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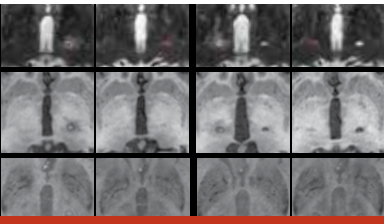
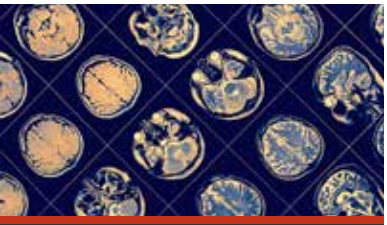
MOVING ALONG

International Parkinson and Movement Disorder Society

Editor, Antonio Strafella, MD, PhD, FRCPC





International Parkinson and Movement Disorder Society
International Secretariat
555 East Wells Street, Suite 1100
Milwaukee, Wisconsin 53202-3823
USA
Tel: +1 414-276-2145
Fax: +1 414-276-3349
info@movementdisorders.org
www.movementdisorders.org

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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:

Editor: *Moving Along*
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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.

We would like to thank the entire MDS community for the enthusiasm demonstrated in contributing to this new issue of *Moving Along* during these challenging times. On behalf of the Editorial Board, we greatly appreciate your participation and contribution.

For this second issue of 2021, the Editorial Board worked tirelessly to pull together new exciting material. Dr. Mark Hallett provided an outstanding contribution on the "History of Clinical Neurophysiology in Movement Disorders" – we are quite sure you will enjoy reading his great piece. The MDS-Africa Section contributed as well with exciting topics related to Parkinson's disease and translational research in the region. This issue also features scientific topics and several recent important developments in the field of neurodegenerative diseases. The "President's Corner", by Prof. Claudia Trenkwalder, continues to introduce young members to our MDS community.

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 making this possible. We hope you enjoy this and the future issues of *Moving Along*.

Warm regards,

Antonio Strafella, MD, PhD, FRCPC
Moving Along Editor, 2019-2021

2019-2021 Moving Along Editorial Board


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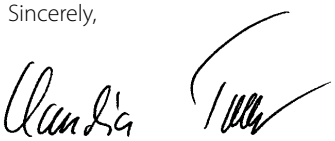
President's Corner

Although we thought, we are getting closer to the end of the pandemic, the situation with the new delta variant keeps us busy and less optimistic than before. Therefore it is very important, that MDS continues in offering more virtual resources and opportunities for engagement until it is once again safe for us to be together in person. Here is a summary of some of the recent highlights and things to look forward to from MDS in the coming months:

- The first **Virtual AOPMC** took place June 4-6, 2021 and welcomed a record attendance over 5,500 participants from 83 countries. I would like to congratulate all of the AOPMC planning committees, and especially MDS-AOS Chair, Roongroj Bhidayasiri, for their tireless efforts in making this virtual event a monumental success for the MDS-AOS region and the Society. If you missed attending the AOPMC, the sessions are available on demand for all MDS members through August 1, 2021 at www.aopmc.org. I encourage members from all regions to log in and view these excellent sessions!
- As I mentioned in my previous update, the Society has been working hard to develop and build a new personalized website experience and learning management system. Thanks to the efforts of Oscar Gershanik, Brandon Barton and Brian Berman, as well as the MDS Secretariat staff, the new and improved **MDS Education Roadmap launched on June 15, 2021!** This new website experience allows members to easily explore resources, learn through e-learning modules, and connect and network with colleagues. If you have not yet taken advantage of this unique new tool, please visit the website and log in to your new "My MDS" page to see everything this has to offer. Thank you to all who contributed to the new website!
- The subject of diversity and inclusion remains extremely important to the Society, and we recently conducted a survey of the membership to seek input regarding your input and perceptions of diversity and inclusion at the MDS Leadership level. Following this survey, MDS plans to form a group to focus on these efforts and create an updated statement, as well as outline how MDS will ensure inclusion moving forward. If you would like to read the current statement, which was updated in 2020, please read it here: **MDS Statement on Diversity and Inclusion**
- On a similar note, the slate of 2021 Nominees for the MDS Leadership positions was released in April for the central MDS leadership and Regional Sections. Members soon will be asked to submit their ballots for these candidates for the 2021 election. Please remember to submit your ballots and attend the annual MDS Business Meeting, as well as the Regional Assemblies during the MDS Virtual Congress 2021 for the official vote and transition of leadership for the 2021-2023 term. You can learn more about this process on the MDS website.
- In June, registration opened for the **MDS Virtual Congress**, which will take place September 17-22, 2021. We look forward to welcoming once again for no fee (complimentary). In addition to the excellent quality scientific sessions, this year's Virtual Congress will offer enhanced interactive components, which will allow you to network with colleagues through live chats and messaging within the platform.
- And finally, we are pleased to announce that the impact factor for the *Movement Disorders* Journal has increased from 8.679 to 10.338, which now ranks 10 out of 208 clinical neurology journals. I would like to congratulate Editor, Jon Stoessl, and his editorial staff for this outstanding achievement. I would also like to acknowledge the previous Editor, José Obeso and his team, who all significantly contributed to this new impact factor as well.

Lastly, I will conclude this message with the introduction of two more active MDS young members on page 5.

Sincerely,



Claudia Trenkwalder, MD
MDS President, 2019-2021

Oscar Gershanik

Brandon Barton

Brian Berman

Jon Stoessl

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President's Corner, *continued from p. 4*

Sara Schaefer, MD, MHS
Yale School of Medicine, USA

I attended Brown University for my bachelor's degree, then The Ohio State University College of Medicine. I completed neurology residency at Yale, culminating in my final year as chief resident, and stayed at Yale to complete my movement disorders fellowship. I am currently an Assistant Professor of Neurology at the Yale School of Medicine in the division of movement disorders. My clinical interests are broad within movement disorders and include botulinum toxin and deep brain stimulation. I also serve as the Movement Disorders Fellowship Director and the Associate Program Director for the Adult Neurology Residency Program. I hold a Masters in Health Sciences with a focus on medical education, which reflects my current main scholarly interest. I have spent several years designing and researching innovative movement disorders curricula and educational tools for neurology residents. My goal is to expand these curricula to include new topics and new audiences.

I got involved in MDS as a movement disorders fellow when I attended the Young Members Group meeting at the MDS Annual Congress in Vancouver. I met other young members through that group with similar interests and have since expanded my role within the MDS, participating in multiple education-focused activities including as a member of the New Learning Formats subcommittee of the Education Committee, as the MDS Podcast co-founder, and as the Movement Disorders Journal CME Editor. I have also worked with other movement disorders program directors on developing milestones for fellows and have worked as the movement disorders section lead for the AAN RITE committee for the last two years.

In my career, I hope to take an increasingly active role in the education of a broad range of trainees, practicing providers, and patients, both within the United States and abroad. I hope to promote movement disorders knowledge by engaging learners with a bottom-up approach to dissecting the examination to determine phenomenological diagnosis, meeting the learners where they are, and to foster interest in our field through interactive, accessible, patient video-based curricula. I appreciate that the MDS is embracing new learning formats, and hope that they will continue to work on creative, pedagogically evidence-based, technologically innovative, and multimodal ways to reach a new generation of trainees, with a diverse representation of educators. I also hope that the MDS will work to expand patient education materials into new formats that are engaging for patients and caregivers.

I live in Guilford, CT, USA with my husband, my 5-year-old, Henry, my 1-year-old, Claire, and our cat, Merlin. In my (admittedly rare!) spare time, I like to sing in the local choir.

Shivam Om Mittal, MD
Cleveland Clinica Abu Dhabi, UAE

I am a consultant Neurologist and section head of Movement disorders division at the Cleveland Clinic Abu Dhabi hospital, which is a tertiary care referral center in the country.

My areas of research includes botulinum toxin injection in tremor conditions including Parkinson's disease, Essential tremor, and other tremor conditions. I completed a post-doctoral research fellowship in movement disorders at the Yale University, New haven, CT, USA, where we initiated several clinical trials using innovative techniques to help patients with tremor conditions. I was able to continue my research during neurology residency at University Hospital, Case Western Reserve University, Cleveland and during the Movement Disorders clinical fellowship at the Mayo Clinic, Rochester, Minnesota, USA.

I got involved with MDS in 2015 when I started attending the MDS International Congresses. It gave me several opportunities to meet and get inspired by the legends in the field of Movement Disorders. MDS educational resources are true asset which nurtured my passion for movement disorders during the years of residency, fellowship and even when I am working as consultant! MDS has helped me to grow as an educator with involvement as a speaker in MDS international and regional conferences, course director for the first virtual botulinum toxin course (MDS-BoNTCon-2020), and MDS scientific committee member. I have learnt values of teamwork and leadership, by working as a steering committee member of the Middle East Working Group, MDS Tremor Study Group, and MDS-AOS Nomination committee member. I am honored to be selected for MDS-LEAP (Leadership Program) class of 2021-2022 ,which I strongly believe will make me more capable to create a comprehensive center "An Oasis of Movement Disorders" in this part of the world!

I believe in the quote by Eleanor Roosevelt "The future belongs to those who believe in the beauty of their dreams". My dream is to be an empathetic and thorough clinician, academician, researcher, teacher and a leader. MDS has helped me tremendously to quench my thirst for academics and passion for teaching, and provided me stepping stones to be a future leader in the field of movement disorders. I am very thankful to the MDS leadership, MDS-AOS leadership and the several MDS committees to believe in me and bring out the best in me. I am hopeful that in future, we have more involvement of clinicians and researchers from the Middle East with resources for epidemiological and genetic studies in Movement Disorders.

On a personal note, I am a father of two lovely sons (Onish and Yuvaan) and live with wife and my mother in the scenic city of Abu Dhabi, United Arab Emirates. I enjoy playing chess, biking and playing on the beach with my family.

The Newly Enhanced 2021 MDS Education Roadmap

— *Brandon Barton MD, MS, Associate Professor at Rush University Medical Center, Chicago, IL, USA*
— *Brian D. Berman MD, MS, FAAN, Professor at Virginia Commonwealth University, Richmond, VA, USA*

The MDS Education Roadmap concept was first conceived in 2016 by Dr. Oscar Gershanik and the initial version was launched in June 2017 with enthusiastic reception. The original Roadmap provided a novel web-based means for MDS members to easily navigate the many available educational resources on the MDS website in a manner according to the learners' level of experience. Seeing the utility and broader potential of the Roadmap, in March 2018 the MDS Officers decided to establish the MDS Education Roadmap Program with the goal of further transforming the Roadmap into a premier educational and training resource in movement disorders. As the current co-chairs of the MDS Education Roadmap Program, selected and advised by Dr. Gershanik, we are thrilled to announce the launch of the newly enhanced MDS Education Roadmap Program on June 15, 2021!

Priorities for the revised MDS Education Roadmap were defined through internal stakeholder meetings, an MDS member's survey, and MDS member interviews conducted in late 2019 and early 2020. The main priorities for the revision included expanded search capability, the development of guided learning via curriculum track to virtually guide learning for users, and an overall enhanced, personalized MDS member experience. New technical specifications for the expanded scope of the Roadmap were also defined and a number of vendors reviewed to help further develop the project. In June of 2020, two vendors were contracted for the project including the Academy for Continued Healthcare Learning to assist in the creation of a new interactive learning management system, and the current MDS website vendor Northwoods to ensure an integrated and cohesive user experience. By integrating all online resources, we are able to ensure a single sign on for the MDS website and MDS Education Roadmap, broaden search functionality between the two systems, and link members to the vast expanding collection of MDS education and resources.

The exciting improvements that MDS members will encounter as part of the launch of the revised MDS Education Roadmap include an updated "My MDS" member page. This page includes information via five personalized panels (Figure 1). This page will provide easy to access information and links to 1) upcoming events and courses relevant to the member, 2) membership details and engagement status, 3) bookmarked or "favorited" pages from across the MDS website, 4) in progress of member engagement in education courses and suggestions for new courses based on the member's profile and activity, and 5) a personalized calendar showing important MDS dates.

