishing the transcriptomic profiles of non-stimulated and TGFβ or BMP-stimulated primary mutant chondrocytes, target gene expressions in both signaling pathways are impaired. Furthermore, the majority of dysregulated genes are linked to the ECM (structural proteins, integrin-reacting proteins, matrix-degrading enzymes, and cytokines).

Conclusion

This new *Smad4* mouse model mimics a Myhre syndrome-like phenotype with short stature and cardiovascular anomalies. BMP signaling pathway being affected in HHT and TGFβ signaling pathway in TAAD, it seems that in Myhre syndrome, both signaling pathways are impaired.

COMPUTATIONAL MODELING FOR THE QUANTIFICATION OF BIOMECHANICS INDEXES ASSOCIATED WITH ADVERSE REMODELING IN VALVE SPARING ROOT REPLACEMENT SURGERY: THE IMPACT OF GRAFT STIFFNESS

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Introduction

Marfan syndrome (MFS) patients commonly develop thoracic aortic aneurysms (TAA): Prosthetic graft replacement provides lifesaving benefit, but risk persists for adverse events in the native distal aorta. One mechanism for such events may stem from graft-induced alterations in aortic biomechanics: Current prosthetic grafts (Dacron) are markedly stiffer than the native aorta, providing a conduit to propagate high energy flow and drive adverse distal remodeling.

Objectives

This study used cardiac MRI (CMR) derived fluid structure interaction (FSI) computational models to test impact of modified graft compliance on the distal aorta.

Materials and Methods

CMR (including MRA, cine, 4D flow) was performed in a genetic TAA patient before and after proximal graft replacement surgery. CMR was used to generate a pre-operative, and 3 post-operative Fluid-Structure Interactions (FSI) models with variable graft compliance (elastic modulus: 1MPa-12MPa [typical Dacron stiffness]). For each model, patient-specific inlet velocity profiles were defined using 4D flow: Intramural stress (IS) and wall shear stress (WSS) were quantified in the native distal aorta.

Results

FSI results were verified against 4D flow, with good matching ($p>0.05$) between velocity patterns. After Dacron graft implantation, distal aortic WSS increased ~2-fold (3.9 [0.5-0.9] vs. 6.9 [0.9-1.7] Pa, $p<0.001$): Simulations using more compliant grafts (1 and 5MPa) yielded lower distal aortic WSS than Dacron (1MPa: 3.1 [0.5-0.9] | 5MPa: 3.2 [0.4-0.9] Pa vs. 6.9 [0.9-1.7] Pa; both $p<0.001$). IS similarly increased after Dacron graft implantation (74.6 [65.6-82.8] vs. 105.8 [84.0-129.9] kPa; $p<0.001$): This was attenuated in simulations using a more compliant (1MPa) graft (81.6 [74.3-88.2]; $p<0.001$ vs. Dacron).

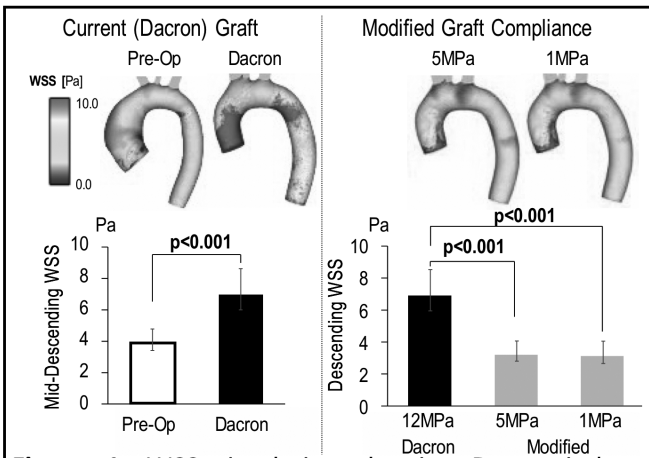

Figure 1. WSS simulation showing Dacron-induced increments in distal aortic WSS and mitigating effect of modified grafts.

Conclusion

Prosthetic graft replacement of TAA using current (non-compliant) materials alters distal aortic flow physiology, providing a potential nidus for adverse downstream remodeling. Attenuation of post-operative increments in distal WSS and IS by grafts with increased compliance suggest that such tailored grafts can mitigate adverse post-operative aortic remodeling.

DEVELOPMENT OF A WEB-BASED MARFAN SYNDROME MOUSE AORTIC ROOT CELL ATLAS TO ENABLE RAPID GENE EXPRESSION ANALYSIS

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Introduction

Single-cell RNA sequencing (scRNAseq) enables deconvolution of complex organs to delineate heterogeneous cell behaviors. While this technique provides high-resolution data for identification of novel disease contributors in Marfan syndrome (MFS), scRNAseq is expensive, technically demanding and requires computational skills and resources to analyze.

Objectives

To generate a robust dataset of aortic scRNAseq data in the commonly studied *Fbn1*$^{C1041G/+}$ MFS mouse model and establish a web-based analysis resource for the MFS research community.

Materials and Methods

We developed inducible vascular SMC fluorescent reporter MFS mice and induced SMC lineage tracing at 6 weeks, enabling SMC fate-mapping *in vivo*. Male MFS mice and littermate controls underwent echocardiography and sacrifice at 24 weeks. Aortic roots were digested and sorted into SMC and non-SMC populations and processed for scRNAseq. Data was analyzed in the Seurat package in R.

Results

Echocardiography confirmed aortic root aneurysm in MFS mice (2.25±0.13mm, n=8) compared to controls (1.87±0.13mm, n=8). Following scRNAseq processing, over 18,000 individual cells were analyzed, identifying 12 discrete cell clusters. We identified three subpopulations in sorted SMCs, including the disease-specific modulated SMC cluster previously reported. The entire dataset, including dimensional reductions, clustering, and expression values for >16,000 genes in each individual cell are hosted online via shinyapps.io. Using this platform, users can investigate expression of specific genes within each cell type, genotype, lineage (SMC vs. non-SMC), and probe co-expression of multiple genes within single cells projected in either uniform manifold approximation and projection (UMAP) or principal component analysis (PCA) projections to capture gene co-regulation. The data resource is open to the public, requires no coding experience, and is free to use.

Conclusion

The generation and public sharing of scRNAseq data in an accessible format provides a new tool for the scientific community studying MFS and other heritable aortopathies toward the goal of accelerating pre-clinical discoveries.

IN VIVO RABBIT ANEURYSMAL MODEL BY USING TUBULAR ENGINEERING VESSELS DERIVED FROM AORTIC SMOOTH MUSCLE CELLS FROM MARFAN SYNDROME (MFS) PATIENTS

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Introduction

Aortic root aneurysm is the major pleiotropic manifestations of MFS that is progressively dilated leading to the catastrophic dissection and rupture. Although the creation of transgenic Marfan mouse has greatly expanded our understanding to mechanism of aortopathy in MFS, there is need for an in vivo aneurysmal analysis platform by combining in vitro engineering VSMCs-based vessels from patient samples and in vivo growing vessel implants in immunosuppressive animals.

Objectives

To study VSMCs contribution for aortopathy development in MFS, we aim to create an in vivo rabbit aneurysmal model by using tubular engineering vessels derived from aortic VSMCs from MFS patients

Materials and Methods

The aortic media were collected from heart transplant donors and MFS patients. Cultured primary VSMCs were seeded on biodegradable PGA-based meshes and engineering vessels were growth in 100mm culture dish(static), or physiological-mimic pulsatile bioreactor(dynamic). The collected vessels were implanted into nude rabbit carotid artery by monolateral or bilateral. The implants were monitored at 2, 4, 6 weeks post-operation by ultrasound, and collected for histology analysis.

Results

Compared to implants derived from VSMCs of donor aortic roots, the ones from MFS demonstrated a progressive dilation in both inner and outer diameters from 2 weeks to 6 weeks post-operation. Histology staining demonstrated that the significant collogen deposition occurred in both MFS tissue samples and implant vessels derived from VSMCs of MFS.

Conclusion

We have created the in vivo aneurysmal rabbit model through implanting engineering vessels derived from aortic VSMCs of MFS that could recapture certain phenotypes of aortopathy in MFS.

ALLOPURINOL BLOCKS THE FORMATION AND PROGRESSION OF AORTIC ANEURYSM IN A MOUSE MODEL OF MARFAN SYNDROME

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Introduction

The pathogenesis and progression of aortic aneurysm in Marfan syndrome (MFS) involves dysregulated TGF-β and nitric oxide signaling, altered hemodynamics, and biomechanical forces. Increasing evidence indicates that redox stress also participates in MFS aortopathy. We previously reported elevated ROS formation and NADPH oxidase NOX4 upregulation in MFS patients and mice aortic samples.

Objectives

To study the contribution of xanthine oxidoreductase (XOR) in the formation and progression of the aortic aneurysm in MFS. XOR is transcribed as dehydrogenase (XDH) and then post-translationally to oxidase (XO) catabolizing purines into uric acid (UA) and ROS.

Material and Methods

We used aortic samples from a murine model of MFS (C1041G) and from MFS patients subjected to reparatory surgery. We evaluated XOR expression levels and enzymatic activity by RT-PCR, fluorimetry-based method and immunohistochemistry, UA plasma levels and ROS production in aortic rings by commercial kits, the aortic reactivity by myography, aortic root diameter by ultrasonography and aortic wall organization by histological staining. **Results**. In MFS patients, XOR protein levels increased in aortic samples. In MFS mice, *XOR* mRNA transcripts and the enzymatic activity of XO was also augmented in the injured aorta. The administration of the XOR inhibitor allopurinol blocked the progression of aortic root aneurysm and it was also protective when administrated before the appearance of aneurysm. Moreover, allopurinol significantly reduced the elastic fiber fragmentation, fibrotic remodeling, nuclear translocation of pNRF2, increased 3'-nitrotyrosine levels, endothelial dysfunction and large production of H2O2. occurring in Marfan aorta. Strikingly, UA plasma levels remained unaltered after allopurinol treatment.

Conclusion

Our study demonstrates the participation of XOR in the MFS aortopathy and strengthens that redox stress is a relevant driving force in the development and progression of the aortic aneurysm in MFS. Moreover, our data supports a clinical trial with allopurinol in the pharmacological treatment of MFS.

LOSARTAN IN MARFAN SYNDROME: A DOSE AND PRODRUG ISSUE?

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Introduction

The angiotensin II receptor type 1 (ATR1) blocker losartan has proven highly effective at preventing aortic widening in Marfan (MFS) mice but efficacy in MFS patients remains underwhelming despite excellent blood pressure (BP) lowering effects. We have provided evidence that activation of protective nitric oxide (NO)-dependent endothelial function by losartan may help prevent MFS aortic root disease, but how this occurs is unknown. Losartan is a prodrug and we suspect that some of its main metabolites - EXP3179 or the dominant BP-lowering EXP3174 – are behind its NO-enhancing properties.

Objective

To show whether EXP3179 or EXP3174 can activate NO release.

Materials and Methods

Smooth muscle cell cultures, wire myographs**,** 2-month-old WT and MFS mice were used to evaluate the AT1R blocking, BP lowering and endothelial NO release properties of EXP3179 and EXP3174 (15uM) .

Results

Both EXP3179 and EXP3174 can fully block AT1R signalling and lower BP, but only EXP3179 can prevent PE-induced contraction (up to 65%; $p < 0.01$) in L-NAME- and endothelium removal-sensitive fashion. In MFS aortas, we observed an 85.5% decrease in PE-induced contraction in MFS mouse aortic rings treated with EXP3179 (15uM) compared to vehicle ($p < 0.001$) whereas L-NAME incubation had a more moderate inhibitory effect on EXP3179, reducing PE-induced contraction by only 62.7% ($p < 0.01$) suggesting that only 23% of EXP3179's effects are NO-dependent in MFS aorta compared to >90% in WT aorta.

Conclusion

Our results show that losartan metabolite EXP3179 has the unique ability to activate aortic NO release, whereas MFS interferes with this pathway. MFS patients may benefit from higher doses of losartan, or switch to a non-prodrug ARB with greater endothelial function activation. This provides a new perspective on improving the management of MFS.

EFFECT OF IRBESARTAN ON TRANSFORMING GROWTH FACTOR BETA (TGF-β) IN PATIENTS WITH MARFAN SYNDROME: SUB STUDY OF AIMS (AORTIC IRBESARTAN MARFAN STUDY) TRIAL

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Introduction

Marfan Syndrome (MFS) is an inherited condition associated with aortic dilatation. This may be mediated by an interaction between the fibrillin-1, and other gene mutations, and transforming growth factor beta (TGF-β). Angiotensin receptor blockers (ARBs) may reduce the risk of aortic expansion by influencing TGF-β signalling. The AIMS trial of 192 participants with MFS aged 6-40 years showed that the ARB irbesartan reduced the rate of aortic expansion compared to placebo.

Objectives

In a subset of patients of the AIMS trial we measured TGF-β levels to explore any effects of irbesartan or other covariates.

Materials and Methods

The primary outcome was a comparison of the change in TGF-β levels between placebo and irbesartan at baseline and one-year. Secondary analyses explored associations between TGF-β levels and covariates such as age, sex, beta blocker use, aortic root size and mutation status.

Results

There were 67 samples available at baseline (prior to treatment) and 89 samples at one-year follow up. Mean log transformed baseline TGF-β levels were 5.43 ng/ml in both the placebo and irbesartan group at baseline and 5.40 and 5.29 ng/ml respectively at one year (geometric mean ratio 0.90; 95% confidence intervals 0.78- 1.05: p=0.18) Potential factors influencing TGF-β levels included age and aortic diameter although these associations were not significant.

Conclusion

This analysis did not demonstrate an association between TGF-β levels in patients with MFS and treatment with irbesartan. These findings may be due to the substudy being underpowered or perhaps because irbesartan does not influence TGF-β levels in MFS. Further research to establish the potential role of TGF-β and other mechanisms in aortic dilatation in MFS is urgently needed.

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NOVEL ASSAY TO ASSESS THE AORTIC RUPTURE OF MICE MODELING AORTIC DISEASES

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Introduction

Thoracic aortic aneurysms and dissections (TAAD) characterized by a weakened aortic wall are a common cause of premature death. TAAD can be divided into syndromic and non-syndromic forms. An example for a syndromic TAAD is vascular Ehlers-Danlos syndrome (vEDS), which is a rare systemic connective tissue disorder, caused by mutations in the *COL3A1* gene, leading to weakened connective tissue, including the aorta.

Objectives

Previously, we have established an objective read-out system to measure the tensile force by stretching short murine thoracic aortic segments until rupture, with the aim of evaluating the effect of various medications on the biomechanical integrity of the aorta. Here, to gain deeper insight into the biomechanical integrity of the aorta, we present an additional, more physiological read-out system of the aortic rupture force.

Materials and Methods

Our novel assay assesses the burst pressure of the murine aorta by creating a fluid-induced load/stress on the aortic wall, thereby enabling the identification of the weakest (rupturing) site in the aortic wall by investigating the entire thoracic aorta. For this, we create a closed *in situ* system in euthanized mice and increase the intraluminal pressure with liquid until aortic rupture. The burst pressure at which the aortic rupture occurs is recorded (in mmHg).

Results

The application of our novel assay to wild-type and untreated heterozygous mice modeling vEDS (*Col3a1*$^{+/m1Lsmi}$) showed that wild-type mice had significantly higher burst pressure than heterozygous mice. The comparison with our previously established method for measuring aortic rupture force will be presented.

Conclusion

Our novel assay of burst pressure measurement can be used as an objective read-out system for assessing the biomechanical integrity of the entire thoracic aorta, enabling the evaluation of drugs to strengthen the weakened aortic wall in mice modeling aortic diseases.

SINGLE-CELL RNA SEQUENCING IDENTIFIES A DISEASE-ASSOCIATED, LOSARTAN-SENSITIVE SUB-POPULATION OF CELLS IN THE THORACIC AORTA OF MARFAN SYNDROME MICE

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We computationally delineated and experimentally validated dynamic alterations of individual cell transcriptomes in the dilating ascending thoracic aorta of mice with severe Marfan syndrome (MFS), *Fbn1*$^{mgR/mgR}$ mice. Data from sc-RNA-seq using P45 MFS and WT aortas segregated the major cell types based on their distinct transcriptional profiles, in addition to revealing that the relative proportions of smooth muscle cells (SMCs) and endothelial cells (ECs) were respectively lower and higher in MFS than WT aortas. SMCs were identified as 3 unique sub-populations displaying distinct transcriptional patterns: SMC1 common to both MFS and WT; SMC2, substantially decreased in MFS mice; SMC3, only present in MFS and uniquely expressing genes encoding ECM proteins. A similar analysis of ECs identified 4 unique subpopulations. Three of them (EC1, EC2 and EC3) are common to both WT and MFS aorta and correspond to the EC sub-populations previously annotated in the single-cell atlas of the normal mouse aorta. The fourth subpopulation (EC4) is similar to a sub-population previously reported in WT mice exposed to chronic disturbed flow. Specifically, EC4 transcriptional profile includes enriched expression of SMC, fibroblast, and immune cell genes. RNAscope in situ hybridization located EC4 in the intima of MFS aortas. Trajectory analysis revealed dynamic changes in EC and SMC and inferred a high degree of similarity between EC4 and SMC3. Genetic evidence from mice without EC-produced fibrillin-1 demonstrated the SMC-origin of EC4. Consistent with the pathogenetic contribution of angiotensin type receptor (AT1r) to aneurysmal disease in MFS, neither EC4 nor SMC3 subpopulations were identified in scRNA-seq data collected from losartan treated MFS mice.

ANGIOTENSIN II RECEPTOR BLOCKERS DEMONSTRATE WIDE HETEROGENEITY AT ACTIVATING ENDOTHELIAL FUNCTION IN THE VASCULATURE: SELECTING THE RIGHT ARB - TELMISARTAN – FOR THE MARFAN JOB

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Introduction

Marfan syndrome (MFS) management with angiotensin II receptor type 1 blocker (ARB) losartan has demonstrated underwhelming efficacy in the clinic, despite promising results in mice. Our laboratory has shown that losartan may be attenuating MFS aortic root pathology by enhancing endothelial function via increased nitric oxide (NO) bioavailability, independent of blood pressure (BP)-lowering. Whether other ARBs are capable of enhancing endothelial function compared to losartan is unknown.

Objectives

To identify the most potent ARB at activating endothelium-dependent NO production and test its anti-aortic root dilation properties at sub-BP-lowering doses.

Materials and Methods

BP dose-response experiments were performed in wild-type (WT) mice treated with 8 clinically available ARBs to determine their EC_5 sub-BP- lowering dose. The EC_5 dose for each ARB was then administered to WT mice for 4 weeks in drinking water. MFS mice were treated with low EC_5 or a high dose of telmisartan to compare their anti-aortic root remodeling effects. BP measurements and isolation of aortic tissues for vessel contractility measurements were done for all groups.

Results

Treatment with all ARBs at an EC_5 dose of BP-lowering resulted in no significant decreases in BP. However, telmisartan treatment resulted in a 70% inhibition of aortic contractility, which was blocked by the NO synthase inhibitor L-NAME. When compared to a high-dose of telmisartan in MFS mice, the EC_5 dose of telmisartan attenuated MFS pathology to the same degree as high-dose telmisartan despite divergent BP-lowering effects.

Conclusion

Telmisartan is the most potent endothelial function enhancing ARB at a sub-BP-lowering EC_5 dose. This dose of telmisartan attenuates mouse MFS aortic root pathology to an equal degree as a high-BP-lowering dose of telmisartan. Titration of ARBs to endothelial function instead of BP-lowering should be further investigated and telmisartan may be a highly effective ARB for MFS management.

A NOVEL MOUSE MODEL OF AORTIC DISSECTION CAUSED BY A POINT MUTATION IN THE HYBRID DOMAIN OF THE FIBRILLIN-1 GENE

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Background and Objective

Aortic dissection (AD) is the primary cause of death for patients with Marfan syndrome, caused by (likely) pathogenic variants in the fibrillin1 gene (*FBN1*). The molecular mechanism for the initiation and progression of AD is poorly understood. Here, we aim to establish a novel mouse model to elucidate the underlying mechanism of AD.

Methods

Based on a newly identified *FBN1* missense variant in a 30-year-old Japanese male patient with familial AD, we introduced the corresponding missense mutation, located in the first hybrid domain of the fibrillin-1 gene (*Fbn1*), in a mouse model. We systematically examined the vascular and extra-vascular lesions in the heterozygous and homozygous mice carrying the mutation.

Results

The elastic fibers in the homozygous mouse aortas were fragmented from 1 week of age, while aortic dilatation was not observed. Heterozygous mice showed no abnormalities. An abnormal blood flow velocity waveform at the mitral valve opening was observed from 4 week of age. 40% of homozygous mice died within 5 weeks after birth due to AD/rupture without aortic aneurysms. In addition, high MMP activity and progressive infiltration of immune cells into the adventitia and intima were observed. In contrast, the TGFβ signaling pathway showed no significant upregulation in the aortas while increased phosphorylation of PKCβ and upregulation of thrombospondin-1 were observed. There were no apparent skeletal abnormalities or eye lesions up to 3 months.

Conclusions

Our data indicate that this new mouse model faithfully reproduces human aortic conditions leading to dissection and rupture and offers a unique opportunity to examine the initial pathological changes of AD. An in-depth analysis of the transcriptomic profile in this novel mouse model will be needed to elucidate the detailed mechanisms of AD in future studies.

VALIDATION OF A GENERALIZED MECHANISTIC MODEL FOR SYNDROMIC PRESENTATIONS OF AORTIC ROOT ANEURYSM USING A CONDITIONAL ALLELIC SERIES OF THE SLOAN KETTERING INSTITUTE PROTOCO-ONCOGENE

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Objectives: Marfan (MFS), Loeys-Dietz (LDS) and Shprintzen-Goldberg (SGS) syndromes show aortic root aneurysm (AoRA) and an aortic wall signature for high TGFβ signaling (TGFβ HiSig). Each condition has a mechanism to reduce TGFβ activity (loss-of-function of signaling effectors in LDS, impaired concentration of TGFβ by microfibrils in MFS, stabilization of SKI – a repressor of the TGFβ transcriptional response – in SGS). We validated a reconciling model in LDS mice in which the second heart field (SHF) VSMC lineage is particularly vulnerable to a relative perturbation of TGFβ signaling, leading to increased AT1R-dependent TGFβ ligand expression and paracrine overdrive of neighboring signaling-competent cardiac neural crest (CNC) VSMCs. Selective antagonism of TGFβ activity in CNC cells is sufficient to prevent aneurysm in LDS mice. We explored generalization of this model to SGS and MFS.

