2018 International Lymphangiomatosis & Gorham’s Disease Alliance Patient & Family Conference

July 27 & 28, 2018
Hilton DFW Lakes Executive Conference Center
Dallas, Texas
Presentation Abstracts from the 2\textsuperscript{nd} International Lymphangiomatosis & Gorham’s Disease Alliance
Patient & Family Conference
July 27 & 28, 2018
Dallas, Texas
AGENDA

Session 1:  Friday, July 27       1:00 pm — 5:00 pm

1:00 pm - 1:15 pm  Welcome
Jack Kelly — President, Lymphangiomatosis & Gorham’s Disease Alliance

1:15 pm - 1:40 pm  Structure and Function of Lymphatic System
Miikka Vikkula

1:40 pm - 2:05 pm  Differentiating the Rare Lymphatic Anomalies
Ionela Iacobas

2:05 pm – 2:30 pm  Imaging in Diagnosis and Management
Matt Hawkins

2:30 pm - 2:45 pm  Refreshment Break

2:45 pm - 3:10 pm  Interventional radiology – Role of MR lymphangiogram
Maxim Itkin

3:10 pm - 3:35 pm  Surgical Intervention: Indications and Risks
Juan Carlos Lopez-Gutierrez

3:35 pm - 5:00 pm  Panel Discussion/Q&A
Moderator: Francine Blei

Session 2:  Saturday, July 28      8:00 am — 1:00 pm

8:00 am - 8:25 am  The Multidisciplinary Team
Michael Briones & Rachel Swerdlin

8:25 am - 8:50 am  Use of Sirolimus in GLA/GSD/KLA
Cameron Trenor

8:50 am - 9:15 am  Use of Bisphosphonates in GLA/GSD/KLA
Yasir Diab

9:15 am - 9:40 am  Coagulopathy in GLA/GSD/KLA
Judith Margolin
9:40 am - 10:05 am  Pulmonary Complications
             David Spielberg

10:05 am - 10:20 am  Refreshment Break

10:20 am - 11:45 am  Panel Discussion/Q&A
             Moderator: Francine Blei

11:45 am - 1:00 pm  Lunch

Session 3:  Saturday, July 28  1:00 pm — 5:00 pm

1:00 pm - 1:25 pm  Discovering the Genetic Basis of Rare Disease
             Michael Dellinger

1:25 pm - 1:50 pm  Use of Patient Cells in Research
             Thuy Phung

1:50 pm - 2:15 pm  International LGDA Registry
             Lisa Klepper

2:15 pm - 2:30 pm  Refreshment Break

2:30 pm - 2:55 pm  Directions in Research
             Michael Dellinger

2:30 pm - 4:30 pm  Panel Discussion/Q&A
             Moderator: Francine Blei

4:30 pm - 4:55 pm  Advancing the Mission
             Planning Committee

4:55 pm - 5:00 pm  Closing Remarks
             Jack Kelly

7:00 pm  Banquet – Austin Ranch
The circulatory system consists of two highly-branched tubular structures: the blood vessels and the lymphatic vessels. Both networks are made of tubes that are covered on the inside by a single layer of endothelial cells, surrounded by variable numbers of layers of vascular smooth muscle cells and/or pericytes. These systems are essential for the transport of fluids, gas, molecules and cells to and from different organs, and for tissue fluid homeostasis.

The lymphatic system consists of lymphatic vessels and lymphatic organs, such as lymph nodes, tonsils and Peyer’s patches. The lymphatic vessels form a blind-ended one-way closed circuit that acts as a drainage system to collect fluid, cells, and plasma proteins from tissues to return them back to the blood circulation. It has an essential role in the maintenance of fluid homeostasis, as well as immune surveillance and fat adsorption. The lymphatic vasculature is divided into several parts according to the histological structure of the vessels wall: lymphatic capillaries, pre-collectors, collectors and lymphatic trunks.

