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MOVING ALONG

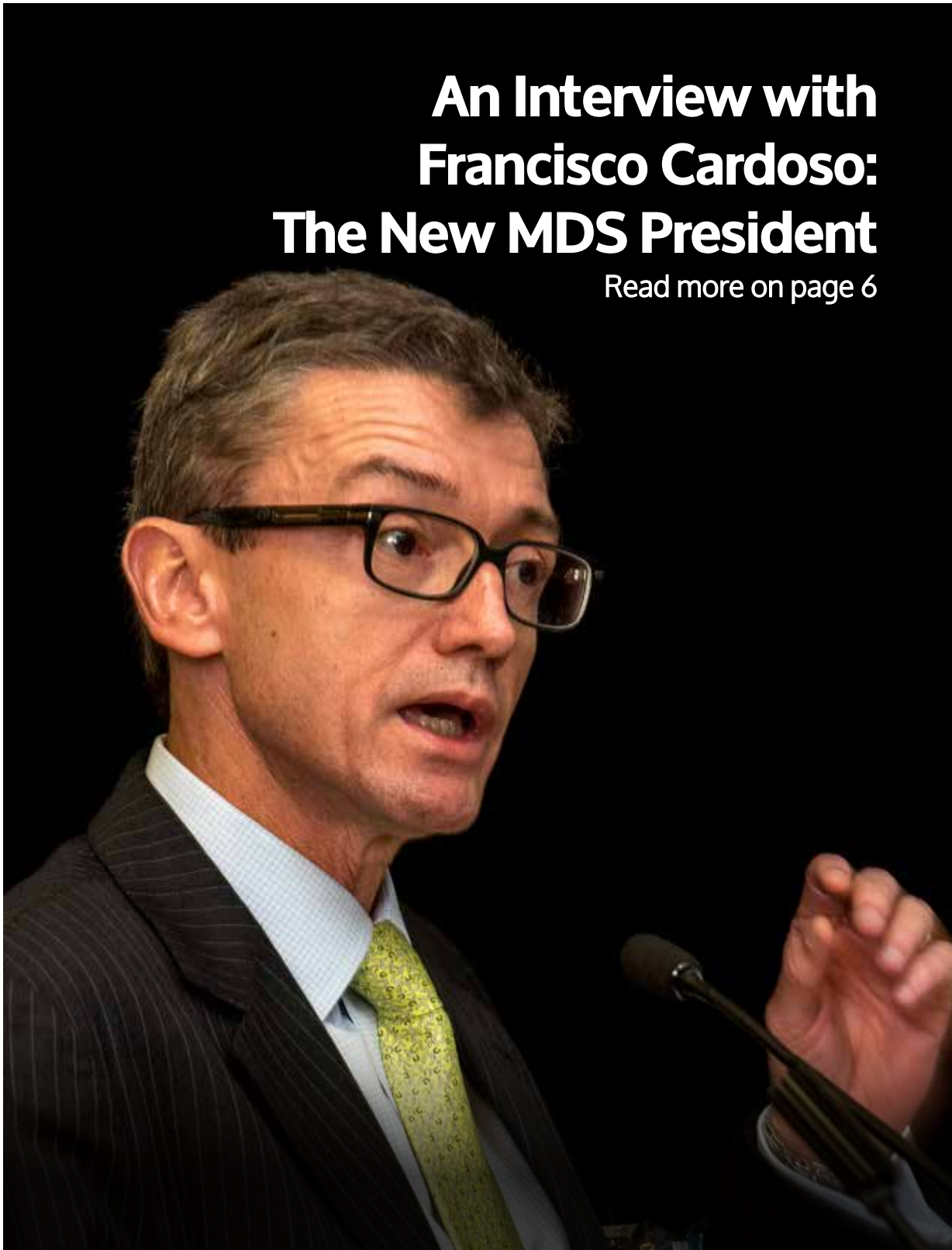
International Parkinson and Movement Disorder Society

Editor, Antonio Strafella, MD, PhD, FRCPC

gp2 Global Parkinson's Genetics Program

An Interview with Francisco Cardoso: The New MDS President

Read more on page 6



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Letters to the Editor *Your comments and questions are always welcome.*

Editorial Policy

As part of its democratic commitment, MDS welcomes the input of all its members about the features and articles that appear in this newsletter. Have a comment or question? Each issue will include responses in the "Letters to the Editor" section. All materials submitted become the property of MDS.

Address your communications to:

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Editorial

On behalf of the *Moving Along* Editorial Board, we hope that you and your family members continue to be healthy and safe during this challenging time of the coronavirus (COVID-19) pandemic.

We would like to thank the entire MDS community for the enthusiasm demonstrated in contributing with new exciting content for this 4th and final issue of *Moving Along* for 2021. The Editorial Board appreciates your participation and worked tirelessly to bring together all of this material.

The 2021 MDS Virtual Congress was a success and attended by over 13,000 participants from 143 countries. Congratulations to the Congress Scientific Program Committee for this truly amazing accomplishment. This issue of *Moving Along* features many of the topics covered during the MDS Virtual Congress, including the Presidential and Junior Award lectures, along with several other scientific activities of the MDS community. The new MDS President, Prof. Francisco Cardoso, provides his insights and vision for MDS for the next two years, and we thank him for his contribution.

We would like to thank some of the members of our Editorial Board (Dr. Margherita Fabbri, Dr. Daniel Martinez-Ramirez, Dr. Carlos Juri, Dr. Jee-Young Lee) who have stepped down at the end of December 2021. In the past three years of their commitments, they have done an outstanding job in improving the *Moving Along* Newsletter.

We would like to thank the MDS Officers, International Executive Committee, Regional Section leadership, and all of the MDS staff for their amazing support in continuing to make this possible. We hope you enjoy this issue of *Moving Along*, and wish you and your families a safe and healthy 2022.

A. Strafella

Antonio Strafella, MD, PhD, FRCPC
Moving Along Editor (2021-2023)

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President's Corner

I would like to start my first column as MDS President by paying homage to my predecessor, Prof. Claudia Trenkwalder. We are still through one of the most dramatic periods of human history as a result of the COVID-19 pandemic. This created unprecedented challenges for our Society. Yet, Claudia steered us with grace, competence, and serenity. The result was not simply to keep MDS afloat: we have achieved many important things such as a record number of members (more than 12,000 as of the writing of this article!) and offering educational activities to an equally record number of people in all corners of the globe. Congratulations, Claudia, and many thanks for the wonderful job!

My vision for MDS over the next to two years is to concentrate on three goals. The first priority is to relaunch the in-person activities of the Society. Despite the increase of new cases in some areas of the world and the emergence of the Omicron variant of the SARS-CoV-2, I remain confident that we'll be able to hold in-person activities in 2022. Of course, this will require following strict sanitary guidelines.

Most likely the new reality will involve a combination of in person activities, that we all are craving for, and a strong online component. During the past two years, MDS learned that despite its shortcomings, virtual activities allowed us to reach out to people who were not able to attend our activities. The Society pledges to continue providing education in the field of movement disorders to people all over the globe.

This leads me to second goal we'll pursue during my term as president: to make even more progress in achieving gender, geographic and ethnic diversity. And, finally, the motto of my term is "to get back to the basics: clinical care". This does not mean that Irene Litvan, MDS Treasurer, Chuck Adler, MDS Secretary, the other Officers, and I will neglect other areas of movement disorders. They will remain relevant to us. Yet, the vast majority of our members are involved with providing care to people with movement disorders. We all are hungry for education that helps us to improve the lives of our patients.

Finally, I invite you to read my conversation with Bettina Balint on page 6. We have discussed not only technical issues but also some aspects of my life I hope you find both interesting and inspirational.

Francisco Cardoso, MD, PhD, FAAN
MDS President, 2021-2023

A Statement from the MDS Officers: Perceptions of Diversity and Inclusion at the MDS Leadership Level

— Francisco Cardoso, MD, PhD, FAAN, President, The Federal University of Minas Gerais, Belo Horizonte, Brazil
— Victor Fung, MBBS, PhD, FRACP, President-Elect, Westmead Hospital, Sydney, Australia
— Claudia Trenkwalder, MD, Past President, University Medical Center Goettingen, Kassel, Germany
— Charles Adler, MD, PhD, Secretary, Mayo Clinic Arizona, Scottsdale, AZ, USA
— Marina de Koning-Tijssen, MD, PhD, Secretary-Elect, University Medical Centre Groningen, Groningen, Netherlands
— Irene Litvan, MD, Treasurer, UC San Diego, San Diego, CA, USA
— Wassilios Meissner, MD, PhD, Treasurer-Elect, CHU Bordeaux, Bordeaux, France

In recent issues of *Moving Along*, the MDS Leadership announced and provided details on the MDS Statement on Diversity and Inclusion. This statement remains important to the leadership and membership of our Society, and drives our decision-making at all levels.

The MDS Officers recently conducted a survey of the membership to seek input regarding your perceptions of diversity and inclusion at the MDS Leadership level. I am happy to share the results of that survey with you now, and to share plans for ensuring diversity and inclusion within MDS in the future.

In total, 534 members completed the survey. The responders were from all MDS Regional Sections, matching closely with the percentage of members that reside in each Section. There was also an even split of male and female respondents, and an age profile that matches our membership. The Officers are pleased with the overall response to the survey and believe that we received a representative response from the membership.

The survey asked members to rate the extent to which they agree with several statements, including whether the MDS membership and leadership match the diversity of movement disorders professionals worldwide. After providing their answers, the responders reviewed statistics on MDS's membership and asked to respond to the same questions.

Before reviewing the statistics, 79.8% of responders agreed or strongly agreed that the MDS membership matched movement disorders professionals worldwide, and 62.7% agreed or strongly agreed that the MDS leadership matched the movement disorders community. After viewing the membership statistics, 78.5% of responders agreed or strongly agreed that the membership matched the movement disorders community, and 63.5% believed the same for the MDS leadership.

The survey also asked for the members to rate their belief that MDS's procedures allowed for diversity, equity and inclusion regarding participation in MDS programs and leadership opportunities. 79.8% of responses agreed or strongly agreed that MDS's procedures allowed for diversity.

The Officers thoroughly reviewed the survey results, along with direct comments from members on their perceptions and ideas to ensure MDS's procedures allow us to be welcoming to all members. While we always strive to improve and involve diverse viewpoints in the Society, the Officers view the survey as a positive result for the Society.

MDS is proud to be an international society, and the leadership is always working to reach out to underserved areas and involve new members in the Society. New initiatives within MDS involve an interest form period for members to volunteer their assistance. We encourage you to visit the MDS Get Involved Webpage, which lists current and upcoming volunteer opportunities as they become available. MDS recently elected its new leadership for the 2021-2023 term, and the nominating committees rely on members to submit candidate profiles that document their credentials and interest in the elected leadership positions. The leadership will always work to include varied perspectives in leadership positions, and we sincerely hope that all members will feel welcome to submit their name and get involved with MDS.

— The MDS Officers (2021-2023)

An Interview with Francisco Cardoso: The New MDS President

— *Francisco Cardoso, MD, PhD, FAAN, Professor of Neurology, The Federal University of Minas Gerais, Belo Horizonte, MG, Brazil*
— *Bettina Balint, MD, Assistant Professor, Department of Neurology, University Hospital Zurich, Switzerland*

Francisco Cardoso, MD, PhD, FAAN

Bettina Balint, MD

Prof. Balint: Thank you very much for agreeing to this interview, and congratulations on your presidency! As the 2021-2023 President, what is your vision for MDS?