Methods: Conditional knock-in, knockout, or transgenic overexpressing *Ski* alleles were assessed in combination with an *Fbn1* allele causing MFS.

Results: As predicted by the model, expression of an SGS allele ($Ski^{G34D/+}$) either globally or specifically in VSMCs caused AoRA in association with a thick collagen-congested aortic wall and overexpression of all assayed TGFβ targeted genes (i.e. TGFβ HiSig); all abnormalities were prevented by an AT1R antagonist. The AoRA and TGFβ HiSig seen in MFS mice were prevented upon overexpression of wild-type SKI in the CNC (where signaling is high), but not in the SHF (where signaling is already impaired). Deletion of *Ski* in the CNC of MFS mice accentuated aneurysm and TGFβ HiSig by amplifying the pathogenic TGFβ transcriptional response, whereas protection from aneurysm was seen upon *Ski* deletion in the SHF via boosting the TGFβ response and hence blunting the paracrine overdrive of the CNC.

Conclusions: These data show that aneurysm severity in multiple conditions specifically titrates TGFβ signaling status in the CNC and support therapeutic strategies aimed at strategic TGFβ antagonism.

IN *VITRO* MODELLING OF MARFAN RELATED CARDIOMYOPATHY POINTS TO ABNORMALITIES IN MECHANOBIOLOGY OF THE HEART MUSCLE CELLS

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Myocardial dysfunction has been demonstrated in a subset of patients with Marfan syndrome (MFS) and in several MFS mouse models but little is known about the intrinsic consequents of the variants on the cardiomyocytes (CMs). CMs were obtained by differentiating human induced pluripotent stem cells (iPSCs) from both MFS and CRISPR-corrected iPSCs, establishing the first human *in vitro* model for MFS-related cardiomyopathy (1).

Several functional analysis were applied on the CMs, including atomic force microscopy, multi-electrode array and Flexcell, revealing functional abnormalities (1). MFS CMs were stiffer, showed a lower beat-to-beat variability and received incomplete matrix support compared to corrected CMs. The improper functioning of the MFS CMs indicate an important role for impaired fibrillin-1 in the extracellular matrix.

The *in vitro* MFS myocardial model was further refined by using 3D co-cultures of CMs and cardiac fibroblasts (CFs) to understand the specific role of each cell type. Preliminary results show distinct differences in CFs derived from MFS iPSCs compared to corrected CFs. The impaired fibrillin-1 matrix production by CFs and the direct cell-cell interaction with CMs is thought to play a major role in the observed abnormalities in MFS CMs. 3D co-culturing MFS CMs with corrected CFs only shows partial rescue by decreased expression of *MMP9*, *ELN*, *TGFβ1* and *PAI-1*, thus implicating an intrinsic role for CMs in the observed cardiomyopathy. Interestingly, 3D cultured MFS CMs exhibit in general decreased *GJA1* (Connexin-43) gene expression compared to corrected CMs. We postulate that abnormal early development of CMs as a consequence of disturbed cell-matrix interactions may lead to MFS-related cardiomyopathy.

(1) Aalders, J. et al. Effects of fibrillin mutations on the behavior of heart muscle cells in Marfan syndrome. Sci Rep 10, 16756 (2020). https://doi.org/10.1038/s41598-020-73802-w

GATA4 AS A MODULATOR OF AORTIC ROOT SENSITIVITY TO MECHANOCHEMICAL DISRUPTIONS IN A MURINE MODEL OF LOEYS-DIETZ SYNDROME

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Introduction

Loeys-Dietz Syndrome (LDS) is a connective tissue disorder characterized by highly penetrant aortic aneurysms. Although dilation can develop in all segments of the arterial tree, the aortic root is one of the regions at higher risk for disease.

Objectives

To identify regional factors underlying aortic root susceptibility to aneurysm in LDS.

Materials and Methods

We performed single cell RNA sequencing on the aortas of 16-week-old control and *Tgfbr1*$^{M318R/+}$ mice, which carry an LDS-causing heterozygous kinase-inactivating mutation in *Tgfbr1*. The region analyzed included the aortic root, ascending aorta, and arch, spanning the region derived from secondary heart field (SHF) and cardiac neural crest (CNC) progenitors.

Results

We identified four vascular smooth muscle cells (VSMCs) clusters regardless of genotype, with two clusters showing increased expression of CNC- and two of SHF-enriched transcripts. SHF-enriched VSMC clusters expressed higher levels of *Gata4*, and GATA4 protein levels were upregulated in the aortic root of LDS mice. To test if excessive GATA4 expression or activity in VSMCs contributed to aortic root dilation in LDS, we analyzed the effect of VSMC-specific *Gata4* postnatal deletion. This intervention significantly reduced aortic root growth from 8 to 20 weeks of age. Transcriptomics data also revealed widespread alterations in expression of matrix proteins, and upregulation of positive regulators of focal adhesion kinase (FAK), including *Rock1*. On the basis of literature evidence linking FAK activity to GATA4 protein stability, we tested the effect of FAK inhibition both in vitro and in vivo. Preliminary data suggests that FAK inhibition reduces levels of GATA4 in aortic LDS VSMCs in vitro and attenuates aortic root growth from 8 to 16 weeks of age in vivo.

Conclusion

Although the mechanisms remain under investigation, expression of regional factors such as *Gata4* may sensitize specific subsets of aortic VSMCs to the effects of an LDS mutation.

DELINEATING MECHANISMS OF THORACIC AORTIC ANEURYSM AND DISSECTION – ROLES OF MEDIAL VULNERABILITY AND ADVENTITIAL INTEGRITY

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Introduction

Thoracic aortic aneurysms and dissections (TAAD) are generally considered together, but they often initiate and progress via very different biological and mechanical mechanisms.

Objectives

A goal of this study is to develop and use novel experimental and computational methods to delineate better the mechanisms of aneurysm progression and dissection potential based on data from multiple complementary mouse models.

Materials and Methods

We have developed two novel computer-controlled biomechanical testing systems to characterize the local biomechanical properties of the murine aorta during development, in health, and during disease progression. Using highly protocolized methods, here we directly contrast histo-mechanical findings from three primary mouse models (*Fbn1*$^{mgR/mgR}$, *Fbn1*$^{C1041G/+}$, *Tgfbr1r2*$^{f/f}$ + Tmx), including both pharmacologic treatments (losartan and rapamycin) and elastase and BAPN exposures. We interpret these many data both directly and via three classes of novel computational models: growth and remodeling simulations, smoothed particle mechanics, and phase-field finite elements. Amongst the many findings, we identify the critical importance of adventitial collagen remodeling in limiting the rate of aneurysmal dilatation and in containing partial medial tears so as to prevent dissections from progressing to aortic rupture.

Conclusion

Although medial degeneration is central to TAADs, collagen remodeling plays multiple critical roles in limiting disease progression and protecting against potentially lethal ruptures. Therapeutic interventions must preserve mural collagen fiber integrity.

INSIGHTS INTO THE BIOMECHANICAL INTEGRITY OF THE AORTA IN MICE MODELLING HEREDITARY AORTIC DISEASES

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Background/Objectives: Individuals suffering from hereditary aortic diseases (ADs) are at increased risk for aortic dissections and ruptures. We established an objective approach to measure the rupture force of the murine thoracic aorta, thereby explaining the outcomes of clinical studies and assessing an added value of old drugs in vascular Ehlers-Danlos syndrome (vEDS). Here, we applied our approach to six additional mouse AD models.

Methods: We used two mouse models for Marfan syndrome (MFS) as well as one smooth-muscle-cell-specific *Efemp2* knockout (SMKO) and three CRISPR/Cas9-engineered knock-in models *(Ltbp1*, *Mfap4*, and *Timp1*). Moreover, one mouse MFS model was subjected to 4-week-long losartan treatment previously shown to reduce aneurysm growth. 1.5-mm-long sections of the murine thoracic aorta were mounted on a tissue puller and uniaxially stretched until rupture as previously described.

Results: The aortic rupture force was significantly lower in both MFS and SMKO models, while mice with knock-in mutations in the genes *Ltbp1*, *Mfap4*, and *Timp1* showed no impairment of aortic integrity. As expected, the losartan treatment of mice modelling MFS led to the reduction of aneurysm formation, which, surprisingly, had no impact on the rupture force of the aorta.

Conclusions: We show for the first time that our read-out system is able to characterize the aortic biomechanical integrity of mice modelling not only vEDS but also related ADs. Furthermore, aneurysm progression alone may not be a sufficient read-out for aortic rupture, as blood-pressure-lowering therapies preventing aortic aneurysms might still not strengthen the weakened aortic wall. These results may contribute to better medical therapies of hereditary ADs.

ABNORMAL CONTRACTILITY AND MECHANOSENSING IN HYPERTENSIVE PATIENT IPSC-DERIVED VASCULAR SMOOTH MUSCLE CELLS BEARING A NOVEL HETEROZYGOUS MUTATION IN THE *PPP1R12A (MYOSIN PHOSPHATASE TARGET SUBUNIT 1)* GENE

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A 5-month old patient with bilateral coronary artery stenosis, was reported to have a *denovo* heterozygous point mutation in the *PPP1R12A* gene. This is a first report of a mutation in *PPP1R12A* with clinical features of vascular involvement, ischemic heart failure and hypertension. Based on the clinical findings and a previous study of mouse knockout of this gene in smooth muscle, we hypothesized that the mutation causes hyperactivity in these human vascular smooth muscle cells (vSMCs). Patient and healthy donor cells were reprogrammed to iPSCs followed by *in vitro* differentiation to vSMCs and phenotypic analyses. Comparing hypercontractile vSMCs to normal cells may hold the key towards understanding functional aspects of contractility and mechanical properties of vSMC in a range of vascular diseases, which remains underappreciated.

Objectives

1) To determine the phenotype the patient's vSMCs by *in-vitro* differentiation from iPSCs,
2) To determine the mechanisms underlying the phenotype,
3) Identify novel therapeutic strategies to restore vSMC contractile phenotype.

Material and methods: iPSC-vSMC differentiation, traction force microscopy, live-imaging, Proteomics

Results

Patient iPSC-derived vSMCs demonstrated hypercontractility. Proteomics data and western blotting also supported the evidence of increased actomyosin-contractility with associated increase in calcium signalling. Mechanosensitive nuclear envelope proteins and mechanoresponsive LIM domain proteins along with YAP pathway members were down-regulated in mutant vSMCs. When subjected to different matrix stiffnesses, mutant vSMCs had difficulty in adapting and continued to show focal adhesions formation and altered nuclear position and morphology on soft substrates. Further, to relax these cells, modulation of mechanosensitive pathways YAP and Piezo1 was more effective than calcium channel blockers.

Conclusions

PPP1R12A mutant vSMC show increased actomyosin activity and it is likely that the contractile-relaxation imbalance leads to abnormal mechanosensing. Better understanding of vSMC function and links between mechano-sensing and contraction are likely to lead to further insights and therapeutic opportunities in a range of vascular diseases including hypertension, atherosclerosis, and aortic aneurysms.

PENTAGALLOYL GLUCOSE (PGG) PREVENTS AND RESTORES MECHANICAL CHANGES CAUSED BY ELASTIC FIBER FRAGMENTATION IN THE MOUSE ASCENDING AORTA

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Introduction

Thoracic aortic aneurysm (TAA) in Marfan Syndrome is characterized by dilation of the aorta that can lead to dissection or rupture. Fragmentation of elastic fibers is a consistent histopathological feature of TAA that likely contributes to disease progression. Pentagalloyl glucose (PGG) shows promise for stabilizing elastic fibers in abdominal aortic aneurysms, but its efficacy and mechanical effects in the ascending aorta are unknown.

Objective

We simulated TAAs using elastase (ELA) to degrade elastic fibers in the mouse ascending aorta and determined the preventative and restorative potential of PGG.

Materials and Methods

Biaxial mechanical tests, constitutive model fitting, and multiphoton imaging were performed on untreated (UNT), PGG, ELA, PGG+ELA, and ELA+PGG treated aortas.

Results

PGG treatment alone does not significantly alter mechanical properties or wall structure compared to UNT. ELA treatment alone causes plastic deformation in the circumferential and axial directions, decreased circumferential compliance, significant changes in the material constants, and separation of the outer layers of the aortic wall compared to UNT. PGG treatment before (PGG+ELA) or after ELA (ELA+PGG) ameliorates the mechanical and structural changes associated with elastic fiber degradation, with preventative PGG (PGG+ELA) treatment being most effective.

Conclusion

These results suggest that PGG may be an effective pharmaceutical option to stabilize elastic fibers in TAA associated with Marfan Syndrome. Ongoing work includes in vivo treatment of a Marfan Syndrome mouse model with PGG-loaded nanoparticles that target degraded elastic fibers.

LMOD1 VARIANTS ASSOCIATED WITH INTERNATIONAL TAAD COHORTS

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Introduction: Thoracic Aortic Aneurysm and Dissection (TAAD) is a severe disease with an increasing incidence (9-15/100,000 patient-years) and accounting for approximately 15,000 deaths per year in the USA. TAAD is typically inherited in an autosomal dominant manner and showing variability in penetrance and severity.

The most common and best characterized syndromic TAAD is Marfan syndrome. In non-syndromic forms of TAAD, a quarter of cases are familial (FTAAD), strongly suggesting a genetic basis in the presence of a normal clinical phenotype. The underlying molecular genetics of TAAD is heterogeneous, with many genes reported to date as sites of pathogenic variants in syndromic and non-syndromic TAAD. However, many families (as much as 84.6%) do not have a causative variant in the reported TAAD genes, suggesting that additional FTAAD genes are yet to be found.

Objectives: TAAD can arise at any time without previous warnings and with fatal consequences. We will describe the genetic cause of TAAD in several international TAAD cohorts.

Materials and Methods: Whole exome sequencing was performed and analysed in a large multigenerational family of British ancestry with autosomal dominant inheritance of TAAD.

Results: N-terminus variants in the TMBS domain & C-terminus variants in the WH2 domain of LMOD1 were enriched in their respective domains in the complete TAAD patient cohort versus the gnomAD genetic database. Myofibroblasts from the proband with variant Val595Ala demonstrated reduced nucleation of actin filaments, mislocalization of LMOD1 protein, and impaired contractility. Knockdown of paralogs *lmod1a/lmod1b* in zebrafish demonstrated delayed development of the aortic precursors, rescued by co-injections with wild-type *LMOD1* mRNA. Conversely, this zebrafish knockdown could not be fully rescued by the mutant c.1784T>C [p.(Val595Ala)] containing *LMOD1* mRNA, strongly suggesting this variant is pathogenic for TAAD.

Conclusion: This study proposes: variants in LMOD1 (TMBS and WH2 domains) predisposes to TAAD due to abnormal LMOD1 functionality.

PATHOGENIC VARIANTS AFFECTING THE TB5 DOMAIN OF FIBRILLIN-1 PROTEIN IN MARFAN SYNDROME AND GELEOPHYSIC/ACROMICRIC DYSPLASIA PATIENTS: FROM TALL TO SHORT

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Introduction

The most known fibrillinopathy, Marfan syndrome (MFS), is a multisystem disease with a unique combination of skeletal, cardiovascular and ocular features. The geleophysic/acromicric dysplasia (GD/AD), characterized by short stature, short extRémities and joint limitation are described as “the mirror image” of MFS. The numerous *FBN1* pathogenic variants identified in MFS are located all along the gene, leading to the same pathophysiological mechanism. Interestingly, in GD/AD patients, the 27 heterozygous *FBN1* pathogenic variants reported all affect the TGFβ-binding protein-like domain #5 (TB5).

Objectives

The main objective is to describe the variants located in this specific domain of fibrillin-1, leading to two opposite phenotypes.

Material and Methods

Between 1996 and 2021, blood samples were obtained for more than 5000 consecutive probands referred nationwide to our laboratory for molecular diagnosis of suspected MFS or related disorders. The *FBN1* gene was originally screened by bidirectional Sanger sequencing and later by a NGS custom capture array.

Results

We identified 5 MFS probands carrying 5 distinct heterozygous variants affecting the TB5 domain of FBN1. The clinical data for these 5 probands and their 7 relatives showed that all the probands displayed a classical form of MFS, with the involvement of skeletal, cardiovascular, and/or ophthalmological systems. At the molecular level, the variants were 3 missense variants and 2 small in-frame deletions. Strikingly, one missense variant affects an amino acid that was previously involved in GD.

Conclusion

Surprisingly, pathogenic variants in the TB5 domain of FBN1 can lead to two opposite phenotypes: GD/AD or MFS suggesting the involvement of tissue specific mechanism and/or a modifier gene. Further functional studies are ongoing to determine the precise role of this domain in the physiopathology of each disease.

TGFB3-RELATED HERITABLE THORACIC AORTIC DISEASE (HTAD): RESULTS FROM THE MONTALCINO AORTIC CONSORTIUM (MAC)

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Introduction: Pathogenic variants in *TGFB3* lead to phenotypes and HTAD overlapping Marfan syndrome (MFS) and TGF-β vasculopathies.

Materials/Methods: Clinical data, phenotypic features, arterial and aortic outcomes in individuals with *TGFB3* variants enrolled in the MAC were reviewed. *TGFB3* rare variants were curated as pathogenic/likely pathogenic by two independent curators.

Results: 40 patients (62.5% male) with *TGFB3* variants and median age 33.5 (IQR 16 – 47) were studied. 31 patients were probands. The median MFS systemic score was 6.5 (IQR 3.5 - 7) and included features such as pectus deformities (20/33), spine abnormalities (14/35), and pes planus (16/33). Features of Loeys-Dietz syndrome included hypertelorism (7/35), abnormal uvula (10/30), cleft palate (6/38), and cutaneous features [doughy skin (8/31), translucent skin (6/32), and widened scars (4/32)]. Mitral valve prolapse was present in 7/40 and a bicuspid aortic valve in 3/40. Arterial tortuosity was present in 5/33; extra-aortic aneurysms in 4/39. A dilated aortic root or a history of aortic root replacement occurred in 9/40. One patient underwent elective root replacement at an aortic diameter 44-mm (age 38-years). Five patients (mean age 63 ± 4) with dilated aortic roots, currently 43-mm, 43-mm, 47-mm, 48-mm, and 49-mm, are being followed. Type A aortic dissection (TAAD) occurred in two patients (ages 59 and 60) and type B aortic dissection (TBAD) in one (age 43-years), all prior to the identification of their *TGFB3* variants. The aortic root size at the time of TAAD was 47-mm in one patient; the descending aorta at the time of TBAD was 43-mm. No deaths from AD occurred. Six of 14 women reported 6 uncomplicated pregnancies.

Conclusions: *TGFB3*-related HTAD shares phenotypic features overlapping MFS and TGF-β related vasculopathies. Aortic root dilatation and aortic dissections occur, but may present with later onset and less penetrance than those associated with *TGFBR1/TGFBR2* variants.

THE FBN1 GENE MUTATIONAL IMPACT AND CLINICAL PATHOGENICITY IN 139 UNRELATED TAIWANESE PATIENTS WITH MARFAN SYNDROME

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Objectives

Building a decision tree model to identify the mutational impact and clinical pathogenicity in Taiwanese Marfan syndrome.

Methods and Results

From May 2007 to Dec 2022, a total of 173 subjects were enrolled, of which 139 had non-synonymous mutations in the FBN1 gene. Further analysis combined with clinical symptoms revealed that (1) FBN1 gene with non-missense mutations were associated with a higher risk of aortic aneurysm or dissection (OR = 5.67, p = 0.0065), but a lower chance of family history (OR = 0.434, p = 0.0324), which may be due to a higher mortality rate that make the offsprings difficult to survive; (2) When FBN1 gene has a missense mutation and is located in the cbEGF-like domain, the patient is prone to have a typical thin and tall appearance (OR = 3.5, p = 0.00825); (3) If the mutation occurs in the 12 conservative sequences of the cbEGF-like domain (Conserved sequence), patients are prone to have cardiovascular disease (OR = 3.38, p = 0.03187) and lens dislocation (OR = 5.5, p = 0.00143).

Conclusions

Genotype information is essential for diagnosis of Marfan syndrome. Detection of gene mutation sites and pathogenicity can provide more information about disease manifestations, helping healthcare, prenatal consultations, and moving towards precision medicine.

GENOTYPE-MITRAL VALVE PHENOTYPE CORRELATIONS IN MARFAN SYNDROME WITH FBN1 PATHOGENIC VARIANTS

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Introduction

Mitral valve prolapse (MVP) is frequent in Marfan syndrome (MFS) and is associated with mitral annular disjunction (MAD) which is a separation between the atrial wall-mitral valve junction and the left ventricular attachment. We recently reported genotype-phenotype correlations in a large MFS population with a difference of survival according to the impact on the cysteine content of fibrillin-1.

Objectives

We report the genotype-phenotype correlations in a subgroup with comprehensive mitral valve evaluation in MFS population.

Materials and Methods

We included MFS patients with *FBN1* pathogenic variant, older than 14 yo without thoracic surgery seen in the French reference center. Using standardised transthoracic echocardiography, we evaluated presence of MVP defined by a mitral leaflet displacement ≥2 mm in systole into the left atrium and presence of MAD. We sought correlations between genotype and mitral valve features, according to the presence of premature termination codon (PTC) variants or in-frame variants (IFV). IFV were divided according to the impact on the cysteine content of fibrillin-1.

Results

A total of 250 MFS patients were included. 99 (39.6%) had PTC variants and 151 patients (60.4%) had IFV. Among patients with IFV, 27 had missense variants that substitute for a cysteine (+Cys), 49 had missense variants that substitute a cysteine for another amino acid (-Cys) and 75 had IFV not modifying the cysteine content of the fibrilline (noCys).

Overall, MVP was observed in 37% and MAD in 22.1%, with a prevalence similar in patients with PTC or IFV.

Among patients with IFV, patients with (-Cys) variants had significantly more MVP compared to patients with (noCys) variants and patients with (+Cys) variants (51% vs 34.7% vs 18.5% respectively; p=0.016). Prevalence of MAD was also more important in patients with (-Cys) variants than patients with (noCys) variants and patients with (+Cys) variants (32.6% vs 19.1% vs 7.4% respectively; p= 0.033).

Conclusion

In this MFS population, mitral valve features are related to the type of variants. In-frame (-Cys) variants were associated with a higher prevalence of MVP and MAD.

PATHOGENIC VARIANTS IN *PLEKHO2* PREDISPOSE TO HERITABLE THORACIC AORTIC DISEASE

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Objectives

To identify novel heritable thoracic aortic disease (HTAD) genes, exome sequencing was pursued on affected individuals in 392 unsolved HTAD families.

