Cleveland Clinic

1st International Fibromuscular Dysplasia Research Network Symposium

MAY 15-16, 2014

InterContinental Hotel and Conference Center
Cleveland, Ohio

1st International Fibromuscular Dysplasia Research Network Symposium

Dear Colleagues:

It is with tremendous enthusiasm that we welcome you to Cleveland, Ohio for the 1st International Fibromuscular Dysplasia (FMD) Research Network Symposium. This meeting has been nearly two years in the making and brings together clinicians and investigators in the field of FMD from across the United States, Canada, and Europe for a state of the clinical science update as well as an opportunity for scientific strategic planning.

FMD is a morbid vascular disease that affects patients at the prime of life. In addition to impairing quality of life through symptoms such as headache and pulsatile tinnitus, FMD is a serious disease that is associated with major cardiovascular events such as stroke and myocardial infarction and other sequelae of poorly controlled hypertension. According to the US FMD Registry, more than 1/3 of FMD patients have an aneurysm and/or an arterial dissection.

The open sessions of the meeting will discuss the major clinical manifestation of FMD and help to define a 2014 approach to diagnosis, medical, endovascular, and surgical therapy. We will discuss optimal nomenclature for FMD. The latest data from US, French, and Canadian registries will be discussed, and the just published multi-specialty FMD scientific statement from the American Heart Association will be presented. We will highlight the relationship between FMD and coronary, visceral, and cervical artery dissection. Emerging concepts of the genetics of FMD will be presented, and researchers at the cutting edge of this field will update you on their work in progress, including some "late breaking" data. We hope that all clinicians who care for patients with FMD will find the open sessions of the meeting useful, and we welcome your participation in the panel discussions.

In addition to the state of the science review, this meeting will allow for much needed in-person conversation and collaboration for our international panel of invited researchers. Four small working groups will meet (hopefully not too) late into the night on Thursday and again Friday afternoon. Each working group will present a summary of their discussions and future plans on Friday afternoon at 3:15 pm. Please try to stay for this special session.

Many of you have come from far away, and we are most grateful for your time. We would like to thank our planning committee and the working group moderators, Jim Froehlich, Santhi Ganesh, and Esther Kim. We thank our meeting supporters, listed below, without whom this international endeavor would not have been possible. Finally, Dr. Gornik would like acknowledge the unwavering support of the Cleveland Clinic FMD Program by Dr. John R. (Jerry) Bartholomew.

This symposium is a momentous occasion. We anticipate that multiple international research projects will be born in the hours that follow, and we hope that this meeting will lead to major advances in our understanding of why FMD develops, how to best diagnose it, and how best to treat our patients to improve their vascular outcomes and quality of life.

And so, the "Cleveland Meeting" begins. Onward!

Heather L. Gornik, MD
Cleveland Clinic Heart and Vascular Institute

Jeffrey W. Olin, DO
Icahn School of Medicine at Mount Sinai

ABOUT CLEVELAND CLINIC

Cleveland Clinic's Miller Family Heart & Vascular Institute is one of the largest cardiovascular specialty groups in the world, providing patients with expert medical management and a full range of therapies. The Department of Peripheral Vascular Disease (PVD) was founded in 1947 by Dr. Fay LeFevre and has a rich history of vascular clinical care, education, and research. PVD was incorporated into the Robert and Suzanne Tomsich Family Department of Cardiovascular Medicine in 2001, and Dr. John R. Bartholomew has served as Section Head of Vascular Medicine since 2004. The Cleveland Clinic FMD Program began in August, 2008 with a dedicated clinic once per month. The clinic is now run twice weekly and follows more than 400 patients with FMD. The program uses vascular medicine specialists as primary vascular care providers and has built an experienced multi-disciplinary team of additional consultants, including nephrologists, neurologists, interventionalists, surgeons, radiologists, and pathologists, who are engaged depending upon the individualized needs of the patient.

The program committee thanks the following individuals and organizations for their support of this meeting:

National Heart, Lung, and Blood Institute (R13)

William Waytena Foundation

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Vascular Medicine Research and Education Fund (Dr. John R. Bartholomew)

MEETING CHAIRS

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PROGRAM PLANNING COMMITTEE

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SPECIAL THANKS

Neil Poria
Cleveland Clinic FMD Program,
Research Assistant – On-site Resource Aide

Kathy Murdakhaev
Course Coordinator, Cleveland Clinic FMD Program

FMD YOUNG INVESTIGATOR TRAVEL AWARD RECIPIENT

The selection committee congratulates Dr. Marysia Tweet, 3rd year fellow in Cardiovascular Medicine at Mayo Clinic. Dr. Tweet will be participating in the Imaging and Clinical Management Working Group. She was 1st author on the description of the Mayo Clinic spontaneous coronary artery dissection (SCAD) cohort with her mentors Drs. Rajiv Gulati and Sharonne Hayes and colleagues, published in Circulation in 2012.

FMD SOCIETY OF AMERICA

The 7th FMDSA Annual Meeting will be held May 16 – 17, 2014 at the Wyndham Playhouse Square Hotel. If you would like more information, please ask the staff to be introduced to Pam Mace, Executive Director, FMDSA.

FRIDAY, MAY 16

There will be closed, working group sessions during lunch and early afternoon on Friday which will allow for you to take advantage of a private tour of Cleveland Clinic's Art Collection. If you have signed up for the tour please meet by the registration desk at 2:30pm. A guide will meet you there. If you choose not to join the tour, you can use the time between lunch and 3:15pm as you please. Presentations from the Working Groups will be shared in the Open Session that follows.

Research Roadmap for Fibromuscular Dysplasia (FMD) and Creation of the FMD Research Network Working Group Participants

There will be four working groups, each chaired by a member of the planning committee. **Dr. Gornik will serve as the liaison between working groups to facilitate inter-disciplinary coordination of projects.**

1) Genetics

Working group charge: To strategize research program for determination of genetic mechanisms of FMD, including optimal use of existing biorepositories of FMD samples.

Chair – Santhi Ganesh, MD, University of Michigan

Participants:

- Juliette Albuisson, MD, National Center for Rare Vascular Diseases and Department of Genetics, Hôpital Européen Georges-Pompidou, France
- Nabila Bouatia-Naji, PhD, INSERM U970 and Paris Cardiovascular Research Centre, France
- Dawn Coleman, MD, University of Michigan
- Valentina D'Escamard, PhD, Mount Sinai Medical Center
- Xavier Jeunemaitre, MD, PhD, National Center for Rare Vascular Diseases and Department of Genetics,Hôpital Européen Georges-Pompidou and INSERM U970, France
- Alex Katz, MD, University of Michigan
- Jason Kovacic, MD, Mount Sinai Medical Center
- Ifitkhar Kullo, MD, Mayo Clinic
- Rocio Moran, MD, Cleveland Clinic

2) Epidemiology

Working group charge: To strategize research program to determine prevalence of FMD (in general population versus selected population subsets) and risk factors for FMD development.