The revised MDS Education Roadmap and new learning management system are seamlessly accessed through the My MDS page of the MDS website, so multiple logins are not required. The fully redesigned Education Roadmap Dashboard (Figure 2) enables members to quickly explore and enroll in the multitude of educational courses and programs, e-learning modules, and other resources available through the MDS, as well as download course transcripts. Additionally, attributes of a member's profile are now being used to help identify and recommend the educational resources that may be of specific interest to the member. A tagging system for all the MDS educational resources and a hierarchy of relevant terms were also established in order to significantly enhance the search capabilities of the Education Roadmap.

In order to provide guided learning and increase member exposure to the extensive amount and variety of educational resources created, sponsored, and curated by the MDS, personalized curriculum tracks based on both topic and content level are being developed. These tracks will roll out regularly as the Roadmap evolves. Curriculum tracks are comprised of a defined set of recommended educational courses and resources covering foundational, intermediate and advanced content for a particular movement disorder along with pre- and post-assessments to augment learning. An initial set of curriculum tracks in Parkinson disease, tremor and dystonia are being developed with help from the MDS Young Members Group, and plans are in place to continue to work with this group to help regularly update these tracks and develop new tracks. Finally,

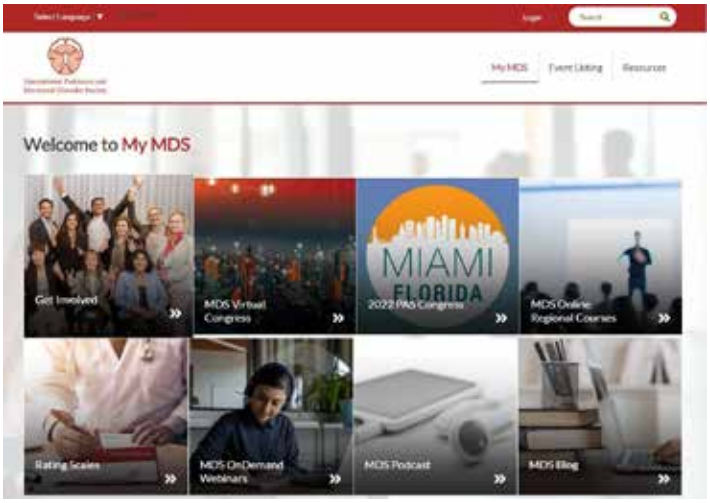

Figure 1

The Newly Enhanced 2021 MDS Education Roadmap, *continued on p. 7*

The Newly Enhanced 2021 MDS Education Roadmap, *continued from p. 6*

virtual discussion boards, chat capabilities with experts in the field, and integrated social media functionality to connect members and facilitate learning, sharing of interests and accomplishments are all in the works.

We are thrilled about the recent launch of the 2021 newly enhanced MDS Education Roadmap and sincerely hope members will use it to **Explore** all the vast number of exceptional educational courses and resources of the MDS, **Learn** about movement disorders across the content spectrum from beginner to advanced, and **Connect** with other learners.

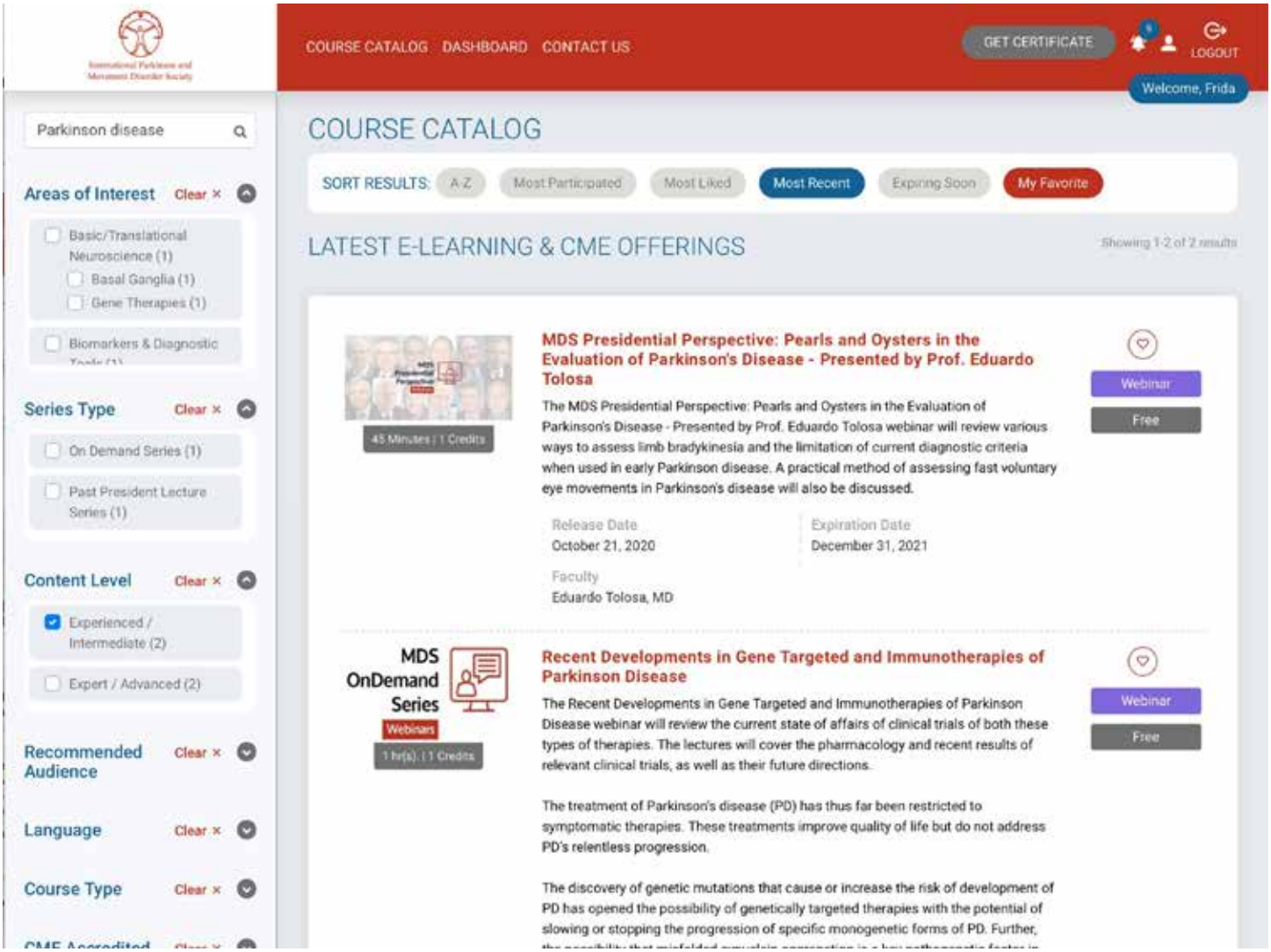

Figure 2

Update on the Activities of the MDS Evidence-Based Medicine Committee

— Rob de Bie, MD, PhD, Neurologist, Amsterdam University Medical Center, Amsterdam, Netherlands
— Regina Katzenschlager, MD, Consultant Neurologist, Klinik Donaustadt Vienna, Vienna, Austria

Rob de Bie, MD, PhD

Regina Katzenschlager, MD

Since 2002, the EBM Committee has regularly provided Systematic Reviews of the evidence for treatments of PD, essential tremor, restless legs, and Huntington´s disease, and will continue to do so. MDS members may be interested to learn what to expect from future MDS Systematic Reviews.

Until recently, a standard method was used for a literature search of randomized controlled trials of interventions commercially available in at least one country, with features such as a minimum of 20 patients treated for at least four weeks. The quality of the evidence was rated using a published Rating Scale for Quality of Evidence. Based on the resulting efficacy conclusions and on safety, implications for clinical practice were formulated.

Over time, the evidence became more difficult to assess using this methodology, particularly in the presence of conflicting results. Following extensive deliberations, the EBM Committee decided to switch its methodology to modified GRADE (Grading of Recommendations, Assessment, Development and Evaluations)[1]. GRADE is based on robust methodological principles, the process is linear and transparent, and it is by far the most commonly used method across medicine. The process includes formulating questions in the PICOT format, involving trained information specialists in the searches, and the Cochrane Risk of Bias tool for the evaluation of included studies. This needs to be applied to the full time frame now, to ensure old and new studies are treated alike.

The aim continues to be the production of Systematic Reviews, not guidelines, in keeping with the mission of MDS as a global society.

During this transition period, no interim updates will be posted on the MDS Website.

A collaboration with Cochrane was established and in 2020 and early 2021, regular online methodology training courses were given by Joao Costa and Goncalo Duarte from Lisbon University. The MDS members involved in this work are based across the globe and all have now had an opportunity to take part. The move to the online format, which had initially been driven by the covid pandemic, has turned out to be highly efficacious for this purpose.

Reference

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso- Coello P, et al. GRADE: an emerging consensus on rating quality of ev- idence and strength of recommendations. BMJ 2008;336:924e6.

(Personal and Partial) History of Clinical Neurophysiology in Movement Disorders

— Mark Hallett, MD, Human Motor Control Section, NINDS, NIH, Bethesda, MD, USA

Clinical Neurophysiology developed as a subspecialty of neurology before movement disorders. EEG and EMG were first used in the early part of the 20th century, EEG for epilepsy and EMG for neuromuscular disease. This led to national societies and to the founding of what is now the International Federation of Clinical Neurophysiology (IFCN) in 1947. Movement disorders began with an interest in Parkinson disease, and interest increased rapidly with the demonstration of L-DOPA as treatment in 1967 by Cotzias. Basal ganglia clubs arose with focus on Parkinson disease and Huntington disease (the British disease and the American disease, respectively).

When I came to David Marsden's Department for my motor control fellowship in 1975, my plan was to study the physiology of normal rapid movements. Lhermitte in France had just found that 5-HTP could markedly reduce myoclonus in patients with post-hypoxic myoclonus, and Marsden wanted to study this in patients in the UK. He had asked Jane Adam, a physiology PhD student in the lab, to look at their physiology, but she wasn't interested, and she asked me to do it – I agreed. The tools were available. Dawson in 1947 had identified that these patients had large somatosensory evoked potentials, but he did not find it satisfying to overlap multiple single trials to show this. He then invented the average for this purpose, originally a mechanical device, but which was eventually computerized as computers developed. EEG spikes had been seen in association with myoclonus. The possibility of averaging EEG activity prior to an EMG event was invented by Kornhuber and Deecke, who were studying brain activity prior to voluntary movement. They recorded the EEG and movement activity on tape, and then played the tape backwards into an average similarly to recording SEPs, triggering on the movement, and in 1965 discovered the Bereitschaftspotential. With the help of development of the delay line, this process was also computerized. Shibasaki and Kuroiwa first used this in 1975 to find a small EEG spike in the EEG not apparent in the ongoing recording.

Marsden got referrals of myoclonus to the lab. David Chadwick, an epilepsy fellow with Ted Reynolds, was co-opted to do clinical assessments and try 5-HTP. I did the physiology. We found multiple physiological types of myoclonus. In the most common post-hypoxic patients, the back averaged premyoclonus EEG activity looked the same as a component of the "giant" SEP. Moreover, somatosensory stimulation could produce myoclonus that looked like spontaneous and reflex myoclonus. The giant component of the SEP looked the same as the back averaged EEG event. Making a calculation of the afferent time from stimulus to cortex and the efferent time from cortex to muscle, it seemed logical that the sensory evoked myoclonus was a hyperactivity of a long latency reflex mediated by the sensorimotor cortex. Sutton and Mayer in 1974 had even proposed that reflex myoclonus was mediated by the cortex and called it a C-reflex. We were primed to confirm that conclusion. Marsden with Merton and Morton had identified such a long latency reflex in their studies of normal physiology, and I had actually come to Marsden's lab to study this reflex in relation to rapid movements. An amazing coincidence. We published this in 1979, and at the same time, Shibasaki was coming to the same conclusion, publishing his report a few months before ours in 1978. I referred to it to our paper in a note added at proof stage. Shibasaki and I met at a myoclonus meeting in New York organized by Stan Fahn, and we have been good friends ever since.