Results

A rare heterozygous variant, p.Gly392Glu, in *PLEKHO2* segregated with HTAD in a large family with a LOD score of 3.26 (variant is present once in 125,000 gnomAD v2.1.1 exomes and predicted to be damaging). Analysis of exome sequencing data from affected probands from 392 unsolved HTAD families and 545 unrelated individuals with early-onset sporadic thoracic aortic dissections ≤ 60 years of age identified four additional rare and damaging *PLEKHO2* missense variants.

PLEKHO2 encodes a protein with no established function. Smooth muscle cells (SMCs) explanted from aorta of a *PLEKHO2* p.Gly392Glu patient had significantly increased expression and protein levels of SMC contractile genes and reduced proliferation compared to that of wild type (WT) SMCs: similar changes were observed in SMCs with *PLEKHO2* knockdown using shRNAs. *Plekho2*$^{-/-}$ mouse aortas had increased expression and protein levels of SMC contractile genes and thicker medial layers that WT aortas. In *PLEKHO2* knockdown SMCs, there was no alterations in phosphorylation of SMAD2/3 with TGF-β1 exposure. Instead, non-canonical TGF-β signaling was constitutively activated in the absence of TGF-β1 exposure based on increased phosphorylation of TAK1 and p38 MAPK, but not JNK or p65. Inhibitors of TAK1 and p38 MAPK, along with knockdown of TRAF6 using shRNAs, decreased p21 and SMC contractile gene expression in *PLEKHO2* knockdown SMCs. Co-immunoprecipitation assays indicate that PLEKHO2 binds directly to TRAF6 and TAK1 and controls TAK1 activation.

Conclusions

Our data indicated that loss of PLEKHO2 function leads to constitutive activation of TAK1-P38 MAPK signaling in SMCs, which ultimately predisposes to HTAD.

HOMOZYGOUS AND COMPOUND HETEROZYGOUS VARIANTS IN *ACTA2* GENE: UNEXPECTED FINDINGS IN EARLY ONSET HERITABLE THORACIC AORTIC DISSECTIONS

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Introduction

Disease-causing heterozygous variants in the *ACTA2* gene cause an autosomal dominant non syndromic heritable thoracic aortic disease (HTAD) with thoracic aortic aneurysm and dissection as main phenotype.

Objectives

We have identified three patients presenting homozygous or compound heterozygous variants in *ACTA2* gene in the context of molecular diagnosis of HTAD. The aim of this study is to describe clinical features associated with these unusual molecular events.

Material and Methods

More than 4000 French probands have been addressed to our laboratory for a suspicion of HTAD since 2016. A custom capture array was used to capture all coding exons and the flanking intronic sequences of 28 genes already known to be associated with HTAD, including *ACTA2* gene.

Results

Among 58 HTAD probands carrying *ACTA2* pathogenic variants, 2 carried homozygous variants (p.Glu59Lys, p.Glu318Lys) and one was a compound heterozygous (p.[(Asp83Asn)];[(Ala140Glu)]). All three presented type A aortic dissection before 30 yo. The heterozygous carriers tested in their families did not present aortic dissection but cases of HTAD or ischemic stroke were reported in the families. Only the 2 variants of the compound hererozygous proband were previously identified in our laboratory or in the literature and each was associated with HTAD. These observations were recently extended to one American proband with early onset aortic dissection carrying another *ACTA2* homozygous variant (p.Trp88Arg).

Conclusion

In the course of molecular diagnosis of HTAD, we describe the original observation of homozygous/compound heterozygous carriers of *ACTA2* variants. Clinical data for these probands and their relatives confirmed that incomplete penetrance is usual in heterozygous *ACTA2* variation carriers. Pathogenic variation at homozygous or compound heterozygous state seems to cause a more severe presentation than a variation at heterozygous state. Although homozygosity and compound heterozygosity are rarely found in molecular diagnosis, they should not be overlooked, especially among consanguineous families.

INTRACRANIAL ANEURYSMS IN PATIENTS WITH LOEYS-DIETZ SYNDROME

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Introduction

Loeys-Dietz syndrome (LDS) is a heritable aortopathy associated with craniofacial abnormalities, vessel tortuosity, and aneurysms. The prevalence and predictors of intracranial aneurysms (ICA) in LDS remain poorly defined.

Objectives

We analyzed patients with LDS due to disease-causing variants in *TGBFR1*, *TGFBR2*, *SMAD3*, *TGFB2* or *TGFB3* for ICA prevalence and risk factors.

Materials and Methods

80 patients with LDS underwent screening for ICA with computed tomography or magnetic resonance angiography. We reviewed records for clinical, genetic, and radiographic data. A craniofacial severity index (CFI) score was calculated, and tonsillar herniation measurements were performed in patients with craniocervical junction imaging.

Results

Overall, 22.5% of patients have at least one and 7.5% have two or more ICAs. ICAs are more frequent with *SMAD3* (46.2%) and *TGFBR2* (20.8%) variants. Patients with an ICA are an average of 37.0 ± 17.0 years old (range 14-74). 28 ICAs are found in 18 patients, and are typically small (average 3.4 ± 2.3 mm). Three patients had an ICA treated via flow-diverting stent, with one treatment complicated by vertebral artery occlusion.

Current tobacco smoking is associated with ICA (OR 7.56, *p=0.01*). While aortic dissection is not associated with ICA, non-aortic vessel dissection is (OR 3.61, *p=0.03*). Historically, higher CFI is associated with worse cardiovascular outcomes, but we found no relationship between CFI and ICA. However, ICA is associated with Chiari malformations (OR 8.43, *p=0.03*). Aorta abnormalities (dilation, dissection, or prior surgery), hypertension, and stroke were common but not associated with ICA.

Conclusion

ICAs are found in >20% of patients with LDS. Current smoking, non-aortic arterial dissection, and Chiari malformation are associated with ICA. Severity of aortic disease or craniofacial findings are poor predictors for ICAs, so serial imaging is appropriate to detect ICAs in LDS, even in patients with mild disease phenotypes.

WHOLE-EXOME SEQUENCING OF 781 UNRELATED ANEURYSM PATIENTS IDENTIFIES MULTIPLE RARE VARIANTS OF THE PROPROTEIN CONVERTASE FURIN CAUSING IMPAIRED TGFB SIGNALING

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Background

Aortic aneurysms (AA) occur frequently in population above 65 years of age. The characteristic loss of elasticity of the aortic wall is caused by complex interactions between genetic predispositions and other risk factors like smoking and hypertension. The genetic causes identified so far are predominantly associated with dysregulation of transforming growth factor-beta (TGFB) signaling, accounting for a small proportion of AA.

Objectives

Determine if pro-protein convertase *FURIN* is a susceptibility gene for aortic aneurysms, based on its role in post-translation modification of TGFB.

Methods

From whole-exome sequencing data of 781 unrelated AA patients and affected relatives, rare variants with predicted pathogenic effects in *FURIN* were selected. The effects of these variants were investigated by structural modeling of protein domains, protein maturation and -activity assays. TFGB maturation, intracellular canonical and non-canonical signaling and downstream gene expression were analysed by immunoblotting and gene expression in patient-derived fibroblast.

Results

WES analysis showed that 31 (3.9%) unrelated index aneurysm patients had 15 different rare heterozygous *FURIN* variants. Two families showed familial segregation of *FURIN* variants. Among 31 index cases, 22 had abdominal aneurysms, 14 had a thoracic aneurysm, 5 a rupture, and 4 a dissection. Overall 23 patients had multiple aneurysms. Constructs of *FURIN* variants showed decrease of steady-state FURIN protein levels, protease activity and shedding. Maturation of proTGFB1, phosphorylation of the downstream targets SMAD2 and ERK1/2 and gene expression of TGFB1-responsive *ACTA2* and *COL4A1* were impaired in fibroblasts, indicating that TGFB family actions were dysregulated. The individual dysregulating effects on TGFB signaling in 5 patients with the recurrent missense p.R745Q highlighted interactions with genetic backgrounds.

Conclusion

FURIN was identified as a novel gene predisposing to aortic aneurysm, with high prevalence in aorta aneurysm patients. The heterogeneity of the effects on TGFB signaling endorses the poly genetic nature of aortic aneurysms.

WHAT IF IT IS NOT ONLY MARFAN SYNDROME?

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Introduction

The diagnosis of Marfan syndrome (MFS) relies on defined clinical criteria (Ghent nosology). It is likely that within the Marfan population other genetic diseases occur with the same frequency as within the normal population; consequently, some of the Marfan patients may suffer from another disease as well. Usually, these patients have additional features outside the Marfan spectrum.

Objectives

To describe the Marfan patients in our hospital with Marfan syndrome and any other genetic diagnosis (Marfan+); and how they were recognized.

Materials and Methods

We collected data on medical history, genetic analysis, and phenotypic features of the patients with Marfan+

Results

In our cohort of around 400 patients with Marfan syndrome we encountered 6 patients with additional diagnoses. Patient 1 has Marfan syndrome, paternally inherited. Because of developmental delay and relatively short stature additional genetic workup was done and a de novo MAP2K1 mutation was found (Noonan/CFC syndrome). In patient 2 a diagnosis of Prader Willi syndrome was established but because of a Marfanoid stature the patient was referred to our centre and a homozygous FBN1 variant was found c.4075A>G, p.(Ile1359Val). In patient 3 a diagnosis of Marfan syndrome was made based on physical signs, aortic dissection and an *FBN1* variant (c.5951_5956dup, p.(Als1985_Pro1986insArgAla). However, in a 3rd degree relative TAAD diagnostic workup showed a *SMAD3* variant (c.728G>C, p.Arg243Pro). Re-analysis showed that our patient carries both (probably pathogenic) variants. In patient 4, genetic work-up was done because of tall stature (+3SD). A de novo *NSD1* mutation (Sotos syndrome) was found, and a maternally inherited *FBN1* variant. This variant has previously been found in patients with aortic root dilatation and families with Marfan/TAAD. Patient 5 was initially referred at age 4 because of relative tall stature, arachnodactyly, camptodactyly, pes plani and ectopia lentis. Genetic work-up revealed a 47,XXY karyotype and a pathogenic de novo p.Cys1420Phe *FBN1* variant. Cardiac follow-up up to the age 14 years shows normal valve function and no aortic root dilatation (Z-score=1.4). Patient 6 has Marfan syndrome and hypochondroplasia. His relative short stature (155 cm) in combination with the skeletal dysplasia brings along challenges in performing and interpreting imaging.

Conclusion

Marfan patients can also have additional (genetic) diagnoses. Extra-ordinary phenotypical features may help to identify these. It is important to recognize additional diagnosis to adjust screening and follow-up.

NATURAL HISTORY AND GENOTYPE-PHENOTYPE CORRELATION IN WEILL-MARCHESANI SYNDROME: RETROSPECTIVE COHORT OF 18 UNREPORTED INDIVIDUALS AND LITERATURE REVIEW OF 42 PREVIOUSLY REPORTED INDIVIDUALS

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Introduction: Weill-Marchesani syndrome (WMS) belongs to the group of acromelic dysplasias, defined by short stature, brachydactyly and joint stiffness. WMS is characterized by ophthalmological abnormalities such as microspherophakia, severe myopia, and lens ectopia. Cardiovascular defects have been reported. Monoallelic variations in *FBN1* are associated with dominant WMS, while biallelic variations in *ADAMTS10*, *ADAMTS17* and *LTBP2* are responsible for recessive of WMS. These four genes code for components of extracellular matrix.

Objective: Natural history description of WMS and genotype-phenotype correlation establishment.

Materials and Methods: Retrospective multicenter study and literature review. Inclusion criteria: clinical diagnosis of WMS with identified mutations.

Results: 60 patients were included in our study: 18 individuals from 17 families from our retrospective cohort and 42 patients from 23 families from literature review. 20 had mutations in *ADAMTS17*, 19 in *FBN1* without specific localization, 19 in *ADAMTS10*, and 2 in *LTBP2*. All individuals presented with eye anomalies including high myopia (38/60), lens ectopy (37/60), microspherophakia (37/60), glaucoma (14/60), and cataract (9/60). Short stature was present in 42/60 patients (70%) ranging from -2 to -5.5 SD. Brachydactyly and joint limitations were observed in 35/60 (58%) and 24/60 (40%) patients, respectively. 10/60 individuals had a valvulopathy, and three patients with *FBN1* mutations developed aortic dissection (2) or aneurysm (1). No clear genotype-phenotype correlation could be established. However, patients with mutation located in TB5 domain of *FBN1* were significantly smaller than patients with *FBN1* mutation outside TB5 domain, who had normal stature for most of them.

Discussion: Apart from the ophthalmological findings, which are mandatory for the diagnosis, the phenotype of WMS seems to be more variable than initially described. Notably, only two-thirds of patients presented with short stature. No genotype-phenotype correlation emerges from this study; apart from mutations located in the TB5 domain of *FBN1*, which are associated with short stature.

CLINVAR AND HGMD VARIANTS IN TAAD GENES: YOU CANNOT INTERPRET WHAT YOU DO NOT DETECT

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Introduction: Whole-exome sequencing (WES), short-read whole-genome sequencing (SR-WGS) and long-read WGS (LR-WGS) enable the detection of sequence variants at unprecedented scale. To identify the cause of Mendelian disorders, such as syndromal and non-syndromal forms of thoracic aortic aneurysms and dissections (TAAD), expert interpretation should not miss (likely) pathogenic variants (LP/P) listed in disease databases like ClinVar or HGMD.

Objectives: The calling of all clinically-relevant ClinVar/HGMD variants is challenging due to the limitations of sequencing and data analysis pipelines. Here, we provide new insights into the performance of the most recent sequencing, alignment, and variant-calling pipelines in the detection of ClinVar/HGMD variants with the focus on established TAAD genes.

Material and Methods: We used raw data of SR-WGS (~60× PE150) of our in-house samples as well as SR-WGS (~60× PE150) and LR-WGS (~30× PacBio HiFi) of publicly available reference samples. We implemented 13 state-of-the-art analysis pipelines for SR-WGS, LR-WGS, or the combination of both as well as developed a workflow to assess the pipelines' performance in the detection of ClinVar/HGMD variants.

Results: For a ~60× SR-WGS, accelerated pipelines decreased the runtime of BWA/GATK from ~2.5 days to ~2-5 hours. LR-WGS outperformed SR-WGS, particularly in regions with mappability <1, while WES, as expected, failed to detect LP/P ClinVar/HGMD variants in non-exonic or GC-rich regions. By analyzing read depth, strand bias, variant allele fraction, and population-based allele frequency, we identified a substantial number of false-positive ClinVar/HGMD entries.

Conclusions: Sequencing, alignment, and variant-calling pipelines can significantly influence the detection of all LP/P ClinVar/HGMD variants, leading to both false-negative and false-positive results. Owing to its inherent advantages in variant detection/calling, LR-WGS should be implemented in clinical practice as soon as it is affordable, either as a standalone solution or to complement SR-WGS.

GROWTH CHARTS FOR MARFAN SYNDROME IN THE NETHERLANDS AND ANALYSIS OF GENOTYPE-PHENOTYPE RELATIONSHIPS

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Objectives

To optimize care for children with MFS in the Netherlands, Dutch MFS growth charts were constructed. We also aimed to investigate the effect of *FBN1* variant type (haploinsufficiency [HI]/dominant negative [DN]) on growth, and compare MFS-related height increase across populations.

Materials and Methods

Height and weight data of individuals with MFS aged 0-21 years were retrospectively collected. GAMLSS was used for growth chart modelling. To investigate genotype-phenotype relationships, *FBN1* variant type was included as an independent variable in height-for-age and BMI-for-age models. MFS-related height increase was compared with that of previous MFS growth studies from the USA, Korea and France.

Results

Height and weight data of 389 individuals with MFS were included (210 males). Height-for-age, BMI-for-age, and weight-for-height charts reflected the tall and slender MFS habitus throughout childhood. Although the Dutch individuals with MFS were on average taller than those living in the other countries, mean increase in height compared with the general Dutch population was significantly lower than in the other three MFS populations compared to their reference populations. *FBN1*-HI variants were associated with taller height in both sexes, and decreased BMI in females (p-values<0.01).

Conclusion

This Dutch MFS growth study broadens the notion that genetic background and MFS variant type (HI/DN) influence tall and slender stature in MFS.

ELASTIN DENUDATION UNDERLIES EARLY AORTIC DEGENERATION IN LOEYS-DIETZ SYNDROME 3

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Introduction

The cellular basis for the aggressive aortic disease in patients with Loeys-Dietz syndrome (LDS) is largely unknown.

Objectives

To determine the early molecular pathology of the aortic wall in patients with LDS3.

Materials and Methods

We identified a missense mutation in the MH2 domain of SMAD3 (p.Arg287>Gln) in 54 members of a Canadian family. We undertook quantitative microarchitecture analysis of the thoracic aorta in seven of whom underwent aortic repair. Findings were compared with aortas from heart transplant recipients and diameter-match aortas from patients with a bicuspid aortic valve (BAV). RNA sequencing and bioinformatic analyses were also undertaken on LDS3 vs normal aortic smooth muscle cells (SMCs).

Results

The median age of the seven LDS3 subjects at the first aortic event was 37 (32-73) years. The mean aortic root diameter at the time of repair was 4.9±0.5 cm. The ascending aorta was smaller (3.6±0.7 cm, $p<0.0001$) with limited medial degeneration and largely intact elastin fibers. However, even in these minimally dilated ascending aortas, 11.1% of SMCs were found to be separated from the elastin laminae by a thin layer of glycosaminoglycan. In contrast, elastin-SMC separation was present in only 2.0% and 1.2% of SMCs in normal ($p=0.044$) and diameter-matched-BAV aortas ($p=0.026$). Moreover, confocal microscopy revealed a striking loss of microfibril proteins that normally decorate elastin, including microfibril-associated glycoprotein-2, fibulin-1, fibulin-2, fibrillin-1, and fibrillin-2. Transcriptomic analysis of LDS3 SMCs revealed that all but fibrillin-1 were down-regulated at the transcript level. In addition, the TGFß-responsive transcription factors, PRRX2, FOXF1 and FOXF2, putative hubs for microfibril genes, were downregulated in LDS3 SMCs.

Conclusion

Elastin denudation of microfibrils is an early feature of the degenerating aorta with mutated SMAD3. Restoring the microfibril sheath could be a framework for aortic stabilization in LDS3.

A CASE SERIES OF LOEYS-DIETZ SYNDROME: HOW CAN WE IMPROVE THE PRACTICAL UTILITY OF DNA DIAGNOSTICS FOR SURGICAL PURPOSES?

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Introduction

Loeys-Dietz syndrome (LDS) is characterized by more severe thoracic aortic disease (TAD) than other connective tissue disorders (CTDs). The definite diagnosis of LDS can be established exclusively by genetic testing. This testing along with strong overlapping of LDS symptoms with those of other CTDs, leads to significant underdiagnosis of LDS in patients with aortic aneurysms.

Objectives

To present the first LDS case series from Russia, to discuss the genotype-phenotype correlations and practical utility of these results.

Materials and Methods

In 10 years of genetic counseling for patients with TAD, we have found 6 genetically confirmed cases of LDS. Genetic testing was performed by next generation sequencing (NGS) followed by Sanger validation of detected variants.

Results

All 6 probands presented with remarkable symptoms of TAD, while extracardiac manifestations were significantly diverse. None had symptoms reported to be unique for LDS (hypertelorism, bifid uvula, cleft palate). Prevalent genetic findings were in the TGFB2 and TGFBR2 genes (2 and 2 of 6 probands, respectively). One proband had a TGFBR1 variant and one had a TGFB3 variant. One of TGFB2-positive patients was compound heterozygote, and one proband with TGFBR2 variant had an additional finding of uncertain significance in the COL3A1 gene. The rest probands were heterozygous. In all cases, except one, the diagnosis of LDS was established retrospectively after aortic surgery. The operated patients demonstrated poor tolerance to surgery, increased blood loss and severe postoperative complications with tendency to further vessel dissection.

Conclusions

The LDS patients demonstrate higher risk of aneurysm progression and early rupture and are more prone to postoperative complications in comparison with other CTDs. Meanwhile, our results indicate a common underestimation of surgical risks in LDS. We believe that low recognition of LDS in routine surgery may be partially overcome by accumulating the data on genotype-phenotype correlations and informing the surgeons.

AORTIC AND ARTERIAL ANEURYSMS AND DISSECTIONS IN PATIENTS WITH LOEYS-DIETZ SYNDROME VARY BY THE PATHOGENIC VARIANT GENE

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Introduction

Loeys Dietz syndrome (LDS) is a heterogeneous group of disorders due to pathogenic variants in the genes coding for TGFβ signaling.

Objective

We describe the aortic and arterial pathology in this population, the phenotypic clinical exam features, interval to aortic/arterial aneurysms/dissections, and extent of repair.

Materials and Methods

Retrospective single academic health care system review of patients with LDS between 2000 and 2021. Individuals with pathogenic/likely pathogenic variants for LDS I-V were included for analysis. Demographics, aortic/arterial pathology, surgical repairs, and survival were abstracted. Groups were compared by presence of aortic/arterial pathology and by genotype (LDS I-II vs. LDS III-V).

Results

A total of 63 patients with LDS (46% male, 77.8 % White, 45.8±14.4 years) were identified: 28.6% LDS I, 23.8% LDS II, 31.7% LDS III, 8% LDS IV, and 8% LDS V. Mean follow up was 7±7 years, Aortic/arterial pathology was diagnosed in 38 (60.3%) patients: 18 aortic dissections (AD) and 26 arterial aneurysms/dissections. AD was type A (n=14), and type B (N=5, one superimposed on a chronic type A). Carotid and iliac arteries were most frequent arteries affected (N=7 each). There were no differences in the extra-aortic phenotypic clinical exam among patients with and without aortic/arterial pathology. Hypertension was more prevalent among those with aortic/arterial pathology (56.8% vs 20%, P=.004). Patients with LDS I-II (N=33) had more aortic/arterial pathology compared to LDS III-V (N=30): 75.8% vs. 43.3%, P=.009 and were younger at occurrence (33.0±15.3 vs. 47.3±5.9 years, P=.003). Surgical repairs included 31 root, ascending, and/or arch repair (49.2%) and 11 descending thoracic and/or thoracoabdominal aortic repair (17.5%). There were 8 deaths (mean age 46.3±10.9 years) with cause of death due to aortic rupture or dissection (N=7) and one unknown.

Conclusions

The genotype and hypertension appear to be associated with aortic/arterial pathology while extra-aortic clinical exam phenotype does not.