Chair – Esther SH Kim, MD, Cleveland Clinic

Participants:

- Sue Duval, PhD, University of Minnesota
- Kevin Meyers, MBBCh, Children's Hospital of Philadelphia
- Marc Pohl, MD, Cleveland Clinic
- Aruna Pradhan, MD, Brigham and Women's Hospital and Harvard Medical School
- Tatjana Rundek, MD, PhD, University of Miami
- Emmanuel Touze, MD, PhD, Université de Caen Basse Normandie, France

3) Maximizing Existing Registries to Advance FMD Knowledge Base

Working group charge: To strategize future analyses and publications of the United States Registry for FMD and to discuss mechanism for collaboration of the United States Registry for FMD with aligned international vascular registries.

Chair – James Froehlich, MD, University of Michigan

Participants:

- Xiaokui Gu, MA, University of Michigan
- Sharonne Hayes, MD, Mayo Clinic
- Andrzej Januszewicz, MD, Institute of Cardiology, Poland
- Eva Kline-Rogers, RN, NP, MS, University of Michigan
- Pamela Mace, RN, FMD Society of America
- Sarah Matthys O'Connor, Cleveland Clinic Lerner College of Medicine
- Pierre-Francois Plouin, MD, Hypertension Unit, Hôpital Européen Georges-Pompidou, France
- Jacqueline Saw, MD, Vancouver General Hospital, Canada
- Aditya Sharma, MBBS, University of Virginia

4) Imaging and Clinical Management

Working group charge: To propose two multi-center clinical research studies addressing top research priorities in FMD diagnosis and therapy.

Chair – Jeffrey Olin, DO, Mount Sinai Medical Center

Participants:

- Michel Azizi, MD, Clinical Investigator Center, Hôpital Européen Georges-Pompidou, France
- Christopher Bajzer, MD, Cleveland Clinic
- Yung-wei Chi, DO, UC Davis Medical Center
- Natalia Fendrikova-Mahlay, Cleveland Clinic
- M. Shazam Hussain, MD, Cleveland Clinic
- Daniella Kadian-Dodov, MD, Mount Sinai Medical Center
- Rebecca Kelso, MD, Cleveland Clinic
- Robert Lookstein, MD, Mount Sinai Medical Center
- Alan Matsumoto, MD, University of Virginia
- Sanjay Misra, MD, Mayo Clinic
- Javier Romero, MD, Massachusetts General Hospital
- John Sperati, MD, MHS, Johns Hopkins University
- Marysia Tweet, MD, Mayo Clinic, Young FMD Investigator Award Winner

AGENDA | THURSDAY, MAY 15, 2014

Each speaker will be allotted 15 minutes for presentation with 5 minutes reserved for questions and topic-related discussion, unless otherwise noted.

Open sessions (Dr. Heather Gornik moderates)		
10:00 a.m.	Registration	
10:30 a.m.	Welcome and introduction of participants	Drs. Gornik and Olin
10:50 a.m.	FMD overview, historical perspective, and AHA scientific statement Top research priorities in FMD	Dr. Jeffrey Olin
11:10 a.m.	Epidemiology of FMD: What do we know? What don't we know?	Dr. Esther SH Kim
11:30 a.m.	Modernizing FMD nomenclature: unifocal versus multifocal FMD	Dr. Pierre-Francois Plouin
11:50 a.m.	Panel Discussion: How common is FMD? Dissemination of modern nomenclature for FMD	
Lunch and free time for open meeting attendees. Working groups (closed sessions, lunch provided)		
12:15 – 1:45 p.m.	• Genetics • Epidemiology • Maximizing Registries • Imaging and Clinical Management	Dr. Heather Gornik gives charge to working groups
Open sessions reconvene (Dr. Jeffrey Olin moderates)		
2:00 p.m.	The FMD Society of America: organization, activities, and partnership opportunities for FMD research	Ms. Pamela Mace
2:20 p.m.	The US Registry for FMD: What have we learned?	Dr. Heather Gornik
2:40 p.m.	French FMD Registry, organizational structure, data elements, summary of findings	Dr. Pierre-Francois Plouin
3:00 p.m.	Genetics of FMD: State of the science in 2014	Dr. Santhi Ganesh
3:20 p.m.	Potential application of genome wide association study to FMD	Dr. Iftikhar Kullo
3:40 p.m.	**REFRESHMENT BREAK**	
4:00 p.m.	Exome sequencing and application to FMD	Dr. Santhi Ganesh
4:20 p.m.	Assessment of the enrichment for rare coding variants in related cases of FMD	Dr. Nabila Bouatia-Naji
4:40 p.m.	The DEFINE FMD study – defining the molecular and cellular basis of FMD using patient-derived fibroblasts	Dr. Jason Kovacic
5:00 p.m.	Prevalence of connective tissue findings in FMD patients: preliminary findings	Ms. Sarah O'Connor
5:20 p.m.	US FMD biorepository activities (5 minutes)	Dr. Heather Gornik
5:25 p.m.	Panel Discussion: Is FMD a connective tissue disorder? Emerging concepts in the pathogenesis of FMD	
5:30 p.m.	**OPEN SESSIONS ADJOURN FOR THE DAY**	
Working groups meet		
5:45 – 8:00 p.m.	• Genetics • Epidemiology • Maximizing Registries • Imaging and Clinical Management	
8:00 p.m.	**WORKING GROUPS ADJOURN FOR THE NIGHT**	