The main processes through which the lymphatic network is developed is called lymphangiogenesis. The first theory for venous origin of the lymphatic vasculature was suggested a century ago by Florence Sabin. She proposed that early in development, isolated primitive lymph sacs originate from endothelial budding from the veins. An alternative theory was proposed some years later by Huntington and McClure. They proposed that the lymphatic vessels form by in situ differentiation of mesenchymal cells which will connect with veins later during development. Recent studies and identification of various lymphatic markers give support for both theories. With the advent of lymphatic markers, our understanding of the precise manner by which the lymphatic system develops has increased importantly. Studies of murine models presenting lymphatic vascular defects have identified several genes implicated in the development of the lymphatic vascular system. This has also shed light into the pathogenesis of lymphatic disorders, such as primary lymphedema.
Differentiating the Various Rare Lymphatic Anomalies

Ionela Iacobas, MD
Assistant Professor
Pediatric Hematology-Oncology
Medical Director, TCH Vascular Anomalies Center
Texas Children’s Hospital
Baylor College of Medicine

A new diagnosis of lymphatic malformation presenting with a micro/macrocystic area AND an additional symptom may trigger very specific diagnostic studies for clear classification. This discussion will try to differentiate the 4 entities (Generalized Lymphatic Anomaly, Gorham-Stout Disease, Kaposiform Lymphangiomatosis and Central Conducting Lymphatic Anomaly) based on clinical features, imaging and coagulopathy. It will particularly focus on bone lesions, effusions, associated lymphedema and risk of bleeding. Assigning the correct diagnosis has clear, practical implications into the procedural and medical management, in the screening for complications and even prognosis.

Imaging in Diagnosis and Management

Matt Hawkins, MD
Director, Pediatric Interventional Radiology, Children’s Healthcare of Atlanta at Egleston
Medical Director – Vascular Anomalies Clinic, Children’s Healthcare of Atlanta
Medical Director – Telemedicine, Children’s Healthcare of Atlanta
Assistant Professor – Emory University School of Medicine Dept of Radiology and Imaging Sciences

Diagnostic imaging has become the primary means by which a number of lymphatic anomalies are diagnosed. More specifically, recent scientific work has further delineated specific imaging characteristics that differentiate GLA, GSD, and KLA as well as factors that can help monitor disease progression. This presentation will focus of recent and emerging science that has improved the diagnosis and management of these diseases.
Lymphatic malformations (LM) are conditions that are characterized by proliferation of the lymphatic tissue in multiple organs. The major cause of mortality and morbidity in patients with LM is deterioration of pulmonary function due to chronic chylous effusions and progressive interstitial lung disease. The etiology of these pulmonary processes is unknown, although lymphatic involvement is certain.

Understanding of the changes in the lymphatic anatomy in patients with LM has been hindered by difficulty of imaging of the lymphatic system. Recently developed Dynamic Contrast Enhanced MR Lymphangiography (DCMRL) allows dynamic MR imaging of the lymphatic system by injecting contrast agent in the groin lymph nodes. Using this technique, pathological lymphatic flow from the central lymphatic system and/or retroperitoneal and mediastinal masses into lung parenchyma (“Pulmonary Lymphatic Perfusion Syndrome”) has been demonstrated in patients with LM. This abnormal lymphatic perfusion overflows pulmonary parenchyma and results in deterioration of pulmonary function due to interstitial process and/or compression effect of chylous effusions.

Percutaneous closure of the thoracic duct in cessation of the pulmonary lymphatic overflow and can significantly improve and prevent deterioration of pulmonary symptoms in LM patients.

The treatment of lymphatic malformations will be soon non-surgical but still remains the best option in a selected group of patients. Indications for surgical management of lymphatic malformations can be preventive or therapeutic and mainly include: recurrent infection, cosmetic disfigurement...
compression of local structures such as the airway, blood vessels, or upper gastrointestinal tract, bone or visceral involvement and failure to control lymphatic leaks by interventional radiology approach.

Interventions cannot be protocolized and must be discussed in an individualized basis depending on factors as age, anatomical location, symptoms or risk of severe complications.

Multidisciplinary management is always preferred and pharmacological treatment, endovascular, laser or other conservative procedures have to be first attempted before establishing the need of surgery.

The eventual risk of significant sequellae has to be taken into consideration as LM frequently arise in critical anatomic areas or in the vicinity of neurovascular bundles.

If, finally, a surgical procedure has to be performed, referral to an expert team with experience in the management of complex lymphatic disorders is mandatory.