AORTIC AND VASCULAR INVOLVEMENT IN LOEYS-DIETZ SYNDROME: RESULTS FROM THE REPAG REGISTRY (SPANISH NETWORK OF GENETIC AORTIC DISEASES).

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Background: Limited information is available regarding the overall aortic and vascular outcome of patients with LDS (TGFB pathway genetic variants)

Objective: To evaluate aortic and vascular complications of patients with genetic variants in the TGFB pathway.

Methods: observational study including (likely) pathogenic (LP/P) variants in TGFbeta pathway from 10 tertiary centers. Clinical and imaging data were reviewed and data on aortic and vascular outcome included.

Results: A total of 163 patients were included (47.9% women, 38.6% index cases), mean age at first evaluation 32.3±20.4yrs, 27.0% with age <16yrs. 70 TGFBR1, 43 TGFBR2, 29 SMAD3, 9 TGFB2 and 12 TGFB3 (Table). Mean follow-up was 4.7±3.7yrs. 54 (33.1%) patients had at least 1 aortic surgery (max 6). Mean age at first aortic surgery was 37.2±16.8yrs (Range 1.2–72.9). First surgery was elective in 42 (77.8%), and included aortic root or ascending aorta in 40 (95.2%) and isolated descending aorta in 2 (4.8%). Emergent surgery included aortic root or ascending aorta in 11 (92.7%). Ascending aorta-root diameter previous to elective surgery was 48.9±4.9mm (range 41-65). 7 patients died during follow-up (2 intracranial bleedings, 1 SD, 2 aortic rupture, 1 post aortic surgery, 1 non-CV). Furthermore, 19 acute aortic syndromes (AAS) were reported (17 dissections , 2haematoma) in 18 patients, 10 type A (52.6%). Mean age at first AAS was 42.3±11.1yrs (min 19.7yrs to 62.9yrs) Median survival free of intervention, dissection or death was 57.1yrs, being worst for men than women (44.7 yrs vs 69.1yrs, p<0.001) (Figure), these gender-difference only remained significant in the TGFBR1 and SMAD3 groups (p=0.005 and p=0.008) Regarding aortic branch and intracranial aneurysms, a total of 383 imaging studies of aortic branches and 223 cranial imaging studies were performed during the clinical follow-up. 21 cranial aneurysms and 73 aortic branch aneurisms were reported. 14 (11.5%) patients suffered 19 aneurysms-related events (3 dissections, 3 ruptures, 13 interventions).

Conclusions: In patients with Loeys-Dietz Syndrome, there's a high prevalence of aortic surgeries and acute aortic events, with high numbers of peripheral and intracranial aneurysms. A worst prognosis in men than in women is observed in TGFBR1 and SMAD3 variants.

	Index cases	Elective ascending aortic surgery (mean age)	Acute aortic syndrome (mean age)	Non-aortic aneurysms-related events
TGFBR1, 70 (42.9%)	22 (31.4%)	18, 25.7% 37.6±18.4yrs	7 (10.0%) 44.9±9.4yrs	6 (9.7%)
TGFBR2, 43 (26.4%)	24 (55.8%)	15, 34.9%) 23.0±14.0yrs	5 (11.6%) 31.1±8.1yrs	5 (12.8%)
SMAD3, 29 (17.8%)	8 (12.5%)	6 (20.7%) 46.6±19.5yrs	4 (13.8%) 49.9±11.2yrs	2 (9.52%)
TGFB2, 9 (5.5%)	3 (33.3%)	1 (11.1%) 30.9yrs	0	0
TGFB3, 12 (7.4%)	6 (50%)	1 (8.3%) 37.9yrs	2 (16.7%) 45.4±4.2yrs	1 (14.3%)

Table. Gene variants and aortic and vascular events

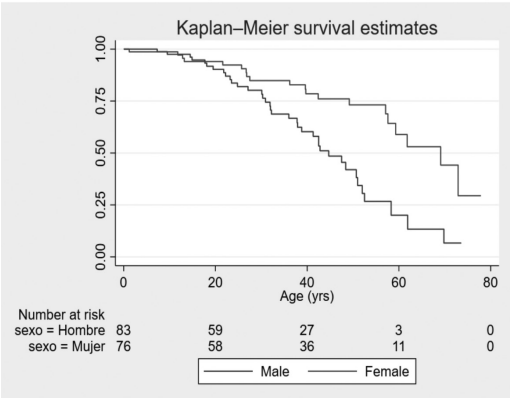

Figure. Survival free of aortic intervention, acute aortic syndrome or death

ISOLATED AORTIC ANEURYSMAL DISEASE AS AN UNDERESTIMATED FINDING IN INDIVIDUALS WITH *JAG1* PATHOGENIC VARIANTS

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Introduction

Pathogenic variants in the Notch ligand *JAG1* are known to cause Alagille syndrome (ALGS), a disorder that primarily affects the liver, lung, kidney and skeleton. Whereas cardiac symptoms are also frequently observed in ALGS, thoracic aortic aneurysms have only been reported sporadically in post-mortem autopsies.

Objectives

We aim to investigate the genetic cause of isolated thoracic aortic aneurysm (TAA) in patients from two different families.

Material and Methods

In family A, whole exome sequencing (WES) was performed in a fetus presenting with left hypoplastic heart syndrome and left renal agenesis and its parents. Segregation analysis of pathogenic variant was performed in other family members. Family B was subjected to a custom-made panel comprising 100 cardiac/aortic conditions-related candidate genes.

Results

We identified two families with segregating *JAG1* variants in family members that present with isolated aneurysmal disease and no ALGS liver, kidney, lung or skeletal findings. Additionally, we report the first histological evaluation of aortic aneurysmal tissue of a *JAG1* variant carrier, which showed fragmentation of elastic fibres with marked decrease in elastin content and abnormal collagen deposition. Because contractile markers of vascular smooth muscle cells (VSMCs) are known to be downregulated upon Notch impairment, we hypothesise that the VSMCs in the aortic media of ALGS patients adopt a synthetic phenotype. This phenotype switching results in tissue damage and subsequent failure to sufficiently dampen hemodynamical pressure, triggering TGFβ signalling, which is supported by increased pSMAD2 in the aortic wall of our patient. Since TGFβ is a well-known mediator of fibrosis and a driver of metalloprotease activity, a destructive cycle will be initiated, leading to further aortic wall degradation.

Conclusion

Our observations shed more light on the pathomechanisms behind aneurysm formation in *JAG1* variant carriers and underline the importance of aortic imaging in the clinical follow-up of *JAG1* variant carrying individuals.

GENOME-WIDE EPISTASIS FOR CARDIOVASCULAR SEVERITY IN MARFAN STUDY DESIGN: PATIENT ORGANIZATION DRIVEN RESEARCH

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Introduction/Objectives

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with manifestations in the ocular, skeletal and cardiovascular system. Morbidity and mortality are mostly determined by aortic disease. Although mutations in *FBN1* are the well-established genetic cause of MFS, there is a poor correlation with regards to phenotypical outcome, especially cardiovascular. Wide intra- and interfamilial phenotypical variability is observed, but the underlying mechanisms remain largely elusive. Consequently, the identification of genetic variation that modifies these effects will provide important novel insights.

Materials and Methods

A worldwide collaborative project driven by researchers and a Belgian patient organization, 'Foundation 101 Genomes' (F101G), was established to maximize the number of patients to participate in the study of the genetic basis of the marked phenotypical variability. RNA-sequencing of iPSC-derived vascular smooth muscle cells (IPSC-VSMCs) will be integrated with WGS to reveal MFS aortopathy genetic modifiers, which will be validated using CRISPR/Cas9 in iPSC-VSMCs.

Results

Our research institutions already gathered DNA for WGS and PBMCs for iPSC-VSMC creation of 50 patients carrying the most common MFS-causing *FBN1* missense variant (p.Ile2585Thr;c.7754T>C). WGS of these samples is ongoing. Based on international collaborations we are aware of at least 200 MFS patients carrying this specific variant and presenting with a wide range in cardiovascular severity. Together with F101G, we created a website to guide patients to participate in our research (https://cst101g.azurewebsites.net).

Conclusion

Despite the large number of patients already included, more patients are needed to identify genetic modifiers for MFS aortopathy. Understanding how mother nature by itself modifies the outcome of the primary *FBN1* mutation will allow for individualization of current treatment protocols to deliver true precision medicine and offer promising new leads to novel therapeutic strategies.

MARFAN MYSTERIES: CLINICAL CHARACTERISTICS, TREATMENT, AND PROGNOSIS OF CHILDREN WITH NEONATAL (EARLY-ONSET) MARFAN SYNDROME

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Introduction

Neonatal Marfan syndrome (nMFS) is a rare form of Marfan syndrome that is caused by variants of the *FBN1* gene. *FBN1* codes for an extracellular matrix protein, therefore variants cause defects in connective tissues. Most studies describing nMFS mention severe atrioventricular valve insufficiency before the age of 1 year, which is almost always the cause of death. The median age of death is 16.3 months. But, there are cases described of children who get a lot older, suggesting early surgical intervention increases the life expectancy.

Objectives

The aim of this study was to evaluate which factors influence survival based on 9 new cases and the existing literature.

Methods

Children with nMFS were identified via our academic network, Genesis, and the social network of a nMFS patient's mother. In addition, nMFS individuals described in the literature presenting with atrioventricular valve insufficiency before the age of 1 year, were included. Data was gathered retrospectively. All individuals were divided into two groups, deceased before 16 months and alive at 16 months, to analyze factors that may influence survival.

Results

We identified 41 children that fit our criteria to include in our study: 9 newly enrolled individuals, and 32 individuals from previously published work. Of these children, 64% were deceased at last follow up. The median age of death was 1 month. 24 children deceased before 16 months, and 13 children were alive at age 16 months. More individuals in the second group did undergo cardiac surgery [77% vs. 8,3%; $p< 0.001$] at an older age [13 vs. 2 months; $p= 0.001$]. Most deceased children already passed away by the time the other children obtained their first cardiac surgery.

Conclusion

While in the group "alive at 16 months" there is a window for surgical intervention, understanding why the group "deceased before 16 months" has so little chance of survival should provide insight into how these children with nMFS may be treated in the future.

AORTIC VERSUS ARTERIAL EVENTS IN INDIVIDUALS WITH PATHOGENIC VARIANTS IN GENES ENCODING PROTEINS IN THE TGFβ SIGNALING PATHWAY: FINDINGS FROM THE MONTALCINO AORTIC CONSORTIUM (MAC)

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Introduction

There is limited information about extra-aortic arterial events in patients with TGFβ pathway pathogenic/likely pathogenic gene variants (PVs).

Objectives

Assess the presentation of aortic and arterial events in patients with PVs in genes for proteins in the TGFβ pathway.

Methods

A retrospective cohort of 178 individuals in MAC with PVs in genes in the TGFβ pathway, including *TGFBR1* (n=20), *TGFBR2* (n=59), *SMAD3* (n=56), and *TGFB2* (n=43), and who experienced vascular events was examined. Aortic events were defined as presentation with an aortic dissection or thoracic aortic aneurysm repair; arterial events were defined as arterial dissections or ruptures or aneurysms requiring repair that did not involve the aorta.

Results

Out of 178 patients, 152 (85%) had an aortic event, 26 had an arterial event (15%), and 20 (11%) patients had both events. Arterial events included 17 patients with arterial dissections, 3 with rupture, and 6 with aneurysm repair. In the majority of patients (20/26), aortic events preceded arterial events. Eight patients had more than one arterial event with half being attributed to *SMAD3* mutations. Additionally, 3 patients who died from an arterial event all had cerebral artery rupture. Although childhood onset aortic events occurred with *TGFBR1* and *TGFBR2,* there were no arterial events < 20 years of age. Time to event curves for aortic versus arterial events stratified by affected gene showed earlier aortic events for *TGFBR1* and *TGFBR2* than for *SMAD3* and *TGFB2*. The earliest onset of arterial events was in *TGFBR1* patients, followed by *TGFBR2*, then later onset of *SMAD3* and *TGFB2*. Five of the 9 SMAD3 patients presented with arterial events involving the iliac arteries.

Conclusions

Arterial events associated with TGFβ gene PVs have a later onset and lower penetrance than aortic events, and cerebrovascular ruptures are the deadliest events. These findings have significant implications for surveillance and prognosis for arterial disease in these patients.

VARIABLE GENETIC UPTAKE RATES IN LOEYS-DIETZ SYNDROME GENES BETWEEN SPONTANEOUS CORONARY ARTERY DISSECTION PATIENT COHORTS

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Introduction

Spontaneous coronary artery dissection (SCAD) is the prime cause of acute myocardial infarction in women below the age of 50 as well as in pregnant or postpartum mothers. While an important health problem, its genetic etiology is relatively poorly studied and remains largely elusive. Recently, we reported that rare variants in the known Loeys-Dietz syndrome (LDS) genes were significantly enriched in SCAD patients as compared to the general population (4.5% versus 1.5%).

Objectives

We aimed to validate our prior findings in an independent cohort of SCAD patients (N=99).

Materials and Methods

Haloplex-based gene panel sequencing of the coding regions and exon/intron boundaries of *TGFB2/3*, *SMAD2/3* and *TGFBR1/2* was performed on an Illumina NextSeq500 system. Subsequent variant filtering involved selection of heterozygous non-synonymous coding or splice site (±2 bp) variants of good quality (~visual inspection in Sequence Pilot) that are either absent in gnomAD v2.1.1 or have a minor allele frequency below 0.1. Subsequently, variant classification was done according to the ACMG guidelines. The discovery and validation cohort were phenotypically compared with respect to the proportion of patients exhibiting connective tissue disease manifestations, fibromuscular dysplasia (FMD), extra-coronary arterial involvement, a positive family history and hypertension by means of Chi^2 statistics.

Results

Our molecular analysis yielded one rare variant in *SMAD2* (variant of unknown significance, 0.5% allele frequency), revealing a significantly lower uptake than what we observed in our discovery cohort (Chi^2 p=0.02). Hitherto, the clinical records of 44 patients (44.4% of the cohort) have been reviewed, suggesting a significantly higher prevalence of FMD in the discovery cohort (38.5% versus 20.4%, Chi^2 p=0.04). Further comparison of the clinical records of both cohorts is currently ongoing.

Conclusion

Our findings suggest that the genetic uptake in LDS genes may differ between discrete SCAD endophenotypes.

IMPACT OF GENOTYPE ON AORTIC DISEASE PROGRESSION IN PATIENTS WITH MARFAN SYNDROME AND LOEYS-DIETZ SYNDROME

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Introduction

Marfan and Loeys-Dietz syndromes are associated connective tissue disorders progressing from childhood. Major morbidity and mortality in both syndromes relate to aorta dilation predisposing to aortic tear.

Objectives

We investigated a putative relationship between genotype and aortic disease progression in young patients that can potentially lead to severe cardio vascular events.

Materials and Methods

100 patients (51 male, 49 female) with pathogenic variants in FBN1 (N=84), TGFβR1 / R2 (N=8) and SMAD3 (N=8) genes were subject to retrospective analysis. The average age at study onset was 13.8 years and data were collected over 5 years. The FBN1 variants were classified as premature termination codon (PTC, N=33) or dominant negative (DN, N=51). Among DN variants 14 cases of cysteine loss (Cys-), severely affecting protein conformation, were analysed separately. Aortic diameters and aortic dilation at the level of the Valsalva sinuses were assessed by echocardiography.

Results

A link was found between gender and aortic diameter evolution (median females 3.8mm vs males 6.3mm; p=0.0089) and growth rate (1.0mm/year females vs 1.4 mm/year males; p=0.0061). No overall differences were found between Marfan and Loeys-Dietz syndrome neither between PTC, DN and Loeys-Dietz patients. However, the aortic diameter evolution over 5 years was significantly higher in Cys-patients, with median 8.70mm against 4.00mm for other genotypes (p=0.0007); OR adjusted for gender was 1.3[1.1-1.5], p=0.003. The median growth rate was 1. 53mm/year in Cys-patients against 1.04mm/year for other patients (p=0.0127), adjusted on gender. No significant difference was found between gender distribution in Cys- and the remaining patients (p=0.15). Interestingly, mitral valve surgery was only reported in PTC patients (3/33, p=0.03).

Conclusion

Our study shows that gender differences in aortic disease progression are significant since childhood. Male patients should be monitored more closely, with emphasis on FBN1 variants with loss of cysteine.

CLINICAL VARIABILITY IN PATIENTS WITH SMAD3 ANEURYSM OSTEOARTHRITIS SYNDROME

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Introduction

Cardiovascular and other clinical outcomes of patients with SMAD3-related aortopathy remain poorly defined. The optimal timing for prophylactic surgery remains unclear due to limited patient data.

Objectives

To examine the clinical outcomes of patients with SMAD3-related aortopathy followed in an Aortopathy Center and assess for predictors of adverse outcome.

Materials and Methods

Individuals with *SMAD3* variants were selected for analysis. Age and aortic size at last followup, prophylactic aortic surgery, aortic dissection (AD), and death were recorded. Demographic, cardiovascular, and cerebrovascular outcomes were noted.

Results

Data was collected on 88 individuals from 13 families with a *SMAD3* variant of known or suspected pathogenicity due to segregation. There were 8 missense variants, 4 haploinsufficiency variants and 1 duplication. Type A AD occurred as the primary cardiac event in 27 (30%) patients with a measured maximal aortic diameter of 5.2 (4.4-6.0 cm) and was fatal in 13 (48%). Of those surviving initial type A AD, 100% required 2 (1-4) subsequent aortic surgeries. Type B AD was the presenting symptom in 3. Prophylactic surgery was performed in 7 patients at an aortic diameter of 5.1 (4.5-6.0 cm). Non-ischemic, non-valvar related cardiomyopathy necessitating advanced therapies including cardiac transplantation was present in 5 patients and pre-dated cardiac surgery in 40%. Cause of death (n=18) included AD in 11 (60%), CNS pathology in 5 (28%), and mitral valve dysfunction in 2 (11%).

Conclusions

There is considerable overlap in the size of the aorta at the time of AD and prophylactic repair. The high rate of AD and the need for multiple surgical redo procedures following AD would suggest the need for surgery at smaller aortic diameters than what occurred in our cohort**.** While type A AD is the most common cause of death, cerebral pathology and mitral valve disease are common.

TRANSCATHETER AORTIC VALVE REPLACEMENT FOR AORTIC REGURGITATION AFTER AORTIC ROOT REPLACEMENT IN HERITABLE THORACIC AORTIC DISEASE

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Introduction

Transcatheter aortic valve replacement (TAVR) for aortic regurgitation (AR) after aortic root replacement (ARR) in heritable thoracic aortic disease (HTAD) is rarely reported. We present 2 cases of TAVR for severe AR, one in Loeys-Dietz syndrome (LDS) and prior valve-sparing root replacement (VSRR) and one in Marfan syndrome (MFS) and prior homograft ARR.

Objectives

To expand treatment options for patients with HTAD, prior ARR, and severe AR.

Materials and Methods

Our 1st patient is a 39-year-old man with LDS who had remote VSRR, prior type B aortic dissection, arch replacement, descending aorta and upper abdominal aortic repair 6 years ago. In 2021, the patient presented with acute CHF and shock. TTE revealed LVEF 10%, marked LV dilation, and severe AR. CTA found a 7.3 cm distal abdominal AD. Surgical AVR and aortic aneurysm repair were considered at prohibitively high risk. Percutaneous transfemoral TAVR with a 29 mm SAPIEN 3 Ultra was uncomplicated. TTE 6-weeks later reported LVEF 30% and mild AR. He underwent open surgical aortoiliac repair without complication. The patient has NYHA class II symptoms at 6-month follow-up.

Our 2nd patient is a 71-year-old man with MFS who had a homograft ARR 20 years ago. He is blind with decreased functional capacity and presented with chronic CHF. TTE showed severe AR and normal LVEF. CT angiography found a calcified aortic annulus and homograft, and a right common iliac dissection. The patient declined surgical AVR. He underwent successful percutaneous transfemoral TAVR with a 26 mm SAPIEN 3 Ultra. He had NYHA class I symptoms at 30-day follow-up. Follow-up TEE demonstrates normal LVEF and no AR.

Conclusions

Severe AR may complicate VSRR or homograft ARR. In carefully selected patients with HTAD facing high-risk reoperation for severe AR after ARR, TAVR appears feasible and safe, but requires further study.

PREDICTORS OF 15-20 YEAR OUTCOMES AFTER T. DAVID VALVE-SPARING AORTIC ROOT REPLACEMENT AMONGST 577 SUBJECTS WITH SPECIFIC FOCUS ON MFS AND LDS PATIENTS

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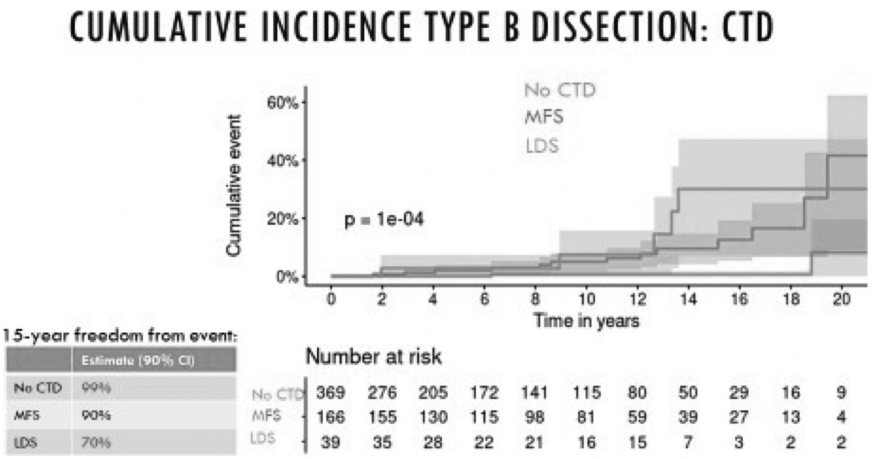
Objectives: Reimplantation valve-sparing aortic root replacement (Tirone David VSARR) has become popular with expanding indications, but 20+ year long-term valve durability remains poorly characterized. More knowledge of long-term outcomes especially in patients with Connective Tissue Disorders (Marfan [MFS] or Loeys-Dietz [LDS]) will allow more intelligent use of VSARR compared to mechanical or bioprosthetic composite valve graft (CVG) aortic root replacement.