AGENDA | FRIDAY, MAY 16, 2014

7:30 a.m.	**CONTINENTAL BREAKFAST**	
Open sessions (Dr. Heather Gornik moderates)		
8:00 a.m.	Duplex ultrasonography for assessment of FMD	Dr. Jeffrey Olin
8:20 a.m.	Clinical manifestations of cerebrovascular FMD and cervical artery dissection	Dr. Emmanuel Touze
8:40 a.m.	Optimal Imaging of cerebrovascular FMD: modalities, evidence, and knowledge gaps	Dr. Javier Romero
9:00 a.m.	Endovascular therapy for cerebrovascular FMD, cervical dissection, and cerebral aneurysm: Indications, emerging techniques, and knowledge gaps	Dr. Shazam Hussain
9:20 a.m.	Coronary artery FMD and spontaneous coronary artery dissection (SCAD): recognition, management, and unanswered questions	Dr. Jacqueline Saw
9:40 a.m.	Mayo Clinic SCAD cohort and maximizing use of the Internet and social media in rare disease research	Dr. Sharonne Hayes
10:00 a.m.	Panel Discussion: cerebrovascular manifestations of FMD, the relationship of SCAD and FMD	
10:20 a.m.	**REFRESHMENT BREAK**	
Open sessions continue (Dr. Jeffrey Olin moderates)		
10:40 a.m.	Optimal imaging of renal FMD: modalities, evidence, and knowledge gaps	Dr. Sanjay Misra
11:00 a.m.	Hemodynamic guided assessment of renal artery FMD	Dr. Christopher Bajzer
11:20 a.m.	Renal angioplasty for FMD: Evidence base and knowledge gaps	Dr. Robert Lookstein
11:40 a.m.	FMD in the pediatric population Evidence base and knowledge gaps	Dr. Kevin Meyers
12:00 p.m.	Panel Discussion: 2014 management of renal FMD – What should be the standard practice?	
Lunch and free time for open meeting attendees Working groups (closed sessions, lunch provided)		
12:30 – 3 p.m.	• Genetics • Epidemiology • Maximizing Registries • Imaging and Clinical Management	Each working group prepares summary presentation
1:30 pm	**CLEVELAND CLINIC ART TOUR FOR OPEN MEETING PARTICIPANTS**	
Open Sessions Reconvene (Dr. Heather Gornik moderates)		
Presentations of the working groups and discussion		
3:15 p.m.	Genetics working group	Dr. Santhi Ganesh
3:30 p.m.	Discussion	All
3:45 p.m.	Epidemiology working group	Dr. Esther Soo Kim
4:00 p.m.	Discussion	All
4:15 p.m.	Maximizing existing registries to advance knowledge working group	Dr. James Froehlich
4:30 p.m.	Discussion	All
4:45 p.m.	Imaging and Clinical Management Working Group	Dr. Jeffrey Olin
5:00 p.m.	Discussion	All
5:15 p.m.	Panel Discussion - next steps	Dr. Heather Gornik to moderate
5:30 p.m.	**WRAP UP AND MEETING ADJOURNS**	Drs. Gornik and Olin

ABSTRACTS

THURSDAY, MAY 15, 2014

10:50 FMD overview, historical perspective, and AHA scientific statement: top research priorities in FMD
Jeffrey Olin, DO, Mount Sinai Medical Center

Fibromuscular dysplasia (FMD) is a non-atherosclerotic, non-inflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm, or dissection. FMD was first described by Leadbetter and Burkland in a 5½-year-old African American boy with severe hypertension and a renal artery partially occluded by an 'intra-arterial mass of smooth muscle'. He underwent a unilateral nephrectomy and his hypertension was cured. Several classifications were introduced in the 1960s and 70s. The most commonly cited was that of Harrison and McCormack in which the angiographic appearance was correlated with the pathological findings leading to a classification divided into the three layers of the blood vessel wall [media (most common), intima and adventitia].

The cause and prevalence of FMD are not known although recent studies have suggested it is more common than generally thought and in an analysis of over 3000 potential kidney donors, FMD was found in approximately 4%. The prevalence in the general population is not known.

The extracranial carotid and vertebral arteries (in ≈65% of cases) and the renal arteries (~70%) are the most commonly involved vessels, although FMD has been reported in almost every vessel in the body. The clinical manifestations of FMD are determined primarily by the vessels that are involved. When the renal artery is involved, the most frequent finding is hypertension, whereas carotid or vertebral artery FMD may lead to dizziness, pulsatile tinnitus, transient ischemic attack (TIA), or stroke. An aneurysm or dissection is found in one of every three persons with FMD.

A striking finding is that there is an average delay from the time of the first symptom or sign to diagnosis of FMD of 4 to 9 years. This is due to the perception that this is a rare disease and thus FMD is not considered in the differential diagnosis, the reality that FMD is poorly understood by many healthcare providers, and the fact that many of the signs and symptoms of FMD are nonspecific

In 2011, an expert French/Belgian consensus panel was convened to review the topic of FMD and to make recommendations on diagnosis and management. Data from the first 447 patients enrolled in the United States Registry for Fibromuscular Dysplasia were reported several months after the European Consensus document. Most recently, the 2014 American Heart Association Scientific Statement entitled Fibromuscular Dysplasia: State of the Science and Critically Unanswered Questions was published. These recent publications have led to a change in the classification of FMD from a pathologic classification scheme to an angiographic classification: Multifocal Fibromuscular Dysplasia represents the "string of beads" appearance on angiography and correlates most often with medial fibroplasia on pathology. Focal Fibromuscular Dysplasia is a focal area of stenosis and correlates with several type of pathology such as intimal fibroplasia, medial hyperplasia and periadventitial fibroplasia.

A list of future research needs and methods to accomplish the goals as outlined in the State of the Science paper will be the focus of this first International Fibromuscular Dysplasia (FMD) Research Network Symposium.

11:10 am: Epidemiology of FMD: what do we know? What don't we know?
Esther SH Kim, MD, Cleveland Clinic

The cause of fibromuscular dysplasia is unknown, and while it has been called a rare disease, the prevalence of FMD in the general population is also unknown. Prior estimates for renal FMD have varied widely from 1% based on autopsy studies to 6.6% in angiographic studies of potential kidney donors. Carotid FMD is less well-studied and estimates of prevalence based on consecutive angiograms ranges from 0.3% to 3.2%. It is well-known that FMD affects women in far greater numbers than men (9:1 ratio based on the US FMD Registry); however, there has been no substantial evidence to support the role of sex hormones in the development of disease. Smoking has also been proposed as a potential risk factor, but large scale studies to explore other risk factors are lacking. The determination of the prevalence of FMD in the general population of women 18-65 years of age has been identified as a top research priority, and one of the specific objectives of the International FMD Research Network Symposium is to develop plans for funding and executing a study to determine the prevalence of FMD in the general population and to determine the risk factors for FMD development. The epidemiology working group will review available research describing the prevalence of and risk factors for FMD, critique the methods used to derive current prevalence estimates, and discuss strategies for developing original studies that will specifically aim to clarify the epidemiology of FMD.

11:30 am: Modernizing FMD nomenclature: unifocal versus multifocal FMD
Pierre-Francois Plouin, MD
On behalf of PF Plouin, S Savard, O Steichen,

Hypertension Unit and Rare Vascular Diseases Reference Center, European Hospital G Pompidou and Paris-Descartes University Paris, France

There is a need to standardize the definition of FMD and FMD subtypes to harmonize clinical practices for FMD and enable cooperative FMD research. The etiology and pathogenesis of FMD are unknown and there is no biochemical test for the condition. Consequently the diagnosis and classification of FMD relies on histological or angiographic findings. FMD is usually treated by percutaneous angioplasty rather than surgery; therefore, histological verification is seldom available and angiographic classification has progressively replaced histological classification. Angiographic diagnosis and classification is based on conventional angiography, computed tomography angiography or magnetic resonance angiography. FMD is diagnosed in patients with non-atherosclerotic stenosing lesions affecting the trunk or branches of renal or cervical arteries in the absence of aortic wall thickening, biochemical evidence of inflammation, and syndromic arterial disease. FMD can be classified as unifocal (presence of a single stenosis on a given vessel, regardless of its length) or multifocal (presence of two or more stenoses on a given vessel segment). Isolated artery aneurysm or dissection is not sufficient to diagnose FMD. The binary classification into unifocal or multifocal FMD is feasible and straightforward, and in patients with renal artery FMD, it discriminates two groups of patients with distinct clinical phenotypes.