Prof. Cardoso: Many thanks for the interview, Bettina. There are three goals I will pursue during my term as MDS President. The first is to relaunch MDS in, hopefully, a post-COVID-19 era. The second, is advance even more in terms of diversity and inclusion. And the third, finally, is to focus on clinical care.

Prof. Balint: Do you have any concrete projects in mind in this regard?

Prof. Cardoso: What I mean by 'relaunching MDS' is to start in person activities. Our dear Past President, Prof. Claudia Trenkwalder, did an outstanding job in keeping the Society alive through the extremely difficulty days of the pandemic. As the global COVID-19 situation is improving it is time to start in-person activities again. Our first event will be the PAS Congress which has now been rescheduled for May 26-28 in Miami, Florida, due to the rising cases. We are also planning to gradually offer in person regional and educational offerings later this year. The most important event, though, will be the 2022 MDS Congress. I am happy to share that it will take place in Madrid, Spain on September 15-18. We are very excited over having the opportunity to see colleagues and friends once more.

As to diversity and inclusion, MDS has made a significant progress in the past few years. I am particularly proud of the role our female members play in the life of our Society. We plan to increase the participation of ethnic minorities in our leadership and educational roles.

Finally, the focus of our educational activities will be to increase the quality of care of people with movement disorders. This goal involves improving the diagnosis ability as well as to enhance the management skills of health care professionals.

Prof. Balint: What do you see as future challenges for MDS, or movement disorders as a neurological specialty?

Prof. Cardoso: Movement Disorders is a quintessentially clinical area. In the developed world, the growing fascination with lab tests is a significant challenge as it carries the risk of neglecting the core of our field. One worrisome sign of this is the decreased number of young physicians willing to pursue a Movement Disorders career in some parts of the world. This leads me back to the need to reinforce the focus on clinical care that I have alluded to in the previous questions. In low to middle-income areas of the world (that concentrate the majority of the world population) the main challenge is the lack of access to health care professionals properly trained in the diagnosis and management of movement disorders.

Prof. Balint: How did you come into the field of movement disorders? What is your personal history with MDS?

Prof. Cardoso: As a Resident in Neurology, one of my teachers, Prof. Gilberto Belisário, had trained in the U.S. and had an interest in what used to be called 'extrapyramidal disorders', although he was a general neurologist. He brought me under his wing, and I started seeing a substantial number of people with movement disorders. Looking back, the main reason for my (ongoing) infatuation with the field is the fascination with phenomenology. Another important aspect is the both Prof. Belisário and another local mentor, Prof. José Teotonio de Oliveira, had trained in the U.S. In an era where there was no such a thing as globalization, their experience opened my eyes to the imperative of having an international experience.

I moved to Houston, Texas in the U.S., where I trained in our field under the supervision of Joe Jankovic. While living in the U.S., I became engaged with MDS. This was initially as a member, but gradually I started my involvement with administration of the Society at multiple levels, including MDS Secretary, MDS-PAS Chair and, finally, President. I really need to highlight the crucial role played by several Past-Presidents in my career with MDS: Eduardo Tolosa, Werner Poewe, Andrew Lees, Chris Goetz, and Claudia Trenkwalder. The most fascinating facet of the Society activity is to be able to interact with friends and colleagues from, literally, all corners of the world.

Prof. Balint: I know of your interest and publications in the field of chorea—particularly in Sydenham´s Chorea (SC); but recently, you also published a piece about movement disorders in relation to SARS-Cov2. Can you speak a little to that, specifically how Brazil's cases relate to the rest of the world?

Prof. Cardoso: As to Sydenham's Chorea (SC), when I came back to Brazil after finishing my training in the U.S., there were still a significant number of cases of rheumatic fever in the country. There was a need to take care of many young patients with SC. At the same time, there were several scientific questions related to this condition: precise details of the underlying immune mechanism, non-motor symptoms, natural history and so on.

This led me to the field of other causes of chorea, both genetic and non-genetic forms. It is true that there has been a remarkable decrease

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An Interview with Francisco Cardoso: The New MDS President, *continued from p. 6*

of the incidence of SC. Curiously enough, it is not clear the reason for this epidemiological change that is not unique to Brazil and occurs in Africa and Indian Subcontinent as well. The improvement of public health conditions is certainly one of the causes, but it does not fully explain what has happened.

Another consequence of my involvement with SC is the interest in movement disorders related to infectious diseases. Unfortunately, Brazil was one of the epicenters of the COVID-19 pandemic. Because of the multitude of patients with this disease, we developed an interest in movement disorders related to SARS-CoV-2. Fortunately, they are not particularly common and can be ascribed mostly to metabolic encephalopathy. Not surprisingly, the most common phenomenology is myoclonus. The second most common mechanism is auto-immune process resulting in cerebellar ataxia and opsoclonus-myoclonus among others.

Finally, there is the intriguing question of a possible relationship between COVID-19 and risk of developing parkinsonism. Of course, the definite answer will be given by careful prospective follow up of people who were infected by SARS-CoV-2. The occurrence of anosmia and a few cases (including one we reported) of COVID-19 related parkinsonism suggest that something similar to post-encephalitic parkinsonism following encephalitis lethargica can occur. My view is that this possibility is unlikely since anosmia is a consequence of reversible lesion of olfactory sustentacular olfactory cells, and very few patients have developed structural CNS lesion.

Prof. Balint: You also published about Stendhal syndrome –is art close to your heart? Or, if I may ask, apart from movement disorders, what are you other interests and hobbies?

Prof. Cardoso: In Brazil, when the student finishes high school, she or he needs to decide what to pursue at the University. At that time, I was torn between going to Medical School or studying literature. I have a great appreciation for music, literature, and art and I am glad you have brought up the name of Stendhal! Although he is now known mostly for "Le rouge et le noir", the best seller during his lifetime was "La vie de Rossini". All this to say that he was fascinated by Italy. The syndrome that bears his name refers to an autonomic reaction involving tachycardia and even syncope after being exposed to artwork. He experienced this when visiting the Basilica di Santa Croce in Florence in 1817. Indeed, I have an interest in literature and am particularly fond of Marcel Proust's work. By the way, near the end of his life Proust went to an exhibition of Vermeer's paintings and had a Stendhal Syndrome when admiring "View of Delft".

The Global Parkinson's Genetics Program

— *Alastair Noyce, MD, Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom*
— *Andrew Singleton, PhD, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA*
— *Christine Klein, MD, FEAN, Institute of Neurogenetics, University of Luebeck, Luebeck, Germany*
— *Cornelis Blauwendraat, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA*
— *Huw Morris, PhD, FRCP, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, United Kingdom*
— *Ignacio Fernandez Mata, PhD, Genomic Medicine Institute, Cleveland Clinic & Molecular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA*
— *Mike Nalls, Data Tecnica International, Glen Echo, MD, USA*
— *Sara Bandres-Ciga, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA*
— *Sumit Dey, , MBPsS, Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom*

gp2 Global Parkinson's Genetics Program


Cornelis Blauwendraat

What is GP2 and when did it start?

GP2 stands for Global Parkinson's Genetics Program. GP2 is an ambitious five-year program to genotype >150,000 volunteers around the world to further understand the genetic architecture of Parkinson's disease (PD). We believe that there is still much to learn about genetic risk factors and the path to further understanding requires working collaboratively and openly sharing data, processes, and results. Officially GP2 started at the beginning of 2020 but planning for GP2 started many years before that.

Can you highlight the work done by GP2 till now?

GP2 is now about one and half years in and we laid the foundation of GP2 and established working groups that will lead GP2 towards its ultimate goals. This foundation includes creating documents and infrastructure ranging from a publication policy to analysis pipelines. We also started several strategic partnerships with other PD consortia and PD related foundations and, of course, also with the Movement Disorders Society (MDS). We set up an online learning platform with a wide variety of courses, funded 6 PhD students and 4 master's students, held a Hackathon, and started the trainee network.


Andrew Singleton, PhD

What influenced the setup of GP2?

An understanding that there were incredible biological and therapeutic opportunities to be had by expanding our genetic understanding of Parkinson's disease, and that we had the tools and skill sets to make a dramatic impact in this space. I think we also understood that while we had come a long way in Parkinson's disease genetics, we had really failed in one regard, our fund of knowledge was largely based on work in populations with limited ancestral diversity. This is not acceptable; how can we hope to treat a global disease if we only know the basis of this disease in one or two populations? We knew we had to do better and the path to doing so was to create a global collaborative network that functioned together to efficiently and fairly understand the genetic basis of the disease.

What were the major hurdles faced by GP2 during its formation and initial years?

In some ways the science is relatively straightforward - certainly it requires hard work, imagination, and a large team of smart, dedicated researchers - but we know approximately what path we're on, and what our destination looks like. We think there are, however, two big challenges, the first involves operations and compliance, this is a large and complicated project with lots of moving parts, and we have to spend a lot of time ensuring that we effectively and efficiently comply with ethical and legal requirements; some of these are ever changing, so it is a continual challenge. Second, we wanted to really democratize this work, so that it wasn't only the investigators with established skill sets and resources who could do meaningful science within GP2; we continue to place a large emphasis on providing and enabling support to a diverse group of investigators through training, resources, and infrastructure. Our aim is to level the research playing field across our global community.

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The Global Parkinson's Genetics Program, *continued from p. 8*

What are the goals of GP2?

In some ways the goal is quite simple: to dramatically expand our understanding of the genetic basis of Parkinson's disease, and to make that understanding globally relevant. This is really divided across understanding the basis of typical genetically complex Parkinson's disease where hundreds of genetic variants influence disease and the rarer forms of disease caused by single mutations. Structurally though, there are some essential aspects of how we reach that goal: democratization of data, global collaboration, safe and responsible data sharing, transparency and reproducibility, creating an actionable and useful resource, and an overarching emphasis on diversity in both the research subjects and the researchers.

Sara Bandres-Ciga

Can you tell us about the organizational structure of GP2?

In order to ensure a functional and efficient structure, GP2 is composed of a series of working groups and hubs that center on achieving specific aims and priorities within GP2. While these groups have clear aims and deliverables, they function as a continuum with shared members. These working groups are: Steering committee, Operations and Compliance, Training, Networking and Communication, Monogenic Disease Hub (including Sample Prioritization, Data Analyses, and Portal Development), Complex Disease Hub (including Cohort Integration and Data Analyses), Underrepresented Populations and Data and Code Dissemination.

Andrew Singleton, PhD

What are the major ongoing projects at this juncture of GP2?

One major goal of GP2 is the identification of novel genetic causes of PD. To this end, we have started sequencing the first set of promising samples from PD patients with a high likelihood of having a genetic origin and where known causes have been excluded. We are using WGS but will also perform long-read sequencing in a subset of patients in whom WGS fails to detect any genetic background. Another focus will be on improving our understanding of known monogenic forms of PD or those associated with strong risk factors, such as LRRK2-linked PD. Carriers of pathogenic variants will be identified through Neurobooster's custom content in both affected and unaffected individuals which will allow large-scale analyses influencing penetrance and age at onset.