Methods: 577 patients (1993-2020) who underwent T. David VSARR (TD-I 137, TD-IV 1, TD-V 25, TD-V Smod 414) were followed for a median of 7 years (IQR 3,13, 100% complete, max= 25 yr, total= 5,366 patient-years); importantly, late echo images were obtained and personally reviewed in 98% (median = 6 years [1,12]). VARC-3 definitions were used for structural valve degeneration (SVD) including more than moderate recurrent/residual AR and/or a mean gradient of 20mmHg.

Results: Median age was 44 (IQR 31,55) years. 26% had a bicuspid aortic valve (BAV), 29% had MFS, and 7% had LDS. Aortic cusp repair was performed in 51% (75% BAV vs. 42% tricuspid). There were five operative deaths (1%). At 15 years, survival was 93% (95% CI= 90%, 96%), cumulative incidence of aortic valve reoperation was 8% (5%, 11%), and cumulative incidence of SVD was 15% (10%, 20%). Multivariable analysis revealed that indexed maximum aortic diameter (HR 5.7 (3-11), p<0.01) and planned CABG (HR 11 (2-66), p=0.03) were associated with mortality while preoperative severe aortic regurgitation (HR 3.2 (1-7), p=0.01), indexed maximum aortic diameter (HR 2.2 (1-4, p=0.04), and surgeon (HR 8.8 (3-24), p<0.01) were associated with SVD. Late type B aortic dissection occurred in 20 patients, which was highly linked with both MFS (HR 5.3 [1-20], p=0.04) and LDS (HR 10.0 [2-44], p=0.01).



Conclusions: T. David VSARR in selected patients provides excellent valve durability out to 15-20 years. Critical determinants for success include seasoned surgical judgment regarding which valves to preserve and severe preop AR. Late postoperative type B dissection remains a major challenge for patients with MFS or LDS; further analysis looking at specific mutations and modes of medical therapy is ongoing.

PROPHYLACTIC AORTIC ARCH REPLACEMENT IN PATIENTS WITH LOEYS-DIETZ SYNDROME: SURGICAL OUTCOMES AND MOLECULAR RATIONALE

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Introduction

Loeys-Dietz syndrome (LDS) patients typically develop focal aortic root aneurysm but have heightened risk of late arch aneurysm and dissection after elective root replacement, prompting consideration of aggressive surgical arch replacement.

Objectives

To examine early clinical experience with prophylactic arch replacement for LDS patients and comprehensively profile aortic cellular phenotypes promoting vascular remodeling in contiguous aneurysmal and non-dilated aortic segments.

Materials and Methods

LDS patients of all genotypes (n=8) were offered prophylactic total arch replacement at time of elective aortic root surgery. Resected tissue was anatomically segmented (root, ascending, arch) and examined via single-cell RNA sequencing ('scRNAseq', n=4 patients), and RNA *in situ* hybridization.

Results

LDS patients had root aneurysm (mean 4.62cm) without arch dilation (mean 2.97cm) and underwent valve-sparing root replacement with branched graft total arch replacement. There were no perioperative deaths or strokes and no distal aortic events or reoperations after median 1.26 years follow-up. scRNAseq analysis identified a continuum of SMC phenotype modulation with progressively reduced contractile gene expression. Pathway analysis of 260 genes enriched during SMC modulation revealed a progressively heightened signature of transforming growth factor-beta-responsiveness, cell adhesion, integrin signaling, and extracellular matrix remodeling. Modulated SMC populations were identified in each aortic segment in the scRNAseq data and histologically using RNA probes specific for this population (the canonical TGF-beta responsive gene *SERPINE1* and glycoprotein *TNFRSF11B*), confirming modulated SMCs in the tunica media layer extending to the arch. Conversely, *TNFRSF11B*+ cells were restricted to macroscopically atherosclerotic tunica intima in donor aortic tissue.

Conclusion

SMC phenotypic modulation is associated with LDS aortopathy. While genetic variants in TGF-beta signaling genes are loss-of-function, single-cell resolution phenotyping suggests paradoxical hyperactivation promotes phenotypic modulation. Ongoing SMC-mediated vascular remodeling in the non-dilated aortic arch provides molecular rationale for aggressive arch replacement given clinical vulnerability for distal aortic events and acceptable surgical risk.

UTILIZATION AND COMPLICATIONS OF THORACIC ENDOVASCULAR REPAIR IN PATIENTS WITH GENETIC AORTOPATHY

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Introduction

Thoracic Endovascular Repair (TEVAR) is contraindicated in patients with genetic aortopathy due to concerns for retrograde aortic dissection (RTAD) and aneurysmal degeneration.

Objective

To investigate the utilization of TEVAR and complications in a cohort of patients with genetic aortopathies.

Materials and Methods

This is a retrospective single system study of patients with genetic aortopathies treated with TEVAR. Genetic aortopathies included Marfan and Loeys Dietz syndromes (MFS, LDS), and non-syndromic heritable aortopathies due to smooth muscle cell ACTA2 and LOX pathogenic variants. Demographics, operative details, and outcomes were abstracted. The primary outcome was a composite retrograde aortic dissection (RTAD), type Ia endoleak, and rupture in the treated aortic segment. Secondary outcomes included RTAD, type Ib endoleak, new distal entry tear, and all-cause and aortic related mortality.

Results

A total of 42 patients (mean age 44.2+14.6 years, 65% male, 65% White) met inclusion criteria (28 MFS, 7 LDS, 6 ACTA2, and 1 LOX) with 13 type A and 29 type B aortic dissections. Median follow up post TEVAR was 54.7 (range 0.2-200) months. Repair indications were aneurysm size (39.5%), aneurysm growth > 5mm in 6 months (30.2%), pain (16.2%), Malperfusion (4.6%), and other (11.6%). Carotid to subclavian transposition was performed in 28 patients. Proximal landing zone was previous Dacron arch repair (n=7, 17%), and antegrade during zone II arch repair (n=12, 29%), and native aortic arch (n=23, 54.7%). Among TEVAR in native aortic arch, the primary outcome occurred in 6 (26%) cases: 4 retrograde aortic dissections (17%) and 2 (9%) type 1a endoleaks. Among the entire cohort, Type 1b endoleak occurred in 2 (5%) and new distal entry tear in 1 (2.3%) case treated with open surgical repair. All-cause mortality was 26% (n=11). Aortic related mortality was 16% (n=7) including 2 aortic ruptures.

Conclusion

This study offers real world data on circumstances in which TEVAR is being used in patients with genetic aortopathies and how these devices can be incorporated into a comprehensive aortic care of this patient population.

ENDOVASCULAR AND HYBRID REPAIR IN PATIENTS WITH HERITABLE THORACIC AORTIC DISEASE

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Introduction

For individuals with heritable thoracic aortic disease (HTAD), endovascular repair of aortic aneurysm and dissection may be lifesaving but is associated with increased risk of device failure and adverse outcomes.

Objectives

To report early and late outcomes of endovascular aortic and branch vessel repair in patients with HTAD from our medical center.

Materials and Methods

A retrospective analysis of patients with HTAD at our institution who underwent endovascular aortic and/or branch vessel repair was performed.

Results

Twenty-nine patients with HTAD (20 male; mean age 45 ± 13 years) underwent 37 endovascular procedures between 2006 and 2020. Underlying conditions included Marfan syndrome (n=16), Loeys-Dietz syndrome (n=14), vascular Ehlers-Danlos syndrome (n=3), and nonsyndromic HTAD (n=4). Indications for repair were acute complications of aortic dissection (AD) (n=10) or aneurysm rupture (n=3), and elective repair (n=18; 10 chronic ADs and 8 aneurysms). Six procedures involved branch vessels. Twenty-five (68%) proximal landing zones were in the native vessel, 11 (30%) were in a surgical graft or elephant trunk, and 1 was in an endograft. Thirty-six (97%) procedures were technically successful and none required emergency surgical conversion. Two patients (7%) died: one from sepsis (33 days post-procedure) and one from presumed late pseudoaneurysm rupture (116 days post-procedure). Two procedures were complicated by stroke and one patient developed paraparesis. Six aortic endografts (16%) developed a stent-induced new entry (SINE) identified 20 ± 15 days post-procedure. Seven endografts (19%) developed a Type I endoleak and 9 (24%) developed a Type II endoleak. Within 30 days, 2 endografts (5%) required reintervention. After 30 days, 15 additional endografts (41%) required reintervention.

Conclusion

Endovascular repair in patients with HTAD can manage acute and chronic complications of aortic aneurysm and dissection with relatively low risk. However, risk of early and late endoleaks and SINE is high. Post-procedural surveillance is required, and many patients will require additional interventions.

MARFAN SYNDROME ACCELERATES CEREBROVASCULAR AGING AND BLOOD-BRAIN BARRIER PERMEABILITY

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Marfan syndrome (MFS) is a connective tissue disorder associated with mutations in fibrillin-1 (*Fbn1*) leading to systemic increases in transforming growth factor-β (TGF-β) availability. Increased TGF-β signaling, in part, induces peripheral vascular dysfunction including vascular wall weakening, stiffening, and endothelial dysfunction by 6-months (6M) of age in MFS mice. TGF-β upregulation has been implicated in cerebrovascular dysfunction, loss of blood-brain barrier (BBB) integrity, and increased neuroinflammation and cognitive impairment in the aging population. Moreover, improvements in MFS care management and life expectancy have uncovered a potential increased risk for cerebrovascular complications such as stroke, cerebral aneurysm, and migraines. This study investigated the impact of MFS on accelerated vascular aging, cerebrovascular integrity, and BBB permeability using a transgenic MFS mouse model (*Fbn1*$^{C1041G/+}$). In male and female 6M and 12M *Fbn1*$^{C1041G/+}$ and *C57BL/6* wildtype (WT) mice, aortic diameters, aortic pulse wave velocity (PWV), posterior cerebral artery (PCA) peak blood flow velocity, PCA rupture point, BBB permeability, microglia activation, and neurological severity scale (NSS) outcomes were assessed.

Using ultrasound imaging, we observed that increased aortic root diameters and exacerbated aortic wall stiffness in *Fbn1*$^{C1041G/+}$ mice were associated with marked decrease in PCA blood flow. Small vessel chamber wire myography demonstrated impaired PCA wall strength. In addition, in *Fbn1*$^{C1041G/+}$ mice, Evans blue extravasation displayed compromised BBB permeability in the hippocampus that was associated with increased iba-1 staining, a marker of neuroinflammation; while increased NSS scores demonstrated neurobehavioral alterations. We also showed that aortic and cerebrovascular phenotypes in 6M-old *Fbn1*$^{C1041G/+}$ mice were more similar to 12M-old WT mice, highlighting accelerated aging effects in the MFS mouse model. These findings signify MFS as a disease of accelerated vascular aging with altered cerebrovascular structure and function, demonstrating potential vulnerability to injuries associated with cerebrovascular dysfunction such as traumatic brain injury, stroke, and longer recovery times post-injury.

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EVALUATION OF LENTICULAR AND ZONULAR CHANGES IN PATIENTS WITH MARFAN SYNDROME USING ULTRASOUND BIOMICROSCOPY

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Objectives

The purpose of this study is to evaluate the utility of ultrasound biomicroscopy (UBM) in quantifying lens shape, subluxation and zonular stability as well as enhancement of zonular fibers in the posterior chamber in Marfan patients attempting to further define the natural history of the disease.

Materials and Methods

We conducted a retrospective review of UBM examinations of 8 eyes of 4 patients with MFS aged 21-43 years. The lens was displaced in all eyes. We measured eight eyes of 4 age-matched normal controls.

Examinations were performed using a Quantel Aviso UBM system with 50 MHz probe. We measured anterior chamber (AC) depth, lens thickness, and displacement from the pupil center as well as appearance of the zonules. Anterior radius of curvature of the lens was determined using ImageJ to mark anterior lens positions within the pupil and solving for best-fit circle.

Results

Central AC depth averaged 2.59±0.39 mm in MFS versus 2.92±0.38 mm in controls; lens thickness averaged 4.3±0.6 mm in MFS patients versus 3.9±0.4 for controls; the anterior radius of curvature averaged 6.3±2.1 mm in MFS versus 9.8±1.5 mm in controls. The difference in anterior lens radius from controls was statistically significant (p=.002). Zonules were enhanced in all MFS eyes compared to normals, particularly in the quadrant opposite to the direction of lens displacement.

Conclusion

MFS patients on average showed decreased central AC depth. The lens tended to be greater in thickness than in age-matched controls and its anterior radius was significantly reduced. The zonules were enhanced in all MFS eyes.

Future studies will seek to correlate DNA results with phenotypic ocular expression. Measurement of the anterior lens radius should be easily obtainable in patients with suspected and confirmed Marfan syndrome. The development of enhancement of the zonules needs to be studied longitudinally. These UBM based anterior segment measurements can serve as parameters during clinical trials.

MARFAN SYNDROME IS ASSOCIATED WITH ALTERED KNEE JOINT MECHANICS DURING GAIT

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Introduction

Marfan syndrome (MFS) negatively impacts muscle composition resulting in muscle weakness leading to decreased quality of life, pain, and fatigue. Poor muscle function may be associated with altered gait mechanics in people with MFS but gait analysis has yet to be performed in people with MFS. This study will provide insight into lower extRémity gait patterns in people with MFS.

Objectives

To assess lower extRémity sagittal plane gait mechanics in people with MFS.

Materials and Methods

Seven females with MFS (age: 38±7.84 yrs; BMI: 22.5±4.61 $kg \cdot m^{-2}$) and 10 female healthy controls (age: 28.4±7.26 yrs; BMI: 23.1±2.73 $kg \cdot m^{-2}$) were tested in this cross-sectional study. Subjects ambulated at a fixed walking speed of 1.35 ms^{-1} while undergoing 3D gait analysis.

Results

People with MFS walked with higher knee flexion at initial contact ($p<0.001$) and during loading response ($p = 0.002$), higher ankle dorsiflexion (DF) during terminal stance ($p = 0.054$), trends of higher ankle plantarflexion (PF) during loading response ($p = 0.069$). People with MFS also exhibited a greater peak quadriceps-to-hamstring strength ratio (QHR) ($p=0.028$). There were no between group differences in hip joint kinematics, lower extRémity joint kinetics (i.e. joint loading) or peak quadriceps and hamstrings strength.

Conclusion

Our results demonstrate that people with MFS walk with altered sagittal plane knee and ankle joint kinematics despite similar quadriceps and hamstrings strength. People with MFS walk with a more flexed knee joint and may indicate quadriceps dysfunction during dynamic activities such as walking. Altered knee joint mechanics and quadriceps function may lead to a compensatory gait strategy, resulting in the altered ankle joint PF and DF observed during walking in our MFS group. Our results suggest that quadriceps dysfunction during dynamic activities, such as walking, may be a potential mechanism of the altered gait mechanics observed in our MFS group.

FIBRILLIN-1 REGULATES WHITE ADIPOSE TISSUE DEVELOPMENT, HOMEOSTASIS, AND FUNCTION

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Introduction and Objective

Mutations in fibrillin-1 cause a wide spectrum of type I fibrillinopathies, including Marfan syndrome characterized by clinical manifestations in adipose tissues, among others. This study addresses the hypothesis that fibrillin-1 regulates adipocyte development and plays a vital role in adipose tissue homeostasis.

Methods and Results

We employed two mouse models - *Fbn1*$^{mgR/mgR}$ (20-25% of normal fibrillin-1) and *Fbn1*$^{C1041G/+}$ (missense mutation in fibrillin-1) to examine the role of fibrillin-1 in adipose tissue development and homeostasis. Fibrillin-1 was detected around mature adipocytes in both mouse and human white adipose tissues. Male *Fbn1*$^{mgR/mgR}$ mice had more white and brown adipose tissues, whereas female *Fbn1*$^{mgR/mgR}$ and both male and female *Fbn1*$^{C1041G/+}$ showed no difference compared to their respective wild-type littermates. Consistent with this data, male *Fbn1*$^{mgR/mgR}$ mice displayed hyperinsulinemia and an insulin resistance phenotype with higher levels of cholesterol and high-density lipoproteins in the serum. Fibrillin-1 deficiency in male *Fbn1*$^{mgR/mgR}$ mice also promoted adipogenic gene expression and led to hypertrophic expansion of mature adipocytes. To further elucidate the fibrillin-1-dependent adipogenic mechanisms in cell culture, we used primary bone marrow derived mesenchymal stem/stromal cells (MSCs) from *Fbn1*$^{mgR/mgR}$, *Fbn1*$^{C1041G/+}$ and wild-type mice. Increased lipid content, adipogenic differentiation and pAKT levels were observed when MSCs from both male and female *Fbn1*$^{mgR/mgR}$ mice were differentiated. Furthermore, a recombinant fragment spanning the C-terminal half of fibrillin-1 significantly reduced adipocyte differentiation i) by binding to MSCs and inhibiting adipogenic commitment, and ii) by sequestering insulin, together suppressing the AKT signaling pathway. This fibrillin-1 fragment also rescued enhanced adipogenic differentiation of MSCs derived from *Fbn1*$^{mgR/mgR}$ mice.

Conclusion

Overall, this study shows that altered adipose tissue homeostasis observed in fibrillin-1 deficient mice depends on the type of fibrillin-1 deficiency and the biological sex, and it shows that fibrillin-1 is a negative regulator of adipogenesis.

AORTIC DISSECTION AND CARDIOVASCULAR OUTCOMES IN WOMEN WITH MARFAN, LOEYS-DIETZ AND VASCULAR EHLERS-DANLOS SYNDROMES: RESULTS FROM PROWGAD (PREGNANCY AND REPRODUCTIVE OUTCOMES IN WOMEN WITH GENETIC-PREDISPOSITION FOR AORTIC DISSECTION)

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Introduction

Pregnancy is a high-risk period for cardiovascular complications in women with heritable aortopathies. Besides aortic root dimensions, risk factors for aortic dissection (AD) have not been well defined.

Objectives

To evaluate pregnancy in women with syndromic heritable thoracic aortic disease cardiovascular to identify characteristics associated with pregnancy-related AD and other cardiovascular complications.

Materials and Methods

PROWGAD is a multi-center, retrospective cohort from 2000-2022 with primary outcomes of cardiovascular and obstetrical complications in women with heritable aortopathies. Individuals with Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS) and vascular Ehlers-Danlos syndrome were selected for analysis. The cardiovascular complications assessed included AD related to pregnancy and composite of other cardiovascular complications in pregnancy (cardiac arrhythmia, heart failure, type A AD, type B AD, descending dissection, other arterial dissection, or worsening mitral valve disease). Demographic and pregnancy characteristics were compared between those with and without pregnancy-related AD.

Results

97 females (58 MFS, 10 LDS, 7 vEDS) with 209 pregnancies (MFS 122, LDS 25, vEDS 15) were included. The overall AD rate was 6.2% of women (2.9% of pregnancies) with 6 dissections total, 5 in MFS (4.1%) and 1 in LDS (4%). The rate of composite of CV complications was 6.8%. Comparing those with AD versus no AD, there were no differences in age at delivery (31 [29-34] vs 28 years [22-33] p=0.28), chronic hypertension (16.7% vs 8.7% p=0.21), gestational hypertension (16.7% vs 5.2% p=0.11), preeclampsia (0% vs 1.2% p=0.29), cesarean (66% vs 51% p=0.10), family history of AD (83% vs 40% p=0.10) or MFM involvement in care (83% vs 71% p=0.59).

Conclusion

There were no demographic or pregnancy characteristics associated with AD or other CV complications however larger studies are needed to confirm this finding.

OBSTETRIC AND NEONATAL OUTCOMES IN WOMEN WITH MARFAN, LOEYS-DIETZ AND VASCULAR EHLERS-DANLOS SYNDROMES: RESULTS FROM PROWGAD (PREGNANCY AND REPRODUCTIVE OUTCOMES IN WOMEN WITH GENETIC-PREDISPOSITION FOR AORTIC DISSECTION)

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Introduction

Obstetric complications have not been well-studied in reproductive-aged patients with heritable aortopathy syndromes.

Objectives

To describe obstetric complications in a large cohort with heritable aortopathy syndromes.

Materials and Methods

PROWGAD is a multi-center, retrospective cohort from 2000-2022 with primary outcomes of cardiovascular and obstetrical complications in women with Marfan syndrome(MFS), Loeys-Dietz syndrome(LDS), Vascular Ehlers-Danlos(vEDS) syndrome, bicuspid aortic valve with aortic dilatation and familial thoracic aortic aneurysm and dissection. Obstetric and neonatal variables were extracted from medical records. Demographics and obstetric outcomes were compared by underlying type of aortopathy.

Results

97 women (58 MFS, 10 LDS, 7 vEDS), 209 pregnancies (MFS 122, LDS 25, vEDS 15) were included. Maternal age at delivery was not significant across groups (MFS 27.5, range 22-31 vs LDS 22.5, range 20-27 vs vEDS 29 years, range 23-32 p=0.116). The rate of preterm delivery was 14.2% overall and differed significantly across groups (MFS 12% vs LDS 33% vs VEDS 21% p=0.018). The mode of delivery was not different across groups between vaginal, operative-vaginal and cesarean delivery (p=0.22). The overall rates of obstetric complications included preterm premature rupture of membranes (3.4%), 3rd and 4th degree vaginal lacerations (1.2%), deep vein thrombosis (1.1%) and pulmonary embolism (0.6%). There were no significance differences in obstetric complications across groups. There were no cases of uterine rupture. The overall rates of stillbirth and neonatal death were 1.5% and 1.2% respectively with no difference across the groups (p=0.14).

Conclusion

Overall outcomes for patients with aortopathy during pregnancy are favorable. Preterm birth, especially amongst patients with LDS, appears to be a major risk.

ACCESS TO APPROPRIATE CARE: AORTIC ROOT ANEURYSM AND PREGNANCY IN MARFAN SYNDROME – A CASE REPORT

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Introduction

During pregnancy and the immediate postpartum period, women with Marfan Syndrome have an increased risk of aortic dissection due to changes in blood volume as well as hormonal mediated changes in aortic elasticity.

Case report

Anamnesis: We present a 32-year-old female patient with the clinical diagnosis of Marfan syndrome, who moved from Romania to Germany few years ago. Genetic testing has not been performed. She presented with craniofacial dysmorphism, tall stature and scoliosis. Several of her siblings had a Marfan-like phenotype and one brother underwent aortic surgery due to aortic aneurysm.

Pregnancy occurred without preconception counselling. Extern echocardiography showed an aortic root aneurysm of 43 mm with a competent aortic valve. She was referred to us in the 21th week of pregnancy. Despite the increased risk for aortic dissection the patient decided to continue the pregnancy.