2:00 pm: The FMD Society of America: organization, activities, and partnership opportunities for FMD research
Pamela Mace, RN, Executive Director, FMDSA

FMDSA was founded on March 11, 2003 and is classified as exempt under IRS Section 501(c) (3) and as a “public charity”. Our vision was to become the recognized leader in the support of Fibromuscular Dysplasia (FMD) awareness, education and research. We have achieved our goal by successfully raising money to develop and fund the United States Registry for Fibromuscular Dysplasia, building awareness programs, and educating the public and medical community about FMD. We have seen the diagnosis rate and knowledge of the disease grow in direct proportion to the growth of our programs.

We are well established as the most extensive FMD resource in the world. and we continue to actively assist with the establishment of FMD Registry Centers and Clinics. The FMDSA website includes patient information, resources and educational videos. This past year we added a Research Network Page where up to date publications and information released from the Patient Registry can be found.

In the 11 years of our existence we have developed a very impressive Medical Advisory Board, Advisory Council, and Board of Directors. We have engaged many resources from all over the world, giving us the ability to assist many patients on a global level.

This weekend we will be holding our 7th Annual Patient Meeting, where patients attend from all over the United States and Canada. In addition to providing the latest information on the disease, our meetings have served as a platform for researchers to meet with patients, giving them the opportunity to participate in FMD related research projects.

ABSTRACTS *(Continued)*

2:20 pm: The US Registry for FMD: what have we learned?
Heather Gornik, MD, Cleveland Clinic
On behalf of the United States Registry for FMD Investigators

The United States Registry for Fibromuscular Dysplasia (FMD) was formed in 2008 among 7 clinical centers. The Registry is funded by the FMD Society of America (FMDSA) and is maintained by the University of Michigan Cardiovascular Outcomes Research and Reporting Program (MCORRP). Its organizational structure includes a Steering Committee (chaired by Dr. Jeffrey Olin) and a Publications Committee. Since the 1st patient enrollment in January, 2009, a total of 1026 FMD patients have been enrolled (as of May 4, 2014), and the Registry has been expanded to a total of 13 active clinical centers. To date, there have been 12 poster or oral abstract publications and two peer reviewed manuscripts from the Registry with multiple additional manuscripts in process. A number of new insights regarding FMD have been gleaned from the US Registry data, including:

- The most common clinical manifestations of FMD are hypertension and headache, followed by pulsatile tinnitus, dizziness, cervical bruit, and neck pain. 32.1% of patients report pulsatile tinnitus ("swooshing") in the ears as a presenting symptom of FMD.
- FMD is an aggressive vascular disease. 36.1% of patients in the US Registry have reported at least one arterial aneurysm or dissection. This statistic has led to a recommendation for all FMD patients to undergo one time brain to pelvis cross-sectional imaging (MRA or CTA) to screen for occult aneurysms or dissections.
- Cerebrovascular FMD is as common as renal FMD. Approximately ~ 65% of Registrants with confirmed renal FMD were found to have cerebrovascular FMD if assessed with imaging and visa versa.
- FMD is primarily a condition of middle age (mean at first symptom 47 years), but can present across the life span, including pediatric and elderly patients.
- The classical clinical presentation of FMD varies by patient sex. Men with FMD are more likely to present with renal or visceral involvement and have a two-fold prevalence of arterial dissection or aneurysm compared to women with FMD.
- Approximately 50% of Registrants have undergone at least one therapeutic vascular procedure, >80% of which are catheter based. The renal artery was the target vessel in 73% of vascular procedures.
- The medical community does a poor job recognizing FMD. The mean length of time from Registrants' first reported FMD-related symptom (by recall) to confirmed diagnosis was 3.6 + 7.4 years.

A current emphasis of the US Registry centers on determination of the prevalence of major vascular events among FMD patients and the frequency of recurrent events in follow-up. Approximately 70% of patients enrolled in the Registry for more than 1 year have had at least one clinical follow-up visit entered, and some patients have been followed for up to 5 years.

On behalf of the Steering Committee, sponsor (FMDSA), and the coordinating center (MCORRP), we hope that the International FMD Research Network Symposium leads to international collaborations between the US Registry for FMD and our colleagues in the FMD and broader cardiovascular research communities.

2:40 pm: French FMD Registry, organizational structure, data elements, summary of findings
Pierre-Francois Plouin, MD
On behalf of PF Plouin, L Toubiana, MC Jaulent, X Jeunemaitre, Hypertension Unit, Department of Genetics and Rare Vascular Diseases Reference Center, Hopital Europeen G Pompidou (HEGP) and Paris-Descartes University; and INSERM UMRS 1142 LIMICS, Centre de Recherche des Cordeliers; Paris, France

The construction of the French FMD registry was a multistep process. First, clinical, hemodynamic and angiographic information and leucocyte DNA were collected from patients with renal artery FMD referred to the HEGP, to document phenotypic, hemodynamic and genetic aspects of the condition. Second, a French network of nephrologists, neurologists, radiologists and specialists in hypertension was organized to document phenotypic and genetic traits of the disease and the progression of FMD lesions in patients with renal and/or cervical artery FMD: ARCADIA, Assessment of Renal and Cervical Artery DysplasIA and PROFILE, PROgression of FIbromuscular Lesions; Programme Hospitalier de Recherche Clinique, French Ministry of Health 2009-2014; achieved/planned inclusions 450/500 patients with FMD. A clinical report form was developed for PROFILE/ARCADIA. Third, a cooperation was established with INSERM UMRS 1142 to develop a quality database to fulfil the following functions: 1) expand the PROFILE/ ARCADIA registry and cohort; 2) expand the national French Rare Diseases database; 3) share data internationally; 4) communicate the activities of the FMD registry; and 5) develop a web service for storage, access and maintenance of the registry. The project faces information management issues related to the heterogeneity

of the structure and semantics of existing databases. Therefore, semantic interoperability solutions will be tested for FMD data, and if successful, they will be extended to other vascular diseases including the vascular Ehlers-Danlos syndrome. Early findings of the French FMD registry include: the observation of carotid and radial artery wall subclinical lesions in patients with renal artery FMD; the association of clinical characteristics with two angiographic subtypes of renal artery FMD; and the association of smoking with phenotype at diagnosis and vascular interventions in patients with renal artery FMD.

