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Multiple System Atrophy: The case for an international collaborative effort

Lucy Norcliffe-Kaufmann, PhD, **Jose-Alberto Palma, MD, PhD**, and **Florian Krismer, MD on behalf of On behalf of the Autonomic Disorders Rare Disease Consortium and European MSA Study Group**

Dysautonomia Center, New York University School of Medicine, New York, NY, USA, Innsbruck University Medical Center, Innsbruck Austria.

"United we stand divided we fall." — Alexandre Dumas, *The Three Musketeers*

Multiple system atrophy (MSA) is a rare neurodegenerative disease that affects both men and women and has no clear ethnic or racial susceptibilities. Cases are geographically spread throughout the world. Age of onset is typically in the mid-50s. Based on MSA prevalence rates [6] and 32% of Americans being over 50, estimates suggest there are around 5,200 Americans suffering from MSA. The rarity of the disease in combination with the geographical spread of the cases is the biggest obstacle when it comes to enrolling patients in clinical trials. It is thought that with so few cases, no single treatment center -and probably no single country- has enough patients to perform well-powered translational research.

MSA is an orphan disease – because it affects less than 200,000 Americans. Orphan diseases are surprisingly common, with an estimated 7,000 different orphan diseases affecting around 30 million Americans. Awareness of rare diseases is growing fast. The National Institutes of Health (NIH) released a position piece recommending that each rare disease has a dedicated global registry and data repository. They emphasized the importance of collecting de-identified clinical data in a standardized fashion overtime and making this information linkable to tissue stored in bio-specimen banks [2].

Gathering specific information from a large pool of patients has obvious advantages when it comes to defining true rates of disease progression as well as the impact of common treatment interventions. Well-defined patient cohorts also lay the foundation for future biomarker research. This strength in numbers approach requires an international collaborative effort that brings together clinical centers conducting research on MSA. Fortunately, in the case of MSA, these collaborative consortia working on the disease already exist.

Corresponding Author: Lucy J. Norcliffe-Kaufmann, PhD, 530 First Avenue, Suite 9Q, New York, NY, 10023, norcll01@nyumc.org, Phone: 212 263 7225.

Links:

Autonomic Disorders Consortium: https://www.rarediseasesnetwork.org/ARDCRC/

European MSA Study Group: http://www.emsa-sg.org

MSA Coalition: https://www.multiplesystematrophy.org

MSA is a central focus of the North American Autonomic Disorders Consortium, created in 2009, as part of the Rare Diseases Clinical Research Network (RDCRN) – a partnership between several NIH Programs [3]. The Consortium has an ongoing prospective natural history study of MSA. The Consortium recently completed a controlled trial to test the neuroprotective potential of the old antibiotic rifampicin. Although the trial ultimately proved negative, the undertaking showed that it was possible to enroll 100 early MSA patients in little under a year [4].

The European counterpart is the European MSA Study Group (EMSA-SG), founded in 1999, from sites in Austria, Denmark, France, Germany, Italy, Portugal, Sweden, Spain and Great Britain. The European MSA Study Group published a report of it's prospective MSA cohort that had been followed for 2-years [5], which defines much of what we know about the motor progression rates in MSA. They have also completed several clinical trials.

In 2013, the MSA Coalition, a patient and caregiver advocacy group, provided support for an initiative to form a transatlantic alliance that would unite US and European MSA Centers. The organization and structure are now in place and a standardized dataset has been agreed upon. Sites in Europe, the US and South America have signed agreements to contribute the standardized data set that will be used to follow the motor and autonomic features of MSA overtime (Figure).

On a day-to-day basis, natural history studies are not the most exciting and require endless hours pouring through case report forms and entering data, but the efforts pay off in the long-term. Large and well-thought natural history studies can provide valuable information for drug development. They are the only way to understand the variability in disease severity amongst patients and reliably estimate the sample size necessary to sufficiently power a study with a clinically meaningful endpoint [1]. They also define rates of progression of affected patients outside a clinical trial. By describing the natural course of the disease, an international prospective study in MSA should help to also define guidelines for clinical care.

The argument for an international registry and natural history study is convincing, Sharing data across academic institutions and international boundary lines requires understanding of local rules and regulations, but is possible. The continued support of the MSA Coalition and the NIH's Rare Diseases Clinical Research Network will make the project feasible.

Bibliography

1. Galpern WR. Clinical trials for multiple system atrophy. Lancet Neurol. 2014
2. Groft SC, Rubinstein YR. New and evolving rare diseases research programs at the National Institutes of Health. Public health genomics. 2013; 16:259–267. [PubMed: 24503586]
3. Krischer JP, Gopal-Srivastava R, Groft SC, Eckstein DJ. Rare Diseases Clinical Research N. The Rare Diseases Clinical Research Network's organization and approach to observational research and health outcomes research. Journal of general internal medicine. 2014; 29(Suppl 3):S739–S744. [PubMed: 25029976]
4. Low PA, Robertson D, Gilman S, Kaufmann H, Singer W, Biaggioni I, Freeman R, Perlman S, Hauser RA, Cheshire W, Lessig S, Vernino S, Mandrekar J, Dupont WD, Chelimsky T, Galpern