Course of pregnancy: Beta-blocker therapy was initiated and repetitive echocardiograms were performed. In the 26th week of pregnancy the aortic diameter was increased to 46 mm diameter. Meanwhile, genetic testing revealed a *FBN1* pathogenic variant. An elective cesarean section in 32nd week was scheduled after a stationary monitoring since week 30 yet. Neonatal assessment revealed a normally developed fetus.

Delivery: Cesarean section went well and the newborn was monitored at the neonatal ward without any events. Three weeks later the patient underwent a root replacement according to David. Besides a postpartal transient global amnesia with complete Rémission after 24 hours no adverse events occurred.

Results: Three years after delivery and David procedure both mother and child are well.

Conclusion

Although current guidelines recommend in case of positive family history, a preconceptional prophylactic David procedure, alternative treatment is feasible. Patient education, multidisciplinary team approach and close monitoring are crucial in high risk pregnancies of patients with Marfan syndrome.

LOSS OF TGFβ SIGNALING IN THE OUTER PERICHONDRIUM CAUSES LONGITUDINAL BONE OVERGROWTH IN MARFAN SYNDROME

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A disproportionate tall stature is the most evident manifestation in Marfan syndrome (MFS). By combining the *Cre-LoxP* recombination system with metatarsal bone cultures, here we identify the outer layer of the perichondrium as the tissue responsible for long bone overgrowth in MFS mice. Analyses of differentially expressed genes in the fibrillin-1 deficient perichondrium predicted that loss of TGFβ signaling may influence chondrogenesis in the neighboring epiphyseal growth plate (GP). Immunohistochemistry revealed that fibrillin-1 deficiency in the outer perichondrium is associated with decreased accumulation of latent TGFβ-binding proteins (LTBPs)-3 and -4, and reduced levels of phosphorylated (activated) Smad2. Consistent with these findings, mutant metatarsal bones grown *in vitro* were longer and released less TGFβ than the wild type counterparts. Moreover, addition of recombinant TGFβ1 normalized longitudinal growth of mutant metatarsal bones. We conclude that longitudinal bone overgrowth in MFS is accounted for by diminished sequestration of LTBP-3 and LTBP-4 into the fibrillin-1 deficient matrix of the outer perichondrium, which results in less TGFβ signaling locally and improper GP differentiation distally.

MUSCULOSKELETAL MANIFESTATIONS OF MARFAN SYNDROME INCLUDING LONG BONE LENGTH AND KYPHOSIS ARE RESCUED BY LOSARTAN TREATMENT DURING ADOLESCENT GROWTH IN MICE.

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Introduction

Musculoskeletal features of Marfan Syndrome (MFS), including excessively tall stature and kyphoscoliosis, present a significant burden to patients but are under-explored. Recent studies suggest that TGF-β is an important pathogenic mediator in MFS. Prophylactic treatment with TGF-β neutralising antibodies or with losartan, which is thought to suppress TGF-β, has been shown to modify cardiovascular manifestations in murine MFS models.

Objectives

Our aim was to characterise the musculoskeletal manifestations of the $Fbn1^{C1039G/+}$ mouse model of MFS and explore the effect of losartan on this phenotype.

Materials and Methods

Whole body microCT was performed at 4, 6, 9, 12, 26 and 52 weeks of age (n=7-35/group) in $Fbn1^{C1039G/+}$ heterozygotes (HETs) and WT littermate controls. Quantitative measures of whole body, tibia and femur length and kyphosis angle were taken. Tibial growth plates (GP) length and cellularity was assessed by histomorphometry. Latency associated peptide (LAP), ColX (hypertrophic chondrocytes) and perlecan (a pericellular matrix marker) expression was assessed by immunohistochemistry. Losartan (0.6g/l) was provided in the drinking water from 4-9 weeks of age. Scoring was blinded and performed independently by AI, ME, and US.

Results

There was a trend towards increased long bone length in all HET mice compared with WT littermate controls. Kyphosis angle was significantly reduced (indicating more severe kyphosis) in MFS mice vs WT. Total body length was not different. The tibial GP length and cellularity were increased at 6 weeks in MFS mice but had normalised by 9 week. LAP was qualitatively increased in MFS GPs. Losartan treatment suppressed long bone length in both WT and MFS mice and led to a significant reduction in GP cellularity.

Conclusion

Musculoskeletal manifestations of MFS were evident in $Fbn1^{C1039G/+}$ mice and could be modified by losartan. These results suggest the potential to reduce the burden of MFS skeletal manifestations in adolescents in clinic.

DOES MODE OF DELIVERY DIFFER FOR PATIENTS WITH MARFAN OR LOEYS-DIETZ SYNDROME BASED ON DELIVERY HOSPITAL SETTING?

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Introduction

Pregnancy is a high-risk time for patients with Marfan syndrome (MFS) or Loeys-Dietz (LDS) syndrome due to risk for cardiovascular complications including risk of aortic dissection. Little is known about differences in obstetric management decisions based on delivery hospital setting (academic/academic-affiliated versus community medical centers).

Objective

To evaluate obstetric management of patients with MFS or LDS based on delivery hospital setting secondary to risks for aortic dissection in pregnancy.

Materials and Methods

This is a secondary analysis of a retrospective, observational cohort study of singleton pregnancies among patients with a diagnosis of MFS or LDS from 1990 to 2016. Patients were identified through the Marfan Foundation, Loeys-Dietz Syndrome Foundation, or Cardiovascular Connective Tissue Clinic at Johns Hopkins Hospital. Data were obtained via self-reported obstetric history and verified by review of medical records. Nonparametric analysis was performed via Fisher's Exact Test and Wilcoxon rank-sum tests.

Results

From this cohort, 188 pregnancies occurred in patients with a known diagnosis of MFS (n=152) or LDS (n=36) prior to their pregnancy. 103 (55%) delivered in an academic medical center, while 85 (45%) delivered in a community hospital. No significant difference was noted between gestational age at delivery between hospital settings (37.2 weeks vs 36.8 weeks, P=0.94). Although there was no significant difference in cesarean delivery rates between the two hospital settings (43.7% and 55.3%, P=0.11), patients with MFS or LDS who delivered an academic hospital were more likely to undergo operative vaginal delivery than patients who delivered at community hospitals (26.2% vs. 10.6%), (p= 0.02).

Conclusions

Delivery planning is critical to optimize obstetric outcomes for patients with genetic-predisposition for aortic dissection. Characterizing the differences in care between delivery settings highlights important areas for further research and education.

ALTERED METABOLISM IN MARFAN SYNDROME MICE FED ON HIGH FAT DIET

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Introduction

Patients with Marfan syndrome (MFS) are typically characterized as very slender. Body weight gain in these patients can be a challenge, and the reason for this is still not fully understood.

Objective

To determine if individuals with MFS have an altered metabolism.

Methods

9-11 weeks old male $Fbn1^{C1041G/+}$ (MFS) mice and wild-type littermates were given either a chow or high fat diet (HFD) for 3 months. These mice were housed individually in metabolic cages for 1 week before euthanasia was performed.

Results

HFD resulted in higher body weights compared to chow diet, and the HFD groups became insulin resistant as measured by the intraperitoneal glucose tolerance test. However, body weight gain was not different in these MFS mice as compared to WT mice on chow or HFD. The HFD groups had increased brown fat weight compared to chow groups. Interestingly, MFS mice had an enhanced heart weight compared to WT mice, independent of the diet. As expected, aortic root diameters were enlarged in MFS compared to WT mice on both diets. However, in the ascending aorta there was a significant increase in diameter in the WT HFD as compared to WT chow, indicating that enhanced lipid levels promote aortic growth. Metabolic cage data showed that the HFD groups had a lower respiratory exchange ratio (RER), indicating that HFD groups used fat as a predominant source of fuel and that chow groups used primarily carbohydrates as an energy source. MFS mice had overall lower RER compared to WT mice, revealing that MFS mice use more lipids under any condition, most likely to manage the significantly elevated activity in the MFS mice.

Conclusions

HFD induced enhanced aortic growth, thus contributing to aorta pathology. In MFS mice, there is increased lipid metabolism, possibly compensating for the enhanced activity, whereas there was no difference in bodyweight.

A NEW THORACIC AORTIC ANEURYSM MOUSE MODEL CAUSED BY THE FBN1Q2467X NONSENSE MUTATION ASSOCIATED WITH MARFAN SYNDROME: MODULATION OF SMC PHENOTYPES, OXIDATIVE STRESS AND INFLAMMATION DURING ANEURYSM PROGRESSION AND RUPTURE

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Introduction

Thoracic aortic aneurysm (TAA) severity and drug responses in Marfan patients vary with FBN1 mutations. Recent clinical studies show that patients with FBN1 haploinsufficiency including nonsense mutations present more severe aneurism phenotypes and better responses to Losartan treatment. More than one thousand pathogenic variants including missense and nonsense mutations have been found in *FBN1*, suggesting that different mutations may trigger different or overlapping pathogenic signaling to cause the phenotypic variation.

Objective

The goal of this study is to elucidate the molecular mechanisms of a FBN1 nonsense mutation in the pathogenesis of aneurysm progression and rupture.

Materials and Methods

Using the CRISPR technology, echocardiogram, histology, molecular biology assays and bioinformatics, we recently generated and characterized a new aneurysm mouse model containing the FBN12467X nonsense mutation found in Marfan patients.

Results

The resulting *Fbn1*$^{Q2469X/+}$ mice appear normal with slightly dilated ascending aorta. The *Fbn1*$^{Q2469X/Q2469X}$ mice develop TAAs at the root-ascending-arch region: these aneurysms progress rapidly from early stage to rupture within 15-21 days. qPCR analyses show that *Fbn1* mRNA is reduced by 50% in *Fbn1*$^{Q2469X/+}$ mice and by > 90% in *Fbn1*$^{Q2469X/Q2469X}$ mice. cDNA sequence chromatogram analysis reveals that *Fbn1*$^{Q2469X/+}$ mutant mRNA is selectively degraded in *Fbn1*$^{Q2469X/+}$ mice. RNA-seq analyses using thoracic aortas from *Fbn1*$^{Q2469X/Q2469X}$ and their control mice show that inflammation and immune responses represent the prominent pathogenic processes in aneurysms. Immunofluorescence and western blot assays identify differential SMC dedifferentiation, oxidative stress and inflammation during aneurysm progression and rupture.

Conclusion

This study provides the first evidence showing that the *FBN1*^{Q2467X} nonsense mutation in Marfan patients causes FBN1 deficiency due to nonsense mediated decay rather than the accumulation of FBN1 truncation protein to promote aneurysm formation. Importantly, this study establishes a new TAA mouse model that will facilitate the investigation of the molecular mechanisms underlying aneurysm progression and rupture.

POSTER PRESENTATION LIST

GenTAC Aortic Summit

Poster Presentation (Posters 1-24)
Thursday, September 1, 2022 • 5:00-7:00pm

TOPIC: BICUSPID AORTIC VALVE

P1 **Endurance Exercise Following Ascending Thoracic Aortic Aneurysm Resection in Bicuspid Aortic Valve Aortopathy**
Alan Braverman, Washington University School of Medicine

P2 **Familial Bicuspid Aortic Valve and Thoracic Aortic Aneurysm Associated with c.221G>A;p.Glu738Lys THSD4 Variant**
Radoslaw Debiec, University of Leicester

P3 **Increased Prevalence of Obesity in Children with Bicuspid Aortic Valve is Associated with Sedentary Behaviors**
Kathryn Holmes, Oregon Health & Science University

P4 **Effect of Losartan or Atenolol on Children and Young Adults with Bicuspid Aortic Valve and Dilated Aorta**
Ronald Lacro, Boston Children's Hospital/Harvard Medical School

P5 **Aortic Tortuosity is Related to the Aortic Phenotype in Patients with Bicuspid Aortic Valve**
Olivier Milleron, CNMR Marfan APHP Hopital Bichat Paris

P6 **Aortic Events During Pregnancy in Women with Bicuspid Aortic Valve and Aortic Dilatation: A Retrospective Study**
Olivier Milleron, CNMR Marfan APHP Hopital Bichat Paris

P7 **Aortic Root Anatomy is Related to the Bicuspid Aortic Valve Phenotype**
Olivier Milleron, CNMR Marfan APHP Hopital Bichat Paris

P8 **Whole Genome Sequencing and Familial Segregation Analysis Reveal CELSR1 Risk Alleles in Familial Bicuspid Aortic Valve and Hypoplastic Left Heart Syndrome**
Talha Niaz, Mayo Clinic

P9 **Concomitant Cardiovascular Malformations in Isolated Bicuspid Aortic Valve Disease: A Retrospective Study and Meta-Analysis**
Katalin Szöcs, University Medical School Hamburg-Eppendorf

TOPIC: GENETICS

P10 **Role and Yield of Clinical Genetic Testing Among Patients with Bicuspid Aortic Valve and Aortic Dilation Referred to the Cardiovascular Genetics Clinic**
Talha Niaz, Texas Children's Hospital

P11 **Genome-wide Epistasis for Cardiovascular Severity in Marfan Study Design: Patient Organization Driven Research**
Lotte Van Den Heuvel, University of Antwerp and Ghent, University Hospital Antwerp and Ghent

P12 **Impact of Adding Dedicated Cardiovascular Genetic Counseling to a Robust Aortic Disease Program at a Tertiary Care Center**
Rajani Aatre, University of Michigan

P13 **Novel Loci Associated with Human Bicuspid Aortic Valve Disease**
Simon Body, Boston University School of Medicine

P14 **Auditing Genetic Testing for Aortopathy at the Genomics Laboratory in Royal Brompton & Harefield Hospital (RBHH)**
Neeti Ghali, Inherited Cardiac Conditions, Royal Brompton and Harefield Hospital

P15 **Yield of Genetic Testing in Individuals with Bicuspid Aortic Valve and Thoracic Aortic Aneurysms and Dissections**
Christina Rigelsky, Cleveland Clinic

P16 **Clinical and Genetic Correlates of Mitral Valve Pathology in Patients with Heritable Thoracic Aortic Disease: Results from the Montalcino Aortic Consortium**
Laura Muiño-Mosquera, Ghent University Hospital

TOPIC: MODELING

P17 **Abstract Proposal for a Future Study: Revisiting the Combination Aortic Dissection Detection Risk Score (ADD-RS) and D-Dimer Algorithm for Acute Aortic Syndrome (AAS) Rule-Out in the Emergency Department**
Robert Pena, George Washington University Hospital

P18 **Computational Modeling for the Quantification of Biomechanics Indexes Associated with Adverse Remodeling in Valve Sparing Root Replacement Surgery: The Impact of Graft Stiffness**
Guido Nannini, Polytecnico di Milano

P19 **Novel Methods for Analyzing Long-Term Outcomes for Thoracic Aortic Aneuryms**
Matthew Solomon, Kaiser Permanente

TOPIC: SURGERY

P20 **Stenting of Infrarenal Aorta Along with Bentall's Procedure in a Case of Acute Stanford Type A Aortic Dissection Complicated By Renal Malperfusion**
Anitha Chandrasekhar, Medanta - The Medicity

P21 **Open Repair of Thoracoabdominal Aortic Aneurysms in Marfan Patients**
Giovanni Soletti Jr, Weill Cornell Medicine

TOPIC: NOVEL RESEARCH STUDIES

P22 **Covid-19 and Aortic Dissection - A Lethal Combination**
Anitha Chandrasekhar, Medanta - The Medicity

P23 **EMILIN-1 (Elastin-Microfibril-Interface-Located-protein-1) is Associated with Aortic Aneurysm**
Kathryn Holmes, Oregon Health & Science University

P24 **Research Priorities Among Patients with Syndromic Heritable Aortopathies with and at Risk for Aortic Dissection**
Sherene Shalhub, University of Washington

ABSTRACTS OF POSTER PRESENTATIONS

GenTAC Aortic Summit

Listed in Order of Presentation

ENDURANCE EXERCISE FOLLOWING ASCENDING THORACIC AORTIC ANEURYSM RESECTION IN BICUSPID AORTIC VALVE AORTOPATHY

[1] Lai, Andrew, MD, [1] Braverman, Alan, MD

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Introduction

Individuals with heritable thoracic aneurysm diseases (HTAD) are advised to avoid physical activity and endurance exercise generating high metabolic equivalents because of aortic disease concerns, even after proximal thoracic aortic aneurysm (TAA) repair. Bicuspid aortic valve (BAV) aortopathy differs from HTAD because the aortic disease is isolated to the ascending aorta or aortic root. The localized aortic disease in BAV aortopathy may predict low-risk for endurance exercise after ascending and/or aortic root resection.

Objectives

We sought to examine clinical and aortic outcomes in athletes participating in endurance exercise and competition after ascending TAA resection for BAV aortopathy.

Materials and Methods

Athletes with BAV aortopathy who participated in endurance exercise and competitions after TAA resection were identified from the Ironheart Foundation and from Washington University School of Medicine. Clinical data and endurance exercise/competition information were obtained from medical records, questionnaires, and telephone calls. Aortic imaging reports from before surgery to the most recent follow-up were reviewed.

Results

21 athletes (17 men) with a mean age of 53 ± 12 years participated. Ascending aortic diameter before surgery (N=16, mean age 46 ± 14) was 50.1 ± 5.4 mm. Athletes returned to exercise at 5.7±3.8 months post-op and they exercised for 1.4 ± 0.6 hours/day, at least 4-6 days/week. After clinical follow-up at 8.0 ± 5.2 years, athletes completed nearly 300 endurance competitions (marathons, Ironman, endurance cycling). During this time, there were no adverse aortic events. The largest native aortic diameter (available in 17 participants) at follow-up of 6.0 ± 4.4 years post-op was 35.4 ± 5.5 mm. Three athletes required repair of a degenerative bioprosthetic AVR at a mean of 8.7 ± 3.7 years post-op.

Conclusion

Among select individuals with isolated BAV aortopathy and without residual aortic disease, endurance exercise after TAA repair was not associated with adverse aortic events.

FAMILIAL BICUSPID AORTIC VALVE AND THORACIC AORTIC ANEURYSM ASSOCIATED WITH C.221G>A;P.GLU738LYS THSD4 VARIANT

Debiec Radoslaw PhD[1,2], Hamby Stephen E PhD[1], Coolman Sue[1], Kharodia Shireen PhD[1], Mariscalco Giovani MD, PhD[1], Suzuki Toru Professor[1], Samani Nilesh J Professor[1], Webb Tom R PhD[1], Bolger Aidan P MD, PhD[1,2]

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Introduction

Hereditary thoracic aortic aneurysm and dissection hTAAD is a group of genetic conditions characterised by significant genetic and phenotypic heterogeneity. Pathogenic variants in *THSD4*, which encodes ADAMTSL6, have recently been reported as a new cause of hTAAD.

Our Bicuspid aoRtic vAlVe gEnetic research (BRAVE) study aims to identify the genetic variants associated with bicuspid aortic valve (BAV), a common congenital heart defect that frequently presents with thoracic aortic aneurysm (TAA). Here, we report the identification of a candidate of a missense variant in *THSD4* as the likely cause of disease in a family with bicuspid aortic valve (BAV) and thoracic aortic aneurysm (TAA).

Methods

Three affected and one unaffected members of a two-generational pedigree with familial BAV and TAA underwent whole exome sequencing (WES) as part of the BRAVE Study.

Results

The 77 year-old female proband underwent aortic valve replacement due to severe stenosis of BAV and tubular ascending aorta replacement (ascending aortic size 43 mm; 27.4 mm/m). The proband's brother underwent aortic valve replacement due to severe stenosis at age 68. His daughter was diagnosed with BAV and ascending aortic dilatation (35 mm, 22 mm/m) as part of the research screening process. WES revealed a *THSD4* variant, c.221G>A;p.Glu738Lys (rs376870646), co-segregating with disease. No variants were identified in other genes associated with hTAAD or familial BAV. The p.Glu738Lys variant has a minor allele frequency of $3.3x10^{-5}$ in gnomAD and a CADD score of 29.4. The highly conserved amino acid is at the border of the 2nd and 3rd thrombospondin type 1 repeat domains.

Conclusion

We provide further genetic validation of *THSD4* as a cause of hTAAD and expand the phenotypic spectrum to BAV. Future studies will explore the frequency of *THSD4* variants in individuals with BAV.

INCREASED PREVALENCE OF OBESITY IN CHILDREN WITH BICUSPID AORTIC VALVE IS ASSOCIATED WITH SEDENTARY BEHAVIORS

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Objective

Compare the prevalence of obesity in a local population of school age children with Bicuspid aortic valve (BAV) in those engaging in competitive sports to sedentary children.

Introduction

(BAV) is the most common congenital heart diseases (CHD) and there is controversy related to recommendation of sports participation. In addition, the prevalence of obesity is increasing in the U.S. population along with increased cardiovascular diseases.

Methods

We performed a retrospective review of pediatric cardiology patients at Oregon Health & Science University with BAV between ages 8 and 18 years. We excluded those with known aortopathies and genetic conditions other than BAV. Demographic information including body mass index was obtained from chart review. Parents were contacted to complete a survey examining level of daily activity, participation in competitive sports and physician prescribed activity restriction.

Results

The initial cohort included 244 patients, 78% male. Of these, 110 (45%) completed telephone surveys. The prevalence of obesity in was 18% (n 43), which is increased compared to 11% in in the local population. Children who participated in competitive sports or the national daily recommended physical activity (60 minutes per day) were associated with a decreased likelihood of obesity (OR 0.26, 95% confidence interval (CI) 0.10-0.83 and OR 0.25, 95% CI 0.060-0.064, respectively). Older children were less likely to be physically active (OR 0.82, 95% CI 0.71-0.94) or participate in competitive sports (OR 0.86, 95% CI 0.76-0.98). While not significant, there was a positive trend when comparing parent worry about exercise and parents who limit their child's activity (OR 3.7, 95% CI 0.96-13.98)

Conclusions

Children with BAV are more obese compared to local population. In addition, older children with BAV more likely to be sedentary. This outlines the critical importance of encouraging daily activity and ongoing participation in competitive sports in children with BAV.

EFFECT OF LOSARTAN OR ATENOLOL ON CHILDREN AND YOUNG ADULTS WITH BICUSPID AORTIC VALVE AND DILATED AORTA

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Introduction

Bicuspid aortic valve aortopathy is defined by dilation of the aortic root (AoRt) and/or ascending aorta (AsAo), and increases risk for aortic aneurysm and dissection. The effects of medical prophylaxis on aortic growth rates in moderate to severe bicuspid aortopathy have not yet been evaluated.

Objective

This was a single-center retrospective study of young patients (1 day to 29 years) with bicuspid aortopathy (AoRt or AsAo z-score ≥ 4 SD, or absolute dimension ≥ 4 cm), treated with either losartan or atenolol.