Huw Morris, PhD, FRCP

We have learnt a huge amount about Parkinson's through case-control analysis, that is comparing Parkinson's cases with unaffected controls. However, we know that Parkinson's is very diverse in terms of age at onset, progression, drug response and the development of complications. We believe that some of this variation relates to genetics and we believe that understanding the genetics of variation will lead to new disease insights. In the complex group, we are working with Parkinson's research groups from around the world to harmonize core clinical data that can be analysed together with the genetic data. Collaborating with clinical researchers in PD from around the world we hope to make major developments in understanding the biology of PD and in developing new treatments.

Alastair Noyce, MD

How can professional societies like MDS contribute to GP2?

To achieve its aims, GP2 must engage with clinicians and researchers from around the world. The MDS is the largest member organization for health professionals and scientists working on PD, with over 10,000 members. GP2 has grown rapidly but in partnership with the MDS, its growth can be even greater. However, it is not just scale that a strategic partnership like this can deliver. For example, through this partnership there will be a physical GP2 presence at MDS meetings and permission to hold satellite meetings, advertising opportunities from GP2 and MDS across web-platforms and social media, as well as coordinating MDS and GP2 training content and access to training. GP2 is open to partnering with other professional organizations, where these partnerships help to achieve our overarching goals.

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The Global Parkinson's Genetics Program, *continued from p. 9*

Ignacio Fernandez Mata, PhD

Where do you see GP2 in the next 5 years?

We believe GP2 will be the largest and most diverse dataset for Parkinson's disease, facilitating the understanding of the genetic basis of PD across the world. In addition to contributing to global advancement, GP2 will also significantly contribute to local research projects, providing the genetic data necessary for their success. We believe the collaborators of GP2 will become leaders of their respective regions, with GP2 being a common thread that unites us in our endeavors.

What is GP2 doing to promote diversity in Parkinson's disease genetics research?

Historically, genetic research has failed to study non-European populations, and this is true for PD genetic research, as well. Promoting diversity is a central component of GP2 as it will fill the gaps in our knowledge about the genetic basis of PD by focusing on the regions and populations that have been underrepresented in the research. Furthermore, GP2 is determined to pay attention to the unique needs of each population to provide appropriate support and information. While there is a specific "Underrepresented Populations Working Group," the entirety of GP2 is committed to this mission by training and supporting local researchers, valuing new contributions to both complex and monogenic cohorts and supporting data analysis.

Mike Nalls

How will GP2 ensure democratization of data resources?

GP2 is working with partners at Verily/Terra and AMP-PD to leverage a convenient single sign on for data and code access. We want to reduce barriers as much as possible to make all data completely and safely analyzed in the cloud platform(s). Additionally, we are working very hard to integrate and work across data silos on a global scale with streamlined federated analysis resources, while respecting GDPR and other logistic constraints.

Sumit Dey, , MBPsS

What is the GP2 action plan for training and networking?

Alongside work to better understand the genetic architecture of PD, there is a need for greater collaboration, shared learning, and communication to maximize the GP2 potential. A major goal of GP2 is to develop training resources and opportunities that will benefit investigators and clinicians around the world to do their own research using GP2 data. In terms of training, we aim to share best practice and learning internationally across a range of existing analytic methods, as well as developing or applying new methods from other fields.

Sara Bandres-Ciga

To do so, we have created a learning management system that offers practical and theoretical courses (https://www.gp2.org/training/) to establish broad and foundation-level knowledge in genetics, bioinformatics, medical statistics and molecular biology. With networking, we want to promote the flow of research ideas and data (in all directions) across the GP2 group and to do so, we have created the GP2 Trainee Network. Furthermore, since it is key to build expertise and capacity in the field, we have offered virtual courses and conferences, PhDs and master's relevant to PD genetics for individuals from underrepresented populations. We also believe that distributing this expertise across sites is important and we will set up sabbaticals once the COVID pandemic resolves.

MDS-AS 1st Virtual Interactive Course; A Visionary New Learning Format Envisioned and Realized

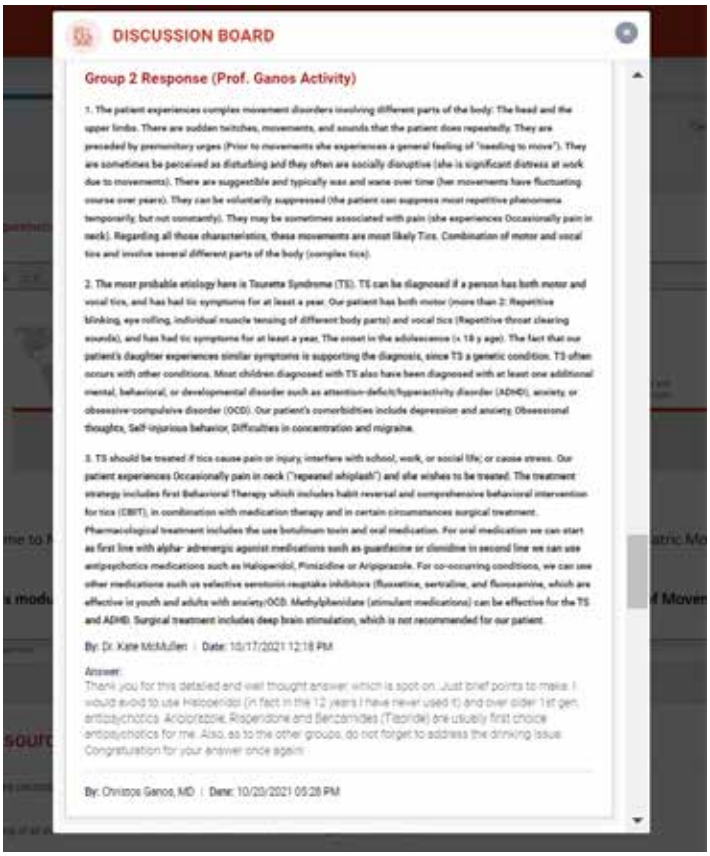
— Ali S. Shalash, MD, PhD, Professor, Ain Shams University, Cairo, Egypt

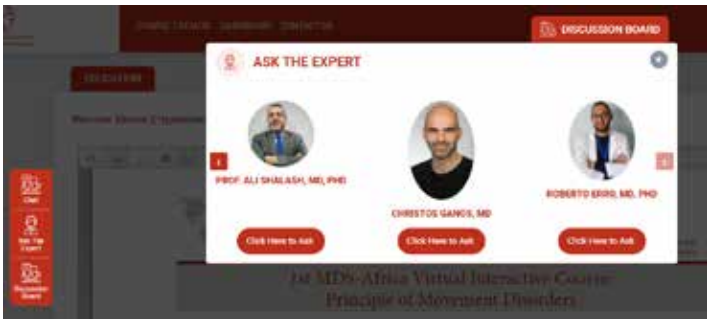
Ali S. Shalash, MD, PhD

The MDS African Section (MDS-AS) recently completed ***the MDS-AS 1st Virtual Interactive Course: Principles of Movement Disorders***, a unique 10-week pilot course that facilitated multi-dimensional interactions between learners, their peers, and global experts using the Society's Learning Management System (LMS) that launched as part of the newly enhanced MDS Education Roadmap.

The MDS-AS 1st Virtual Interactive Course, envisioned and led by Ali Shalash, consisted of 5 separate module topics each structured over a two-week period and comprised of an innovate course format. All course interactions occurred on the new MDS Learning Management System (LMS) entirely through participant group activities, participants' completion of independent work that were moderated by module faculty via the course discussion board.

Ali Shalash, Chair of the MDS-AS Education Committee and a member on the MDS-AS Steering Committee, envisioned a course to provide access to global experts and provide multiple forums for feedback. The proposal





was supported by the then MDS Education Committee Chairs and Co-Chairs, Wassilios Meissner and Ronald Postuma.

Given the recent impact of the COVID-19 pandemic, this course become even more necessary and relevant for underserved audiences across the globe.

Module Topics were structured over two weeks. During the first week, participants were instructed to review lectures presented by faculty, complete MDS articles/supplemental materials related to module topics and submit Ask the Expert questions to be answered by faculty in the course discussion board. During the second week, participants completed module activities prepared by the faculty and also prepared interesting cases for discussion. Participants were assigned into seven groups to encourage interaction and peer-to-peer collaborations. Throughout the entire module duration individualized feedback and commentary from faculty were made visible on the course discussion board for participants viewing.

The first of its kind, the MDS-AS 1st Virtual Interactive Course attracted 105 applicants, among whom 86 were selected across 29 African countries. Participants were highly enthusiastic and committed and engaged with 100% completion rate of modules' activities for which excellent answers were thoughtfully crafted. In the post-course evaluation, students indicated appreciation for the course format as the module activities and continuous engagement with faculty allowed for effective consolidation of the learned material. Additionally, 93% of students were likely to recommend this online course to a colleague. This was illustrated in several statements from students:

"This was a very educative course. I would recommend that it is offered every year with updates and a fast-track option for those who have attended the course before"; and "More people from the region can benefit from this program"

The faculty represented by a panel of internationally recognized movement disorder experts facilitated module topics (each topic led by two faculty members) and engaged with students by providing expert

MDS-AS 1st Virtual Interactive Course; A Visionary New Learning Format Envisioned and Realized, *continued on p. 12*

MDS-AS 1st Virtual Interactive Course; A Visionary New Learning Format Envisioned and Realized, *continued from p. 11*

guidance and mentorship throughout the two-week module duration. Even faculty enjoyed their unique roles and appreciation for this new course format. Francesca Morgante who served as the faculty for Module 4 (Hyperkinetic Disorders: Dystonia; Chorea/Drug Induced) shared:

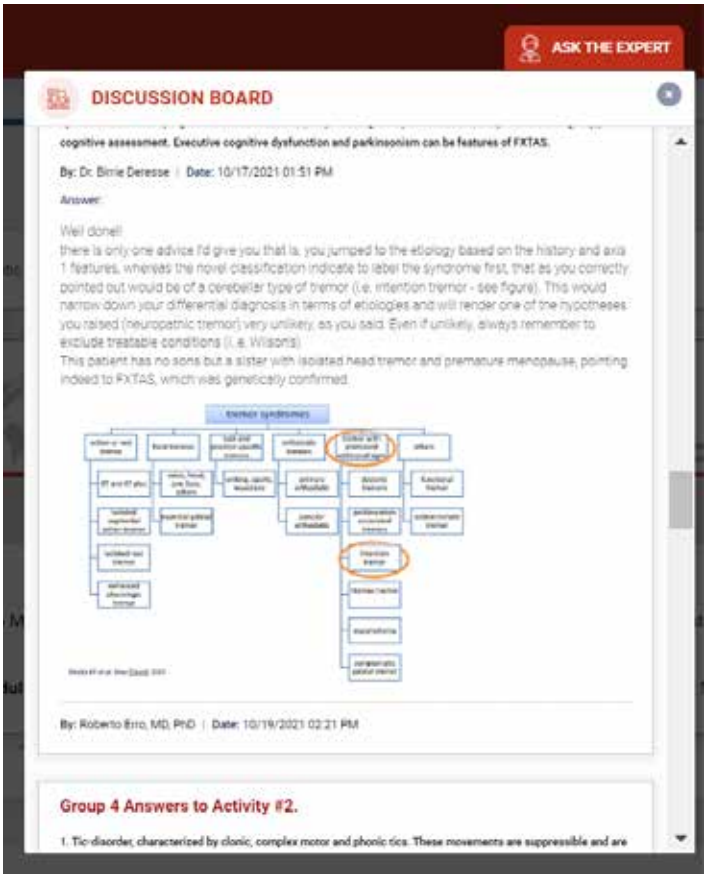
"I was impressed by the level of the participants when reading the [group] answers to the case scenario [activity]. Also, they have interacted a lot by asking many questions. I like the idea of an interactive dashboard [course platform] where we can add all educational material. Surely this formula is a great success"