Since that time, clinical neurophysiology of myoclonus, including evaluating the EMG, the C-reflex, the SEP, and the back averaged EEG has been used to characterize and classify myoclonus.

In the 1970s and 1980s, there were many small motor physiology meetings, often focusing on specific topics. John Desmedt, who made contributions in virtually all fields of clinical neurophysiology, organized many of them and produced books with the speakers' papers. I recall one particularly important meeting in Liege organized by Paul Delwaide on the topic of increased tone, how spasticity and rigidity differed and what were their physiologies. Long discussions led to the conclusion, and current understanding, that increased tone had three components, increased reflexes to stretch, increased background contraction due to failure to be able to relax, and changes in the muscles themselves.

In 1985, Stan Fahn together with David Marsden founded the Movement Disorder Society (MODIS), and Reiner Benecke and Bastian Conrad together with David Marsden founded the International Medical Society for Motor Disturbances (ISMD). MODIS would start with a journal, and ISMD would start with meetings, but there was also a difference in focus. MODIS was clinical and pharmacological, while ISMD was physiological. ISMD had meetings in Lausanne in 1986 (where spasticity was a major topic) and in Rome in 1988. MODIS joined ISMD for the next meeting in Washington in 1990, and that was called the first International Congress of Movement Disorders (although it was actually the third meeting). Meanwhile, the journal Movement Disorders rapidly became successful. An illustration of the difference of focus of the two societies is the proposal of Johannes Noth to publish the proceedings of a meeting that he organized on spasticity in Movement Disorders as a supplement. After a contentious discussion at an Editorial Board meeting, the supplement was turned down because spasticity was not a movement disorder. Nevertheless, the two societies merged after negotiations from 1992 to 1994 to form a new society also called the Movement Disorder Society but now abbreviated MDS to indicate that it was different from the two original societies. The idea was to foster all fields of movement disorders, but the focus on clinical neurophysiology has faded over the

(Personal and Partial) History of Clinical Neurophysiology in Movement Disorders, *continued on p. 10*

(Personal and Partial) History of Clinical Neurophysiology in Movement Disorders, *continued from p. 9*

years, and MDS now has a new Task Force on Clinical Neurophysiology to assess the current situation and to advocate for more use of clinical neurophysiology in clinical practice of movement disorders.

Back to the clinical neurophysiology. Much of the work in clinical neurophysiology has been in understanding the pathophysiology of different movement disorders, similar to the interest in increased tone described above. Why are patients with Parkinson disease slow? What is the fundamental disturbance in cerebellar ataxia? Why do patients with dystonia have abnormal postures? I will discuss here one more theme, functional movement disorders, which, similar to myoclonus, is a personal interest and a disorder where clinical neurophysiology can usefully extend the neurologic exam.

Functional neurological disorders, first called hysteria, have been known since the early days of medicine. They were of particular interest to Charcot, Janet, and Freud. Freud devoted himself to the disorder, and, on the basis of his theory of psychological causation, called them conversion disorders. Then, bound up in the development of psychoanalysis and Freud's evolution of thinking to the Oedipus complex, the disorders became relatively neglected by the rest of medicine. Neither neurologists or psychiatrists were trained in these disorders, and, has been well documented the topic disappeared from neurology and psychiatry textbooks. In the late 1970s and early 1980s, many of the focal dystonias were thought to be of psychogenic origin, and Marsden and Fahn rightly argued that they belonged in the dystonia spectrum, but they recognized that some patients did have psychogenic dystonia. Fahn, together with Williams in 1988, developed the first formal criteria for the diagnosis of psychogenic dystonia, and the term psychogenic movement disorder arose. What to call these disorders has always been controversial. Marsden in 1986 opined about the name, and suggested staying with hysteria, but psychogenic movement disorders stuck until the last few years when the consensus changed to functional movement disorders.

The clinical neurophysiology of functional movement disorders developed alongside the clinical aspects. In relation to functional myoclonus, Thompson and Marsden in 1992 first drew attention to the fact that functional sensory provoked myoclonus had latencies that looked like voluntary reaction time responses even though they were involuntary. They were longer and more variable than the latencies of cortical myoclonus. Terada and Shibasaki in 1995 back averaged the EEG in functional myoclonus and found a Bereitschaftspotential (BP). This was remarkable since the BP had been described for voluntary movements and not before in relation to an involuntary movement. These two observations together continue to be useful to identify functional myoclonus, but also reveal that the movements of functional myoclonus use voluntary mechanisms. In 2012, van der Salm and Tijssen looked at the sensitivity and specificity of the BP for analyzing jerky movements and found it to be valuable.

In regard functional tremor, it had first been observed clinically by Koller that tapping with one hand might entrain the tremor to that frequency. O'Suilleabhain and Matsumoto in 1998 showed this with EMG recordings. Zeuner in my laboratory in 2003 showed this as well with accelerometry and noted that that the tremor might be altered in frequency and not necessarily entrained at the same frequency as the tapping. She also pointed out that patients did not necessarily do their voluntary tapping correctly, and this itself might be a useful sign. Schwingenschuh with Bhatia and Edwards put these signs together with a few others and came up with a combined functional tremor score with high sensitivity and specificity.

With the development of these clinical neurophysiological methods, in 2009 Gupta and Lang suggested that there should be a category of diagnostic certainty called "laboratory supported."

There have been three international meetings with a focus on functional movement disorders that I organized together with leaders of MDS, including past presidents Fahn, Jankovic, and Lang, and others. The International Parkinson and Movement Disorder Society supported all of them and served as the Secretariat, although they were not official MDS meetings. The first meeting in 2003 included much physiology including a major session on how the brain might make movements without developing the sense of voluntariness. The second was in 2009, and the third in 2017 which was broader in scope to include all functional neurological disorders. The third meeting generated sufficient enthusiasm to give birth to a new society, the Functional Neurological Disorder Society, which was founded in 2019 with blessing from its parent, MDS.

In 2006, I wrote an article, *"Functional Movement Disorders, A Crisis for Neurology"*. I noted our collective ignorance about the nature of the disorder and the difficulties of diagnosis and treatment. In 2019, by invitation of Jose Obeso, I wrote another article for Movement Disorders, asking whether the crisis was resolved. I concluded that it is resolving, and clearly clinical neurophysiology is helping, both with diagnosis and with insights into the nature of this interesting disorder.

Sleep Cycle

— *Prof Christian Baumann, MD, Neurologist, Department of Neurology, University Hospital Zurich, University of Zurich, Switzerland*
— *Dr Fabian Buechele, MD, Senior Physician, Department of Neurology, University Hospital Zurich, University of Zurich, Switzerland*
— *Elena Antelmi, MD, PhD, Assistant Professor, Parkinson Disease and Movement Disorders Division, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy*

Three sleep experts were invited for a roundtable discussion about the expanding role of sleep science in neurodegenerative disease.


Christian Baumann, MD


Fabian Buechele, MD


Elena Antelmi, MD, PhD

Fabian Buechele: I read with great interest your work on biomarkers in patients with polysomnographically confirmed idiopathic REM sleep behavior disorder (iRBD) who are at risk to develop a neurodegenerative synucleinopathy such as Parkinson's disease (PD), Multi-system atrophy or Lewy body dementia1–3. Given that this risk is high (up to 90% in 15 years4), iRBD cohorts are of great value to identify, measure and thereby validate other prodromal markers.

Your studies focus on tissue-based (phosphorylated a-synuclein deposits in skin biopsy)1, fluid-based (serum protein signature profile)2 and imaging-based markers3. They add important insights to a growing body of literature on biomarkers in prodromal Parkinson's disease.

Given the great variety of emerging markers: What are your thoughts on the "ideal" biomarker? Where specifically can they help us today and in the future? When and in which setting will we use them?

Elena Antelmi: Thank you for your comments and for this question, which is indeed a "hot topic". Unfortunately, my answer is that the "ideal biomarker" is missing yet. Overall, the "ideal biomarker" should be sensitive, specific, not invasive and not expensive. Moreover, it has to cover different roles. For example, in iRBB we need diagnostic biomarkers that confirm the presence of a disease (i.e. of an underlying synucleinopathy), prognostic biomarkers that identify the likelihood of a clinical event (i.e subtypes of PD and time of phenoconversion) and therapy-responsive biomarkers that show a biological response - i.e. for example, reduction of alpha-synuclein deposits - to a certain medication).

IRBD patients are the ideal candidates to observe the natural history of synucleinopathies and to try neuroprotective strategies, as most of the patients will convert to a clinical synucleinopathy. However, the percentage of iRBD patients that converts is not 100% (considering the possibility also of RBD mimics), additionally we do not know which subtype of parkinsonism the patient will develop and also when the patient will convert.

Currently, we have different biomarkers that can be very powerful to answer these questions, but none can cover all of them at the same time. For example, skin biopsy has an excellent economic and safety profile as well as in terms of sensitivity and specificity, but we do not know if it can be used as a treatment-responsive biomarker. Similarly, other biomarkers, like the cognitive, autonomic or genetic profile can serve as diagnostic biomarkers to predict the subtypes of parkinsonism, while others like ^{123}I-Ioflupane-SPECT or motor tests are useful to predict an imminent phenoconversion (prognostic biomarkers). It is therefore clear that there is not a single biomarker by itself to cover all the issues.

So far, the majority of iRBD studies evaluated biomarkers in isolation, but I think that in the imminent future the only way to have an "ideal biomarker" will be to combine different biomarkers. Of course, this approach requires the collaboration of several centers and harmonization of data collection and analysis, but it is time to do the effort!

This combination of biomarkers can inform on proximity to phenoconversion and track therapy response. Indeed, disease modifying trials are currently ongoing in de novo PD populations and the next step will be to apply these treatments on iRBD, to prevent or slow down neurodegeneration.

Fabian Buechele: Our work relies partially on the notion that the accumulation of "bad proteins" (in our case of alpha-synuclein) is causally involved in specific neurodegenerative diseases (such as Parkinson's disease). More recently, this concept has been questioned and criticized as oversimplified8. Rather, it has been proposed that PD represents a group of diseases that exhibit unique genetic, biological and molecular abnormalities, which probably respond differentially to a given therapy, particularly for strategies aimed at neuroprotection9.

What are your thoughts on alpha-synuclein-based biomarkers in this context? Are iRBD cohorts helpful in identifying biomarkers to define subgroups? What is the relevance of genetic studies in RBD cohorts in this context?

Elena Antelmi: This is a very crucial question.

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Sleep Cycle, *continued from p. 11*

I totally agree with the view that PD is a group of disorders with unique genetic, biological, and molecular abnormalities. It is therefore likely that these different diseases (coming under the umbrella of parkinsonian disorders) will respond differentially to neuroprotective strategies. Taking into account this prospective, patients with iRBD are precious for identifying a particular subtype of PD. Indeed, not all PD patients have RBD and iRBD patients have most likely an underlying synucleinopathy[1] and will likely develop a subtype of parkinsonian conditions with a different genetic and a proteomic background. Recent studies suggest that the genetic background of iRBD does not completely overlap with the one of PD. Indeed, genetic variants in ***LRRK2*** and ***MAPT*** while being associated with PD have not been found in iRBD[10,11]mainly Parkinson's disease (PD, while ***GBA*** variants are found in approximately ten percent of iRBD[12]. Similarly, iRBD patients show a unique protein expression profile, consistent with alterations in the norepinephrinergic and dopaminergic systems and in the inflammatory response[2]capable of providing new insights into the underlying pathogenic mechanisms and putative α-synuclein-related neurodegenerative processes.\nMethods Serum samples from patients with idiopathic RBD (n = 9.

Of course, iRBD cohorts should be further stratified by means of additional biomarkers able to predict the subtype of PD. To this regard, for example cognitive, autonomic and genetic tests may be of help.

Fabian Buechele: How do you see the role of RBD as an indicator for a more malignant disease course? Does the presence of RBD change how you counsel and treat a PD patient?

