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MEETING REPORTS

Meeting Report for the 2016 Conference on GLA and Gorham–Stout Disease

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Meeting Report for the second International Conference on Generalized Lymphatic Anomaly and Gorham–Stout Disease, held in Atlanta from 10 to 11 June 2016.

Introduction

Generalized lymphatic anomaly (GLA); formerly known as lymphangiomatosis is a rare disease of unknown etiology characterized by the proliferation of lymphatic vessels in tissues and frequently involves bone.[1] Gorham–Stout disease (GSD) is a related disease characterized by the presence of lymphatic vessels in bone and by the gradual resorption of bone.[2] Unfortunately, the natural histories of GLA and GSD are poorly understood and patients with these diseases have limited therapeutic options. To help address these gaps in knowledge, the Lymphatic Malformation Institute (LMI), the Lymphangiomatosis & Gorham's Disease Alliance (LGDA) and the Alfie Milne Lymphangiomatosis Trust sponsored the second International Conference on GLA and GSD. This conference was held from 10 to 11 June 2016 in Atlanta, Georgia; it had 59 participants from around the world; and it was chaired by Drs Ionela Iacobas and Michael Dellinger. The objectives of this conference were as follows: (1) to share and discuss recent unpublished clinical and basic science research on GLA and GSD; (2) to discuss questions related to the diagnosis, management and treatment of patients with GLA or GSD; and (3) to catalyze the formation of collaborations among investigators studying these rare diseases. The highlights of this exciting conference are presented in this meeting report.

Session I: Review of GLA and GSD

The conference began with a session focused on reviewing the clinical features and management of GLA and GSD. Kaposiform lymphangiomatosis and central conducting lymphatic anomaly were included in several of the discussions during this session because of their similarities to GLA and GSD. The first speaker of the session was Cameron Trenor. He reviewed several of the distinctive clinical features of GLA and GSD. Although GLA and GSD have overlapping symptoms and complications, they display differences in how bone is affected. Cortical bone is spared in patients with GLA but is destroyed in patients with GSD.[3] Also, the appendicular skeleton is more frequently affected in GLA patients than GSD patients.[3] In addition to reviewing the published data, Dr Trenor presented new findings from a lymphatic anomalies registry (www.lymphaticregistry.org). This registry contains the clinical data from hundreds of patients with complicated lymphatic anomalies. The LGDA also has a patient registry (www.lgdalliance.org/registry) and patients with GLA or GSD are encouraged to participate in both registries. Denise Adams was the next speaker of the session and she started her presentation by reviewing a few of the therapies (steroids, interferon and vincristine) that have been used to treat either GLA or GSD. Next, she presented the findings from a phase II clinical trial with sirolimus[4] and the unpublished data from a combined retrospective and prospective study on the use of sirolimus in GLA and GSD. Dr Adams ended her presentation with ideas on how to advance the field and care of patients with GLA or GSD. Next, Juan Carlos Lopez-Gutierrez reviewed the surgical management of GLA and GSD. Chylothorax is a common complication of GLA and GSD, and can cause severe respiratory problems and death. Dr Lopez-Gutierrez discussed surgical approaches to manage chylothorax in patients with GLA or GSD. He also discussed how surgery could be used to stabilize the skeleton to prevent paralysis in patients with spine involvement. The session ended with Patricia Burrows discussing the radiologic diagnostic challenges in GLA and GSD. She also reviewed several of the endovascular procedures and sclerosis-inducing agents used to treat complications of complex lymphatic anomalies.

Session II: Advances in Clinical Research

Presentations in this session were focused on the latest advances in clinical research. The session started with Maxim Itkin discussing dynamic contrast-enhanced MR lymphangiography, a new technique that allows detailed imaging of the central lymphatic system.[5] He reported that lymph spilled into the lung parenchyma in several of the lymphatic anomaly patients he has imaged. Presentations on imaging continued with Michael Collins. He showed that 18F-Na PET/CT imaging could be used to identify and monitor osteolytic lesions in a patient with GSD. In addition, he discussed the use of the potent antiresorptive drug, denosumab, in the treatment of GSD. Erik