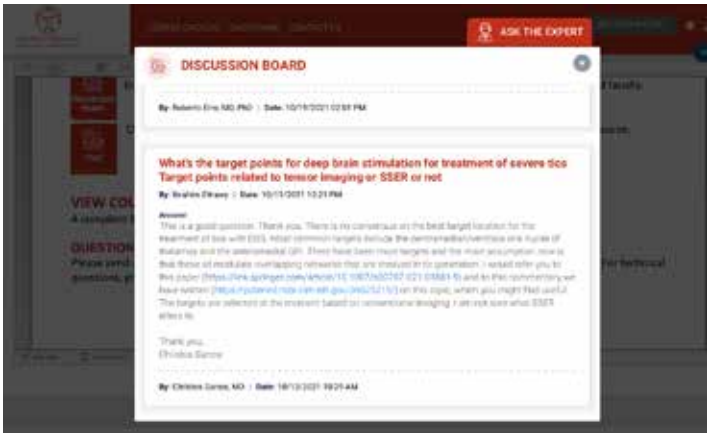
Susanne Schneider who led Module 4 alongside Prof. Morgante shared:

"Thank you for inviting me to contribute to this fantastic course. It has been an honor and pleasure. I am excited to see new learning formats made possible through the MDS Education Roadmap. And more excited to see that there is an increasing number of movement disorders experts in the African region. I agree with what Francesca said about the high quality of cases. It was good to see the sensible answers given by the teams and the high-quality cases they had submitted".

The MDS-AS 1st Virtual Interactive Course was a successful program due to the vision of Ali Shalash, the mentorship of the MDS Education Chairs, the engagement and dedication of the invited faculty, the secretarial support from the MDS-AS Liaison, Nura Said, and the dedication and enthusiasm of the participants. Through the investment in the MDS Education Roadmap is providing new and interactive learning formats.

The MDS-AS also looks forward to organizing a second iteration of this highly successful course as part of their 2022 regional education programming.





MDS Virtual Congress 2021: *Towards Personalized Medicine for Movement Disorders*

— *Vincenzo Bonifati, MD, PhD, Professor, Erasmus University Medical Center, Chair, MDS Congress Scientific Program Committee, 2019-2021, Rotterdam, The Netherlands*

Vincenzo Bonifati, MD, PhD

The MDS Virtual Congress 2021 (September 17-22, 2021) was a great success with an amazing number of 13,000 registered participants from 143 countries. The theme of this year was *"Towards Personalized Medicine for Movement Disorders"*, and the program included 64 scientific sessions, featuring 221 faculty and chairs from 38 countries, as well as 1,320 accepted abstracts and 16 guided poster tours. Of note, the Virtual Congress platform will remain available to all MDS members through April 1, 2022, including access to all on-demand sessions, posters, guided poster tours, exhibits and sponsored symposia.

While we miss the beauty of traveling and the joy of meeting colleagues and friends in-person, during these challenging times of the COVID-19 pandemics the virtual format allows our society to continue to fulfil its mandates of disseminating knowledge, promoting research and ultimately improving the management of our patients worldwide. Leveraging the experience gained during the 2020 edition, the 2021 Congress was intended as a virtual event from the beginning of its development. The Congress Scientific Program Committee (CSPC) has been working hard to put together the best program possible in terms of scientific excellence, while at the same time promoting the younger talents, and remaining mindful of the importance of the gender balance and the global spread and diversity of MDS.

The 64 sessions were all great and highly attended, and many more views are expected 'on demand' in the next few months. Among the highlights of 2021, I like to mention two memorable Fahn and Marsden Award lectures, presented immediately after the Opening Ceremony on Sept.17, respectively, by Dr. Oscar Gershanik, Argentina (titled: *Opening the Pandora's Box of Parkinsonism*) and Dr. Etienne Hirsch, France (titled: *Seven Solutions for Neuroprotection in Parkinson's Disease*). Furthermore, the 'Neuroscience Bridges' award lectures were presented by Dr. Madeline Lancaster, United Kingdom (titled: *Investigating Human Brain Development and Function Through the Lens of Cerebral Organoids*), and Dr. Don Cleveland, USA (titled: *Development of Designer DNA Drug Therapy for Neurodegenerative Disease*), on two hot topics in the current neuroscience research, in which they did pioneering research. The highly popular Video Challenge was led this year by Dr. Tony Lang and Prof. Kailash Bhatia as Masters of Ceremony, together with a stellar panel of expert discussants.

Also this year, we aimed at highlighting the richness and diversity of the original scientific research. In addition to sixteen thematic Guided Poster Tours, 36 abstracts selected from those with the highest scores (Top Abstracts) were given the opportunity to be presented during the Parallel sessions, together with the invited lectures, and the presenters could also join the live discussion and question and answer session together with the invited faculty.

The other overarching aim was to promote and facilitate networking, by a number of features embedded in the virtual platform, such as the Networking Lounge, a great Young Delegates Hub, several 'Meet the Expert Roundtable Discussions', and other discussion boards. Furthermore, after Plenary and Parallel sessions, a new feature termed 'post-session discussion' moderated by Young Members from several countries, offered further opportunity for networking and conversation to discuss the learnings and highlights of the sessions.

In addition to the above considerations, and in my view one of the most valuable aspects of going virtual with no registration fee has been the fact that we could reach unprecedented numbers of colleagues and students in underserved areas of the world, who could not have afforded travelling to an in-person International Congress.

After the 2021 Congress, it is time for me to pass the baton to the incoming CSPC chair, Dr. Steven Frucht, who has taken on the challenge of developing the International Congress of the next two years. My deepest gratitude goes to Claudia Trenkwalder, our President, and to Oscar Gershanik, Chair of the Congress Oversight Committee for 2019-2021, to the MDS Officers and the MDS leadership, for their trust and support; to the members of the 2019-2021 CSPC, all the Speakers and Chairs, and, last but not least, to the MDS International Secretariat, particularly Kate Hausner, Jenny Quebbeman, and Jennie Socha, for their amazing work and great dedication. It has been a pleasure working with you!

Thank you all very much, please keep enjoying the 2021 Congress on-demand, and I look forward to seeing you all in 2022!

Reflections on Being Awarded the 2021 Stanley Fahn Presidential Lecture Award: Oscar Gershanik

— *Oscar Gershanik, MD, Professor & Scientific Director, Institute for Neuroscience, Buenos Aires, Argentina*

Oscar Gershanik, MD

Being invited to deliver this lecture is one of the highest honors one can aspire as a Neurologist dedicated to the field of Parkinson's disease and Movement Disorders. For me it has been the culmination of a career spanning 45 years. The name Stanley Fahn carries for me an important symbolic value, both from an academic and personal perspective. Dr. Stanley Fahn epitomizes what a clinician-scientist should be. During my entire professional career his name has been associated with our sub-specialty, having contributed to the advancement of our field in every conceivable aspect.

Whether directly or indirectly he has been the mentor of many generations of Movement disorder specialists. He has been an example to follow as a clinician-scientist, as well as for his personal qualities. Above and beyond that he has been and is a dear colleague and a personal friend. Despite his professional and academic stature, his modesty and understated demeanor, make him an endearing figure in our Society. It is admirable to see Stan seated in the first row of the Congress auditorium, at every single meeting, taking notes, thirsty for new knowledge, his considerable experience notwithstanding.

The Stanley Fahn Presidential Lecture was an opportunity to provide a personal view, based on my own experience, of the challenges involved in the diagnosis of Parkinsonism, which has become, through the years, an ever-expanding universe. As the title of my lecture stated, a true "Pandora's Box".

In the absence of robust and definitive biomarkers, we have to rely on distinctive clinical features, clinical criteria, and supportive elements, both from the personal and family history, the age, mode of onset, clinical course, imaging findings, response to dopaminergic therapy and in some cases, specialized laboratory determinations.

I found it very helpful to develop a taxonomy based primarily on whether the clinical features are typical, as seen in Parkinson's disease (PD), or atypical. However, as experience shows us, many atypical disorders may initially present with features indistinguishable from PD, and contrariwise PD may not present itself with the classical features we recognize as typical. The same applies to the traditionally labeled "Atypical Parkinsonisms" which in some cases have atypical clinical features at onset. That led me to separate Parkinsonisms into the following categories: "Typical Parkinsonism", "Atypical-typical" Parkinsonism, "Typical-atypical" Parkinsonism, "Atypical-typical-atypical" Parkinsonism, and a final category encompassing a wide range of disorders (genetic, metabolic, autoimmune, infectious, vascular, etc.) which I label as "Atypical-atypical" Parkinsonisms (1).

To underline the difficulties, we face in diagnosing PD or "Typical" Parkinsonism I refer the readership to the paper published in 2014 by Adler et al which found that only 26% of "possible" PD cases diagnosed on first visit and 53% of "probable" PD cases with less than 5 years of disease duration were found to have pathologically confirmed PD (2). I believe that says it all.

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Reflections on Being Awarded the 2021 C. David Marsden Presidential Lecture Award: Etienne Hirsch

— Etienne Hirsch, PhD, ICM - Hospital De La Salpetriere, Paris, France

Etienne Hirsch, PhD

I am greatly honored to have been selected to receive the C. David Marsden Presidential Lecture Award at the MDS Virtual Congress 2021. It has been a real privilege to be able to honor the memory of such a great clinician and scientist in the field of Parkinson's disease. His work was highly influential to my research, especially for studies on the mechanisms of neurodegeneration in PD and the identification for deleterious factors involved in cell death such as neuromelanin, rise in iron and oxidative stress.

I had the privilege to meet Dr. Marsden at the beginning of my career at several congresses and he suggested to me to focus my work on the role of neuroinflammatory processes in the early 90's. This was highly original at that time and it has driven the way we conduct research for almost 30 years in my team.

The title of my lecture is, "Ways to improve neuroprotection in Parkinson disease". I chose this topic because it allowed to include some concepts developed by Dr. Marsden himself and to give an overview of my own research. I tried to discuss the reasons for the failure of the clinical trials and to provide solutions to improve the efficacy of neuroprotection in PD. Seven solutions to improve neuroprotection in Parkinson's disease can be found in a review article published this year in Movement disorders (2021; 36(2):306-316).

Some of the solutions are:

1. to perform studies on subgroup of patients with known etiology,
2. to test neuroprotection as soon as possible during the evolution of the disease,
3. to deliver drugs in the right place in the brain, the right cell and the right organelle,
4. to combat dopaminergic but also non-dopaminergic cell death,
5. to choose drugs counteracting both initial cause and propagation of cell death,
6. to use cocktails of molecules or multifunctional drugs and
7. to take into account changes in BBB.

I would like to thank Claudia Trenkwalder, MD and the program committee for this award.

