SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 359-363

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The 2014 annual meeting of the Americas Association of Sarcoidosis and Other Granulomatous Disorders (AASOG) was held on September 19th and 20th at The Ohio State University in Columbus, Ohio, U.S.A. The theme of the meeting was "Sarcoidosis Health Care Disparities and Clinical Research Challenges" that was endorsed by leading healthcare and research organizations, including the American Thoracic Society (ATS), American College of Chest Physicians (ACCP) and was conducted through support provided by the National Institutes of Health (NIH), particularly the National Heart Lung and Blood Institute (NHLBI).

The meeting participants were predominantly from North America, and included preeminent experts and emerging clinical scientists engaged in sarcoidosis research. With respect to the latter, a number of high quality scientific abstracts were presented, among which 5 were selected for oral presentation and Travel Awards. In total, over two-dozen oral presentations and ~20 abstracts were presented during the two day meeting. The AASOG meeting was held in parallel with a patient-oriented meeting sponsored by the Foundation for Sarcoidosis Research (FSR), based in Chicago, which was held in an auditorium less then 100 meters away. A number of sarcoidosis experts contributed significantly to both meetings. In total, over 200 scientists, clinicians and patients were engaged in the AASOG and FSR meetings. A brief overview and selected excerpts of the 2014 AASOG meeting proceedings are provided herein.

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Sarcoidosis and Health Care Disparities

Sarcoidosis is microcosm of the healthcare problems facing the Americas in that the disease disproportionately afflicts underserved populations who have limited access to personalized healthcare in large urban communities. The additional burden of undertreated and often undiagnosed sarcoidosis, including the inability to sustain employment and associated healthcare insurance, further exacerbates their plight by limiting access to routine medical care. Consequently, many sarcoidosis patients are undertreated, and present with more advanced disease for emergency and often futile medical care.

Limited access to healthcare also undermines governmental support for sarcoidosis research and clinical care by obscuring the magnitude and various phenotypic expressions of the disease from view. This phenomenon was demonstrated in two major efforts to better characterize the epidemiology of sarcoidosis in representative American populations.

Dr. Yvette Cozier, principal investigator of the Black Women's Health Study, which monitors over 59,000 black women living in U.S.A., reported an astounding statistic relating to the burden of sarcoidosis in this population. Despite selective representation of wealthy and well-educated members of the population, the prevalence of sarcoidosis was ~2,000/100,000 in this American Black female cohort (1) and the all cause mortality rate was nearly double that of the non-sarcoidosis consortium members within all age groups. Specific challenges relating the recruitment of underprivileged members of society to participate in clinical research trials were underscored in the epidemiological study of Dr. Cozier and in a national survey conducted by Dr. Alicia Gerke at the University of Iowa, wherein limited access to the internet, failure to complete the surveys, disengagement from healthcare providers and a related lack of trust, such as concerns about protection of their personal information, were identified as common deterrents. Hence, the prevalence of sarcoidosis and related healthcare implications in the underserved remains unknown, and will require alternative methods to accurately measure.

Dr. Robert Winn, a plenary speaker from the University of Illinois Chicago, shared his firsthand experience a director of the Mile Square Health Centers, a group of Federally Qualified Health Centers that have been established to address healthcare disparities among ~2 million citizens of Chicago using an approach that was pioneered over 100 years ago. The solution is very simple, said Dr. Winn, "…we need to bring healthcare to the patients!" Dr. Winn noted that primary and specialized healthcare needs in the inner cities are currently rendered by large, centralized medical centers wherein the patients are inappropriately viewed, from a Ptolemaic perspective, as celestial bodies (e.g., the sun) orbiting the central medical center and its physicians (the earth). For many of the reasons previously mentioned, the Ptolemaic model is diametrically opposed to the optimal healthcare model. Per Dr. Winn's recommendations, smaller satellite health centers, with associated pharmacies and, ideally, fitness centers and grocery stores (i.e., instead of fast food restaurants), would be strategically placed in close proximity to the patients. Such models of urban planning were introduced in the U.S.A and Britain over 100 years ago to address health care as a social and political issue wherein the patients become directly engaged in all aspects of healthy living, including the positioning of physicians as engaged members of their community. Accordingly, the patient is viewed as the solar center, with the physicians and their health centers the orbiting planets in this revised, Copernican view of healthcare.

The same concepts of engendering patient access and trust while promoting physician integration have important implications for addressing disparities in the context of research. It is self-evident that integration of the physician scientist within the community medical system would provide underprivileged patients with greater access to cutting edge, investigational therapies, and would provide more accurate estimates of the varied phenotypes and the burden of granulomatous diseases, such as sarcoidosis, in these communities.