Elena Antelmi: As said, iRBD represent a cohort of patients prone to develop a more malignant subtype of PD. However, since even under the umbrella of iRBD we can recognize different subtypes of PD, I do not think that this should change the clinical and therapeutic approach to the patients. Treatments should anyway be targeted on patients' complains and counseling to the patients should be based on clinical follow up rather than on the presence of RBD or not. Of course, I advise to follow them up more frequently and to perform cognitive and autonomic tests in order to highlight subclinical abnormalities also in these domains.

Fabian Buechele: Counseling patients with iRBD is challenging with respect to communicating the potential development of an incurable neurodegenerative disease[13,14]. What is your personal approach?

Elena Antelmi: This is a hard topic and several viewpoints and reviews have addressed this issue [3,13,14].

The question is even more delicate, since currently we do not have any neuroprotective treatments or strategies and therefore counseling does not have a practical consequences.

Having said this, I personally behave like for all the other diseases. I try to build an empathic dialogue with the patient aiming at better understanding his/her willing to know in deeper his/her condition and his/her resources to understand and face the counseling. Therefore, what I usually do is to explain that he/she is suffering from a movement disorder during nighttime and that this disorder can eventually evolve towards a more complex condition with the possibility to develop a movement disorder also during daytime. Then, based on the cultural and emotional background of the patient and on the feelings and feedbacks emerging from the empathic dialogue I go or do not go deeper into details.

Fabian Buechele: Based on more recent studies[15,16] there is an ongoing debate on how to symptomatically treat RBD in PD. What are your experiences and what is your personal approach?

Elena Antelmi: Currently we do not have any data coming from the literature to support the use of clonazepam or melatonin for RBD in PD, and well-designed studies including not only the evaluation of clinical outcome but also of neurophysiological parameters, like REM sleep without atonia measured on polysomnography are lacking.

Even in iRBD, we do not have much data to support the use of clonazepam and melatonin. From the clinical practice we know that clonazepam 0,5-2 mg, even without having a direct effect on muscle tone during REM sleep, is quite effective as well as melatonin up to 12 mg.

What I personally did in PD patients with RBD is firstly the counseling, i.e. advising to modify bedroom environment in order to reduce the risk of injury. Then, considering that clonazepam should be used with caution, especially in older adults with neurodegeneration, as it can aggravate confusion, cognitive symptoms, falls and respiratory problems during sleep, I prefer to start with melatonin up to 4 mg, to be eventually increased.

This is because, at least, melatonin has a much safer profile and also because it can help with the circadian dysregulation seen in PD.

Elena Antelmi: I read with interest your latest article on the potential protective role of slow wave sleep (SWS) evaluated by means of the computed slow sleep energy (SWE) in Parkinson's disease - PD[17]. The paper shows that higher SWE was associated with slower motor progression over a mean observation time of almost five years. Even considering the retrospective nature of the study, I do appreciate the brilliant and far-sighted idea underling this paper.

Can you explain briefly the implication of the study and the possible next step of your researches on the matter?

Christian Baumann: Thank you for this great summary of our study. This study is retrospective, and it is burdened with many limitations. Therefore, and although we were surprised ourselves to find such a significant outcome, we must interpret it with utmost caution. Nevertheless, it shall evoke new ideas on how to think about the role of (deep) sleep in

Sleep Cycle, *continued on p. 13*

Sleep Cycle, *continued from p. 12*

neurodegenerative protein aggregation disorders, for there is a growing pile of evidence from preclinical and clinical Alzheimer disease studies: ever since the seminal study of Kang and colleagues[18], many groups found that sleep plays a role in protein turnover and aggregation in relation to neurodegenerative disease.

Elena Antelmi: Neurodegeneration is usually associated with reduced sleep duration, quality and efficiency in what appears to underlie a bidirectional relationship. This is supported by a great body of literature in animal models and lately in patients with Alzheimer's disease[19–21]deposition of insoluble amyloid-β (Aβ. Quoting the old question of "the chicken and the eggs", what do you think comes first?

Christian Baumann: There is still no definitive answer for this important question, and given the complexity of nature, I guess that there will never be one. In other words, given the insights we do have these days, I assume that in some patients, poor sleep quality might in fact be heralding (or even contributing to) neurodegenerative disease, whereas in others, it is well conceivable that neurodegenerative disease affecting sleep-wake regulating nuclei causes sleep-wake problems in former good sleepers. In this line, others have convincingly shown that loss of hypocretin cells in the hypothalamus is present in Parkinson patients, and that this loss deteriorates with the progression of disease[22,23].

Elena Antelmi: Which can be the best study design to analyze the protective role of SWS?

Christian Baumann: The problem is that such studies are, as usual, very extensive and expensive. Therefore, as it already happened in the field of Alzheimer disease, it is first important to deliver good evidence from preclinical and human studies that sleep in fact affects the underlying neuropathology of neurodegenerative disease. This has been shown in animals[18] and in human subjects[20,24]. We found a similar effect of sleep modulation on synucleinopathy in transgenic mice (revised manuscript in review), and the correlation study in Parkinson patients has been discussed above. Once such evidence is present and considered strong enough, carefully designed prospective interventional randomized studies are necessary, maybe with a delayed start design, over a long period of time, with optimal outcome (bio-)markers such as functional imaging or cerebrospinal fluid markers.

Elena Antelmi: As you stated, your study was motivated by the lack of studies on the importance of SWS in PD, although growing evidence supports a role of SWS in Alzheimer disease. This is also related to the lack of an easy to perform and dynamic biomarker in order to test p-alpha-syn clearance? How do you think we might overcome this? Which is the most promising biomarker to that regard in your view?

Christian Baumann: This is again a crucial question. We still do not have functional neuroimaging for synuclein burden or clearance at hand, and cerebrospinal fluid biomarkers may be promising, but no one is available to reliably detect disease and measure its progression. Thus, we need such biomarkers badly, and many groups worldwide are working in this direction, supported by national funding institutions and important foundations such as the Michael J Fox Foundation or the Chan Zuckerberg Initiative.

Elena Antelmi: Acute sleep deprivation has been shown to hamper the clearance of "bad" proteins even in healthy subjects[24,25]. Which do you think can be the consequence of chronic sleep deprivation for people without genetic predisposition for neurodegeneration?

Christian Baumann: The definitive answer for this question again is missing as of now, but I expect that sleep quality is only one determinant for the development of neurodegenerative disease. It is most probably the interplay between behavior (physical activity, diet, sleep etc), environmental and genetic factors which determines the risk for disease. Not every smoker develops lung carcinoma.

Elena Antelmi: Having said this, why do you think that sleep deprivation in patients with obstructive sleep apnea or insomnia is not associated with cognitive decline or neurodegeneration[26], even though also these populations showed reduction of the clearance of proteins of accumulation[27]?

Christian Baumann: As so often, when scientific studies or retrospective analyses are performed, the outcomes are not unambiguous. Differences in included populations, methods, observation times, outcome parameters and many other factors have an effect on the overall outcome. Thus, I would not over-interpret the above-mentioned discrepancies. On the other hand, I assume that current evidence is strong enough to state that there is a link between more fragmented (less deep) sleep and turnover or aggregation of proteins that are related to neurodegenerative disease. Whether or not poor sleep is a major risk factor for neurodegeneration, whether sleep modulation might constitute a disease-modifying approach, and whether clearance of protein or other mechanisms are underlying this observation, must be elucidated in the future.

Elena Antelmi: Given these premises, do you think that a pharmacological or behavioral approach aiming at improving sleep efficiency can be used as a "neuroprotective" strategy in the prodromal stage of neurodegeneration or in the early stages of PD?

Christian Baumann: Whether such a sleep improving strategy should be pharmacological, non-pharmacological or behavioral, remains to be tested. But given the fact that better sleep is likely to improve quality of life and to exert close to no unwanted side effects, I guess that such strategies should be tested whenever possible.

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Elena Antelmi: Would you expect a stronger effect coming from Z-drugs, melatonin or drug acting mainly on SWS (like sodium oxybate)?

Christian Baumann: Given the insights from many studies including our own[28], I would try to deepen sleep, i.e. to enhance slow-wave activity. Z drugs and melatonin are therefore not my first candidates for such an intervention. Sodium oxybate, on the other hand, produces a slow-wave sleep-like behavioral state and is an interesting option, but this compound (like the other slow wave sleep-promoting drugs) has tolerance, dependency and to some extent safety issues which are critical if we start thinking about population-wide prevention strategies.

Elena Antelmi: Bet for the future! I'd like to know your prediction on where all this will drive us.

Christian Baumann: I will consult my crystal ball and let you know its answer as soon as it has produced it. For the time being, at least, there is some hope that sleep will play a good role in the field of neurodegenerative disease, and I bet that we have not yet come to the end of manifold new insights.

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Bilateral Staged Magnetic Resonance-Guided Focused Ultrasound Thalamotomy: The First Step

— *Raúl Martinez-Fernandez, MD, PhD; Jose Ángel Pineda-Pardo, PhD; Michele Matarazzo, MD, HM CINAC (Centro Integral de Neurociencias Abarca Campal), Hospital Universitario HM Puerta del Sur, HM Hospitales, Madrid, Spain*

Raúl Martinez-Fernandez, MD, PhD

Jose Ángel Pineda-Pardo, PhD

Michele Matarazzo, MD, HM CINAC

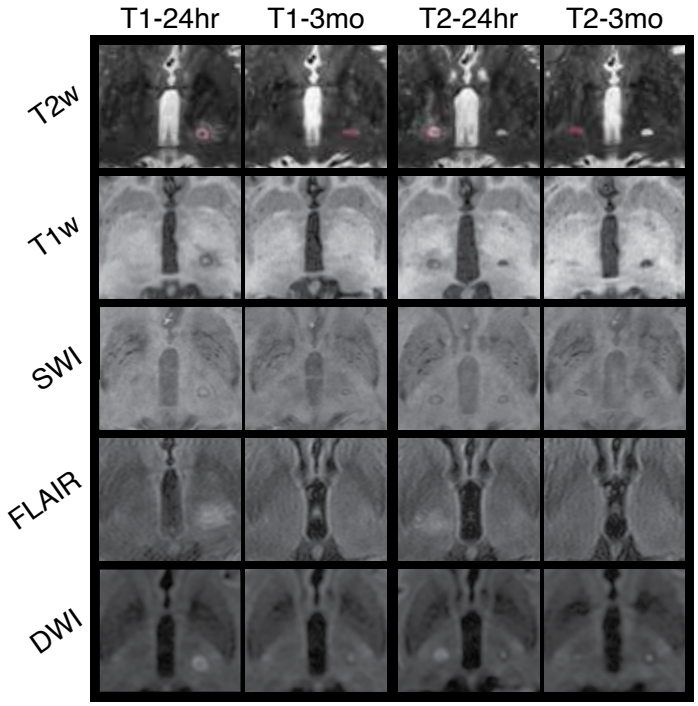
Magnetic Resonance-guided focused ultrasound (MRgFUS) has emerged in the last few years as a new therapy for neurological conditions and, specifically, for movement disorders[1]. MRgFUS technology employs a phased array ultrasound transducer to efficiently deliver ultrasound energy into a small brain target in order to produce a focal therapeutic thermoablation. Lesions are initially planned on intra-procedural MR imaging, and while the target is being sonicated, MR thermometry together with real-time clinical assessment provide control, safety, and clinical efficacy feedback on lesion placement. The rationale for the therapeutic use of brain lesions is based on the elimination of disease-related abnormal neural activity which underlies the occurrence of motor signs.

So far MRgFUS has been mainly applied to perform thalamotomy for tremor, including essential tremor[2], parkinsonian tremor[3], and secondary tremors[4,5]2 with dystonic tremor in the context of cervicobrachial dystonia and writer's cramp, and 1 with dystonia gene-associated tremor underwent MRgFUS targeting the ventro-intermedius nucleus (Vim. However, in the last few years applications have been expanded progressively, including thalamotomy for dystonia[6], and subthalamotomy and pallidotomy for the treatment of all Parkinson's disease motor signs and complications[7-10]. Conceptually, any condition that can be treated with deep brain stimulation could be approached using ultrasound ablation.