3:00 pm: Genetics of FMD: state of the science in 2014
Santhi Ganesh, MD, University of Michigan

On behalf of Ganesh SK, Morissette R, Xu Z, Schoenhoff F, Griswold BF, Yang J, Tong L, Yang ML, Hunker K, Sloper L, Kuo S, Raza R, Milewicz DM, Francomano CA, Dietz HC, Van Eyk J, McDonnell NB

In this talk, we will review current data informing our approaches to a genetic analysis of FMD. We will cover recent data published on TGF-β expression and systemic findings in FMD patients, the abstract of which is provided below. Finally, we will review research approaches to Mendelian and complex genetic diseases and impact on study design considerations.

Fibromuscular dysplasia (FMD) is a rare, non-atherosclerotic arterial disease for which the molecular basis is unknown. Therefore, we comprehensively studied 47 FMD subjects, including physical examination, spine magnetic resonance imaging, bone densitometry and brain magnetic resonance angiography. Inflammatory biomarkers in plasma and transforming growth factor-β (TGF-β) cytokines in patient-derived dermal fibroblasts were measured by ELISA. Arterial pathology other than medial fibrodysplasia with multifocal stenosis included cerebral aneurysm found in 12.8% of human subjects. Extra-arterial pathology included low bone density ($P < 0.001$); early onset degenerative spine disease (95.7%); increased incidence of Chiari I malformation (6.4%) and dural ectasia (42.6%); and physical examination findings of a mild connective tissue dysplasia (95.7%). Screening for mutations causing known genetically mediated arteriopathies was unrevealing. We found elevated plasma TGF-β1 ($P = 0.009$), TGF-□2 ($P = 0.004$) and additional inflammatory markers, and increased TGF-β1 ($P = 0.0009$) and TGF-β2 ($P = 0.0001$) secretion in dermal fibroblast cell lines from FMD subjects compared to age- and gender-matched controls. Detailed phenotyping of FMD patients allowed us to demonstrate that FMD is a systemic disease with alterations in common with the spectrum of genetic syndromes that involve altered TGF-β signaling, and offers TGF-β as a marker of FMD.

3:20 pm: Potential application of genome wide association study to FMD
Iftikhar Kullo, MD, Mayo Clinic

The molecular basis of fibromuscular dysplasia (FMD) is unknown. Genetic factors appear to play a role, although the degree of familial clustering has varied in different studies. In the (US) FMD registry, only 7.3% of FMD patients reported a confirmed diagnosis by a physician of FMD among a family member but there was a high prevalence of a family history of stroke (53.5%), aneurysm (23.5%), and sudden death (19.8%). In my talk, I will present an update on a collaborative effort between Mayo Clinic and Cleveland Clinic which began in 2009 with the goal of establishing a collection of DNA and plasma samples to enable genetic studies of FMD including genome wide association studies (GWAS). I will discuss how a GWAS approach, made possible by knowledge of linkage disequilibrium across the genome as well as the availability of high density genotyping platforms, may provide insights into the genetic basis of FMD. Typically in a GWAS half a million or more single nucleotide polymorphisms (SNPs) with a minor allele frequency of >5% are genotyped in relatively large numbers of cases and controls. Statistical methods are then used to identify SNPs that differ in frequency between cases and controls. SNPs that differ in frequency at a significance level of $P<5x10\text{-}8$ are considered to be associated with disease of interest. The GWAS approach is unbiased in nature and has the potential to discover novel disease susceptibility genes. Identifying such genes will provide insights into disease pathophysiology and thereby enable new diagnostic and therapeutic strategies.

4:00 pm: Exome sequencing and application to FMD
Santhi Ganesh, MD, University of Michigan

After introducing relevant background information in the session titled, “Genetics of FMD: State of the Science,” I will discuss genome sequencing in the application to FMD research. We will discuss the advantages of sequencing based approaches to study rare diseases, study design issues, analytic approaches and important caveats to consider in the analysis of these data.

ABSTRACTS *(Continued)*

4:20 pm: Assessment of the enrichment for rare coding variants in related cases of FMD

Nabila Bouatia-Naji, PhD, Paris Cardiovascular Research Centre

On behalf of Bouatia-Naji N, Kiando R, Plouin PF, Jeunemaitre X, INSERM, UMR970 Paris Cardiovascular Research Center; Paris Descartes University, Paris Cité Sorbonne; Center for Rare Vascular Diseases, Hopital Européen Georges Pompidou, Paris, France

The genetics of FMD is under-investigated because of the lack of large families and cohorts due to the rarity of the disease and the complexity of the diagnosis. The causes of FMD are unknown and it occurs predominantly in females with a prevalence of ˜4/1000 for the clinical forms. There are strong arguments in favour of the genetic origin of FMD, based on documented and reported family history, although the precise estimation of its heritability is missing. FMD is probably a typical complex genetic disease, and it is challenging to investigate because it is also a rare disease.

I will comment upon our recent assessment of the enrichment for rare coding variants that we have recently performed using exome sequencing and genotyping by the exome chip, a genotyping array enriched for rare and predicted functional variants. Exome sequencing generated 85 genes with at least four rare (MAF<0.01) and predicted functional variants in 16 familial cases of FMD (five sibs and two sib-trios). None of these genes was mutated in at least three out of seven families, nor were 14 known causative genes of vascular diseases and syndromes (e.g. FBN1, TGFB2 and MYH11). Then, we aimed to assess these genes in a larger sample of 259 FMD unrelated cases and 698 controls using genotyping data. Neither gene-based association analyses of rare variants (MAF<0.01) using SKAT and Burden tests nor single SNP association of common SNPs (MAF>=0.05) support a role of the ˜100 genes tested in our study (N=816 SNPs, including 189 common SNPs). These findings support strong genetic heterogeneity for FMD and encourage more powerful and comprehensive genomic approaches, such as genome-wide association studies, to decipher the genetic architecture of FMD.

4:40 pm: The DEFINE FMD study – defining the molecular and cellular basis of FMD using patient-derived fibroblasts

Jason Kovacic, MD, Mount Sinai Medical Center

Fibromuscular dysplasia (FMD) is a non-inflammatory vascular disease of unknown cause. Despite an improved clinical knowledge of the disease, there has been surprisingly little progress in understanding the genetic and molecular basis of FMD since its first description. However, a genetic contribution is strongly anticipated, as up to 15% of cases display familial inheritance. As potentially one of a number of reasons why FMD has so far evaded attempts at unraveling its cause, family pedigrees pose unique challenges and are not ideally suited to traditional molecular and genetic approaches that may be applied to other undefined conditions. In response to these issues, we initiated the DEFINE FMD study, which aims to define the molecular and cellular basis of FMD using patient-derived fibroblasts.