Virtual Congress 2021: Junior Awards Recipient: Alba Tristán Noguero

— Alba Tristán-Noguero, PhD, Postdoctoral Researcher, Fundació Sant Joan de Déu, Barcelona, Spain

Alba Tristán-Noguero, PhD

Dr. Alba Tristán Noguero has been awarded the MDS Junior Award 2021 for the work presented at the MD SVirtual Congress 2021, "Cellular Modeling of Tyrosine Hydroxylase Deficiency Recapitulates Patient Phenotypes and Response to Treatment ". She is currently working as a postdoctoral researcher at the Sant Joan de Déu Hospital within the synaptic metabolism group led by Dr. Àngels García Cazorla. This collaborative work has been developed in the laboratory of Dr. Antonella Consiglio at IDIBELL.

The awarded work describes the first human cellular model of Tyrosine Hydroxylase deficiency (THD) based on the technology of induced pluripotent stem cells (iPSC). Tyrosine Hydroxylase deficiency is an inborn error of metabolism characterized by a defect in the enzyme tyrosine hydroxylase, which catalyzes the rate-limiting step in the biosynthesis of dopamine (DA). Two clinical phenotypes have been described: i) "Type A" which refers to a progressive hypokinetic-rigid syndrome and dystonia with an onset in infancy or childhood and L-Dopa responsiveness; ii) "Type B" which produces a severe early-onset encephalopathy, mental retardation, oculogyric crises and parkinsonism with sub-optimal L-Dopa response.

We established induced pluripotent stem cells (iPSCs) lines from fibroblasts derived from one THD Type A patient, one THD Type B patient, two healthy young individuals and one isogenic control where the mutation was corrected with CRISPR/Cas9 technology. Those iPSC were further differentiated to dopaminergic neurons (DAn). THD Type A and B neurons exhibited THD-related phenotypes such as decreased TH protein expression, reduced levels of DA metabolites and altered expression levels of DA-related genes compared to control iPSC- derived neurons. In addition, in this spontaneous THD human model, both type A and B cultures presented a reduction in the total neurite length. Moreover Type B shows a reduction in TH neuronal arborization whereas Type A mutant neurons present an abnormal proximodistal TH gradient in neurites. L-Dopa + Carbidopa treatment in THD A derived neurons, normalized TH protein expression, DA metabolites levels and neuronal phenotypes. However, the treatment did not rescue neuronal deficits in THD B derived neurons, thus suggesting that early pathological events in THD B mutant neural cells may be crucial for the pathogenesis of the disease.

This human iPSC-based model mimics not only the disease phenotype observed in THD patients but also the response to the existent treatment. Therefore highlighting new possible molecular mechanisms of the disease that could disclose new opportunities for future preclinical studies.

2021 MDS Honorary Membership Award Recipient: Ray Chaudhuri

— *Ray Chaudhuri, MD, FRCP, DSc, Professor and Director, Movement Disorders, The Maurice Wohl Clinical Neuroscience Institute, King's College, London, United Kingdom*

Ray Chaudhuri, MD, FRCP, DSc

From the days I grew up in India in Kolkata, research was driven into me by my father, a professor of medicine with a keen interest in neurodegeneration. It so happened that in my training period as a junior doctor in neurology working in Leicester in the midlands of the UK, I was asked to take over a project on apomorphine injection in the late 1980's. I did it and the data was published in Lancet in 1988, the same year Andrew Lees, Katarina Stibe and colleagues published their seminal work on apomorphine infusion and Parkinson's Disease in Lancet. I had noted the dramatic effect apomorphine showed when reversing off related dysphoria, pain, fatigue and anxiety. I was hooked on work in Parkinson's non-motor arena.

In the 1990's, I moved to London to work in the Pickering unit at St Mary's hospital and the National Hospital of Neurology at Queen Square to start my research career addressing autonomic dysfunction in humans, healthy and those with neurodegeneration. I then moved to Kings College in London where I still am and it is here my long awaited research in nonmotor symptoms (NMS) of PD really took hold, inspired by the comments of a patient of mine . The patient, a famous female saxophone player of the seminal 1970's jazz band paraphernalia, told me "can you do something about my pain, sleep and memory ? I am so worried !". She had been recently diagnosed to have PD.

I realized there was no specific guidelines for management of these symptoms in PD, there were no high quality trials and most importantly no comprehensive or "holistic" patient or health care professional (HCP) tools available to address these range of nonmotor symptoms that blight the lives of people with Parkinson's although such tools and evidences were well established to manage the motor symptoms of PD. This led me to assemble what in hindsight was the first international truly multidisciplinary team of HCP's (neurologists, neuropsychiatrists and psychologists, nurse specialists, sleep physicians, basic scientists, epidemiologists, patient representative) from across the globe to assemble in a meeting in the periphery of London to discuss this massive unmet need and ways to address these issues. This meeting in 2003-2004 led to the birth of now globally used NMS questionnaire, still the only PD validated patient completed tool to declare NMS while a series of global validation of the NMS scale (NMSS) followed with superb clinimetrics support from the group of my colleague and friend Pablo Martinez-Martin in Madrid.

We set up the worlds first cohort study entirely focused on validated NMS assessment using NMSS and other motor and specific NMS measured to track the longitudinal natural history of NMS as well as stratifying patients using NMS scores. The NILS global cohort study is now 12 years in progress having produced important data such as characterization of early morning off period, development of the first pain scale for PD, helping in cluster analysis for nonmotor subtypes as well as prognostic work such as emergence of the concept of idiopathic constipation can be linked to cognitive dysfunction as a nonmotor predictor. Measurement is now key to the concept of value based healthcare and I can now rightfully state that these initial measures at quantifying and recognizing the burden of NMS as opposed to focusing on a single NMS changed the landscape of clinical care and research in PD.

NMS is now a well established part of all Parkinson's related clinical meetings and the Movement Disorders Congresses and I was lucky to be enabled by the MDS to set up the first research study group, the MDS nonmotor PD study group (Non-Motor Parkinson's Disease Study Group) which is now one of the largest of the Society and spans membership in over 20 countries. In addition, drug development programmes of pharmaceutical industries are also increasingly considering NMS measurements as an outcome measure while in many countries such as the UK national mandatory audit protocols include NMS as a quality standard. Another key development and honour is that in 2017 the MDS commissioned our group to develop a more updated version of the NMSS which has now been developed and published; the MDS-NMS which I hope will become mandatory measure of the NMS burden and characterization in clinical trials across the world. I cannot thank the presidents of the MDS and the executives for support of our work.

The work carries on, and we all now recognize the critical role of some NMS in the prodromal phase of PD where precise characterization may hold the key to successful neuroprotection trials. I and others have championed the concept of personalized medicine encompassing genomic precision medicine , nonmotor subtype based delivery as well as pharmacogenomic medicine underpinned by enablers such as bodyweight, age, ethnicity, personality and comorbidity, the so called "circle of personalized medicine". One of these strategy is specific nonmotor subtype based treatment and has been highlighted in several reviews

I would very much hope NMS assessment becomes routine in clinical practice and we slowly move away from the "one size fits all" dopaminergic approach to management of PD, a heterogeneous condition, to a truly personalized delivery of care in future. Dr. James Parkinson was born and lived in my city London, not far away from where I practice and identified a range of NMS in all his cases described in his essay. Two-hundred and fourteen years have passed since he wrote his masterpiece and we need now to ensure that management of Parkinson's becomes a truly 21st century concept embracing care of non-motor and motor symptoms together.

Virtual Congress 2021: The Young Delegates Hub: A Virtual Space Created to Maximize the Congress Experience

— Margherita Fabbri, MD, PhD, Neurologist, Toulouse University Hospital, Toulouse, France
— Shaimaa El-Jaafary, MD, Associate Professor of Neurology, Cairo University, Egypt

Margherita Fabbri, MD, PhD

Shaimaa El-Jaafary, MD

The MDS Young Members Group is a special interest group that supports and expands the network of outstanding young MDS members. It addresses members from different backgrounds, including neurologists, basic scientists and other allied health care providers who have an interest in the field of movement disorders.

This highly active group is led by the following Steering Committee members: Margherita Fabbri, MD (Chair), Tomás De La Riestra, MD (Co-Chair), Bruno Bergmans, MD, PhD, Miryam Carecchio, MD, PhD, Shaimaa Ibrahim El-Jaafary, MD, Michele Matarazzo, MD, Roopa Rajan, MD, DM, Houyam Tibar, MD, PhD-Candidate, Nirosen Vijiaratnam, MBBS, BMedSci, FRACP, Prof. Bastiaan Bloem, and MDS Secretariat liaison, Drew Whalen.

Annually, at each International Congress of Parkinson's Disease and Movement Disorders®, the MDS Young Members Group is an active part of the Congress, offering different activities, in order to reach members of the target age from all over the world. Traditionally during in-person events, they participate in pavilion talks, young members' committee meetings, and young member networking events. Unfortunately, these activities were not possible this year due to the virtual format of 2021.

However, there was a long discussion on how to keep the MDS Young Members Group equally as engaged during the MDS Virtual Congress 2021 as they were before the pandemic. Hence the idea of the Young Delegates Hub!

The Young Delegates Hub was created to provide opportunities for networking between attendees of the MDS Virtual Congress 2021. It included focused discussions with other young members and senior faculty on a variety of topics and provided easy access to scientific content.

The Young Delegates Hub included three main areas that housed a variety of resources: Virtual Congress Education and Resources, Networking and Connecting with Peers, and MDS Information.

Virtual Congress Education and Resources

Within the first section of the Young Delegates Hub the visitors found the Cyber Talks. These were short on-demand educational sessions given by MDS Leadership featuring a variety of topics such as the MDS Education Roadmap and the LEAP program. Cyber Talks also included: how to submit a paper to a journal, the MDS study groups and how to get involved, how to pursuit a career in movement disorders, finding the suitable fellowship and a good mentor, career advice and learned lessons, and MDS offers for basic and how to combine clinical and research activities.

These talks can still be watched anytime and will remain on the Hub until April 1, 2022. Additionally, in this area, there were suggestions for sessions within the Congress scientific program that could be of interest for Young Members. It also included the roundtable discussion.

Networking and Connecting with Peers

In the second area, Networking and Connecting with Peers, there included a general chat area for visitors to interact with other colleagues as well as a Twitter feed for the hashtag #YDHub. Throughout the day, MDS Leadership were available on this general chat board for 30 minutes and interacted with the young members through the chat to answer a variety of questions about clinical findings and diagnostic methods, the career of movement disorders, further questions on the society and active involvement as well as more information about the LEAP program. The "Ask the Professor" schedule was also listed in this area with two faculty available each day for a Q&A session.

MDS Information

Lastly, in the third section of the Hub, MDS Information, and the visitors could find out how to become more involved with MDS, learn about upcoming courses and how to become a member of the Society if they aren't already.

The last day on the MDS Virtual Congress 2021, the MDS Young Members Group and the Steering Committee Members got together (virtually) for an interactive event for networking and social interaction including introducing all members and playing short videos by participants on their activities during the pandemic. Then participants recapped descriptions of the objectives of the MDS Young Members Group including the past and the current activities, current projects, and how to join and actively participate as a member.

Overall, **the Young Delegates Hub acted as an excellent virtual space for the** activities of the attendees and visitors who found the information and resources on the hub useful at the MDS Virtual Congress 2021.

Virtual Congress 2021: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?

In the plenary session at the MDS Virtual Congress, Patrik Brundin and Alberto Espay discussed the question: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?