Like any new therapeutic approach (especially those which are invasive) ultrasound thermoablation has raised several legitimate concerns. The most relevant have been: 1. Unlike DBS, brain ablation by its very nature implies a permanent lesion and therefore the risk of permanent neurological complications; 2. The long-term effect of the therapy is still uncertain, especially considering that, unlike DBS, ablation cannot be "adapted" according to the patient's needs and clinical progression; 3. Bilateral ablative treatments might not be feasible as they have been associated with neurological side effects when performed with classical ablative techniques. Again, DBS is not constrained by this limitation.

Even though the literature on FUS is still relatively scarce, in the case of thalamotomy for ET the two former arguments have been addressed by studies reporting a very low rate (0.7%) of permanent severe side effects in large series[11] and by long-term follow-up studies (up to 4 years) showing that benefit is maintained over time[12]. Also, if there is a relapse in tremor, patients can effectively be retreated to reshape the scope of the lesion (authors own clinical experience).

Nevertheless, concerns regarding bilateral ablations have not been investigated yet. Our recently published case series shows that staged bilateral thalamotomy might be safe and effective for the treatment of ET[13]. In the context of a pilot study, nine patients (5 from HM CINAC, HM Puerta del Sur, and 4 from University of Zürich Hospital) who had received unilateral MRgFUS thalamotomy at least 5 months previously, underwent a contralateral ultrasound thalamic ablation. Lesions were produced in a staged manner because acute FUS thermoablation is associated with perilesional edema, and two simultaneous impacts in each brain hemisphere might not be well tolerated. Also, we selected patients who had not experienced any permanent side effect after the first intervention, in order to maximize safety. Our results showed that



Axial MRI slices on (from upper to lower row) T2- weighted, T1-weighted, SWI, FLAIR and diffusion weighted sequences showing the lesion's appearance at 24hr and at 3 months after the first (T1) and the second (T2) interventions (left columns and right columns, respectively) in a representative patient (P1). The axial images are oriented along AC-PC. The red line in the T2w images (upper row) indicates the edges of the lesion. [13]

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staged bilateral ablation improved tremor in both hands, remarkably, without the occurrence of any permanent adverse event. Although several patients presented gait instability after the second treatment (which is also frequent after unilateral ablation[11] they all completely recovered. Interestingly, axial tremors such as voice and head tremor also improved, which is not the case with a unilateral approach. Supposedly, the main reason why bilateral ultrasound lesions were not associated with permanent neurological complications is related to the reduced invasiveness of this incisionless technique that avoids skull opening and electrode penetration, unlike ablative surgical procedures performed in the past.

Our report has obvious limitations, such as the small sample size and the open-label design. For those reasons, we should proceed with caution regarding the interpretation of the results, and further validation must be pursued, as the potential occurrence of adverse events cannot be ignored. However, this initial experience warrants a more ambitious trial (i.e. larger sample, with a control group) to define the risk-to-benefit ratio of bilateral thalamic ablation for ET and determine whether this approach can be translated into regular clinical practice.

Summarizing, our study constituted a necessary initial step to hopefully pave the way toward a new therapeutic option for patients with ET.

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Huntington's Disease in Africa and the Middle East: A Call for Action

— *Shaimaa El-Jaafary, MD, Associate Professor of Neurology, Cairo University, Egypt*

Huntington's disease (HD) is an autosomal dominant fatal neurodegenerative disorder, characterized by motor, psychiatric, behavioral and cognitive symptoms. The disease is underreported in Africa and the Middle East, where the information on epidemiology and management of HD is scarce. Here we are trying to focus on Huntington's disease in the region highlighting some of its challenges.

The Prevalence:

The worldwide prevalence of Huntington's disease is heterogenous and it differs from region to another, with more than tenfold difference between regions across the world[1].

Though there are many case reports with confirmed CAG repeat expansions have been described in different countries across Africa, the prevalence of Huntington's disease is still underestimated.

In their systematic review, Rawlins and colleagues reported very low prevalence rates among blacks in South Africa (0.02, 95% CI 0–0.5 per 100,000) and Zimbabwe (1.00, 95% CI 0.48–1.84 per 100,000). On the other hand, Baine et al. reported higher prevalence reached 5.1, 2.1 and 0.25 (per 100,000 individuals) for the white, mixed ancestry and black population groups respectively in South Africa.

Reports from North Africa are non-conclusive with a study done in 1994, from which the prevalence of the disease in Egypt was estimated to be 21 per 100,000, which is considered the highest prevalence reported worldwide, since that no other epidemiological studies were done to confirm. Other countries in the region including Tunisia and Morocco[2] have some reported cases of HD, still lacking a proximate prevalence of the disease.

Concerning the prevalence of the disease in the Middle East, it is not yet clear. In 2009, Scrimgeour[3] reported an estimate of 3-4 per 100,000 based on few available studies from some countries in the region. In 2019 Squitieri et. al,[4] reported a prevalence estimate of 7.36 per 100,000 inhabitants from the Muscat region of the Sultanate of Oman.

There is a need to start national and regional registries for HD cases and to conduct more epidemiological studies to estimate the incidence and prevalence of the disease in Africa and the Middle East.

The Genetics:

HD is caused by the presence of an expanded number of CAG repeats in the HTT gene on chromosome 4p16.3.

It worth mentioning that there is high ethnolinguistic and genetic diversity in Africa. Genetic testing for Huntington's disease was performed in Africa as early as in 1994, mainly in South Africa[5], where direct mutation testing for HD has been available. Diagnostic, prenatal, and predictive testing for HD is available in south Africa[6], but not in every African country, making the diagnosis even more challenging. Genetic counselling services are provided also in South Africa but very deficient or even absent in other African countries.

Concerning HTT CAG expanded alleles and haplotypes, compared to European and Caucasian populations, where they are typically found on haplogroup A, in Black African and East Asian populations, they are more commonly found on specific variants of haplogroups AB and C[7,8].

Squitieri and colleagues[9] investigated the ancestral origin of HD expanded alleles in some families in Oman (a middle eastern country) and showed that most HD families from the Middle East, including three from Oman, shared an A2b haplotype that was similar to Europeans.

A lot of work is needed in these regions to identify the common haplotypes and alleles for future allele specific antisense oligonucleotides therapies for Huntington's disease.

Another challenge in genetics of HD in Africa is the presence of phenocopies especially Huntington's disease like type 2 (HDL2) which has different gene location and different repeats; a CTG/CAG expansion mutation in exon 2A of the junctophilin-3 (JPH3) gene on chromosome16q24.3[10]. HDL2 has a clinical picture and radiological findings similar to HD with some subtle changes[11].

The availability of genetic services for diagnosis and counselling is highly required in the region in a reasonable price. This necessitates providing good equipment and sufficient training in more centers distributed across the region in Africa and the Middle East and facilitate sample transfer when needed.

Clinical Presentation:

The presentation of the disease is variable, with some reports showed psychiatric manifestations were the presenting symptoms at onset, while others reported the abnormal movement to be the first symptoms. Still there is a need to have cohorts to characterize the phenotypes of HD in different countries in the region.

Awareness and Support Groups:

There is marked lack of awareness about Huntington's disease in Africa and the Middle East, this also contributes to the underreported cases in the region. There is a problem in seeking medical advice, and also a lack of trained neurologists who can recognize and diagnose the disease. There is also lack of the supportive care provided for patients and their caregivers across Africa and middle east. The knowledge about the disease is still in its infancy, with very little resources in local languages to spread awareness.

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Huntington's Disease in Africa and the Middle East: A Call for Action, *continued from p. 18*

Recently there are some efforts and initiatives to raise awareness about the disease, for example the Huntington's disease Africa as an advocacy group https://hd-africa.org/ , for the Middle East there are the Oman's Huntington's disease association. There are some initiatives in Egypt to raise awareness by translating some articles and creating some educational materials about the disease in Arabic languages, with some translated articles from HDBuzz are now available in Arabic. https://ar.hdbuzz.net.

There is a need to connect to the international associations providing support to patients with HD and their families e.g. the international Huntington's disease association (IHA), The European Huntington's disease association (EHA) and the Huntington's disease youth organization (HDYO), and to encourage founding more local and regional associations.

Access to Care:

The access to care is still limited to patients in Africa and some of other Middle Eastern countries. Not all patients in these regions are covered by health insurance, and they have to pay the high cost of the treatment[12]. The Multidisciplinary care of managing the disease is also not well established, with little known about the role of non-pharmacological intervention (e.g physiotherapy and speech therapy and how to apply them in different stages of the disease).

Social Aspects of the Disease:

Since 1980 when Hyden and colleagues[13] reported the social aspects of HD nothing was mentioned. In their report they discuss the social burden, the suicidality, crimes, and the economic burden. The burden of HD is not discussed at all in the Middle East.

Trained Neurologists and Specialized Centers

As reported by Scrimgeour 2009 the average doctor in the Middle East may never encounter or recognize a case with HD, though there are many cases reported from different countries, this applies also to Africa. Another problem is the inadequate numbers of neurologists in relation to the population number in different countries in Africa and the Middle East.

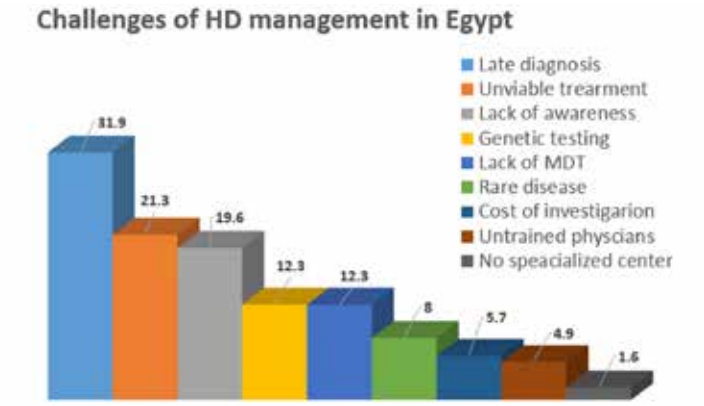
In order to overcome the problem of inadequate trained neurologists, educational courses and fellowships are important and to encourage the enrollment of neurologists as well as non-neurologists involved in the management of HD from the region. This is nicely done by the Movement disorders society (MDS) providing a variety of teaching courses and educational materials about HD. This effort was even more appreciated at the time of COVID-19 pandemic where all courses were available online for free for all MDS members.

Another good opportunity for young neurologists is the EHDN-MDS Fellowship, which provide training on Huntington's disease at one of expert European centers. Applicants from countries with fewer resources have the chance to stay for six weeks or so and train on the diagnosis and management of the disease, many different aspects of the disease and the current clinical trials.

Another initiative taken by the IHA is to hold meetings for Arabic countries, to introduce the disease from its different aspects and how to deal with patients in different stages.

The first meeting was held on June 25, 2021, in English, hosted by Prof. Bernhard Landwehrmeyer from Ulm, Germany, where many expert speakers in the field were invited to give talks. The meeting provided an overview on HD and its different stages, the motor manifestations, the cognitive and behavioral manifestations, the genetic diagnosis and counselling, caregiver experience in some of Arabic countries, the status of HD in the Middle East, and how to decrease the gap between the Eastern and western countries in HD management.

It is worth mentioning that short survey was conducted on the challenges facing neurologists while managing Huntington's disease in Egypt. The responses from 140 participants showed that results late diagnosis (31.9%) or misdiagnosed cases, unavailable treatment and no cure (21.3%), lack of awareness about the disease among physicians and public (19.6%), the genetic testing is inadequate, not present in every center (12.3%), lack of multidisciplinary and supportive care (12.3%), less frequent responses included; lack of experienced specialists, rare disease without funding for researches, no specialized centers, lack of facilities for the patients and their families[14].



In conclusion, action is needed in Africa as well as most of countries in the middle to achieve following: implementing national registries, spreading more awareness, providing more educational courses and training opportunities, encouraging collaboration across Africa and middle east as well as international collaboration in fields of patient care and research, creating more supportive groups for the patients and families for more awareness and to erase the stigma, providing more information about the disease in different local languages, fund raising for research on Huntington's disease in Africa and the Middle East, and to establish specialized HD centers for better care and research.