Methods

Maximal diameters and BSA-adjusted z-scores obtained from serial echocardiograms were utilized in a mixed linear effects regression model. The primary outcome was the annual rate of change in AoRt and AsAo z-scores during treatment, compared with before treatment.

Results

The mean ages (years) at treatment initiation were 14.2 ± 5.1 (losartan; n = 27) and 15.2 ± 4.9 (atenolol; n = 18). Median treatment duration (years) was 3.1 (IQR 2.4, 6.0) for losartan, and 3.7 (IQR 1.4, 6.6) for atenolol. Treatment was associated with decreases in AoRt and AsAo z-scores (SD/year), for both losartan and atenolol (pre- vs post-treatment): losartan/AoRt: +0.06 ± 0.02 vs -0.14 ± 0.03, $p < 0.001$; losartan/AsAo: +0.20 ± 0.03 vs -0.09 ± 0.05, $p < 0.001$; atenolol/AoRt: +0.07 ± 0.03 vs -0.02 ± 0.04, $p = 0.04$; atenolol/AsAo: +0.21 ± 0.04 vs -0.06 ± 0.06, $p < 0.001$. Treatment was also associated with decreases in absolute growth rates (cm/year) for all comparisons ($p \leq 0.02$).

Conclusion

Medical prophylaxis reduced proximal aortic growth rates in young patients with at least moderate and progressive bicuspid aortopathy. Additional larger clinical studies are warranted to confirm this finding and to determine if early medical prophylaxis can decrease the rate of serious aortic events during adulthood, including aortic surgery, aortic dissection, and sudden death.

AORTIC TORTUOSITY IS RELATED TO THE AORTIC PHENOTYPE IN PATIENTS WITH BICUSPID AORTIC VALVE

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Introduction: Although the incidence of aortic dissection is higher in patients with bicuspid aortic valve (BAV) compared to tricuspid aortic valve (TAV), risk stratification remains unclear. Aortic tortuosity (AT) is emerging as a novel risk marker in patients with genetic thoracic aortic aneurysm (TAA) but has not been assessed in BAV.

Objectives: Our aim is to describe the relationship between AT, BAV type and ascending aortic phenotype in patients with BAV.

Materials and Methods: Patients with BAV and aortic dilatation but without significant aortic valve disease nor aortic surgery history were included, as well as age and sex matched TAV controls. Aortic diameters, aortic length, and AT index (ATI) were measured on CT scans. ATI was defined as the ratio between actual length and geometric length, measured for the ascending, descending and the entire aorta. Aortic phenotype was classified as “root phenotype” (RP) when the Z score >2 at the root level and < 2 at the tubular level and “tubular phenotype” (TP) when the Zscore is >2 at the tubular level.

Results: 61 patients (43 ± 16 years, 15 women) with BAV (84% of typical BAV) and aortic dilatation and 22 TAV controls were included. Tubular phenotype was found in 49 (80%) of BAV patients.

Aortic diameters and ATI were similar in L-R and N-R BAV.

Total ATI was correlated with age (r = 0.53, p <0.0001) and BSA (r = -0.31, p = 0.014) and was higher in BAV patients compared with age- and sex-matched controls (n = 31) (1.98 ± 0.19 vs 1.84 ± 0.19, p = 0.004).

Total ATI was higher in patients with Tubular Phenotype compared to patients Root Phenotype (2.01 vs 1.85; p = 0.013). In addition, Total ATI was correlated with tubular Z-score (r= 0.31; p = 0.014) but not with Root Z-score (p = 0.55).

Conclusion: Aortic tortuosity is increased in BAV patients with ascending aorta enlargement and seems to be related with tubular dilatation but not with root dilatation, suggesting that tubular phenotype may be at higher risk of aortic complication. Further studies evaluating the association between ATI and clinical outcomes in BAV are needed.

AORTIC EVENTS DURING PREGNANCY IN WOMEN WITH BICUSPID AORTIC VALVE AND AORTIC DILATATION: A RETROSPECTIVE STUDY

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Introduction: The risk of aortic dissection during pregnancy remains poorly appreciated in women with BAV.

Objectives: to investigate aortic events associated with pregnancy in women with BAV and aortic dilatation and to estimate ascending aortic diameter at the time of pregnancy.

Materials and Methods: We performed a retrospective study using data of women with BAV and aortic dilatation, not affected by a genetic syndrome and who have been pregnant, seen//treated in our center between 1996 and 2020. Assuming from the literature an annual aortic dilation rate of 0.2 mm at the sinuses of Valsalva and 0.4 mm at the tubular ascending aorta, we estimated ascending aortic diameters and Z- score at the time of pregnancy.

Results: We identified 47 women with BAV and aortic dilatation with an occurrence of 103 pregnancies.

The median age at the time of pregnancy was 29 (26-33) years. No aortic dissection occurred during pregnancy or during the postpartum period. At distance of pregnancy and post partum, acute aortic dissection occurred in 2 women and elective aortic surgery was performed on 8 women, associated with aortic valve replacement for 6 of them.

The median age at first visit in our center was 43 (35-56) years old. Median largest ascending aortic diameter (root or tubular aorta) was 44 (40-47) mm corresponding to a median Z-score of 4.4 (3.6-5.1).

At the time of pregnancy, the estimated median largest diameter of the ascending aorta was 37.2 (33.4-42.3) mm and the estimated median Z-score was 3.4 (2.3-4.7). The largest aortic diameter was estimated to be ≥40mm in 40/103 pregnancies, ≥45 mm in 15/103, and ≥50 mm in 0/103; Z-score was estimated to be ≥2 in 86/103 and ≥4 in 40/103 at the time of pregnancy.

Conclusion: In our population of women with BAV and aortic dilatation, no aortic complication occurred during 103 pregnancies, even though, when estimating aortic diameter at the time of pregnancy, the rate of aortic dilation was high.

AORTIC ROOT ANATOMY IS RELATED TO THE BICUSPID AORTIC VALVE PHENOTYPE

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Introduction: Bicuspid Aortic Valve (BAV) is associated with an asymmetrical (not circular) aortic root, resulting in variability in the aortic root diameter measurements obtained using different techniques.

Objectives: to describe the aortic root asymmetry, including its orientation in the thorax, in relation to the various phenotypes of BAV and its impact on aortic root diameter measurements obtained using TTE.

Materials and Methods: Aortic root asymmetry, orientation of the largest root diameter, and orientation of the valve opening were studied using CT scans of BAV patients without significant aortic valve dysfunction referred for evaluation of a thoracic aortic aneurysm. 85 BAV patients were evaluated: BAV with fusion of the left and the right coronary cusps (L-R BAV), with or without raphe (n=63), were compared with BAV with fusion of the right coronary and non-coronary cusps (N-R BAV), with or without raphe (n=22).

Results: Asymmetry of the aortic root and its orientation in the thorax can be predicted from the BAV phenotype: orientation of the valve opening differed from orientation of the largest root diameter by nearly 75° in both groups. The angle of the largest root diameter with the reference sagittal plane was 64.3° in the L-R BAV group versus 143.1° in the N-R BAV group ($p<0.0001$).

Therefore, using TTE parasternal long axis view, in N-R BAV, the ultrasonic beam is roughly parallel to the valve opening orientation and almost orthogonal to the maximum diameter of the root. On the contrary, in the L-R BAV, the ultrasonic beam is roughly perpendicular to the valve opening orientation and almost parallel to the maximum diameter of the root. Consequently, TTE parasternal long axis view significantly underestimates the maximum aortic root diameter in the N-R BAV, and modestly underestimates the root diameter in L-R BAV (-6.1 ± 0.96 vs - 2.3 ± 0.47 mm; $p=0.0008$).

Conclusions: Aortic root morphology in BAV patients can be predicted by the BAV phenotype: the largest root diameter is roughly perpendicular to the orientation of the valve opening. Therefore, echocardiographic measurements according to present recommendations (parasternal long axis view) underestimate maximal diameter in patients with N-R BAV.

WHOLE GENOME SEQUENCING AND FAMILIAL SEGREGATION ANALYSIS REVEAL CELSR1 RISK ALLELES IN FAMILIAL BICUSPID AORTIC VALVE AND HYPOPLASTIC LEFT HEART SYNDROME

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Background: Bicuspid aortic valve (BAV) is a common congenital heart disease (CHD); however, a complex genetic architecture evident by incomplete penetrance, variable expression, and genetic heterogeneity has hampered BAV gene discovery. Whole- genome sequencing (WGS) in families enables deciphering of CHD causes.

Objective: To determine genetic basis for familial bicuspid aortic valve (BAV) and hypoplastic left heart syndrome (HLHS).

Methods: WGS was performed in affected members of 6 multiplex BAV families, an HLHS cohort of 197 probands and 546 relatives, and 813 controls. Data were filtered for rare, predicted-damaging variants that cosegregated with familial BAV and disrupted genes associated with CHD in humans and mice. Candidate genes were further prioritized by rare variant burden testing in HLHS cases versus controls. Modifier variants in HLHS proband-parent trios were sought to account for the severe developmental phenotype.

Results: In 5 BAV families, missense variants in 6 ontologically diverse genes for structural (*SPTBN1*, *PAXIP1*, and *FBLN1*) and signaling (*CELSR1*, *PLXND1*, and *NOS3*) proteins fulfilled filtering metrics. *CELSR1*, encoding cadherin epidermal growth factor laminin G seven-pass G-type receptor, was identified as a candidate gene in 2 families and was the only gene demonstrating rare variant enrichment in HLHS probands (P=0.003575). HLHS-associated *CELSR1* variants included 16 missense, one splice site, and 3 noncoding variants predicted to disrupt canonical transcription factor binding sites, most of which were inherited from a parent without congenital heart disease. Filtering whole-genome sequencing data for rare, predicted-damaging variants inherited from the other parent revealed 2 cases of *CELSR1* compound heterozygosity, one case of *CELSR1-CELSR3* synergistic heterozygosity, and 4 cases of *CELSR1-MYO15A* digenic heterozygosity.

Conclusions: *CELSR1* is a susceptibility gene for familial BAV and HLHS, further implicating planar cell polarity pathway perturbation in congenital heart disease.

CONCOMITANT CARDIOVASCULAR MALFORMATIONS IN ISOLATED BICUSPID AORTIC VALVE DISEASE: A RETROSPECTIVE STUDY AND META-ANALYSIS

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Introduction

Congenital bicuspid aortic valve affects up to 2% of the general population. It occurs in complex congenital heart defects or in syndromes such as Turner, Marfan, or Loeys-Dietz. However, the majority of bicuspid aortic valves are considered to manifest as isolated malformations

Objectives

We aimed to assess retrospectively associated cardiovascular malformations in 200 individuals with bicuspid aortic valve considered to occur as an isolated manifestation.

Methods

All individuals underwent transthoracic echocardiography, 164 thoracoabdominal tomographic imaging, and 84 coronary artery imaging. In addition, we also performed a meta- analysis of data from the literature to assess the occurrence of associate malformations.

Results

In our retrospective study collective, the mean age was 45 ± 15 years, 154 (77%) individuals were male. Anatomy of bicuspid aortic valve according to Schaefer was type 1 in 142 (71%), type 2 in 35 (18%), type 3 in 2 (1%), unicuspid in 6 (3%), and unclassified in 15 (8%) individuals. Coarctation of the aorta had 4.2% of individuals, 3.6% had coronary anomalies. No individual had a patent ductus arteriosus, 0.5% had atrial and ventricular septal defect each, 1.5% mitral valve prolapse. No individual had a tricuspid valve prolapse. Our meta-analysis identified in cohorts with isolated bicuspid aortic valve 11.8% (95% CI: 7.6%-16.0%) individuals with aortic coarctation, 3.7% (95% CI: 1.2%-6.1%) with coronary anomalies, 3.3% (95% CI: 0.0%-6.7%) with patent ductus arteriosus, 5.3% (95% CI: 0.8%-9.7%) with ventricular septal defect and 1.6% (95% CI: 1.1%-2.1%) with mitral valve prolapse.

Conclusion

Individuals with isolated bicuspid aortic valve may exhibit a variety of associated cardiovascular malformations and therefore screening for associated malformations may be warranted.

ROLE AND YIELD OF CLINICAL GENETIC TESTING AMONG PATIENTS WITH BICUSPID AORTIC VALVE AND AORTIC DILATION REFERRED TO THE CARDIOVASCULAR GENETICS CLINIC

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Introduction: Bicuspid aortic valve (BAV) is one of the most common causes of aortic dilation and can occur concomitantly with other heritable thoracic aortic diseases (HTAD). Therefore, it is critical to rule out concomitant HTAD among patients with BAV to guide clinical management.

Objective: To describe the yield of clinical genetic testing among patients with BAV referred to the Cardiovascular Genetics (CVG) clinic.

Methods: We retrospectively identified 125 patients with BAV, without a known genetic diagnosis, who were referred to the CVG clinic at Texas Children's Hospital between January 2010 - December 2021. We subsequently identified 83 patients where the primary referral question was evaluation for a concomitant HTAD or associated genetic condition.

Results: Among 83 patients with BAV and aortic dilation, 71 (86%) underwent genetic testing after detailed phenotypic evaluation at a median age of 10 years (IQR 5-13 years). Most common form of initial genetic testing was panel of genes associated with aortopathy in 59 (83%), followed by whole exome sequencing (WES) in 8 (11%), and other forms of testing in 4 (6%) patients. A total of 16 (19%) patients underwent chromosomal microarray (CMA) irrespective of other genetic testing. Overall yield of genetic testing relevant to the clinical phenotype of patients, including variants of uncertain significance (VUS), was 24% (17/71). After meticulous interpretation of the variants, the diagnostic yield of genetic testing in terms of pathogenic or likely pathogenic variants and clinically actionable findings was 13% (9/71). While the remaining 11% (8/71) patients had a VUS associated with the phenotype, with probable clinical impact, but lacking enough evidence to be classified as pathogenic or likely pathogenic.

Conclusions: Among patients with BAV, genetic testing can provide a considerable clinically relevant and actionable diagnostic yield when guided by a detailed phenotypic evaluation for HTAD or associated genetic conditions.

GENOME-WIDE EPISTASIS FOR CARDIOVASCULAR SEVERITY IN MARFAN STUDY DESIGN: PATIENT ORGANIZATION DRIVEN RESEARCH

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Introduction/Objectives

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with manifestations in the ocular, skeletal and cardiovascular system. Morbidity and mortality are mostly determined by aortic disease. Although mutations in *FBN1* are the well-established genetic cause of MFS, there is a poor correlation with regards to phenotypical outcome, especially cardiovascular. Wide intra- and interfamilial phenotypical variability is observed, but the underlying mechanisms remain largely elusive. Consequently, the identification of genetic variation that modifies these effects will provide important novel insights.

Materials and Methods

A worldwide collaborative project driven by researchers and a Belgian patient organization, 'Foundation 101 Genomes' (F101G), was established to maximize the number of patients to participate in the study of the genetic basis of the marked phenotypical variability. RNA-sequencing of iPSC-derived vascular smooth muscle cells (IPSC-VSMCs) will be integrated with WGS to reveal MFS aortopathy genetic modifiers, which will be validated using CRISPR/Cas9 in iPSC-VSMCs.

Results

Our research institutions already gathered DNA for WGS and PBMCs for iPSC-VSMC creation of 50 patients carrying the most common MFS-causing *FBN1* missense variant (p.Ile2585Thr;c.7754T>C). WGS of these samples is ongoing. Based on international collaborations we are aware of at least 200 MFS patients carrying this specific variant and presenting with a wide range in cardiovascular severity. Together with F101G, we created a website to guide patients to participate in our research (https://cst101g.azurewebsites.net).

Conclusion

Despite the large number of patients already included, more patients are needed to identify genetic modifiers for MFS aortopathy. Understanding how mother nature by itself modifies the outcome of the primary *FBN1* mutation will allow for individualization of current treatment protocols to deliver true precision medicine and offer promising new leads to novel therapeutic strategies.

IMPACT OF ADDING DEDICATED CARDIOVASCULAR GENETIC COUNSELING TO A ROBUST AORTIC DISEASE PROGRAM AT A TERTIARY CARE CENTER

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Introduction

The University of Michigan had an aortic surgery and disease program with Genetic counseling (GC) and testing provided through Medical Genetics in the obvious cases but not as part of the regular care team. In 2016, we piloted having a certified genetic counselor (CGC) with expertise in cardiovascular genetics meet with aortic patients. In 2017, the CGC became part of the care team.

Objectives

To retrospectively evaluate the impact of a dedicated CGC on enhancing care in an established aortic disease program.

Methods

GC case logs were evaluated over a 5-yr period (2017-2021) to determine the number of patients seeing the genetic counselor, pursing testing and subsequent family cascade screening.

Results

The number of patients seen annually increased from 127 to 183 (44%) from 2017-19 and150 during the pandemic. Number of patients seen in the 1st quarter predict an increase to greater than 230 (83%) in 2022. The percentage of index patients pursing genetic testing rose from 65% to 87%. Most revealing was the increase in family cascade testing from 25% to 65% in 2019 and about 50% subsequently. On average, 15% of cases tested had a causative change, while 27% had a VUS with 6% reclassified to pathogenic over 5 years by familial segregation. All relatives who tested positive went on to pursue clinical screening.

Conclusion

While genetic counseling and testing has been recommended as an integral part of the care of patients and families with thoracic aortic disease by AHA guidelines, having a dedicated cardiovascular CGC (as opposed to a referral to a separate location) increases identification of families at risk and optimizes medical management and screening. This will translate to lives saved, even in a robust and experienced aortic care center of excellence.

NOVEL LOCI ASSOCIATED WITH HUMAN BICUSPID AORTIC VALVE DISEASE

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Introduction

Bicuspid Aortic Valve (BAV) is the moist common congenital valvular abnormality in humans. BAV is associated with many-fold increase in early calcific aortic stenosis (CAS), thoracic aortic disease (TAD) and surgery for same. BAV incurs life-time morbidity and mortality.

Objectives

We wished to identify genetic loci associated with non-syndromic BAV, to facilitate further identification of loci for BAV-associated CAS and TAD.

Materials and Methods

Using cohorts of individuals with non-syndromic BAV and population controls identified in Europe, Canada and USA, including from GenTAC, we used or performed genome-wide genotyping of >1.6M SNPs. Genotypes were further imputed using the TopMed Imputation Server. QC was performed using PLINK and analysis performed with SAIGE. SNPs with $P<5*10^{-8}$ and MAF>0.01 were identified.

Results

Loci identified included replication of previously-identified associations with *GATA4* and *PALMD* at 8p23 and 1p21.2, respectively. Additional loci were identified (Table 1).

Table 1:

Position	tagSNP	P value	Potential gene of interest
chr3:195,760,320	rs2641716	P=2.36E-08	Unknown
chr9:134,873,131	rs11351893	P=3.86E-16	*COL5A1*
chr9:136,480,886	rs35219967	P=2.95E-08	*NOTCH1*
chr17:41,815,787	rs111544145	P=3.53E-10	Unknown
chr17:82,117,684	rs35882870	P=6.11E-10	Unknown

Conclusion

This is the largest multi-institutional BAV cohort yet genotyped. Loci identified in this study may facilitate further identification of loci for BAV-associated CAS and TAD. For example, the locus at 3q29 (peak SNP rs2641716) is in proximity to *SMCO1*, a gene highly expressed in human atria and ventricles with unknown function. The region is located in proximity to the 3q29 microdeletion locus. Confounding by presenting disease including CAS and TAD is likely present, thus amplifying the expression of *PALMD* and *COL5A1* in this cohort.

AUDITING GENETIC TESTING FOR AORTOPATHY AT THE GENOMICS LABORATORY IN ROYAL BROMPTON & HAREFIELD HOSPITAL (RBHH)

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Introduction: Familial aortopathies can be syndromic or non-syndromic. In the presence of factors such as family history or early age of onset without environmental triggers, best practice is to refer patients for genetic testing, usually via a multigene next-generation sequencing (NGS) panel.

Patients carrying deleterious variants in known aortopathy-associated genes may be more prone to aortic dissections at younger ages and at smaller diameters. Timely genetic testing helps guide management to prevent further complications and enables some prediction of risk in family members. However, identifying variants of unknown significance (VUS) cannot meaningfully guide management and causes further uncertainty for patients, families, and healthcare professionals. Therefore, the panel must be carefully designed and curated to exclude genes without strong evidence bases.

Objectives: To examine the number and nature of aortopathy testing referrals in the UK, and to compare identification rates of (likely) pathogenic variants and VUS between a 63- gene Vasculopathy & Aortopathy (V&A) and a more focussed and curated 34-gene FTAA panel (R125) in a laboratory dedicated to aortopathy gene testing (RBHH).

Materials and Methods: Data from July to December 2019 (n=82) when the V&A panel was used was compared to that from February to July 2021 (n=110) after switching to R125. A chi- squared comparison of proportions test was conducted on the percentages of (likely) pathogenic and VUS detected.

Results: The R125 panel detected fewer VUS, with a rate of 9.1% compared to 20.7% using the V&A panel. Pick-up rates of (likely) pathogenic variants were 10.9% using the R125 panel and 17.1% using the V&A panel, and this difference was not statistically significant.

Conclusion: Aortopathy testing using the 34-gene R125 panel identified fewer VUS than the 63- gene V&A panel, while preserving identification rates of (likely) pathogenic variants. This audit highlights the importance of carefully and frequently curating diagnostic gene panels to only include genes with strong evidence of association.

YIELD OF GENETIC TESTING IN INDIVIDUALS WITH BICUSPID AORTIC VALVE AND THORACIC AORTIC ANEURYSMS AND DISSECTIONS

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Introduction

Bicuspid aortic valve (BAV) is a common congenital anomaly affecting 1- 2% of the population. BAV increases the risk of thoracic aortic aneurysms and dissections (TAAD). While understood to have a hereditary component, the underlying genetic cause remains largely unknown. Limited data exists on the likelihood of identifying a pathogenic variant in individuals with a personal history of BAV with TAAD (BAV/TAAD).

Objectives

Determine the yield of genetic testing for individuals with BAV/TAAD.

Materials and Methods

Between April 8, 2015 and February 27, 2019, 464 patients were referred to cardiovascular genetic counseling for TAAD. Of these, 49 had BAV and 37 underwent genetic testing that examined at least 10 genes associated with TAAD.