— Patrik Brundin, MD, PhD, Deputy Chief Scientific Officer, Van Andel Research Institute, Grand Rapids, MI, USA

Patrik Brundin, MD, PhD

YES:

In 1912, Fritz Jakob Heinrich Lewy described intraneuronal hyaline inclusion bodies in PD that became known as Lewy bodies and Lewy neurites, depending on their intracellular location. In 1997, alpha-synuclein was identified as the main protein constituent of Lewy pathology. In Lewy pathology, alpha-synuclein is present as misfolded fibrils that are considered the result of gradual assembly of oligomers into small protofibrils, although several other proteins and lipids are also found in these inclusion bodies. While these observations are fundamentally important for the diagnosis (post-mortem) of PD and might shed light on the pathogenesis of the disease, they do not explain if Lewy pathology is mechanistically involved in the disease process. Some would argue that alpha-synuclein aggregates might just be an epiphenomenon indicating that the cells are under some form of stress, or that they are protective by sequestering potentially toxic alpha-synuclein oligomers or disarming invading pathogens.

Genetics might shed some light on the possible causative role(s) of alpha-synuclein in adult-onset progressive neurodegenerative diseases. There are several facets of genetic evidence linking alpha-synuclein to neurodegenerative diseases. For example, several rare point mutations in the alpha-synuclein gene – which are inherited in an autosomal dominant fashion – are associated with adult-onset neurodegenerative conditions that include parkinsonism as a feature. Furthermore, duplications and triplications of the alpha-synuclein gene locus, leading to elevated cytosolic levels of the protein, are found in rare familial forms of neurodegeneration with parkinsonism. The greater the gene dosage, the earlier the onset of disease and the more rapid the progression of symptoms. These findings indicate that mutations that make the protein more aggregation-prone lead to neurodegenerative disease, and that highlights the important fact - merely the presence of increased alpha-synuclein causes predisposition to misfolding of the protein and neurodegeneration.

Furthermore, genome wide association studies (GWAS) in sporadic PD have consistently identified a relatively strong association between polymorphisms in the genome close to the alpha-synuclein gene locus and increased PD risk. There is some evidence that the risk alleles are related to slightly increased levels of alpha-synuclein expression, which would be in line with observations in people with gene multiplications. Finally, several other gene loci identified in GWAS as being associated with increased PD risk are located close to genes involved in the lysosomal-autophagy pathway, which is one cellular mechanism that controls the accumulation of alpha-synuclein, adding further weight to the idea that alpha-synuclein aggregation might be involved in the pathogenesis of sporadic PD. Finally, normal aging is the greatest risk factor for PD, and studies in normal non-human primates and human brains have shown that soluble alpha-synuclein levels in substantia nigra dopamine neurons increase with age.

Additionally, the historical diagnosis of PD frequently included hyposmia and constipation as early signs, which suggests that the disease might first affect olfactory structures and enteric nerves. Notably, aggregated alpha-synuclein is a frequent finding in enteric nerves and Lewy pathology is often abundant in olfactory structures in early PD. This tentatively suggests that alpha-synuclein might first misfold in these structures. Braak and colleagues suggested that these anatomical sites were trigger sites for the pathogenesis and that the pathology then slowly spread along neural tracts to other parts of the nervous system.

Consequently, the Braak team proposed that most PD patients will exhibit a stereotypic anatomical pattern distribution of Lewy pathology in accordance with six predefined stages related to the duration of the disease and severity of symptoms. Since histopathological examination of patient samples can only be done postmortem, and it is not possible to follow the progressive development of Lewy pathology using in vivo imaging, the concept of stereotypical Braak stages has not been examined in a more definitive fashion. Some subsequent studies have also shown that not all patients adhere to the patterns of pathology proposed by the six Braak stages.

Nonetheless, Braak staging has provided a conceptual framework which has been interesting to use when trying to understand how PD pathology progresses over time. While Braak and coworkers did not identify the "propagating factor", findings in experimental animals (described below) several years later indicate that alpha-synuclein aggregates in the gut and olfactory bulb can trigger a progressive aggregation, possibly through a prion-like propagation of misfolded alpha-synuclein species, in interconnected structures in the brainstem (including the substantia nigra) and forebrain. Cell culture studies have convincingly demonstrated that misfolded alpha-synuclein can indeed move from one neuron to another and cause endogenous alpha-synuclein in the recipient cell to aggregate via a "permissive templating" mechanism.

Virtual Congress 2021: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?, *continued on p. 20*

Virtual Congress 2021: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?, *continued from p. 19*

An important question is whether alpha-synuclein aggregates are both necessary and sufficient for PD to develop? Several studies over recent years have shown that alpha-synuclein aggregates are present in all familial forms of Parkinsonism that involve point mutations or multiplications in the alpha-synuclein gene. However, in other forms of inherited parkinsonism such as those associated with mutations in the LRRK2 or parkin genes, Lewy pathology is present in around half or none, respectively, of the patients. In large series of autopsies of sporadic PD where no familial inheritance of gene mutations has been identified, it is estimated that 92-100% exhibit Lewy pathology in the brain at the time of death.

It is also notable that the presence of Lewy pathology in cortical regions has a high (around 90%) sensitivity and specificity for dementia in people with PD, which tentatively suggests that the aggregates are either directly involved in the development of cognitive decline or represent markers for another related pathogenic process that causes the symptoms. Recent studies have shown that there are aggregation-prone assemblies of alpha-synuclein in the cerebrospinal fluid of PD patients that can lead to generation of more alpha-synuclein aggregates in so-called alpha-synuclein seeding assays. The emerging picture is that these seeding assays can identify patients with PD and related synucleinopathies with a high degree of sensitivity, suggesting that the presence of aggregation-prone alpha-synuclein in the central nervous system is closely linked to disease. Taken together, the current neuropathology and seeding assay data suggest that Lewy pathology containing aggregation-prone alpha-synuclein species can be viewed as "necessary" in almost all sporadic PD cases. However, at autopsy the brains of around 8-12% of elderly people contain Lewy pathology ('incidental Lewy body disease') without any evidence of neurological disease prior to death. This suggests that Lewy pathology is not "sufficient" for the clinical neurological features of PD to develop.

That said, independent studies have shown that individuals with incidental Lewy body disease at death have fewer dopamine neurons in the substantia nigra, which can be taken to suggest that they are on a path towards PD but have not yet reached a critical threshold for nigral cell death required for motor deficits to develop. Thus, it has been argued these people were on a path towards clinical features of PD but died before the disease process had significantly advanced to cause motor deficits.

So far, we have described several observations from human genetics and tissue samples which show that alpha-synuclein is strongly associated with PD. Have animal models taught us anything about the potential role of alpha-synuclein in PD, and have they provided further mechanistic insight into where alpha-synuclein plays a role in the pathogenic cascade? A very large body of experiments in numerous animal species over the past two decades have demonstrated that transgenic overexpression of wildtype or mutant alpha-synuclein leads to the development of Lewy-like pathology in neurons. This artificial overexpression can be achieved either by germline manipulations ("transgenic mice") or by intracerebral injections of viral vectors that express alpha-synuclein. Generally, in animal models, high alpha-synuclein protein expression levels and point mutations (like those seen in patients) are associated with more extensive and rapid development of pathology.

Moreover, in several models there is progressive loss of neurons over time, analogous to what is seen in human patients. During the past decade, it has also been shown that injections of misfolded alpha-synuclein, either generated from Lewy bodies derived from patient brains or from recombinant alpha-synuclein protein allowed to aggregate in a test tube, can trigger the misfolding of endogenous alpha-synuclein in neurons. The resulting aggregates stain positive for numerous markers that are characteristic of bona fide Lewy bodies. These findings are consistent with observations of Lewy bodies in dopamine neurons transplanted into the striatum of PD patients, a decade after the grafting surgery.

By contrast, grafted dopamine neurons did not contain Lewy pathology in patients who died two to five years after transplantation surgery, which led to the idea that alpha-synuclein aggregates had propagated from the host brain to transplant in a prion-like fashion. Notably, injections of alpha-synuclein fibrils can be made into the striatum, gut, olfactory bulb, peripheral sites (liver, muscle, intraperitoneal cavity, etc) of experimental animals, and they typically result in the progressive development of Lewy-like pathology in the central nervous system over weeks to months after the injection. Accumulating evidence supports that the spread of Lewy pathology is dependent upon axonal transport and trans-synaptic propagation of aggregation prone alpha-synuclein conformers, although some recent studies suggest that migrating glial cells might also participate in the spread of aggregated proteins. Notably, many animal models of synucleinopathy exhibit signs of neuroinflammation, as is also the case in human PD brains. Furthermore, neuroinflammation has been shown in laboratory settings to increase alpha-synuclein accumulation and aggregation, which is suggestive of a vicious cycle. Most importantly, the development of the Lewy-like pathology has been shown to correlate with a variety of neurological deficits depending on the anatomical regions involved, either due to the dysfunction, or death of neurons.

In summary, numerous studies in a wide variety of experimental animal

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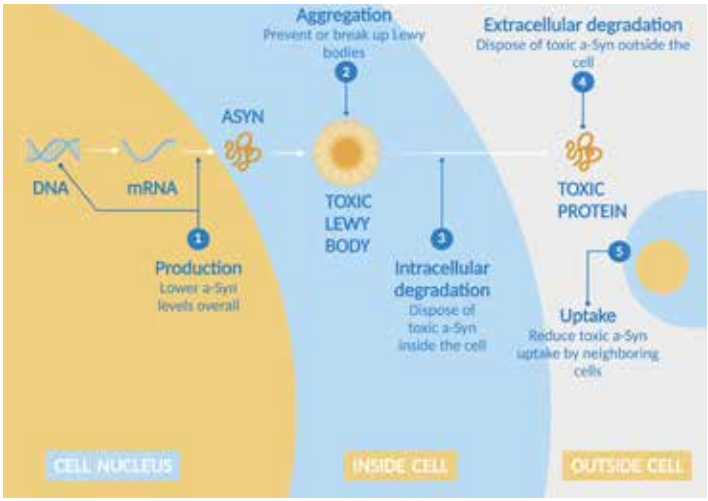
Virtual Congress 2021: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?, *continued from p. 20*



Schematic illustrating five ways in which experimental therapeutics that currently are in clinical development or already in human trials are targeting alpha-synuclein pathology. Modified from Brundin ***et al*** *(2017) Therapeutic approaches to target alpha-synuclein pathology.* ***Exp Neurol*** *298, 225–235.*

models have shown that artificial overexpression of alpha-synuclein and the injection of alpha-synuclein fibrils can trigger Lewy-like pathology and neurodegeneration, which supports the idea that alpha-synuclein aggregation might play a role upstream in PD pathogenesis. A critique of these types of experiments is often that the concentration and total amounts of alpha-synuclein that are injected by far exceed what is seen in the brain of PD patients. However, it needs to be emphasized that most of the injected material is most likely cleared within a few days and the gradual development of Lewy pathology in interconnected brain structures is entirely dependent upon the presence of endogenous alpha-synuclein that can use misfolded molecules as a template. Unsurprisingly, this type of propagation of alpha-synuclein pathology does not occur in animals that are null mutants for alpha-synuclein.

Considering the substantial body of aforementioned evidence from genetics, neuropathology and experimental cell and animal models that points towards alpha-synuclein aggregation being associated with neural dysfunction and death, the pharmaceutical industry is currently assessing whether alpha-synuclein is a valid therapeutic target for PD. As a result, several programs that target at least five principally different steps in alpha-synuclein pathology are being developed.