As suggested by the name “Fibromuscular Dysplasia”, it is likely that fibroblasts play an important role in this disease. In the DEFINE-FMD study, we are collecting DNA, plasma, serum, fibroblasts (via skin punch biopsy) and culture supernatant from rigorously phenotyped FMD patients with multifocal disease and healthy controls. Healthy controls have been matched to FMD patients by gender, race/ethnicity, age, smoking status, body mass index and number of anti-hypertensive medications. All fibroblasts are grown from skin biopsy samples under standardized conditions by a single technician, and fibroblast RNA is then harvested under both quiescent and stimulated cell culture conditions. As of April 2014 over 100 subjects have been enrolled and recruitment is ongoing. Sample analysis will commence in July 2014 and will initially comprise fibroblast gene expression analysis (RNA sequencing) of quiescent and stimulated cells to understand differential expression patterns between patients and controls. A systems-based bioinformatics approach will be applied to build gene expression models of FMD and to understand regulatory gene networks that orchestrate this disease, which we expect will permit us to make inroads on defining the molecular and cellular basis of FMD.

5:00 pm: Prevalence of connective tissue findings in FMD patients: preliminary findings
Sarah O'Connor, MS4, Cleveland Clinic Lerner College of Medicine

Background: Fibromuscular dysplasia (FMD) is a non-atherosclerotic disease of the arteries that can present with stenosis, occlusion, dissection, or aneurysm. The molecular basis of FMD remains unknown. Several case reports suggest an underlying connective tissue disorder among patients with FMD. A recently published study of 47 patients by Ganesh and Morissette and colleagues found increased TGF β signaling in fibroblasts derived from FMD patients and also reported a mild connective tissue dysplasia phenotype (FASEB J 2014). We sought to test the hypothesis that patients with FMD have more abnormal connective tissue physical findings than the general population. A secondary hypothesis is that FMD patients with a high vascular risk profile have more connective tissue physical findings compared to those with a standard vascular risk profile. Methods: Patients with a confirmed diagnosis of FMD who enrolled in the Cleveland Clinic FMD Biorepository Study were approached and consented for this project. A brief medical history was completed assessing for complications associated with connective tissue disorder, including history of joint dislocation, non-traumatic bone fracture, hernia, scoliosis, cleft palate, club foot, myopia, early onset arthritis, and post-partum hemorrhage. A brief physical assessment was completed. Facial morphology was assessed with mandibular measurements. Interpupillary distance was measured using a digital pupillometer. Head circumference was measured using a standard retractable tape measure. The palate was inspected for abnormalities, including high arch, tori, and variations of the uvula. Joint hypermobility was assessed using the Beighton score. Joint extension was measured with a goniometer. Patients were categorized into high vascular risk profile and standard vascular risk profile. High vascular risk profile was defined as ≥1 arterial dissection and/or ≥2 arterial aneurysms. Prevalence of connective tissue features in this cohort of FMD patients was compared to historical published controls, and prevalence of features was compared between the FMD patients with high and standard vascular risk profile. Results and Conclusion: Late breaking preliminary data from this study will be presented at the International FMD Research Network Symposium.

FRIDAY, MAY 16, 2014

8:00 am: Duplex ultrasonography for assessment of FMD
Jeffrey Olin, DO, Mount Sinai Medical Center

Duplex ultrasonography is an accurate, safe and inexpensive way to diagnosis and follow the course of fibromuscular dysplasia (FMD). The examination of the renal arteries by duplex ultrasound requires a high level of skill by the ultrasound technologist and experience by the interpreting physician because the standard criteria for determining the degree of stenosis does not apply to patients with FMD. Whereas atherosclerosis occurs at the origin and proximal portion of the renal and internal carotid artery, FMD occurs in the mid and distal portions of these arteries and in the case of the renal arteries, in the branches as well. Thus in many vascular laboratories, the distal portions of these arteries are not routinely imaged, and thus, the diagnosis of FMD is overlooked.

Duplex ultrasound of the renal arteries typically reveals evidence of arterial stenosis in the affected renal artery, including a step-up in peak systolic velocity in the mid to distal portion of the main renal artery or a delayed systolic upstroke (tardus et parvus waveform- not sensitive but very specific) in arterial branches distal to the stenosis. It is important to image the renal artery in its entirety from the origin to the kidney parenchyma. The degree of velocity increase is not as important as how the artery looks on color Doppler. When the PRF is set correctly, one sees tortuosity and turbulence in the mid and distal renal artery leading to the diagnosis of FMD. The string of beads appearance on ultrasound is rarely seen in the renal arteries on ultrasound. It is important to recognize that the Doppler velocity derived criteria used for atherosclerotic renal artery stenosis is not accurate in determining the severity of stenosis in FMD.

The principles of carotid/vertebral artery duplex ultrasound in FMD are the same as for the renal artery. The most important aspect is to recognize that one must image as far distally as possible in the carotid and vertebral arteries. The appearance on color Doppler is similar to that seen in the renal arteries. There is often marked tortuosity and turbulence in the mid and distal vessels. Dissections may also often be identified. The criteria for determining the degree of stenosis for atherosclerotic disease at the origin of the internal carotid artery do not apply for abnormalities visualized in the mid and distal internal carotid arteries. Since atherosclerosis does not occur distally, if abnormalities are seen in the mid and distal part of the carotid or vertebral arteries, it must be due to FMD and/or dissection. The 'string of beads' appearance is rarely visualized on ultrasound.

ABSTRACTS *(Continued)*

For both renal artery and carotid artery multifocal FMD, It is not possible to give an accurate percentage stenosis since the criteria used for atherosclerosis has not been validated in patients with FMD. Therefore, a more appropriate interpretation would be a statement such as: "There are elevated velocities, tortuosity, and turbulence in the mid and distal renal (internal carotid) artery consistent with FMD."

Duplex ultrasound is also an excellent test to follow patients with known FMD (to assure there is no progression) and those who have undergone angioplasty and/or stenting (to look for restenosis).