Eklund was the next speaker of the session. He presented work on the histological differences between pulmonary and pleural samples from pediatric and adult patients with GLA/GSD.[6] First, he described the creation of a biobank of formalin-fixed paraffin-embedded tissue with material from 23 patients with GLA/GSD. Importantly, material from this biobank is available to researchers for collaborative ventures. Using material from this biobank, he found that the number of proliferating lymphatic endothelial cells (LECs) was greater in tissues from GLA/GSD patients than tissues from unaffected individuals.[6] In addition, he found that the number of proliferating LECs was greater in tissues from pediatric GLA/GSD patients than adult GLA/GSD patients.[6] Next, Tim Le Cras presented results from a collaboration with Denise Adams, which is focused on identifying serum biomarkers for lymphatic anomalies. Non-invasive biomarkers could replace the need for tissue biopsies for diagnosing lymphatic anomalies and provide insight into the molecular pathways driving the pathogenesis of these diseases. Drs Le Cras and Adams have identified a factor that is markedly elevated in serum from patients with kaposiform lymphangiomatosis. They also found that the level of this factor decreased following treatment with sirolimus. This biomarker may facilitate the diagnosis of patients with kaposiform lymphangiomatosis and could potentially be used to monitor response to therapies such as sirolimus. The focus of the session then switched to genetics. Victor Martinez-Glez and Michael Levine gave separate presentations on the search for the genetic underpinnings of GLA and GSD. Both investigators have identified numerous genetic differences between affected and unaffected tissue by whole-exome sequencing and are working on determining the significance of these changes.

Sessions III and IV: Group Discussions and Presentations

The conference featured a breakout session that allowed participants to discuss questions related to the diagnosis and management of GLA and GSD. During the session, participants segregated into the following specialty groups: (1) Hematology Oncology, (2) Medical (Non-Hematology Oncology), (3) Surgery, (4) Radiology and (5) Pathology, Genetics and Basic Science. Each group had a moderator to help guide the discussion. Ionela Iacobas, Michael Collins, Steven Fishman, Sheena Pimpalwar and Michael Dellinger served as moderators. After the breakout session, each moderator presented their group's answers and recommendations to the rest of the attendees. This resulted in several lively discussions and exposed a few controversies in the field (for example, nomenclature and so on). The suggestions from these productive discussions are going to be compiled into a separate report.

Session V: Advances in Basic Science Research

Talks in this session focused on recent advances in basic science research on GLA/GSD. The session began with Lianping Xing presenting her work on the crosstalk between LECs and osteoclasts. Her group has identified a factor secreted by LECs that induces the formation of osteoclasts and has found that inhibition of this factor prevents LEC-induced osteoclast differentiation. She also found that intratibial injection of LECs leads to the destruction of bone. Thuy Phung was the next speaker of the session and she described how she isolated, characterized and immortalized LECs from affected tissue from a patient with lymphangiomatosis. These cells could potentially serve as a valuable biological resource for the study of lymphangiomatosis and could be used to identify therapies for lymphangiomatosis and the genetic underpinnings of this disease. The focus of the session then switched to animal models. Donald McDonald previously reported that *CCSP-rtTA; TetO-Vegfc* transgenic mice develop hyperplastic lymphatic vessels in their airways.[7] At this meeting, he described the beneficial effects of rapamycin on the lymphatic abnormalities in *CCSP-rtTA;TetO-Vegfc* transgenic mice. He also presented work on a new animal model of inducible chylothorax. This animal model should yield new insight into the cause of this common complication of GLA/GSD. Presentations on animal models continued with Michael Dellinger reporting that transgenic mice that overexpress a lymphatic growth factor in their bones develop lymphatic vessels in their bones. Using this model, he has identified a potential biomarker of disease activity and is starting to evaluate this factor in patients with GLA/GSD. The session ended with a presentation by Sarindr Bhumiratana, the Chief Scientific Officer of EpiBone. He gave an exciting presentation on how EpiBone is using anatomically shaped scaffolds and stem cells isolated from adipose tissue to engineer bone.

Conclusions

The presentations at the meeting revealed that substantial progress has been made in the field since the first International Meeting on GLA and GSD in 2013.[8] Potential biomarkers have been identified, several animal models have been created, and a LEC line has been generated and immortalized. Despite this progress, many questions and controversies still exist. Importantly, the meeting gave clinicians and scientists an opportunity to discuss solutions to problems and controversies, to identify new avenues of research and to form new collaborations. We hope that these conversations and new collaborations will lead to the development of new research projects that will increase our understanding of GLA and GSD, and accelerate the discovery of new therapies for these devastating diseases.

Conflict of Interest

The authors declare no conflict of interest.

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