First, some approaches are designed to reduce the expression levels of alpha-synuclein, either using genetic strategies or small molecules. In different animal models of PD, reducing the levels of endogenous alpha-synuclein has been found to be neuroprotective. There has been justified concern that excessive reduction of alpha-synuclein levels could lead to undesirable side effects. While alpha-synuclein knock out mice have a relatively normal phenotype, and injections of antisense oligonucleotides in the adult mouse brain appear to have no major side-effects, the use of viral vectors to reduce alpha-synuclein via siRNA has been suggested by some studies to lead to neuronal death. This might be related to inflammation coupled to the use of viral vectors, but it is also possible that such purported toxic effects can be reduced by a less extensive knockdown of the alpha-synuclein protein. One concern is that the role of alpha-synuclein in the immune system is still not well understood and any therapy that also reduces alpha-synuclein in these cells could potentially have unexpected side effects.

Second, approaches that prevent the intraneuronal misfolding (e.g., by chaperone proteins) are being tested. Third, treatments focused on enhanced degradation of intracellular alpha-synuclein, especially aggregated assemblies, are another priority. These frequently involve acting on the lysosomal-autophagy pathway. One challenge with this approach is that the lysosomal-autophagy pathway plays an integral role in the function of most cells throughout the body, and therefore, undesirable side-effects of drugs that potentially target its activity are a potential concern.

Fourth, several clinical development programs are focused on degradation of extracellular alpha-synuclein. These include numerous programs that use active and passive immunization against different epitopes present on aggregated alpha-synuclein, in an attempt to reduce aggregates. While data from several early trials have indicated that immunotherapy against alpha-synuclein aggregates is safe and well-tolerated, this approach saw a setback in early 2021, when one of the clinical trials targeting alpha-synuclein oligomers with monthly antibody infusions did not meet its primary endpoint. At the same time, it is important to emphasize that only a small fraction (estimated at <1%) of the infused antibody is predicted to reach the central nervous system. Several immunotherapy programs will present results from Phase II trials in the coming two years. When evaluating these, it will be important to consider which precise epitopes on alpha-synuclein assemblies are being targeted and how much of the antibody is reaching the intended neurons.

Fifth, one emerging therapeutic target is the process whereby potentially pathogenic alpha-synuclein assemblies are taken up by neurons from the extracellular space, which could be a crucial step in the proposed prion-like propagation of pathology described above. By slowing the propagation of pathology from one neuron to another, it is conceivable that the progression of symptoms would decelerate, and the types of symptoms associated with advanced disease stages (e.g., cognitive decline) might be prevented. However, the cellular mechanisms that underlie cell-to-cell transmission of alpha-synuclein are yet to be identified, with multiple contenders in the running (e.g., tunneling nanotubes, exosomes, and endocytosis). The molecular mechanisms required for endocytosis of alpha-synuclein assemblies are currently being elucidated, and it might be possible to reduce the process of uptake with some degree of specificity (without inhibiting endocytosis in general), which then potentially could ameliorate the prion-like spread of pathology between neurons and brain regions.

One can predict that the outcomes of several ongoing and planned

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clinical trials that target alpha-synuclein will reveal if alpha-synuclein aggregation is a viable therapeutic target in PD. It is possible that the stage (prodromal, early, late) of the disease will be important when selecting patients in the trials focusing on alpha-synuclein, because as illustrated above, the experimental treatments interfere with different parts of the proposed pathogenic cascade. Furthermore, the clinical presentation and rate of progression differ greatly between PD patients, and it is possible that biomarkers (e.g. alpha-synuclein seeding assays) can be used to stratify those most suited for therapies targeting alpha-synuclein. Undoubtedly, the coming years will be very informative and provide answers to several questions related to the role of alpha-synuclein in PD.

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Virtual Congress 2021: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?

In the plenary session at the MDS Virtual Congress, Patrik Brundin and Alberto Espay discussed the question: Is Clearing Of A-Synuclein Aggregates An Adequate Therapeutic Strategy In Parkinson's Disease?

— Alberto J. Espay, MD, MSc, FAAN, Professor of Neurology, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

Alberto J. Espay, MD, MSc, FAAN

NO:

In 1999, Bob Burke and collaborators at Columbia University demonstrated in a rodent model of apoptosis that synuclein was "likely to play a role in protection or restoration of neurons destined to survive."[1,2] These observations were overshadowed by two others, published around the same time: that α-synuclein was the key constituent of Lewy bodies[3] and that a point mutation in the 53rd amino acid of *SNCA* caused an aggressive form of Parkinson's disease.[4] The neuroprotective-to-neurotoxic narrative migration was completed in 2003. Braak and colleagues examined the distribution of Lewy pathology in 41 brains of patients with Parkinson's disease and 69 of individuals with Lewy pathology without neurological disease. They organized the brains from least to most α-synuclein staining and succumbed to pareidolia: Lewy pathology *moved* cephalad in six stages, explaining parkinsonian motor features once half way through, upon reaching the midbrain.[5]

What's the inconvenience? A lack of correlation between Lewy pathology and parkinsonism or neurodegeneration. Since 2005, we have known that neither the presence nor distribution of Lewy pathology predicts motor or cognitive symptoms,[6] that the Braak and Hoehn & Yahr stages bear no relationship to each other,[7] and that the proportion of neurons with Lewy pathology has nothing to do with disease duration.[8] In fact, the more Lewy pathology in the nigra, the more nigral neurons there are.[8] Even my esteemed opponent, Prof. Patrik Brundin, admitted that α-synuclein aggregation is neither necessary nor sufficient for parkinsonism or for neurodegeneration.

Historically, the bar for the concept that neurodegeneration was about a *gain* of anything —the gain of toxic proteins— should have been much higher than the more logical premise: that degeneration was about ***loss***, including of proteins and neurons. Loss of proteins is universal in Parkinson's disease: α-synuclein, amyloid-β42, total tau, and phosphorylated tau are low when compared to healthy controls.[9] This loss occurs because soluble proteins misfold into insoluble, highly stable cross-β clumps. We have had to "embrace complexity"[10] to defend the convoluted idea that a depleting peptide can be toxic and to reconcile the paradox that higher levels of α-synuclein, not lower, are associated with the preservation of normal brain volume.[11]

Normal α-synuclein must be rather important: it has been preserved since prehistoric genomes and rendered redundant with β- and γ-synuclein. What are the odds α-synuclein was evolutionarily protected so that it can turn toxic the minute a brain is under biological stress?[12] Lewy pathology is formed from previously normal, monomeric soluble α-synuclein. Once polymerized into Lewy pathology, any function α-synuclein had is lost. Pathology, therefore, represents the end of functional α-synuclein –not the beginning of its transformation into a virus- or prion-like agent.

The clinico-pathological framework on which Parkinson's and other neurodegenerative disorders were conceived remains a tribute to the creativity of our forebears. At a time when the only research tool

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available was scavenging for clues at a crime scene, creating the fine art of interpreting histopathology, no one could have been faulted for assuming that whatever was abnormal under a microscope was the source of the problem, not its consequence. All of us, at least some of the time, still use the word *pathology* as implicitly meaning *pathogenesis*.

Clearing pathology cannot restore the health of a degenerating brain any more than clearing tree stumps can restore the health of a ravaged forest. Increasing levels of depleting α-synuclein, its *reforestation*, might instead offer potential biophysical and functional advantages. But shifting disease-modifying efforts from anti-aggregation to protein replacement will require a shift in paradigm from a gain-of-function *proteinopathy* to a loss-of-function *proteinopenia*. Can we Break from Braak and get back to Burke?

Neurodegenerative diseases are classified according to the shapes of fibrils. A forensic approach creates narratives about the nature of a crime, but can it uncover the perpetrator?

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The COVID Controversy: SARS-CoV-2 and Neurotropism: Is it a Myth?

In the plenary session at the MDS Virtual Congress, Elena Moro and Andrea Pilotto discussed the question: SARS-CoV-2 and Neurotropism: Is it a Myth?

— Elena Moro, MD, PhD, Professor of Neurology, Grenoble Alpes University, Grenoble, France

Elena Moro is full Professor of Neurology at the Grenoble Alpes University, Grenoble, France. Currently, she is the Director of the Movement Disorders Center, and the Head of the Department of Psychiatry, Neurology, Neurological Rehabilitation and Forensic Medicine at the CHUGA. Her main research has been focused on restoring brain function, especially with deep brain stimulation. She is currently the Secretary General of the European Academy of Neurology. In the EAN, she is also co-Chair of the EAN core COVID-19 Task Force and the Gender and Diversity Issues in Neurology Task Force. In the International Movement Disorders Society, she is co-Chair of the Women in Movement Disorders Working Group, the Neuromodulation of gait Study Group, and the Bylaws Committee.

YES

Background: Almost two years have passed by since the occurrence of the first cases of SARS-CoV-2 (COVID-19) infection in Wuhan, China. To date, the WHO reports about almost 251 million confirmed cases of COVID-19 including 5 million deaths. Besides the general common symptoms and signs of a flu-like infection (fever, headache, myalgia, cough, fatigue), it is well known that COVID-19 can have a very broad degree of infection severity (from asymptomatic cases to death) and of organs involvement (lungs, heart, intestine, Kidney, skin, brain, etcetera).[1] Focusing on neurological aspects, it has become increasingly evident that COVID-19 infection has also a wide spectrum of neurological symptoms, signs and diseases.

For example, anosmia, headache and myalgia are very common signs of infection whereas encephalopathy and stroke are among the most common neurological manifestations.[2-3] Interestingly, people with COVID-19 who are hospitalized and have also neurological manifestation are likely to have severe infection and bad outcome.[4] Therefore, there has been a grown interest in the neuropathological mechanism of the viral infection, with the scientific community divided between supporters of a direct neurotropism of the virus and supporters of indirect mechanisms of the central and peripheric nervous system also shared by several other organs and systems involved in the infection.[5] To date, accumulating evidence strongly supports an indirect involvement of the nervous system by COVID-19. There are at least five good reasons to support this statement.

First, the neuropathology is mainly showing systemic and local inflammation and immunoreaction, thus supporting the growing evidence that SARS-CoV-2 main pathological activity is related to systemic activation of the inflammatory and immunity systems.[5-6] Neuroinflammation and blood brain barrier disruption are the critical factors linked to the neurological symptoms.[7]

Second, concerning the supposed direct nasal entry, there is no finding of the virus inside the olfactory nerve. Indeed, the sustentacular cells and not the olfactory neurons are targeted by the virus.[8]

Third, neurons are not directly targeted by SARS-CoV-2, since the current evidence does not support direct neuronal damage. Most damage seems to be related to the blood brain barrier endothelial cells disruption, cytokine release, local microglia activation and altered neurotransmission with secondary neuronal damage.[9]

Fourth, not much virus has been found in pathological brain samples. Indeed, brain autopsies have failed in finding evidence of direct CNS damage from SARS-CoV-2. No virus has been found inside neurons or glia.[10-11]

Fifth, the main neurological manifestations are present in severe SARs-CoV-2 infection, thus related to systemic infection with secondary brain involvement.[3-4]

In conclusion, the statement that SARS-CoV-2 has a direct neurotropism is a myth for the reasons discussed above. Moreover, also the post-COVID-19 neurological symptoms (so called long-COVID)[12] are likely related to the massive neuroinflammatory response (cytokine storm), endotheliopathy, secondary brain hypoxia, and neurotransmitter disturbances.