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Huntington's Disease in Africa and the Middle East: A Call for Action, *continued on p. 20*

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https://huntington-disease.org/
http://www.ehdn.org/
https://en.hdyo.org/

MJFF Editorial in the *Journal of Parkinson's Disease* Emphasizes the Need for Diversity, Equity and Inclusion in Research

— Bernadette Siddiqi, MA, Senior Associate Director, Research Engagement, The Michael J. Fox Foundation for Parkinson's Research, New York, NY, USA
— Andrew Koemeter-Cox, PhD, Senior Associate Director, Research Programs, The Michael J. Fox Foundation for Parkinson's Research, New York, NY, USA

Bernadette Siddiqi, MA

Andrew Koemeter-Cox, PhD

Though knowledge of the causes and progression of Parkinson's disease (PD) is growing, most research has not been inclusive of the broader community of people with Parkinson's. As a result, our understanding of how PD affects patients and families across racial, ethnic, socioeconomic, gender, sexuality and geographic spectrums is incomplete. In a new position paper published in the ***Journal of Parkinson's Disease***, we discuss the critical need to close this gap by engaging diverse people in clinical studies of the disease. To ensure that the breakthrough treatments we seek benefit the widest possible range of people living with Parkinson's, studies must include the widest possible range of participants.

Though factors driving disparities in society are complex, researchers, doctors and patient communities must make concerted efforts to eliminate inequities in healthcare. Making research more representative of the community will broaden our understanding of PD, which can only lead to strategies for reducing risk and developing treatments for all.

The Michael J. Fox Foundation (MJFF) is committed to reducing health disparities and advancing treatments for everyone with PD. To help achieve these goals, the paper outlines four major areas of action:

- identifying barriers and solutions to research participation
- enrolling representative research groups affected by disease
- building a diverse and inclusive clinician/researcher workforce
- supporting a more holistic understanding of PD

The position paper also highlights steps the Foundation is taking in each of these areas, including a new funding program to promote diversity, equity and inclusion in Parkinson's disease research that was launched earlier this year.

Despite being new and taking a unique angle to research, the program received 98 preproposals, which was on par with our established programs. This included many new to Parkinson's research and a strong international presence from 25 countries in six continents. This program will support interdisciplinary teams of PD researchers, physicians and community organizations engaging Black, Latino, Asian, Indigenous groups and LGBTQ+ communities, as well as individuals from underprivileged socioeconomic circumstances. Such collaborative efforts aim to identify and implement strategies that can dismantle barriers to participation for underrepresented groups. Selected projects are expected to be funded in late 2021.

This position paper is the first in a series of perspective pieces that will be published in the *Journal of Parkinson's Disease* to increase awareness of the current state of Parkinson's research along with available resources and infrastructure for investigators. The partnership is a unique opportunity to underscore the greatest unmet needs of the Parkinson's community and galvanize researchers to address them.

Read the full editorial : A Call to Action: Promoting Diversity, Equity and Inclusion in Parkinson's Research and Care

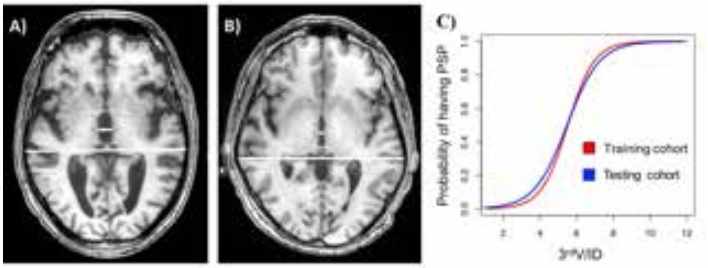
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

MR Imaging Biomarkers for Parkinsonisms: It's Time to Use Them in Clinical Practice

— *Andrea Quattrone, MD, Institute of Neurology, University "Magna Graecia", Catanzaro, Italy*

Over the last decade, a plethora of imaging biomarkers to differentiate among neurodegenerative parkinsonisms have been developed.[1-6] The majority of these biomarkers are based on the combination of imaging data (atrophy, DTI alterations, FDG-PET metabolism) of different brain structures, and require machine learning algorithms.[5-8] The main advantage of this approach is the possibility to maximize the diagnostic accuracy, moving beyond the group-difference level and allowing to use these biomarkers for the differential diagnosis at the individual level. On the other hand, the disadvantage is the complexity of these biomarkers, which often requires high-level technology and engineering expertise to perform the MRI post-processing procedures, limiting their use in clinical settings.

In an effort to develop a biomarker which could be performed directly by clinicians in the absence of specific expertise, a very recent study[9] proposed a new simple MR measure to early distinguish between Parkinson's disease (PD) and progressive supranuclear palsy (PSP) patients, based only on the 3rd ventricle width, normalized by the internal skull diameter (3rdV/ID = 3rdV width*100/internal skull diameter). The 3rdV is a structure typically enlarged in PSP and spared in PD, and its width can be easily measured on routine axial T1-weighted MR images, combining high diagnostic accuracy with extreme simplicity. In this study, the 3rdV/ID has been validated in two large independent patient cohorts, one from a single Italian center and the other from several international research groups, to ensure the generalizability of this biomarker. The study showed a strong association between 3rdV/ID values and PSP diagnosis, demonstrating that the higher the 3rdV/ID value, the higher the probability of having PSP rather than PD. This biomarker yielded high diagnostic performances in distinguishing PSP from PD in both cohorts (AUC: 0.94 and 0.91, respectively), and the optimal cut-off was 5.88. A key result of this study was that the 3rdV/ID accurately differentiated patients in the early stage of the disease (PSP patients in the first years from the disease onset and de novo PD patients). This is of great importance because the differential diagnosis between PD and PSP is much more challenging in the early stage of the disease, when the typical PSP clinical features (postural instability and vertical ocular dysfunction) are still mild or absent. Of course, the 3rdV/ID is not the first MR biomarker to differentiate between PSP and PD to be proposed. A recent review[1] summarized the current radiological biomarkers for PSP, and pointed at the Magnetic Resonance Parkinsonism Index (MRPI) as one of the most reliable imaging biomarkers for the diagnosis of PSP, also in the early stages. The MRPI[10] and its new version (MRPI 2.0, which includes also the 3rdV measurement)[11] are extremely powerful biomarkers for PSP diagnosis, but their complexity is the reason why MRPI biomarkers are only used for research purposes. This study provides a strong impetus for using simple biomarkers in clinical practice in addition to clinical criteria for improving differential diagnosis and selection of patients in clinical trials on disease-modifying treatments.



Subcallosal axial T1-weighted volumetric MR images showing the measurement of the third ventricle width and the internal skull diameter (ID) in a patient with PSP (A), and in a patient with PD (B). Measurements were performed at the level of the third ventricle's maximum dilatation as the largest left-to-right width between the lateral borders of the ventricle in its central portion. The maximum ID was also measured on the same axial slice. Images show marked dilatation of third ventricle in the PSP patient in comparison with the PD patient. Figure 1C shows the probability of having PSP for each 3rdV/ID value in the training (red) and testing (blue) cohorts obtained using logistic regression models. The probability of having PSP increased with higher 3rdV/ID values.

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Parkinson's Disease Awareness in Africa: The SEE Initiatives

— Omotola Thomas, African Parkinson's Advocate, Founder & Executive Director of Parkinson's Disease Africa
— Mie Rizig, PhD, Senior Clinical Research Fellow, University College London; Lead Coordinator, IPDGC – Africa

On World Parkinson's Day, April 11, 2021, Parkinson's Africa and the IPDGC-Africa[1] launched a collaborative project called **S.E.E. Parkinson's** - a health literacy initiative seeking to provide the Support, Education, and Empowerment resources needed to improve the health outcomes of Africans affected by Parkinson's disease. The initiative, designed to break through language barriers by providing Parkinson's disease educational resources in several different African languages, is being sponsored by the UCL Grand Challenges and Global Engagement Offices.

The World Parkinson's day launch was very successful and well attended by Parkinson's patients, relatives, and healthcare workers from Africa and around the world. The purpose behind the initiative was jointly introduced and explained by Mrs. Omotola Thomas (Founder and Executive Director of Parkinson's Africa) and Dr. Mie Rizig (Senior Clinical Research Fellow at UCL and Lead Coordinator of the IPDGC - Africa).

Health literacy (HL) is described by the World Health Organization as the ability of individuals to "gain access to, understand, and use information in ways which promote and maintain good health". HL skills are especially important when it comes to managing complex chronic illnesses like Parkinson's disease; yet, across many parts of Africa, the resources required to develop these HL skills are largely unavailable or inaccessible. The **S.E.E. Parkinson's** initiative seeks to change that dynamic by creating educational resources in print, digital, and video formats, which will then be translated into several different African languages. With Parkinson's disease being the fastest growing neurological condition in the world, and as the number of diagnosed cases in Africa increase, the **S.E.E. Parkinson's** initiative seeks to provide the growing population the **S**upport, **E**ducation, and **E**mpowerment resources they will need to make informed health decisions about Parkinson's disease.

The launch also featured the release of "Faces of Parkinson's - Africa" - a moving Parkinson's disease awareness video shot and produced in Kumasi, Ghana. The video, created to highlight the realities of living with Parkinson's in Africa, featured several Parkinson's patients and relatives from the Anidaso Parkinson's Disease Foundation (founded by Dr. Vida Obese).

The program closed with a recognition of different Parkinson's support groups that are serving their communities in Nigeria, Uganda, Ghana, Cameroon, Kenya, South Africa, and Ethiopia. Following the official close of the event, the organizers stayed on and gave the attendees to ask any questions. This impromptu session lasted for about 45 minutes and was a very engaging session. Several questions were asked by patients and their relatives; healthcare workers in attendance, in addition to the organizers, answered these questions. The questions covered a broad range of topics including the lack of PD awareness in Africa, the lack of access to healthcare and medication, and the lack of educational resources.

For more information about the S.E.E. Parkinson's initiative, please visit: www.parkinsonsafrica.com

https://www.ipdgc-africa.com/

Link to the video: https://youtu.be/GlCa_rErykI

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How Would You Approach This Case? Follow-Up: Sunflower Syndrome

— *Fiona Baumer, MD, Assistant Professor, Department of Neurology, Division of Child Neurology, Standford University, Palo Alto, CA, USA*
— *Sonal Bhatia, MD, Division of Pediatric Neurology, Medical University of South Carolina, Charleston, SC, USA*
— *Mahesh Chikkannaiah, MD, Assistant Professor, Neurology and Pediatrics, Boonshoft School of Medicine, Wright State University, Dayton Children's Hospital, Dayton, OH, USA*
— *Charuta Joshi, MD, Professor, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO, USA*
— *Kristina Julich, MD, Assistant Professor, Department of Neurology, University of Texas Health Austin Pediatric Neurosciences, Dell Children's Hospital, Austin, TX, USA*
— *Jennifer Friedman, MD, Clinical Professor, University of California San Diego, Del Mar, CA, USA*

The video link in the last issue's survey demonstrated a case of Sunflower Syndrome. This condition is a rare and fascinating photosensitive epilepsy in which affected patients have a strong attraction to bright light, particularly sunlight, and wave their hands with fingers abducted in front of their face while facing the light. The action creates a flicker effect and is associated with onset of spikes on EEG. During this EEG discharge, patients' response time may slow or they may exhibit eyelid fluttering (epileptic myoclonus of the eyelids), but they usually remain responsive. Typical onset of seizures is in early to mid-childhood, and only some patients develop additional seizure types.[1] While the "hand-waving" movement is the best described motor phenomenon associated with the syndrome, some children present with more subtle movements such as rubbing the forehead while facing a light source.[2] Given the highly stereotyped semiology of the movements and childhood onset of these episodes, patients are often diagnosed as having stereotypies or tics rather than epilepsy.