8:20 am: Clinical manifestations of cerebrovascular FMD and cervical artery dissection
Emmanuel Touze, MD, PhD, University Hospital Center of Caen, France

FMD and dissection of carotid, vertebral, and intracranial arteries have been known for several decades. The two conditions can sometimes be encountered concomitantly and are believed to result from an underlying vasculopathy. Arterial dissections occur in patients about 20% with FMD, and up to 20% of patients with cervical artery dissection have signs of FMD on imaging. However, the diagnosis of FMD can be challenging in case of acute dissection, as angiographic features of both diseases can be similar. The most serious clinical manifestations of cerebrovascular FMD include ischemic or subarachnoid hemorrhage (SAH). Cerebral ischemic events can result from a thromboembolic mechanism or a haemodynamic compromise of the distal circulation due to FMD lesions or from spontaneous dissection. SAH is usually in relation to ruptured intracranial aneurysm. More occasionally, FMD can be revealed by a pulsatile tinnitus or carotid-cavernous fistula. There is also an atypical form of intimal FMD involving the origin of the carotid internal artery, often revealed by an ischemic stroke, with a "web-like" aspect on angiograms. However, the majority of patients seem to be asymptomatic or to have nonspecific symptoms. In the old literature, cervical FMD was often found in patients who had headaches, vertigo, syncope, seizures, or several neurological diseases that required cerebral angiography at that time. Intracranial FMD is very rare and most often corresponds to an intracranial extension of extracranial FMD. Isolated intracranial FMD has been reported in a few cases, but the diagnosis is very challenging. Similarly, intracranial artery dissection is rare although potentially very serious. Clinical manifestations mainly include ischemic stroke, SAH, and isolated headache.

8:40 am: Optimal imaging of cerebrovascular FMD: modalities, evidence, and knowledge gaps
Javier Romero, MD, Massachusetts General Hospital

In the absence of definite non-invasive testing or direct genetic profile for FMD, imaging has certainly taken a predominant range not only in the diagnosis of FMD but also in the follow up of patients with this disease. Advances in the diagnosis include and array of high resolution CTA, MRA and Ultrasound.

In this conference we will go over the basic diagnosis and the current use of contrast, high resolution CT angiography and PET in the diagnosis of these processes. New cervical MRI coils used to detect carotid plaque morphologic changes are being used to look into the wall of patients with FMD and to differentiate them from other vascular collagen processes. Sequences such as PD, T1, T2 SE and post gado images show alterations in the wall that could be use in many of these patients. Differential diagnosis with vasculitic processes can be made with PET study, which show inflammatory components particularly when the involvement is uni-vessel. We will also explore the other vascular beds that are involved in FMD and consider a probable comprehensive screening algorithm.

9:00 am: Endovascular therapy for cerebrovascular FMD, cervical dissection, and cerebral aneurysm: indications, emerging techniques, and knowledge gaps
M. Shazam Hussain, MD, Cleveland Clinic

Cervical artery involvement in fibromuscular dysplasia (FMD) is common, often accounting for the presentation of the condition. Symptoms can result directly from changes in these arteries related to the FMD, or related to complications of the condition such as dissection. Management of cervical artery disease is generally medical, with endovascular and surgical management reserved for those with symptomatic disease refractory to medical therapy. Developing a greater understanding of the factors leading to various presentations (i.e. collateral circulation) may lead to refinement of our treatment strategies. Careful patient selection may allow us to intervene earlier on patients at high risk for cerebrovascular complications of the disease.

Cerebral aneurysms are also seen at increased frequency than that of the general population, and rates of subarachnoid hemorrhage may also be higher. Cerebral aneurysms are generally managed according to similar strategies as in the general population. Little data exists that is specific to the FMD population regarding both natural history and management strategies of cerebral aneruysms, representing an opportunity for better understanding and research. In addition, new device technology (such as flow diverting stents) is rapidly advancing, and may provide opportunity to treat a wider range of patients.

9:20 am: Coronary artery FMD and spontaneous coronary artery dissection (SCAD): recognition, management, and unanswered questions
Jacqueline Saw, MD, Vancouver General Hospital, Canada

Spontaneous coronary artery dissection (SCAD) is underdiagnosed and an important cause of myocardial infarction in young women. We discovered a strong association of SCAD with fibromuscular dysplasia (FMD). The frequency of predisposing and precipitating conditions, and cardiovascular outcomes remain poorly described. Patients with non-atherosclerotic SCAD who were identified at or referred to Vancouver General Hospital were prospectively evaluated and screened for predisposing arteriopathies and precipitating stressors. We found that FMD is commonly observed in our cohort of SCAD patients. Precipitating stressors were prevalent prior to the SCAD event. The most common angiographic appearance was diffuse smooth stenosis. The majority of patients was treated conservatively, and was associated with spontaneous arterial healing. However, SCAD survivors are at risk for recurrent cardiovascular events including recurrent SCAD.

9:40 am: Mayo Clinic SCAD cohort and maximizing use of the Internet and social media in rare disease research
Sharonne Hayes, MD, Mayo Clinic

E-Patients: those who are engaged, enabled, educated, empowered, and typically, e-connected, are uniquely positioned to be powerful drivers of research and practice innovation. The Mayo Clinic Spontaneous Coronary Artery Dissection (SCAD) Collaborative Project originated out of activated patients who spurred the development of what is now a multidisciplinary collaborative research network.

SCAD is a rare and poorly understood nonatherosclerotic cause of acute coronary syndrome, myocardial infarction, and sudden cardiac death. Recent observations from our group and others have identified an association and possible causal relationship between FMD and SCAD. SCAD and FMD patients have similar demographics: typically young women who do not have risk factors for atherosclerosis. Until 2010, little was known about the prevalence, causes, prognosis, recurrence rate, and optimal management of SCAD and it was considered too rare to study in any meaningful way.

In 2009 over 70 women with SCAD had organized on WomenHeart's online community (www.WomenHeart.org) and representatives reached out to our team. Since then we have endeavored to advance not only the science and health care of women and men with SCAD, but also explored the novel role of social media in health care and research studies. We have successfully recruited research participants via social media, dramatically exceeding initial estimates of enrollees (and our need for resources) and through our SCAD Clinic practice, accelerated our understanding of both SCAD and FMD.

This session will describe the origins, perpetuation, advantages and limitations of patient-driven (as opposed to investigator) research via social media and online communities, and describe our SCAD and FMD clinical practice experience. Challenges, pitfalls, IRB and patient protection issues will also be highlighted as we explore this novel method of studying rare conditions using social media for recruitment and patient (rather than provider) initiated enrollment.

10:40 am: Optimal imaging of renal FMD: modalities, evidence, and knowledge gaps
Sanjay Misra, MD, Mayo Clinic

The most common vascular bed affected by fibromuscular dysplasia (FMD) is the renal arteries. Patients suspected of having renal artery FMD can present with symptoms of hypertension but often are asymptomatic. Today, the diagnosis of renal FMD is made using some type of an imaging modality. The different imaging modalities which can be used to diagnose renal artery FMD include computed tomography angiography (CTA), magnetic resonance imaging (MRI), duplex ultrasound, and digital angiography. This talk will discuss the strengths and weaknesses of each of these modalities. These include patient body habitus, baseline kidney function, the use of ionizing radiation, and other factors. The result from recent studies from our institution using CTA to identify FMD in patients donating their kidneys for transplantation will be discussed. In addition, a new study on the treatment of iliac artery FMD with angioplasty will also be highlighted. Finally, knowledge gaps in imaging and advanced imaging techniques which maybe beneficial for assessing patients with FMD will be discussed.