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— Andrea Pilotto, MD, Department of Clinical and Experimental Sciences, Neurology Unit, University of Brescia, Italy

Andrea Pilotto is Assistant Professor of Neurology at the Brescia University, Brescia, Italy. His main research has been focused on biological, imaging and digital biomarkers of neurodegenerative disorders, especially Parkinson's and Alzheimer's diseases. He is leading the ENCOVID network- a multicenter study on encephalopathies associated with SARS-CoV-2 infection and the "Neuro-Covid Next" project on long-term manifestations of COVID-19 disease. He is an active member of Movement Disorder Society, the ISTAART- Professional interest Area taskforce on prodromal Lewy and trial definition, member of COVID-Neuronetwork for neurological syndromes associated with COVID-19 and active member of the WHO-Essential-Services COVID-19 taskforce.

NO

Background: With the increasing number of confirmed cases and the accumulating clinical data, it is now well established that, in addition to the predominant respiratory symptoms, a significant proportion of COVID-19 patients experience neurological symptoms. The wide spectrum of COVID-19 neurological manifestations ranges from acute disorders such as cerebrovascular disease, Guillain-Barrè syndrome, encephalopathies or encephalitis[1,2] to long-term symptoms including fatigue, myalgias, sleep disorders or memory complaints.[3,4] Since the first cases described, several preclinical and clinical studies addressed the brain involvement of SARS-Cov-2 with contrasting and debated results. Thus, the neurotropism SARS-CoV-2 is still a very controversial issue for the research community. In the last decades, SARS-CoV-2 related b-coronaviruses such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) exhibited neuro-invasive potential.[5] The high brain expression of the SARS-CoV-2 major cell entry receptor angiotensin-converting enzyme 2 (ACE2) over glial cells and neurons makes them a potential target of COVID-19.[6]

These are the findings supporting the neurotropism of SARS-CoV-2.

First, several independent postmortem brain studies in severe COVID-19 found evidence of SARS-CoV-2 infection of neuronal and other cell types using real-time PCR including cortical, subcortical areas and brainstem.[7-9]

Second, biophysical and structural studies demonstrate a higher affinity of SARS-Cov-2 S protein to ACE2 compared to SARS-CoV and other types of coronaviruses. These structural characteristics increase the ability of SARS-CoV-2 virus to enter in neurons and glial cells compared to other viral agents.[10] Organoids and in vivo studies in human ACE2 transgenic mice have been shown that SARS-CoV-2 can infect neurons and cause neuronal death in an ACE2-dependent manner.[11]

Third, besides ACE2, SARS-CoV-2 may utilize basign, neruophilin-1 as docking receptor with the involvement of several proteases including TMPRSS11A/B, cathepsin B and furin.[11] These proteins are expressed in different brain regions, including nasal mucosal epithelial cells thus representing an alternative entry route for SARS-CoV-2 virus.[12]

Fourth, the presence of SAR-CoV-2 in olfactory bulb has been demonstrated by different techniques for virus-specific nucleocapsid and spike, RNA transcript and proteins. In vitro and in vivo studies claimed

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that SARS-CoV-2 can enter the nervous system by crossing the neuronal-mucosal interface in olfactory mucosa, exploiting the close vicinity of endothelial and nervous tissues[11-13]

Fifth, studies in brain organoids and postmortem COVID-19 brains have reported the presence of SARS-Cov-2 related transcript in choroid plexus and subependymal regions, highly vascularized with an important role in blood-CSF barrier in close vicinity to cerebrospinal fluid spaces.[14] This suggested choroid plexus and blood brain barrier as a putative alternative route and an important barrier to SARS-cov-2 infection.[14,15]

In conclusion, several research evidences supported the claim of neurotropic properties of SARS-CoV-2 virus. Still, the evidences linking the viral RNA presence in neuropathological samples, inflammatory alterations and neurological symptoms and syndromes are highly controversial. Larger on-going studies addressing brain tissue and CSF in COVID-19 patients with and without neurological acute and long-term symptoms are warranted to clarify this very important issue to the research community.

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The Association of Tourette Syndrome (TS) and Group A Streptococcus (GAS)

— *Davide Martino, MD, PhD, Director, Movement Disorders Program and Lead, Calgary Parkinson's Research Initiative; Associate Professor, University of Calgary, Calgary, AB, Canada*

Davide Martino, MD, PhD

Tourette syndrome (TS) and other persistent primary tic disorders are amongst the most common neurodevelopmental disorders, with a 0.3%-0.9% prevalence for TS in childhood/adolescence. As shown by their comorbidity profile, persistent tic disorders belong to a broad impulsivity-compulsivity spectrum encompassing attention deficits, hyperactivity, impulsivity, obsessions, compulsions, and autistic traits. This spectrum has a multifactorial etiology that includes genetic, epigenetic, and environmental factors. Switching from a single-disease to a transdiagnostic approach seems higher-yielding to identify larger effect causative and risk-modifying factors across the spectrum, as shown by a recent meta-analysis of genome-wide association studies.1

The different behavioral symptoms of the impulsivity-compulsivity spectrum are known to fluctuate in severity during youth. These fluctuations might be associated with the chronic, low-grade inflammatory state observed in TS and related disorders, consisting of enhanced immune responses to both exogenous (pathogens, allergens) and endogenous triggers (self-antigens targeted by autoimmune processes; Figure).2,3 Moreover, acute-onset neuropsychiatric syndromes that encompass these symptoms (e.g. Pediatric Acute Neuropsychiatric Syndrome or PANS) have been related to an underlying pathological immune-mediated mechanism. Of all the environmental factors that could act as 'second hits' within the postnatal exposome to sustaining this chronic, low-grade inflammation, Group A Streptococcus (GAS) pharyngeal infections are probably the most explored in relation to tics and obsessive-compulsive symptoms. This is due to the proposed 'post-streptococcal' subtype of PANS, also known as PANDAS, the diagnosis and management of which has consistently generated heated debate over the past 25 years.

The European Multicentre Tics Study (EMTICS) was launched in 2012 by a consortium of 15 different institutions to elucidate gene-environment interactions in persistent tic disorders.4 A major focus of this program was to explore the influence of GAS in the course and onset of tics and

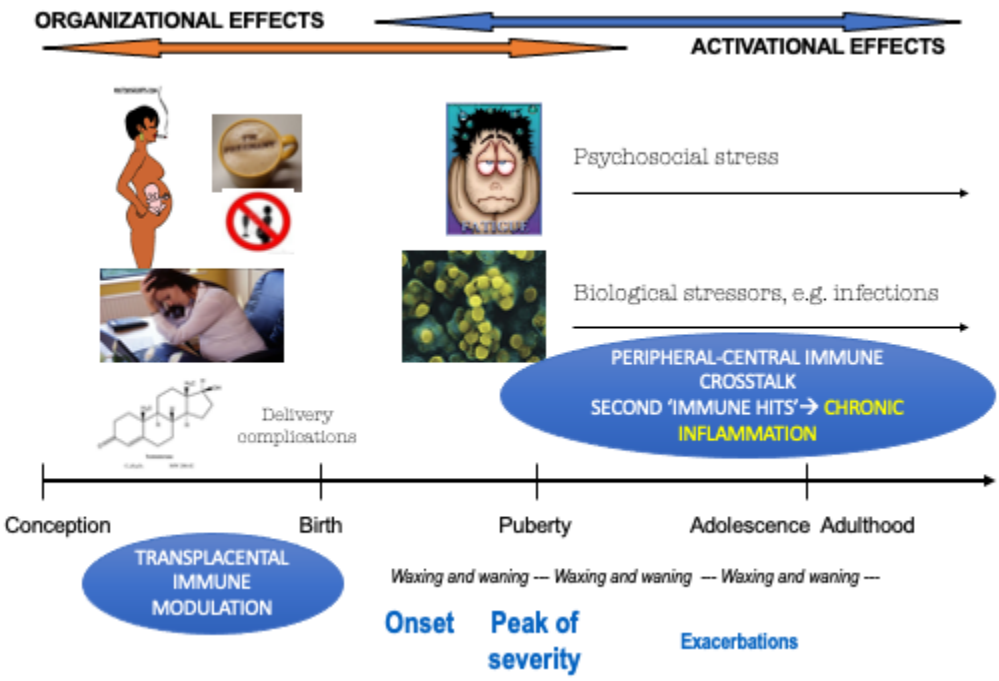

Figure legend. Enhanced immune-inflammatory responses in Tourette syndrome and related disorders may have a developmental origin, particularly in an abnormal imprinting of the immune system, which could depend on both epigenetic modifications (hence, gene expression profiles) and extra-genetic factors consisting with external (i.e. environmental) exposures. This may begin already with mechanisms through which materno-fetal immune modulation may occur at the level of the placenta. The resulting outcome during postnatal life will be the long-lasting co-existence of behavioral and cognitive deficits and of hypersensitive innate and adaptive responses to antigens or allergens of sufficient immunogenic potency, leading to a chronic state of low-grade inflammation, in the brain and in the periphery. Modified from Hoekstra PJ, Dietrich A, Edwards MJ, Elamin I, Martino D. Environmental factors in Tourette syndrome. Neurosci Biobehav Rev. 2013 Jul;37(6):1040-9.

The Association of Tourette Syndrome (TS) and Group A Streptococcus (GAS), *continued on p. 25*

The Association of Tourette Syndrome (TS) and Group A Streptococcus (GAS), *continued from p. 27*

related symptoms with an unprecedented statistical power. In the first of two prospective studies on this topic, we followed up for an average of 16 months 715 children with persistent tic disorders (mean age 10.7 years), recruited by 16 specialist clinics from 9 countries.5 The severity of tics, obsessive-compulsive and ADHD symptoms was assessed during 4-monthly study visits, intercalated every two months by telephone interviews. Exposure to GAS was analyzed adopting four different combinations of measures based on pharyngeal swab and serological testing, from the most conservative to the most lenient. Applying this design, we captured in real time 409 exacerbations of tics and analyzed the association of any of the four GAS exposure definitions with tic exacerbations and with longitudinal changes of symptom severity across the different behavioral domains.

Our results showed that the effect of GAS exposure is symptom specific. Whereas we did not observe any association with changes in tic or obsessive-compulsive symptoms severity, the three less conservative definitions of GAS exposures were associated with prospective increases of hyperactivity-impulsivity symptom severity, ranging from 17% to 21% depending on the definition of GAS exposure. A second prospective study (currently in press) followed up for 3 years younger, unaffected siblings of TS patients, showing lack of association between GAS and first onset of tics.

Our study of the largest prospective cohort of youth with persistent tic disorders ever documented to date carries two main take-home messages. First, the lack of temporal association between GAS exposure and clinically relevant tic exacerbations should hopefully discourage clinicians from unnecessary diagnostic work-up and antibiotic management of GAS infections with the specific objective of improving tics in youth with established tic disorders. Second, like for genomic factors, the behavioral effect of environmental influences may be relevant only for specific symptom dimensions. This should further encourage clinicians and scientists to think across diagnostic boxes when exploring exogenous and endogenous (e.g. microbiome) environmental factors along the impulsivity-compulsivity spectrum.

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