SESSION 2: SATURDAY, JULY 28, 2018 8:00 AM — 11:30 AM

The Multidisciplinary Team

Michael Briones, D.O.
Medical Director Scottish Rite Campus
Associate Professor of Pediatrics
Aflac Cancer and Blood Disorders Center
Emory University School of Medicine

Rachel Swerdlin, MS, RN, CPNP
Pediatric Nurse Practitioner
Vascular Anomalies Clinic Coordinator
Children’s Healthcare of Atlanta

Gorham-Stout disease (GSD) is a rare vascular disorder of lymphatic origin characterized by bone destruction with massive osteolysis due to progression of lymphangiomatous tissue while Generalized Lymphatic Anomaly (GLA) is a multisystem disorder that also commonly affects bone and KLA is a subset of GLA with associated coagulopathy and a more aggressive course. In GSD,
osteolytic lesions are progressive and consecutive. Both GLA and KLA have osteolytic lesions that are multifocal with non-progressive osteolysis. All of these disorders can present with swelling (edema) of a localized area, although generalized swelling is also possible. There are varying degrees of bone and soft tissue involvement seen in each of these disorders. Bone involvement can be severe enough to cause bone to dissolve/disappear as in GSD or to become weak enough to spontaneously break (fracture). Chylous effusions (accumulation of liquid made up of fat, water and lymphocytes) are frequently seen, and often there is spontaneous drainage either externally (leakage from the skin) or from one internal compartment to another. If the lung cavity or pericardial sack fills with fluid there can be significant problems with the function of these organs (resulting in shortness of breath and exercise intolerance). When the GI tract is involved there can be significant leakage of chylous fluid into the bowel which can cause problems with nutrition (from protein and fat loss) as well as diarrhea/bowel incontinence. Because these disorders can affect multiple organs, there is a need for experienced providers working in the context of a coordinated and structured multidisciplinary team that can treat these complex patients successfully and offer highly specialized care, potential access to leading clinical trials, and a comprehensive multidisciplinary team approach with expert consultation. We will present the development of a multi-disciplinary, in-person vascular anomalies program built for clinical collaboration, prospective data collection, outcomes tracking, and optimizing clinical.

Use of Sirolimus in GLA/GSD/KLA

Cameron Trenor, MD, MMSc

Pediatric Hematology/Oncology
Vascular Anomalies Center
Boston Children's Hospital

Director, Senior TME 1
Novartis Institutes of BioMedical Institute

Sirolimus has been FDA-approved since 1999 for immunosuppression but has many appreciated off-label uses, including for lymphatic disorders. Based on clinical study results and reported cases, sirolimus is often used for Gorham-Stout disease (GSD), generalized lymphatic anomaly (GLA)/lymphangiomatosis and other lymphatic conditions. Many lymphatic malformations are associated with activating somatic mutations in PIK3CA, for which it is logical to treat with an mTOR inhibitor, such as sirolimus. The genetics and biology of GSD and GLA are still only partially understood, though new discoveries of PIK3CA and NRAS mutations have been reported. There is no known effect of diet on disease, except that fat intake can increase lymphatic (especially chylous) leak volume. Related to sirolimus therapy, fat intake may be lowered to assist in cholesterol control and grapefruit should be avoided. Our current approach to medical therapies for these disorders is to treat certain complications, rather than the genetics or disease entity itself. Pleural effusions,
bone disease, soft tissue lesions and other areas of lymphatic leak may respond to sirolimus. It is important to agree upon goals of therapy and how to measure response before starting. Close follow-up including laboratory follow-up is necessary to delivery sirolimus therapy safely. We will review known side effects in this talk, all of which are dose-related and reversible. Sirolimus is well-tolerated by the majority of patients. The future of medical therapy for GSD and GLA is likely to involve combination therapies and novel drugs targeting genetic and biologic discoveries.