There is significant debate as to whether the hand-waving seen in Sunflower Syndrome is a voluntary movement over which patients have some control or whether it is part of the seizure. The corollary of this question is whether or not seizures are "self-induced." Early case series dating back to the 1950s describe patients who reported either a pleasurable sensation or reduction in stress during the episodes, leading some physicians to conclude that the hand-waving was purposeful or a tic.[3] In support of this theory, some children continue to have spontaneous hand-waving episodes even when anti-seizure medication therapy has successfully suppressed epileptiform abnormalities.[2] In contrast, several authors[3,4]photosensitive epilepsy characterized by an attraction to light and highly stereotyped seizures with associated hand-waving (HW have argued that the hand-waving must be part of the seizure because it precedes EEG abnormalities only by a few seconds, which would be too short of an exposure to flickering lights to induce a seizure by itself. These authors suggest that while the light-seeking behavior itself may be a compulsion, the hand-waving is "light-induced" rather than "self-induced."

Characterizing the nature of the hand-waving is of great interest, because the seizures in Sunflower Syndrome are notoriously difficult to treat. While most photosensitive epilepsies respond to one of several antiseizure medications (most typically valproic acid, ethosuximide, benzodiazepines, lamotrigine, or levetiracetam),[5–7] hand-waving episodes are often refractory to these therapies; we have seen the best response to valproate.[2] Several groups have tried treatments more typically used for movement disorders, including pimozide,[8] stimulant therapy,[9] and various forms of psychotherapy,[10] but there is not yet strong data supporting these practices. Recently there has also been a resurgence of interest in fenfluramine,[11] and we are awaiting results of an open-label trial of this agent. Regardless of the etiology of these movements, care of these patients requires thorough counseling on trigger avoidance,[12,13] including the use of brimmed-hats and sunglasses. In Europe, Zeiss[14] blue lenses have been shown to limit photic-induced seizures, but these are unfortunately not readily available and very expensive in the United States.

The semiology of Sunflower Syndrome overlaps significantly with common pediatric movement disorders: tics and stereotypies. The commonalities, however, extend beyond superficial appearances to also include the internal trigger that initiates the repetitive movement. As noted for Sunflower Syndrome, whether the origin is voluntary or due to epileptic phenomena is uncertain. For tics too, the genesis of the urge defies clear categorization leading some authors to coin the term "un-voluntary" reflecting the combination of both voluntary and involuntary drives to perform the movement.[15] Some have concluded that though the premonitory sensation is involuntary, the movement is typically perceived by the patient as a voluntary action to relieve the preceding, underlying discomfort.[16,17] Whether these shared features

How Would You Approach This Case? Follow-Up: Sunflower Syndrome, *continued on p. 25*

How Would You Approach This Case? Follow-Up: Sunflower Syndrome, *continued from p. 24*

are a clue to underlying overlapping brain circuitry remains to be seen. Improved recognition of Sunflower Syndrome and increased study of both conditions will lead to improved treatment options for patients.

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Translational Research in Africa: An Interview with Mohamad Salama

Mohamad Salama, MD, PhD

Shaimaa El-Jaafary, a member of the Moving Along Editorial Board, recently sat down for a virtual interview with Mohamad Salama, MD, PhD, Associate Professor at The American University in Cairo, Egypt, to discuss translational research and neuroscience in Africa.

Shaimaa: Dr. Mohamed Salama is Professor at the Institute of Global Health and in Human Ecology in the American University of Cairo. The founder of the Egyptian Network for Neurodegenerative Diseases. The founder of the Egyptian Genome Project. Awardee of many awards for Parkinson's disease and the founder of many international collaborations, including a steering committee member of the MDS Basic Science Special Interest Group. We are very happy and excited about your presence with us today, talking about the translational neuroscience in Africa and the gap between the basic science and clinical science. Let me start by asking, how did you become interested in this field, translational and neuroscience?

Mohamed Salama: First of all, thank you for the invitation and willingness to have this interview with me. The point here is, why I was interested in transnational neurodegeneration. Initially, I started trying to get engaged with a lab in Europe, in Germany. To be honest, first step I was looking for working as a basic neuroscientist, lab man. But once I entered the lab, My professors there asked me one question, "Why are you wasting all your previous studies as a medical graduate? One of your strengths is, you are a physician, so why are you wasting all your time, study and efforts and so on, and just focusing on basic research?" And he made a model for himself, because he is a physician and in the meanwhile he's a professor for neuroscience and he has a very active lab, working with animal models and cell culture. So he said, "Okay you can keep both tracks. You can play the role of crossing the gap between basic scientists, because you will see many of our researchers here, working in the lab, and they have no clues about what's happening in clinics and on the other hand you will find of our neurologists working in the hospital and they don't understand very well the main mechanisms or the main techniques working in the lab. Why not crossing this gap?"

So, I started thinking and the other important point he told me is that, "If you focused mainly on basic science, you will not be competitive to those who are hardcore scientists, those who are working mainly in the lab, and they have all their training as basic scientists. So it's better to gather all your strength points and come up with new model." He was establishing by that time a department called "Translational Neurodegeneration." And I found that according to him, the quality of papers, the quality of research projects, the number of funding, or funded grants he achieved, is increasing or getting higher, because he's targeting this critical point, which is Translational Neurodegeneration. Not mainly working in the lab, not mainly working in the clinic, but crossing this gap between the two areas. And most important, it is a so far unmet need in most of areas, not only in Africa, but everywhere, you will find this missing person, who can cross this bridge.

And I thought, "Why not, since it is still missing also in Europe. Certainly, it will be missing in Egypt and Africa. Let's return to Egypt and start to implement the same model I joined in Germany for a while." This is how I started being interested in translational neuroscience for neurodegenerative diseases.

Shaimaa: I think you have already covered the second question, which is "How do you see the gap between the basic and the clinical research in Africa?"

Mohamed Salama: When we are talking about active neuroscientists in Africa, you will find that the majority are working in the field of neurology. So they are in fact, neurologists. We do not have this critical mass of neuroscientists who are interested in working in the field of neuroscience, or basic neuroscience. We are not very similar to Europe or America where we have two large groups. Basic neuroscientists and neurologists for example. No, we have, let's say 80% as neurologists and only 20, or even 10% those who are specialized in neuroscience.

The second issue here is that I have been chatting with many of my colleagues, or researchers and when I start talking about translational research in general, they feel very excited and say, "Yes, certainly, it's very important." However, when you start asking them, "Do you know examples for translational research?" they do not answer. Yeah, they think it is something very new, it's a totally new discipline, but they don't know what it is.

And because most of them do not know the concept of translational neuroscience, or in general, translational research, they prefer not to approach this vague area. This is another major issue. They think that is a totally different branch of science. So, I am working as basic neuroscientist, why am I changing my career? I am working as a clinical neurologist, why am I changing my career? They do not understand that the idea is, you are not changing your role at all, just you are accepting to work with others. So, instead of working mainly in clinical research, or working mainly in basic neuroscience research, you have the appetite to collaborate with others from different disciplines.

Shaimaa: How can we decrease this gap between the clinical and the basic neuroscientists in Egypt and in Africa?

Mohamed Salama: I guess the first thing is to start bringing both sides to this, and we have to invite basic neuroscientists to neurology

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conferences and start bringing neurologists or clinicians to basic neuroscience conferences. Also, dedicating some sessions for the introduction of this concept translational research, translational neuroscience. Try to introduce concepts to both sides. And to underline the most important point here, is that we are not starting a new research. You are not changing your role at all; just we are making bigger teams. So instead of one person or two persons working in the lab, no we are bringing clinicians, artificial intelligence experts, geneticist, and we are establishing one team.

So, you will still continue doing the same thing you have learned to do for the past 10 years. But we are piecing together those pieces of the puzzle to have the whole picture. So this is the most important to, I do not want to say teach, but at least increase awareness about how it works. How we can do translational research and on the meanwhile, each one is preserving his rights, his quality of work, his type he is doing, or the style he's doing his work.

Shaimaa: Is this one objectives of the MDS Basic Science Special Interest Group?

Mohamed Salama: Yes, exactly. And according to last discussion, we thought it's very important to underline or emphasize this, and that is why we are starting to hold several meetings and we are trying to even organize separate sessions in different international meetings to increase awareness about this. As I poked them last meeting, we have also the other problem that we don't have enough critical mass of neuroscientists in Africa, so we have at least to understand or evaluate the current situation. How many neuroscientists are working in Egypt, in Tunisia, in other African countries? Start bringing them to the board and trying to attract them or make it more appealing to join their clinical colleagues in one thing.

Shaimaa: How do you evaluate the infrastructure for translational research in Egypt and in Africa? Are we ready or we are still lacking resources?

Mohamed Salama: I do not think we are lacking resources in term of equipment or machines or even scientists. Maybe some high-tech specialties, but in general, the experts are there. Most important is that we are lacking the understanding of the concept itself. As I mentioned previously, when you start talking about translational research, they think that it is a totally different way of doing research, a different discipline. No, we have just to emphasize that it is a new concept of how you could do your work through joining bigger groups. We are missing this concept. We are missing the appetite to join big team, for example. Each one will say, "No okay, no I prefer to continue working with my own team, just two or three partners working in this area," and others, same way. So we are missing this interest in expanding, in collaborating, in working with other countries. Maybe I would say, also, somehow we are missing the confidence, the total trust on other partners.

Sometimes I speak with the basic scientists and they feel, "Okay, those clinicians are very arrogant. They don't want to listen to us." On the other hand, when I start talking with clinicians, they said, "Okay, those scientists are always talking about mechanisms and signaling and genetics, and we feel we are superficial." We are not missing the infrastructure regarding the money, the funding or the equipment. The more part we are missing is the appetite to collaborate, and I think we have to encourage this in the coming years.

Shaimaa: You are very active about bringing international collaboration into the continent, not only Egypt. What are the values of having this international collaboration, and what are they bringing to us, and how to make good use of this international collaboration?

Mohamed Salama: We have first to differentiate between international collaboration and exploitation. Because many times, you are eager to bring international collaborators and you feel that, okay they are not offering capacity building or bidirectional collaboration, no, they are just aiming at bringing some samples from the African continent and they do their research outside Africa, publish a work and then put your name and that's it. This is not a collaboration. From my perspective, a collaboration means that the international partner, let's say European or American, has a need to understand, to have better understanding for the disease aspects in Africa, and we as African researcher want to learn more and increase our capacities to do research. In this regard, certainly, it would be a valuable collaboration and we are in a great need of it. We are in need of money for funding. We still need to learn more in different aspects, especially high tech and cutting-edge technology and so on, and we need to send African junior scientists to get more training. For Europeans or for Western scientists as well, they need to learn more about the disease.

I remember I had a chat many years ago with one expert in Parkinson's disease genetics and he was telling me that, "Okay, we didn't know everything about Parkinson's disease, because we are doing our homework in Europe. We are discovering new genes and new mechanisms of the disease and new risk factors. But in Africa, for example, and some other areas of the world, it is unexplored disease, so we don't know about the risk factors in African genetics, and certainly there should be some changes or differences between genes for different diseases in Africa and in Europe, so they need to learn more about other aspects of disease in order to have the whole picture, and we need to improve our capacities. So, international collaboration or partnership is highly needed, highly required, but as I mentioned, we have to differentiate between a scientific, respectful partnership and what we call exploitation. Someone's coming to take few samples and run away back to his country and that's it. This is totally unacceptable. For us the most important, certainly number one is capacity building and also providing expertise and funding. Yes I understand that we cannot do everything inside Africa.

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100% of the work tasks, the task needed. However, you have to judge the quality of such collaboration by the increase of the percentage of work you are doing at the time of collaboration proceeding. So, in the first year, I understand that maybe 50% of the work should be done in Europe. In the second year, let's say 30%. In the third year, 10% and that's it. If we are progressing, if we are improving the percentages we are contributing to the work, this means we are improving our capacities. I would say that hopefully in five years or 10 years we should be able to do everything technically. In South Africa, the rule of the European partner would be, the data analysis finally, so we sit together and we say, "We did this part in Africa, you did your work in Europe. We are comparing between both worlds." This should be the ultimate goal of such collaboration.

Shaimaa: It's a very, very optimistic view for the future and I hope we can establish this in the real world, because it's not impossible.