Clinical Research Challenges and Opportunities

Integral to the issue of healthcare disparities is the notion of "scientific relevance", a phrase coined by Dr. Winn, to describe the type of science that directly influences the health and wellbeing of sarcoidosis patients.

Many of the featured speakers within the session entitled "Novel, Cutting Edge Research" are relatively new to the field of sarcoidosis. Dr. Naftali Kaminski from Yale University, a world leader in genomics research relating to the pathogenesis of idiopathic pulmonary fibrosis, has recently assumed a leadership role in the NIH-sponsored Genomic Research in Alpha-1-Antitrypsin Deficiency and Sarcoidosis (GRADS) project. Dr. Kaminski reported that subject recruitment is on track towards the goal of recruiting 400 carefully-phenotyped sarcoidosis patients, while establishing a biobank and genomic database resource for ongoing and future research. Dr. Kaminski shared exciting preliminary data demonstrating the promise of genomic and bioinformatic research for discovering novel biomarkers, unraveling disease mechanisms and identifying potential therapeutic targets.

Other featured speakers within this session addressed challenging aspects of sarcoidosis managment. Cardiac sarcoidosis is emerging as a major

clinical dilemma in that it is a potentially lethal complication of sarcoidosis that is difficult to detect and for which standardized treatments are lacking. Dr. Subha Raman, a cardiologist and professor of internal medicine, biomedical informatics and radiology at The Ohio State University, reviewed the current options for detecting sub-clinical and symptomatic cardiac sarcoidosis. While no diagnostic modality is perfect, cardiac MRI has the advantages of no radiation exposure, high anatomical resolution, and the ability to discriminate potentially reversible disease (inflammation) from irreversible manifestations (necrosis or fibrosis), that has implications for prognosis and treatment (2).

Neurological and psychological manifestations of sarcoidosis are common and strongly influence the patients' quality-of-life. In this regard, the concept of "paraneurosarcoidosis" has been proposed to describe neurological symptoms that arise as an indirect consequence of systemic granulomatous inflammation, such as fatigue, impaired concentration, and neurosensory pain. Dr. Jinny Tavee, a neurologist at the Cleveland Clinic provided insight into the clinical manifestations, modes of detection, and experimental treatments that she is evaluating for the small fiber neuropathy that frequently complicates sarcoidosis. The sarcoidosis experts in attendance acknowledged the need for greater access to well-trained neurologists to help distinguish sarcoidosis-related small fiber neuropathy from other common disorders (e.g., diabetic or steroid-induced neuropathy).

Given the strong influence of race on sarcoidosis disease prevalence and severity and the observed familial predisposition, genetic and genomic tools are considered by most investigators to be essential for understanding the pathogenesis of sarcoidosis. Genetic variability strongly influences the sarcoidosis clinical phenotype, and is shown to play a causal role in some individuals (i.e., a subset of Germans with the BTNL2 mutation (3)). Genetic variability is strongly dictated by functionally distinct polymorphisms, collectively referred to as SNPs (single nucleotide polymorphisms), including those directly altering the protein coding sequence resulting in altered protein function (cSNPs), regulatory polymorphisms that alter gene expression (rSNPs), and structural RNA variants (srSNPS) that alter RNA processing and thereby, expression. Candidate, potentially disease-modifying cSNPs are typically identified by genome wide association studies (GWAS) based upon the implied functional implications of the altered protein product. The availability of GWAS data from sarcoidosis populations are limited; however, novel analytical techniques being applied to existing databases by new investigator, Dr. Albert Levin and colleagues at the Henry Ford Health System, provided further resolution within established regions of linkage disequilibrium, and have thereby incriminated novel SNPs with credible disease modifying potential. As noted by Dr. Mike Iannuzzi from the State University of New York Upstate in Syracuse, the meeting's keynote speaker and a leading geneticist in the field of sarcoidosis, more work in this area is needed to further exploit existing GWAS databases to identify novel disease modifying SNPs and validate previously identified SNPs.

Dr. Wolfgang Sadee, a world renowned pharmacogenomic researcher at The Ohio State University, discussed how innovations relating to next generation sequencing (NGS) provides insight into "missing heritability" that may not be evident from GWAS by identifying unexpected changes in gene expression in the context of disease. NGS comprehensively and quantitatively measures all tissue RNA transcripts. Detection of allelic mRNA expression imbalance provides clues for the identification of cis-acting factors, including genetic (e.g., rSNP or intrinsic srSNP, which may be further imputed from GWAS) and epigenetic (e.g., inhibitory microRNA), which are primarily responsible for most human phenotypic variability. Pharmacogenomics refers to the targeting of therapies, either existing drugs or new ones, based upon newly discovered genomic mechanisms such that the disease manifestations are minimized. Thus, genomic and pharmacogenomics approaches add to information provided by GWAS by considering tissue-and environment-specific changes in gene expression and related gene networks to discover post-transcriptional regulatory mechanisms which represent novel treatment targets. These approaches are yet to be considered in the context of sarcoidosis.