Use of Bisphosphonates in GLA/GSD/KLA

Yaser A. Diab, M.B.B.S.
Attending Hematologist
Director, Thrombosis Program
Center for Cancer and Blood Disorders
Children’s National Health System
Assistant Professor of Pediatrics

Complex lymphatic anomalies including Generalized Lymphatic Anomaly (GLA), Gorham–Stout disease (GSD), and Kaposiform Lymphangiomatosis (KLA) can involve the bones leading to bone destruction which can negatively impact the quality of life for patients with these lymphatic anomalies. At present, no standard treatment for these diseases exist, and due to the rarity of these diseases, no clinical trials are available. Sirolimus has been shown to be effective in the treatment of various types of lymphatic anomalies. Bisphosphonates are medications that can slow down normal bone destruction and are commonly used to treat bone diseases, such as thin or fragile bones. Administration of bisphosphonates may help in treating the bone disease in patients with GLA, GSD or KLA. In addition, there is some evidence that suggests that bisphosphonates may enhance the effect of sirolimus. New treatment regimens that include sirolimus in combination with a bisphosphonate have been recently introduced and used for treatment of refractory or high risk GLA, GSD and KLA. In this talk, I will review the potential role of bisphosphonate for treating these lymphatic anomalies. I will also present the experience from various centers in using these medications in combination with sirolimus and discuss potential side effects and risks of bisphosphonate therapy. Lastly, I will discuss the efforts to lunch a multicenter pilot study aimed at defining the role of bisphosphonate therapy and the optimal regimen to use for treating patients with these complex lymphatic anomalies.
Patients and their families face a veritable alphabet soup of acronyms starting with diagnoses (GLA/GSD/KLA), including diverse tests for diagnoses and monitoring (e.g., PT, PTT, Factors I-XII, d-dimers, DIC, LIC), and culminating with a host of procedures and drugs (generic and brand names)! Many of these terms, drugs, and procedures are related to coagulation. This reflects the unfortunate complexity of lymphatic disorders.

Coagulation, also called thrombosis, is the process of forming platelet and protein plugs on torn or damaged blood vessels and tissues. It acts constantly as part of our body’s defenses, but it’s hard to get the right balance. Too little leaves bleeding and inflammation unaddressed; too much can impair circulation in the wrong place or, in the right place, but with disastrous effect. Either type of problem contributes to pain and disability. Lymphatic disorders often trigger both bleeding and clotting simultaneously. Doctors and scientists have struggled for years to understand, predict, and alas, only partially control this complex sets of interactions. Fortunately, despite the limits of our knowledge, and the sometimes, unavoidable side effects of our therapies, it is possible to discern trends with the tests, intervene with drugs and procedures to “turn the tables” on the internal chaos of malfunctioning coagulation.

I hope to shed some light on the terms families and patients in the LGDA hear every day as they work with their care teams. This brief talk can only skim the surface of a topic like this, but hopefully learning what is behind some of the jargon will clarify how we help patients with these disorders make progress towards living pain-free, normal lives.
Often the pulmonary complications of the lymphatic malformations can manifest as or mimic other common disorders: cough or wheezing, thus mimicking asthma or non-specific chronic cough. Lack of response to the usual treatments for these disorders may be a clue to the presence of some other process. This being said, anecdotally, I cared for a KLA patient whom, on top of her other problems, manifested as having asthma that required extremely aggressive treatment to control symptoms.

The most significant pulmonary complication in the lymphatic malformations is pleural effusion. This can be chylous (fatty) fluid in GLA or bloody in KLA. The effusions are challenging to manage because they tend to re-accumulate rapidly with drainage. Effusions themselves compress the lungs and can directly reduce lung function.

KLA being particularly aggressive can directly involve lung tissue or airways, which can further complicate managing these patients.

SESSION 3: SATURDAY, JULY 28, 2018 1:00 PM — 5:00 PM

Discovering the Genetic Basis of Rare Diseases

Michael Dellinger, Ph.D.

Assistant Professor
Department of Surgery
UT Southwestern Medical Center

Director of Research
The Lymphatic Malformation Institute

DNA carries all of the instructions for the development of an organism. DNA is a long polymer made up of the building blocks, G, A, T, and C. Genetic mutations are changes to the sequence of DNA. Some genetic mutations are germline mutations (heritable), whereas other mutations are somatic
mutations (non-heritable). Germline mutations cause inherited diseases that are passed from one generation to the next. In contrast, somatic mutations cause sporadic diseases that are not inherited. Recently, several vascular anomalies have been found to be caused by somatic mutations. This has led researchers to hypothesize that GLA, KLA, and GSD are also caused by somatic mutations. In my presentation, I will discuss how patient samples have been used to try to identify the genetic mutations that cause GLA, KLA, and GSD.