WR. Efficacy and safety of rifampicin for multiple system atrophy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014; 13:268–275. [PubMed: 24507091]

5. Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, Kollensperger M, Goebel G, Pfeiffer KP, Barone P, Pellecchia MT, Quinn NP, Koukouni V, Fowler CJ, Schrag A, Mathias CJ, Giladi N, Gurevich T, Dupont E, Ostergaard K, Nilsson CF, Widner H, Oertel W, Eggert KM, Albanese A, del Sorbo F, Tolosa E, Cardozo A, Deuschl G, Hellriegel H, Klockgether T, Dodel R, Sampaio C, Coelho M, Djaldetti R, Melamed E, Gasser T, Kamm C, Meco G, Colosimo C, Rascol O, Meissner WG, Tison F, Poewe W. European Multiple System Atrophy Study G. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013; 12:264–274. [PubMed: 23391524]
6. Wenning GK, Krismer F. Multiple system atrophy. Handbook of clinical neurology. 2013; 117:229–241. [PubMed: 24095129]

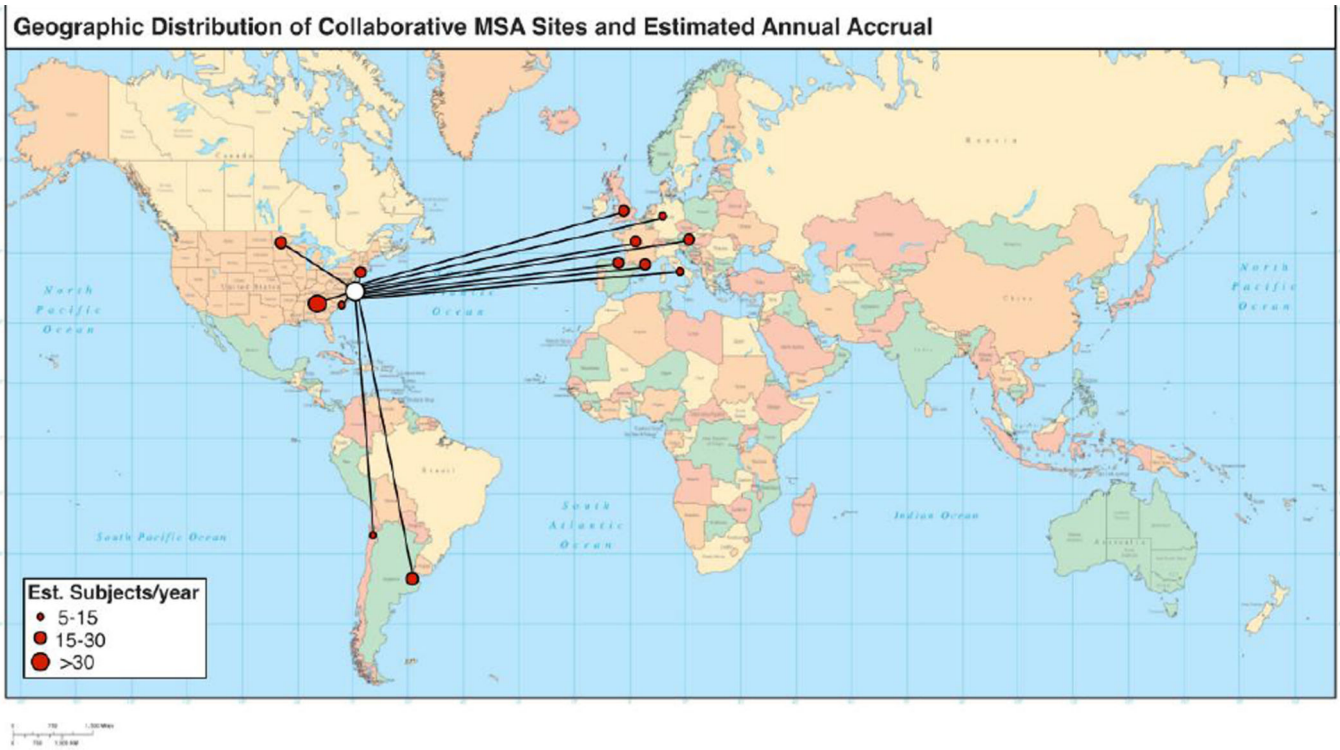

Figure.

Collaborating sites in the Global MSA Natural History Study include: New York University Medical Center (Coordinating site: Horacio Kaufmann), Vanderbilt University Medical Center (PI Autonomic RDCRC: David Robertson & Italo Biaggioni), Beth Israel Deaconess (Roy Freeman & Christopher Gibbons), Mayo Clinic Rochester (Phillip Low & Wolfgang Singer), Intramural NIH (David Goldstein), Columbia University (Un Jung Kang), Innsbruck Medical Center (Gregor Wenning & Florian Krismer), Toulouse University (Olivier Rascol), Bonn University Hospital (Thomas Klockgether), University of Bologna (Pietro Cortelli), University College London (Kailash Bhatia), University Hospital Bordeaux (Wassilios Meissner), Cruces University Hospital (Juan Carlos Gomez-Esteban), University of Valparaiso (Juan Idiaquez), and FLENI (Marcelo Merello)