A major barrier to understanding the pathogenesis and treatment of sarcoidosis is the reliance on resource-intensive and time-consuming human research in lieu of relevant animal or *in vitro* models of sarcoidosis. Progress towards more useful models of

sarcoidosis was offered by investigator Evelyn Guirado, Ph.D., from The Ohio State University, who has developed a human *in vitro* granuloma model for the investigation of tuberculosis that promises to be useful for exploring the earliest stages of granuloma formation in the context of sarcoidosis. The earliest stages of granuloma formation are difficult to assess *in vivo* or from tissue samples and are thought to be critical determinants of disease pathogenesis and progression. In this context, Andrew Fontenot, M.D. at the University of Colorado, a preeminent leader in the field of berylliosis, provided a template for exploring the host/environment interactions relating to genetic MHC class II variability, which is a strong determinant of sarcoidosis phenotypic variation. As demonstrated by complex investigations conducted by Dr. Fontenot's laboratory in the context of berylliosis, MHC variability is readily tested in modified cell lines and modeled in genetically altered mice to consider putative disease causing host/antigen interactions. Taking a very different approach, Wenrui Hao, Ph.D., a new investigator under the mentorship of National Academies of Science member, Avner Friedman Ph.D. from The Ohio State University, shared a newly developed mathematical model of sarcoidosis that is based upon the current scientific evidence. The model, presented in abstract form at AASOG and since accepted for publication in the *Proceedings of the National Academy of Science, USA*, is shown to closely approximate the human condition and is capable of predicting the effects of genetic diversity or the response to novel treatments in the setting of sarcoidosis research (4).

Several promising new treatment strategies for sarcoidosis were unveiled at the AASOG meeting. Wonder Drake, M.D. (Vanderbilt University), the principal investigator, and co-investigator Robert Baughman, M.D. (University of Cincinnati), presented progress relating to their ongoing NIH/NHLBI sponsored clinical trial that will treat sarcoidosis patients with Concomitant Levaquin, Ethambutol, Azithromycin, and Rifabutin (i.e., the CLEAR trial). Preliminary data suggests CLEAR is effective for the treatment of cutaneous sarcoidosis, albeit through unclear mechanisms. In this regard, components of CLEAR (e.g., azithromycin) have known immune modulatory actions. Alternatively, Dr. Drake and others have proposed that CLEAR may lead to the eradication of an undetectable (by available means) atypical mycobacterial infection that is linked to the pathogenesis of sarcoidosis. In this regard, Dr. Drake also shared new human data, recently published in the *American Journal of Respiratory and Critical Care Medicine*, suggesting that "immune cell exhaustion", relating in part to programmed death receptor (PD)-1 and programmed death ligand (PDL)-1 interactions between antigen presenting cells and T cells, may play a role in failure to clear infectious antigens, thereby resulting in sustained granulomatous inflammation in the context of sarcoidosis (5). It follows that anti-PD-1 or anti-PD-L1 therapies, currently under investigation for the treatment of chronic viral infections and various cancers, could play a role in the treatment of sarcoidosis.

At the conclusion of the AASOG meeting, the challenges and opportunities facing the field of sarcoidosis were eloquently summarized by Dr. Jerry Eu, a Program Director within the Lung Biology and Disease Branch at the National Heart Lung and Blood Institute (NHLBI) Division of Lung Diseases, who further shared 5 primary sarcoidosis research themes that are prioritized by the NIH/NHLBI for future support: 1) research that will facilitate personalized medicine, 2) discoveries and mechanisms promoting disease prevention, 3) investigation of programs and treatments to promote health, 4) training of future investigators, and 5) initiation of programs that will address health care disparities. As per Dr. Winn, the goal should be to conduct "relevant science" that will ultimately improve the health and wellbeing of sarcoidosis patients. Examples of relevant science being discoveries relating to genetics/genomics, identification of predisposing environmental factors, development of better health care models (to access the patients who are excluded from clinical trials and detached from the healthcare system), and most importantly, public awareness and access to better training programs to prepare the next generation of sarcoidosis researchers.

The AASOG meeting was a showcase for the depth of thought in the Americas concerning both the science of sarcoidosis as well as its impact on the sarcoidosis patient. AASOG recognizes its role as a subsidiary to WASOG in an international effort to understand and eradicate sarcoidosis. AASOG has an additional mission as an important forum in the

Americas for promoting research and clinical care of sarcoidosis within the Western Hemisphere, with attention to unique challenges that we encounter. We look forward to the 2015 AASOG meeting in Denver, Colorado on September 11th and 12th, and the 2016 meeting to be held in Chicago.

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