ABSTRACTS *(Continued)*

11:00 am: Hemodynamic guided assessment of renal artery FMD

Christopher Bajzer, MD, Cleveland Clinic

Angiography is the gold standard for evaluation of vascular disease. The appearance of fibromuscular dysplasia on digital subtraction angiography is pathognomic for the diagnosis of the disease. Unfortunately digital subtraction angiography falls short of being able to determine which patient will benefit from endovascular intervention.

Endovascular repair of the renal artery is and of itself a controversial topic. The determination of which patient will benefit from endovascular intervention requires the synthesis of clinical and noninvasive as well as invasive evaluations.

Without additional supplementary information, the appearance of FMD on digital subtraction angiography could lead an operator to be biased towards a revascularization strategy that may provide no benefit to the patient and will come at the risk of procedural harm. Clinical information, such as resistant hypertension on 3 to 4 agents at reasonable to high doses helps to identify one subset of patients may benefit from intervention.

Noninvasive imaging data such as the appearance of decreasing renal parenchyma with normal resistive indices in the parenchyma help to identify a patient who may benefit from revascularization.

Functional data such as rising serum creatinine or more sensitive declining creatinine clearance help identify patients with renal stenoses who would benefit from renal revascularization.

Hemodynamic invasive interrogation of a suspected lesion with pressure measurements historically has provided a good indication of the lesion that is restricting flow. Originally the placement of a small catheter across a restrictive lesion enabled an operator to measure a peek translational gradient. If the gradient was greater than 20 mmHg lesion was considered to be significant. This type of vascular hemodynamic interrogation dates back to Dotter.

In the current age, we can borrow technology from our cardiology colleagues who have established the utility of measuring fractional flow reserve to identify lesions warranting intervention. There are problems with translating techniques from the coronary circulation to its use in the renal circulation. First, almost all of the flow to the heart occurs in diastole. Renal blood flow is more evenly parsed out between systole and diastole. So, when determining fractional flow reserve in a renal artery, one needs to carefully delineate whether the measurement is mean pressure or diastolic pressure versus systolic pressures gradients.

Another challenge with determining hemodynamic measurements in the renal artery is related to renal motion. One is accustomed to thinking that the heart is constantly moving and not accustomed to thinking that the kidney is also always moving. This movement is driven by respiratory function and causes elongation in and flexion of the artery. This movement-akin to a child playing with a Chinese finger cuff-will alter the measurements of pressure gradients and fractional flow reserve. The most accurate measurement period in the respiratory cycle would be at the functional residual volume which is not a breath hold. Standardization of protocols for measurements of fractional flow reserve need to identify the precise pressure measurement taken and its location within the respiratory cycle.

An additional tool borrowed from our cardiology colleagues is that of intra-vascular ultrasound. This tool allows the operator to view a cross-sectional appearance of the entire renal artery from its ostium to the renal pelvis. One can identify renal aneurysms and the pathognomonic fibrous bands or webs which appear as crescentic shapes in cross-section of the renal artery. Minimal luminal diameters and minimal luminal areas may be calculated and compared to reference values within the same artery.

In summary, determination of which patient with fibromuscular dysplasia of the renal artery will benefit from revascularization requires a synthesis of information. Information must be culled from clinical data, noninvasive imaging data, invasive imaging data including hemodynamic data and other adjunctive invasive imaging modalities.

11:20 am: Renal angioplasty for FMD: Evidence base and knowledge gaps

Robert Lookstein, MD, Mount Sinai Medical Center

Since first described in 1979, angioplasty for the treatment of renal artery fibromuscular dysplasia has become the default revascularization strategy for symptomatic patients presenting with either new-onset hypertension, medically resistant hypertension, or renal insufficiency. Angioplasty has largely replaced surgical bypass as the primary revascularization strategy due to high technical success rates and low incidence of peri-procedural morbidity.

In the past 40 years, numerous single center series and meta-analyses have demonstrated excellent safety of the angioplasty procedure and reproducibility of outcomes. Despite these advancements, the cure rate for patients with new-onset or refractory hypertension is rarely over 40%. In addition, a trial-randomizing patients between best medical therapy and endovascular therapy has never been conducted. One criticism of the available data regarding angioplasty for renal artery fibromuscular dysplasia has focused on the technique employed by endovascular operators. A paucity of data has been generated defining the role of the translesional gradient across the diseased segment. Only recently have reports attempted to describe translesional gradient's effect on the acute outcome of the revascularization procedure and the long-term prognosis for the patient.

Less common indications for renal artery intervention include renal artery dissection and renal artery aneurysms. Modern endovascular techniques are increasingly being utilized to preserve renal function and prevent complications such as renal failure and renal artery rupture.

11:40 am: FMD in the pediatric population: evidence base and knowledge gaps

Kevin Meyers, MBBCh, Children's Hospital of Philadelphia

What we know about pediatric FMD comes from single case descriptions and retrospective case series. There are no prospective studies and very little registry data collected on pediatric FMD. The true age, sex, ethnic and geographic distribution of pediatric FMD is unknown at the present time. The presenting symptoms of FMD in children include that of stage two hypertension associated with renal artery stenosis and focal neurological findings related to stroke. Of importance, children with severe hypertension may present with Bell's palsy. Intracranial stenoses are extremely rare in adults with medial fibroplasia however findings of a Moyamoya appearance is well described in children with presumed FMD. Occasionally presentation of FMD in children can resemble a systemic necrotizing vasculitis (intimal fibroplasia) and may be difficult to distinguish from Takayasu's arteritis. The differential diagnosis of FMD in the pediatric population includes inflammatory vasculitides such as Takayasu's arteritis as well as other non-inflammatory systemic vasculopathies that includes Neurofibromatosis Type 1, Turner's syndrome, Williams' syndrome, and Alagille syndrome. Arterial stenosis, arterial dissection and aneurysmal formation may occur in children with FMD. Stenotic lesions in the aorta present with the middle aortic syndrome (MAS) and often affect multiple large feeder arteries (renal, celiac, SMA, IMA); these findings are not seen in FMD in the adult population. In children, FMD usually presents with intimal fibroplasia or perimedial fibroplasia (long tubular stenosis)

with adolescents somewhat more likely to have medial fibroplasia (string-of-beads) as seen in the young adult population. It is likely that what we call pediatric FMD represents a number of separate clinical entities with unique genetic and other pathogenic factors that have yet to be elucidated.

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