Results

A pathogenic variant was identified in 6 individuals (16.2%). Pathogenic variants were detected in the following genes: FBN1 (4), ACTA2 (1), PRKG1 (1). Variants of unknown significance were identified in 8 individuals (21.6%). All four individuals with a pathogenic FBN1 variant had features suggestive of Marfan syndrome. Family history of TAAD or sudden death in a first degree relative (FDR) was present in 6 (16%) who underwent genetic testing (2 individuals with a pathogenic variant and 4 individuals with a negative genetic test result).

Conclusions

Genetic testing using a TAAD panel identified a pathogenic variant contributing to BAV/TAAD in 16.2% of individuals. The majority of the pathogenic variants identified were in FBN1 and had features suggestive of Marfan syndrome. The two remaining pathogenic variants identified were in individuals with family history of sudden death or TAAD in FDR. The presences of features suggestive of Marfan syndrome or family history of TAAD or sudden in FDR should prompt recommendations for genetic testing related to TAAD. This has a number of limitations including small sample size and the genes available during the timeframe studied.

CLINICAL AND GENETIC CORRELATES OF MITRAL VALVE PATHOLOGY IN PATIENTS WITH HERITABLE THORACIC AORTIC DISEASE: RESULTS FROM THE MONTALCINO AORTIC CONSORTIUM

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Introduction: Mitral valve (MV) pathology, is a well-known cardiovascular manifestation associated with the genes that predispose to Heritable Thoracic Aortic Disease (HTAD). MV pathology as a function of the underlying genetic cause has not been investigated in detail.

Objectives: Assess the prevalence, presenting features and outcome of MV pathology according to the underlying genetic defect in HTAD.

Materials and Methods: We leveraged clinical and genetic data of a large international multicenter retrospective cohort study. Probands and relatives with a (likely) pathogenic (LP/P) variant in 8 HTAD genes were included. Genes were categorized in 2 groups: Group 1, TGF-β pathway genes (*TGFBR1, TGFBR2, SMAD3 and TGFB2*) and Group 2, VSMC genes (*ACTA2, MYLK, PRKG1, MYH11*). MV pathology was defined as at least moderate MV regurgitation, MV prolapse and past MV surgeries.

Results: 459 patients with a LP/P variant were included. 68,8% carried a variant in a Group 1 gene and 31,2% in a Group 2 gene. 52 patients (11,3%) had MV pathology. Significant differences in MV status according to gene group were present: 15,5% in group 1, versus 2,1% in group 2, ($p<0,001$). Within Group 1, variants in SMAD3 were most common (32,7%), followed by TGFBR2 (25,0%) and TGFB2 (23,1%) ($p=0,006$). Compared to patients without MV pathology, patients with MV pathology more often underwent aortic aneurysm repair (34,6% vs 15,5%, $p<0,001$) but less frequently presented aortic dissection/rupture (7,7% vs 26,8%, $p<0,001$).

Conclusion: Patients with HTAD carrying LP/P variants in TGF β pathway genes present more frequently with MV pathology than patients with variants in VSMC genes. Patients with MV pathology more often undergo aortic aneurysm repair and present less frequently with aortic dissection/rupture. Whether the presence of MV pathology accelerates the diagnosis and hence leads to a stricter management and/or whether biological differences explain these differences requires further study.

ABSTRACT PROPOSAL FOR A FUTURE STUDY: REVISITING THE COMBINATION AORTIC DISSECTION DETECTION RISK SCORE (ADD-RS) AND D-DIMER ALGORITHM FOR ACUTE AORTIC SYNDROME (AAS) RULE-OUT IN THE EMERGENCY DEPARTMENT

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Introduction

Acute aortic syndrome (AAS) remains one of the most challenging, life-threatening, and easily misdiagnosed pathologies in the Emergency Department. The ADvISED Trial (2018) by Nazerian et al. has evaluated an AAS rule-out algorithm to reduce time-to- diagnosis and unnecessary studies (CTA, MRA, TTE) through a combined Aortic Dissection Detection Risk Score (ADD-RS) and D-dimer protocol (Sn(98.8%), Sp(57.3%), failure rate (0.3%), and efficiency (49.9%)). However, its adoption is limited due to lack of external, prospective validation, restricted generalizability, no US hospital involvement, and limited conclusive imaging studies (46.8%) with brief clinical follow-up (14d).

Objectives

Our objective is the reproduction and external validation of the ADvISED Trial through a multicenter, prospective US clinical trial, while also addressing limitations through expanded confirmatory imaging ($\geq$75%) and follow-up (30-90d). Developing a modified ADD-RS to include known AAS risk factors (age, race, cocaine) will also be considered.

Materials and Methods

Our study design and analyses are derived from Nazerian et al. to parallel their work. This is a proposed multicenter, prospective clinical trial (6 potential US sites) with the null hypothesis “ADD-RS/D-dimer algorithm failure rate > 2%” and sample size ($n \geq 1767$) to achieve types I (0.05) and II error (0.2). Primary and secondary outcomes are failure rate and efficiency of AAS rule-out via ADD-RS=0 + D-dimer<500ng/mL and ADD-RS$\leq$1 + D- dimer<500ng/mL. Statistical analyses include characteristics assessments ($\bar{x}\pm$SD, IQR, proportions), OR between AAS and categorical vs. continuous independent variables (univariate logistic regression models), and differences across independent samples (2- tailed student *t* or X^2 tests).

Results

We aim for equivalent/superior metrics as the ADvISED Trial with potential improvement thorough a modified ADD-RS.

Conclusion

The timely diagnosis and rule-out of AAS warrants further investigation and this research will hopefully validate the work by Nazerian et al. so it may achieve greater acceptance in medical practice.

COMPUTATIONAL MODELING FOR THE QUANTIFICATION OF BIOMECHANICS INDEXES ASSOCIATED WITH ADVERSE REMODELING IN VALVE SPARING ROOT REPLACEMENT SURGERY: THE IMPACT OF GRAFT STIFFNESS

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Introduction

Marfan syndrome (MFS) patients commonly develop thoracic aortic aneurysms (TAA): Prosthetic graft replacement provides lifesaving benefit, but risk persists for adverse events in the native distal aorta. One mechanism for such events may stem from graft-induced alterations in aortic biomechanics: Current prosthetic grafts (Dacron) are markedly stiffer than the native aorta, providing a conduit to propagate high energy flow and drive adverse distal remodeling.

Objectives

This study used cardiac MRI (CMR) derived fluid structure interaction (FSI) computational models to test impact of modified graft compliance on the distal aorta.

Materials and Methods

CMR (including MRA, cine, 4D flow) was performed in a genetic TAA patient before and after proximal graft replacement surgery. CMR was used to generate a pre-operative, and 3 post-operative Fluid-Structure Interactions (FSI) models with variable graft compliance (elastic modulus: 1MPa-12MPa [typical Dacron stiffness]). For each model, patient-specific inlet velocity profiles were defined using 4D flow: Intramural stress (IS) and wall shear stress (WSS) were quantified in the native distal aorta.

Results

FSI results were verified against 4D flow, with good matching ($p>0.05$) between velocity patterns. After Dacron graft implantation, distal aortic WSS increased ~2-fold (3.9 [0.5-0.9] vs. 6.9 [0.9-1.7] Pa, $p<0.001$): Simulations using more compliant grafts (1 and 5MPa) yielded lower distal aortic WSS than Dacron (1MPa: 3.1 [0.5-0.9] | 5MPa: 3.2 [0.4-0.9] Pa vs. 6.9 [0.9-1.7] Pa; both $p<0.001$). IS similarly increased after Dacron graft implantation (74.6 [65.6-82.8] vs. 105.8 [84.0-129.9] kPa; $p<0.001$): This was attenuated in simulations using a more compliant (1MPa) graft (81.6 [74.3-88.2]; $p<0.001$ vs. Dacron).

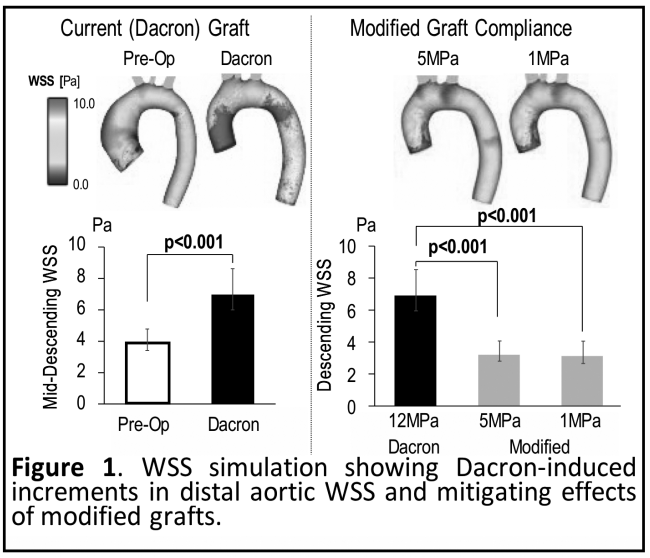

Figure 1. WSS simulation showing Dacron-induced increments in distal aortic WSS and mitigating effects of modified grafts.

Conclusion

Prosthetic graft replacement of TAA using current (non-compliant) materials alters distal aortic flow physiology, providing a potential nidus for adverse downstream remodeling. Attenuation of post-operative increments in distal WSS and IS by grafts with increased compliance suggest that such tailored grafts can mitigate adverse post-operative aortic remodeling.

NOVEL METHODS FOR ANALYZING LONG-TERM OUTCOMES FOR THORACIC AORTIC ANEURYMS

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Introduction

Discrepant measurements of thoracic aortic aneurysms (TAA) size occur depending upon the imaging modality, interpreting physician, and whether a study was dedicated for aortic measurement, making analysis of natural history and long-term outcomes challenging.

Objective

Estimate the risk of aortic dissection (AD) by aortic size using all available information on aortic size over time, which includes follow-up studies that may be more precise since they are dedicated for aortic measurement.

Materials and Methods

Using a safety net system tracking TAA patients in Kaiser Permanente Northern California, an integrated healthcare delivery system caring for >4.5M persons, imaging data was abstracted for date and maximum TAA size. We merged EHR data for demographics, clinical characteristics, and the outcome of AD. We estimated the association of TAA size (as a time-updated variable) with AD in multivariable, Cox competing risk models, and predicted the 5-year risk of AD if TAA size remained unchanged over follow-up or if TAA size increased by one size category at 2 years after baseline.

Results

Among 6,372 TAA patients from 2000-2016, (mean [SD] age 69 [13] years; 32% women), mean baseline TAA size was 4.4cm (13% of cohort >5.0cm; 4.4% > 5.5cm). Rates of AD were low across mean (SD) 3.7 (2.5) years of follow-up (0.7% of cohort, incidence 0.23 events/100 person-yrs). In multivariable models, larger aortic size was associated with increasing risk of AD and a size increase at Year 2 of follow-up resulted in higher risks.

Conclusion

Incorporating baseline and follow-up TAA imaging data in analyses provided improved understanding of risks from static vs changing TAA size, and can better inform patients on risks from TAA.

STENTING OF INFRARENAL AORTA ALONG WITH BENTALL'S PROCEDURE IN A CASE OF ACUTE STANFORD TYPE A AORTIC DISSECTION COMPLICATED BY RENAL MALPERFUSION

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The mortality rate among patients who undergo surgical repair of acute type A aortic dissection is approximately 35%. However, for acute disease complicated by end-organ ischemia, the surgical mortality rate exceeds 50%. We report a case of percutaneous transluminal angioplasty with stent placement to treat obliteration of the aortic true lumen that was causing acute kidney infarct in a patient with Stanford Type A dissection. This 28 years old gentleman, presented to ER with lower limb paraparesis, anuria and severe lactic acidosis. CT Angiography of aorta revealed Aortic Dissection with intimal flap extending from coronary sinus of valsalva to the entire aorta and further into the left common iliac artery with complete obliteration of true lumen in suprarenal abdominal aorta and thrombotic false lumen in left common iliac artery. Perfusion defects were noted in both the kidneys with an organised infarct in the lower pole of left kidney.

Echocardiography revealed ascending aorta of five cm with non-cooptation of aortic leaflets leading to moderate aortic regurgitation with normal ventricular function. He was immediately taken up in the hybrid operating room for emergency high risk Bentall's procedure using a 25 mm mechanical valved conduit with surgical fenestration. Axillary artery cannulation and antegrade cerebral perfusion was employed. His surgery was uneventful. In the same setting, he subsequently underwent Percutaneous Transluminal Angioplasty to infrarenal aorta with bare metal stenting with good end result. This restored blood flow to the true lumen and recovered bilateral lower limb flow. His post-operative course was prolonged and required multiple dialysis sessions after which his kidneys recovered. Aggressive physiotherapy for paraparesis and meticulous care with multi- disciplinary reviews were immensely beneficial. Renal malperfusion is a known but dangerous complication of aortic dissection. Timely restoration of blood supply to the true lumen is paramount.

OPEN REPAIR OF THORACOABDOMINAL AORTIC ANEURYSMS IN MARFAN PATIENTS

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Introduction

Outcomes for open repair of thoracoabdominal aortic aneurysms (TAAA) are progressively improving, but little is known about outcomes in patients with Marfan syndrome.

Objectives

To assess outcomes of Marfan patients undergoing open TAAA repair at a specialized institution and to compare results with non-Marfan patients.

Materials and Methods

All consecutive patients with and without Marfan syndrome who underwent open TAAA repair at our institution between 1997 and 2022 were included in the analysis. Propensity score weighting was used to account for differences in baseline characteristics between groups. Multivariable analysis was used to identify associations with postoperative major adverse events (MAE) including perioperative mortality, myocardial infarction, stroke, dialysis, tracheostomy, and re-exploration for bleeding. Long-term survival was estimated using the Kaplan-Meier method.

Results

Of 684 patients, 90 (13.1%) had Marfan syndrome. Marfan patients were younger ($p<0.001$), had lower left ventricular ejection fraction ($p=0.03$), had more frequently undergone previous open-heart surgery ($p<0.001$), and had lower prevalence of hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, and renal dysfunction ($p<0.001$ for all variables). Extent II-IV aneurysms were more common in Marfan patients ($p<0.001$). Operative mortality was similar in the two groups (Marfan vs non-Marfan, 3.3% vs 4.7%, $p=0.75$). There were no significant differences in MAE (Marfan vs non-Marfan, 13.3% vs 16.8%, $p=0.5$). Multivariable analysis identified preoperative renal dysfunction (odds ratio [OR]: 2.29; confidence interval [CI]: 1.43- 3.68, $p<0.01$) and urgent/emergent procedure (OR: 2.17; CI: 1.35-3.48, $p<0.01$) to be significantly associated with MAE, while Marfan syndrome was not (OR: 1.56; CI: 0.69-3.49, $p=0.28$). Weighted Kaplan-Meier curves showed no difference in long-term survival between the groups at 14-year follow-up (adjusted hazard ratio: 0.79; CI: 0.32-1.99, $p=0.62$).

Conclusion

In Marfan patients, open TAAA repair can be performed with acceptable risk at a specialized institution. Marfan syndrome is not associated with worse postoperative outcomes or long-term mortality.

COVID-19 AND TYPE A AORTIC DISSECTION: A LETHAL COMBINATION

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Covid-19 disease, declared as a pandemic since March 2020, has multiple extra-pulmonary manifestations, of which the cardiovascular ones are significant. The cardiovascular complications of Covid-19 include acute pericarditis, acute coronary syndrome, myocardial infarction, cardiac arrest, cardiogenic shock, arrhythmias and thromboembolic events. Rarely, it can also cause aortic dissection. We report a case of a 37 years old lady, who presented with Gastrointestinal symptoms and was tested Covid positive. She was initially treated with high flow oxygen at an outside hospital. She deteriorated, required mechanical ventilation and was subsequently tracheostomised. CT chest revealed Type A Aortic Dissection with dissecting flap originating from aortic root and extending to arch vessels. She sustained acute kidney injury necessitating hemodialysis. She subsequently developed hepatic encephalopathy, altered sensorium and polymicrobial sepsis. Echocardiography revealed dissecting flap arising from the aortic root at the sinus, causing non- coaptation of aortic leaflets, severe aortic regurgitation and moderate mitral regurgitation. After optimization with multi-disciplinary consultations, she underwent high risk, complex Bentall's procedure with Hemiarch replacement and mitral valve repair. Cardiopulmonary bypass was established with axillary artery-bicaval cannulation. Surgery was performed with integrate cerebral perfusion using 23mm mechanical valved conduit along with mitral valve repair using 28mm ring. The procedure was uneventful but her post-operative course was prolonged and intense. The double whammy of Covid infection and Aortic Dissection affecting almost every organ in the body leading to prolonged bed ridden status, required sustained and earnest efforts in the recovery phase. Aortic dissection is a relatively rare but life-threatening complication in Covid-19 patients. The similarities between the inflammatory pathologic pathway of Covid-19 and aortic dissection are compelling. Suspicion must be based on the clinical features. Prompt diagnosis, meticulous surgery and post-operative care at experienced hands can produce successful outcomes.

EMILIN-1 (ELASTIN-MICROFIBRIL-INTERFACE-LOCATED-PROTEIN-1) IS ASSOCIATED WITH AORTIC ANEURYSM.

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Introduction: EMILIN-1 (Elastin-Microfibril-Interface-Located-proteIN-1) is a structural component of the elastic fiber network and localizes to the interface between the fibrillin microfibril scaffold and the elastin core. How EMILIN-1 contributes to connective tissue integrity is not fully understood.

Objective: Describe the pathogenesis of a single family with a mutation in EMLIN-1

Materials and Methods: Data was abstracted from the patient record. Aortic tissue for histology and immunohistochemistry from the index patient was derived during surgery.

Results: Genetic testing of the index case demonstrated homozygous variant in the *EMILIN1* gene (c.1606C>T, p.Gln536Ter). The index case presented in utero with dilated aorta and concern for coarctation. Initial aortic root and ascending aorta were dilated at birth with Z scores 5.02 and 2.24 respectively. He was placed initially on Losartan followed by Atenolol. Tortuosity score was 1.1. He was taken to the operating room for valve sparing proximal aortic and hemi arch replacement at 18 months as the ascending aorta grew at a rate of 1.2 cm per year (from 1.14 cm to 2.95cm). In the operating room, it was demonstrated that he had a long intramural right coronary that ran parallel to the ascending aorta that was unroofed. Electron microscopy of the resected aorta (full thickness) showed pronounced fragmentation of the medial elastic lamellae with lamellar elastic fibers closest to the intima. The post-operative course was complicated by cardiac arrest necessitating ECMO cannulation for recovery. The patient with discharged to rehabilitation then home after a month-long hospital stay. At 2 years of age, they are doing well with good surgical result and minimal residual effects.

Conclusion: In our patient, loss of function of EMILIN-1 is critical for ascending aortic integrity. These results extend other patient accounts of EMILIN-1 variants (Adamo, et al., 2022). Down-stream effects of early aortic replacement will be determined in the future.

RESEARCH PRIORITIES AMONG PATIENTS WITH SYNDROMIC HERITABLE AORTOPATHIES WITH AND AT RISK FOR AORTIC DISSECTION

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Introduction

The AD Collaborative built a research infrastructure to facilitate patient centered outcomes research (PCOR) and identify priorities for aortic dissection (AD) research. Little is known about what patients with syndromic heritable aortopathies find most important from a research perspective.

Objectives

We report the PCOR priorities identified by patients with syndromic heritable aortopathies including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Vascular Ehlers-Danlos syndrome (VEDS).

Materials and Methods

The foundational engagement work identified 7 PCOR topic: Education, Genetics, Pregnancy, Medications, Mental health, Surgery, and Telemedicine. Evidence gaps were identified and 8 PCOR research questions were designed. An anonymous research prioritization survey was disseminated from 11/22/2021 to 2/28/2022 globally to the virtual research network of patients to rank the research questions. Responses by patients with syndromic heritable aortopathies were selected for analysis. The percentage of respondents ranking each question among their top three priorities was analyzed to derive the final ranked order of research questions.

Results

A total of 239 respondents met inclusion criteria: 139 with MFS, 61 with LDs, and 39 with VEDS (mean age 47.4±12.7 years, 66.9% in the United States). Educational resources for doctors was the highest ranked research priority (61.1%). Other highly ranked topics were genetic testing for underlying AD risk factors (51.9%), educational resources for patients (48.5%). The timing of surgery, impact of exercise, and mediations ranked lower (45.2%, 38.9%, and 38.5% respectively). Mental health and telehealth research ranked last (12.6% and 3.3%). These research priorities were no different when compared to patients with aortic dissection who did not have a genetic diagnosis.

Conclusions

Through stakeholder engagement, we identified the PCOR priorities of the AD community and found that research priorities of patients with syndromic heritable aortopati3es closely align with patients without such diagnosis. Educating physicians on AD was ranked highest among all research priorities.

GENERAL INFORMATION

Hotel

Le Méridien Etoile, Paris, France
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Ideally situated in the heart of Paris and facing the Palais des Congrès de Paris, the hotel is located near the La Défense business district and within walking distance of the Arc de Triomphe and Champs-Elysées. It is also near the Louvre Museum, Eiffel Tower, and Montmartre – all of which make Paris one of the most beautiful cities in the world.

Charles de Gaulle and Orly Airports are only 30-45 minutes from the hotel. The Le Bus Direct shuttle to Charles de Gaulle stops across the street every 30 minutes. The famed Gare du Nord train station is a mere 20 minutes away for those traveling to or from other cities aboard the Eurostar.

Seine River Cruise with Canapés and Cocktails – Le Paris

Between cruise and cuisine, a complete Parisian immersion awaits you for the Science in Paris dinner cruise on Tuesday, August 30, 2022. Facing the Eiffel Tower, Le Paris is the most innovative and modern of the boats on the Seine.

A beautiful evening of cocktails, hor d'oeuvres and beautiful Seine River scenery with fellow colleagues. The three-hour excursion is from 6:00-10:00 pm. Departing in front of the Eiffel Tower at 2 Port Debilly, approximately a 40 minute walk from the hotel. Discover Paris while tasting finely prepared dishes. The cruise allows you to observe the most famous monuments of the capital. During the cruise, you will be able to admire the Eiffel Tower, the Notre-Dame Cathedral, the Louvre, the Conciergerie, the Musée d'Orsay...and many other places that make the charm of Paris.

Speaker Presentations

Presentation timers will be used. All speakers will be required to load their presentations onto a single computer between 7:00 and 7:45 AM or during the breaks. Please bring your presentation on a USB.

Poster Presentations

A poster presentation session has been planned for each day. Posters have been assigned a number and a poster presentation session. This information can be found on the Poster Lists included in this booklet. Set up must be conducted prior to plenary sessions or during lunch or breaks. Please place your poster on the appropriate numbered board. Please remove your board after the poster session ends.

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