Use of Patient Cells in Research

Thuy Phung, MD, PhD
Associate Professor
Department of Pathology
Baylor College of Medicine and Texas Children’s Hospital

Generalized lymphatic anomaly (GLA) is a rare condition caused by pathologic growth of lymphatic vessels in the lungs, bones and soft tissues. The overgrowth leads to the formation of abnormal lymphatic vessels that can cause serious medical problems. Our goal is to understand the molecular causes of GLA, which would give us insights into how to better manage and treat patients with this disorder.

To study the biology of GLA, we isolated lymphatic endothelial cells derived from lesional tissues of GLA. We demonstrated that GLA endothelial cells have increased growth as compared with normal endothelial cells. GLA cells also have increased ability to form vascular sprouts in vitro. The growth and sprout formation of GLA cells can be significantly inhibited by the drug rapamycin that blocks the mammalian target of rapamycin (mTOR) signaling pathway, which is important for cell proliferation and survival. Because cells isolated from human GLA tissues typically do not survive long when grown in vitro, we successfully "immortalized" GLA cells so that they can be perpetually propagated. We are currently using these cells to establish an animal model of GLA to further investigate the biology of GLA cells in an intact in vivo system.
International LGDA Registry for Lymphatic Malformations

Lisa K. Klepper, BSN, RN
Director of Patient Programs
Patient Registry Coordinator
Lymphangiomatosis & Gorham’s Disease Alliance

The International LGDA Registry for Lymphatic Malformations was established for the purposes of helping to (1) establish the number of individuals who have lymphangiomatosis and Gorham-Stout disease, (2) tabulate the symptoms, complications, and co-morbidities reported by patients (or parents, in the case of minors) and how these impact the participants, and (3) to establish and maintain a database of known patients who are willing to share their de-identified information in order to accelerate the pace of basic and clinical research. Now in its fifth year, the registry has enrolled more than 300 patients around the world and has been accessed to identify individuals who meet initial inclusion criteria for 5 studies.

Directions in Research

Michael Dellinger, Ph.D.
Assistant Professor
Department of Surgery
UT Southwestern Medical Center

In the past, there were limited resources available for research on generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA), and Gorham-Stout disease (GSD). The Lymphatic Malformation Institute (LMI, www.lmiresearch.org) was created in 2011 to address this need. The LMI fosters collaborations among scientists and promotes the dissemination of knowledge on GLA, KLA, and GSD. Additionally, the LMI funds research on these rare diseases. Since 2011, the LMI has invested over 3.5 million dollars in basic science, preclinical, and clinical research on GLA, KLA, and GSD. This research has yielded valuable insight into the biology of lymphatic anomalies. In my presentation, I will discuss the latest advances in research on GLA, KLA, and GSD.
PATIENT RESOURCES

The LGDA has a number of ways for members of our community to connect and learn. We hope you will find these resources helpful and welcome you to utilize those with which you are most comfortable.

**Lymphangiomatosis & Gorham’s Disease Alliance**
Website: www.lgdalliance.org
Facebook: www.facebook.com/LGDAlliance
Twitter: www.twitter.com/LGDAlliance
Email: support@lgdalliance.org
Phone: 1-844-588-5771

**Alfie Milne Lymphangiomatosis Trust**
Website: www.alfiemilne.org.uk
Facebook: www.facebook.com/alfiemilne.lymphangiomatosisstrust.9
Twitter: www.twitter.com/alfiemilne
Email: support@lgdalliance.org
Phone: 01224 735038

**Lymphangiomatosis & Gorham’s Disease Alliance – Europe**
Website: http://www.lgdalliance-europe.org
Facebook: www.facebook.com/LGDAllianceEurope
Twitter: www.twitter.com/lgda_eu
Email: info@lgdalliance-europe.org

**Lymphatic Malformation Institute (LMI)**
Website: www.lmiresearch.org
Email: mdellinger@lmiresearch.org

**CONFERENCE COMMITTEE**

**Conference Chair:** Lisa K. Klepper (United States)

**Conference Committee Planning Members:**
Diane Bomberg (United States)
Ange van der Velden (Netherlands)
Tracy Milne (Scotland)
Jack Kelly (United States)
Sandy Goldfarb (United States)