Mohamed Salama: Not impossible, and we have a very good example in Latin America. I know my very good friend Agustin Ibañez, he established the ReDLat. It's a Latin America consortium for dementia. Certainly, they depend on expertise in the United States, but step-by-step, now, they have increased their capacities, they have improved their research potentials and they are thinking now of establishing a separate institute inside Latin America that is more or less on equal footage with similar instate in the States. So, this is a model. We can replicate somewhere, it's not a problem. I guess we have brilliant minds and we have excellent minds who have just returned from Europe. They have their PHDs or postdocs, so why not invest on those people?

Shaimaa: Yes, that is very inspirational. What are the challenges about the international collaboration? Is it a challenge in establishing the collaboration, or implementing the projects from that collaboration?

Mohamed Salama: No, not establishing the collaboration, because as I know, there is a high tendency among Europeans and Western world now, to start collaboration with Africa, to explore more the unexplored features of the disease, so there is a tendency to start a collaboration. Many of the funding organization are initiating funding programs for underrepresented populations, so there is an opportunity to get money. The challenge as I mentioned, is to differentiate between a real collaboration that's built on equal partnership and the other types of, not collaboration as I said, it's exploitation, where you are trying just to get some data from me and I'm not your partner.

To differentiate between real partners and those who are not looking at African scientists as real scientists. Once we identify those who can really start a partnership, those who are keen to start a capacity building program, those who are happy that you are increasing your percentage of work, you are improving your potentials and those who are looking at you as real scientists, that one day you could do everything inside your continent and then we start discussing and chatting and trying to analyze the data together. Those are real partners.

Those who are the ones who we should invest in their partnerships. So the challenge is to identify those who are the real partners, the real scientists, the real European or American scientists, who are looking for a real or equal footage partnership. This is the main challenge. Another important challenge as well, is to convince authorities in different African countries that international partnership and collaboration is a must. To be honest, we cannot do high quality research without that help. At least in the current stage. So, no harm with collaboration as far as we have the regulations and guidelines that control everything.

So, there's no harm to start collaboration for example in a huge project regarding genetics, regarding risk factors with international experts to understand and learn from them. Guided that everything is approved officially and everything is under control and everything is transparent, the protocols are there available and we have official agreement between different institution. And to convince authorities that this international collaboration is a step for capacity building. Without such initial step, we cannot move forward.

So, the two major challenges are to differentiate between real and unreal partnership, and to convince authorities with the value of partnerships.

Shaimaa: Moving to the important project of Parkinson's disease genetics in Africa. Let us talk about the IBDCG Africa: What is the importance of this project for genetics of Parkinson's in Africa?

Mohamed Salama: Thank you very much for bringing this to the discussion. As we mentioned, the genetics of Parkinson's disease is still understudied. We don't know many things about the genetics and different patterns of Parkinson's Disease, and in world where we are talking about precision and personalized medicine and personalized health and so on, this would be a huge gap, a huge missing group of data that will endanger our ability to enter the precision health. If we don't know the types of patients, if we don't know the genetics of patients, how come we are going to advise individualized patterns of treatments? The IPDGC Africa, International Parkinson's Disease Genomic Consortium African Chapter, is an initiative. A huge project certainly to cover this area. So the plan is that, as I mentioned previously, we will start a capacity building program. Initially, we will try to explore the available capacities all over Africa.

Those who are willing to collaborate in this consortium, I guess now we are talking about ten or eleven African countries willing to collaborate. Step-by-step, the ultimate goal of IBDGC Africa is that all African neurologists working in the area of Parkinson's Disease who are actively working in the area, can conduct research inside Africa. That we eventually have a whole understanding of the genetics of Parkinson's disease inside Africa.

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Certainly, we will have several activities. Some of them is training and some internship and some fellowships, and certainly some genotyping activities and analysis. But the very nice thing about IBDGC Africa is that we aim that most of the work is done already by African scientists, clinicians, potential geneticists, neuroscientists, data analysts and now I guess we are starting to offer some potential capacity building programs, activities and fellowships as I mentioned. So, this is the right track to start with. I guess IPDGC Africa is very nice platform to give an example of what is meant by international collaboration. We are collaborating with international partners, European partners but in term of capacity building, in term of improving our potentials, hopefully by the end of five years, we have a much better understanding of generics of Parkinson's Disease in Africa, in addition to a higher capacities of African scientists to conduct similar studies in their own countries, by the end of the five years.

It's a very, very, very strong initiative. Hopefully, it will succeed to bring African neurologists, neuroscientists and geneticists together. Hopefully by the end we would say that we have now the capacity to conduct our research inside the African continent.

Shaimaa:This takes us to the Egyptian genome project. What is peculiar about the Egyptian genome by itself?

Mohamed Salama: I like this, but first I have to say that I am one of the partners, or one of those who were working on the research initially, and now I am on with the national project of the reference gene. There is nothing peculiar in term that we have strong genes, or we have better genes or worse genes, certainly not. But the issue here is that each population should have a group of common variants that differentiates them from others. And that's why, for example, you will find that certain gene risks are higher, for example for Parkinson's disease than other countries, and you find this in everywhere. The genes contributing to Parkinson's disease in China is different, is different from America, is different from North Africa and so on. The concept here, is that before we identify the disease genes, we have to identify the normal pattern of gene. And this is a reference genome.

Initially it was thought that, "Okay, we will have a human reference genome, and this will cover everything." And then step-by-step geneticists started to understand that no, it will not cover everything. The reference genome built on European ancestors, are somehow different from the reference genome form North Africa for example, for South Africa, and so on. That's why different countries worldwide are starting to establish or assemble their own reference genome. This is the first step to start analyzing the data you have from your patients' cords, to identify risk genes, or genes responsible for this.

First, we have to know our normal pattern of genes, our set of normal variants and then say "Okay, we can now compare the patients' genetics with the normal variants and try to filtrate and try to identify possible pathogenic variants. And this is not something new, as I mentioned, so we have different countries, so even the Middle East started their own project. Our research, our initial research identified, I would say the very early base for such activity, Certainly with the national project now handled by the Minister of Higher Education and Academy of Scientific Research, we hope that we will enlarge this number of recruited subjects and certainly we we'll have more confidence in the data. More robust data that we can finally say that we have a reference Egyptian genome comparable, for example to the UK reference genome, the genome built on 100,000 case. We can do the same in Egypt, I guess, especially with the resources available now by the Egyptian government.

And for those who have been working in genetics of diseases for years, we were missing such a thing. We were facing problems, trying to imputing the data we have done in studies or similar studies. Now, I guess we have the first step and on completion of this project, we will have a better idea on the different risky genes for different disease in Egypt, and this even could help in the Middle East area.

Shaimaa: Talking about the Middle East and Africa, we have this concept of the increasing aging population, and we need to start thinking about the concept of active aging and how to promote the healthy aging in Africa and the Middle East. We know that you have stepped toward this project of active aging. Could you please focus on promoting active aging in Africa?

Mohamed Salama: As you mentioned, for years this was also a missing part in Africa and even Middle East, because we were considered younger population, so the life expectancy was not high as Europe for example, so the concerns of aging populations and how they contribute to society and so on, was missing. We felt that we have a lot of other priorities. Now we are moving to the direction of being somehow older population, now the life expectancy is increasing. Are we already prepared? As an easy answer would be, "No, certainly not." Why? Because actually we do not know everything about the current situation. Again, we are not reinventing the wheel. This is something that has been done previously in different countries. We have the aging study in America, in UK, in Ireland and Europe and so on. So why not starting an aging study in Egypt and even in the Middle East?

Recently, I started such initiative, talking about launching, or starting a pilot for understanding the features of aging in Egypt. I am trying to follow up this through a study for 10 years. Now successfully we have initial funding, very good funding from the DRD in collaboration with the European longitudinal study, which is called CHAIR. So, we will start a capacity building program. As I mentioned previously, such studies cannot be done through international partners. The role of an international partner is to start capacity building. So the funding we have got from the DRD to collaborate with CHAIR, is just to start improve our capacities to conduct a longitudinal study inside Egypt.

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And not only inside Egypt, we called it the Eastern Mediterranean Aging Study. The hope here is that we will start collaboration between Egypt, Lebanon and Jordan to better understand the current situations, the capacities, potential stakeholders, potential players and researchers. Then, hopefully we will harmonize, or coordinate activities between the three countries to start or launch a longitudinal studies in the three countries. The aim is to study aging population from 50 to 60 years old, over a ten year period. Every two years, we will have one wave, evaluates the progress of the aging population. What is the difference between you when you were in age of 50 and 52 and 54 and so on. We will evaluate clinically through a questionnaire for socio-economic and demographic values. We will try to have samples for bio-markers studies, genetics and everything. And as I mentioned, we will establish patterns of HRS studies in the States, in the UK and Germany, certainly, because now we are staring this capacity building program.

Hopefully, by the end of the capacity building program, we have the potentials, and we have also the interest of other countries, so why not instead of starting with Egypt, Lebanon and Jordan only, to also include other countries in North Africa and the Middle East? Why not include other countries in Africa and so on? This is an initial start. 2021 is the kick-off of such a project. Hopefully by the end of 2022, we are ready to start a real longitudinal aging study in Egypt.

Shaimaa: I would like to ask you some personal questions. Who is your role model?

Mohamed Salama: Let's see. It is changing, according to your age, so I remember when I was starting my PHD, I guess every Egyptian researches has a role model, Ahmed Zeweil for example. Certainly a brilliant scientist. He got the Nobel prize and he has brilliant vision. But when you grow older, you start to appreciate that we have really here some very good role models inside Egypt, that started to work while they are living here in Egypt.

They start to battle and face the challenge. For me, for example, I have a unique role model, Dr. Mohammed Sobh. He is the founder of Medical Research Center in Mansoura University. I remembered why he is considered a role model, because he kept working from inside Egypt, in Mansoura, in Delta. Where the situations are not very favorable and he start thinking, he has a vision, and I like a man who has a vision. He is a brilliant clinician. He is very successful in his clinical world, however, he mentions that why not, in the school of medicine, why don't we have a basic research lab? Why don't we start encouraging clinician to work somehow, to dedicate some of their time in there.

And by the time he started talking about this, most of the faculty considered him somehow crazy and somehow very over-ambitious, but at certain moment, he established a center. At the very beginning, it was not such a high esteemed center for research, but now it is improving and developing international reputation partnership, and gaining funding. This is what I liked about the guy, that he had a vision and he struggled, and had many fights until he fulfilled his vision.

And after resigning or leaving the research center, his vision is moving forward. His dream is growing, so this is what I liked about him. This could be one of my role models certainly. Finally, the last one I would mention as a role model is Brian Lawler. Brian was my mentor in Global Brain House Institute, and the most critical thing about him is empathy. He is very helpful, he's very modest. I guess he is my role model from the ethical aspect. He is always there to help you, and you never feel that he is this prestigious and highly esteemed professor. He is a founder of St. James hospital in Ireland, so he is a highly esteemed psychiatrist and scientist.

However, when you start talking with him, he looks like a very, very old friend who you have known for many years. He is very modest, and he is very, as I mentioned, empathetic. Sometimes when you start talking about someone elderly, or those living in less favorable conditions, you feel that he is going to cry.

Shaimaa: I have two important questions. One of them is about your activities, and how can you achieve this balance between your active life in research and your personal life? How do you find time for your family? How can you achieve this balance?

Mohamed Salama: No. I am sorry to say, I did not achieve this balance. I cannot say I am achieving this balance, because honestly, I'm taking from the family all the day. Even when I am staying in home as my son is saying, I'm working on my laptop, but I guess, the good thing about this is an understanding wife. My wife can understand the value of what I am doing. She is always pushing me, and most of the time you feel confident. Okay she is backing you and everything is okay in the home, so you can start focusing on your work. So, I guess this is the secret, but no, certainly I didn't achieve this balance.

Shaimaa: Lastly, what is your advice for the younger generation of clinicians and basic scientists?

Mohamed Salama: Okay, first for all types of scientists or those who are working in science, dream. And dream high. You have the potential. Now it's much easier, but now though internet and through different free courses and even you can send an email and receive the reply within few minutes, so you have more access. You have better potential and I remember when I was a medical student, we understand that the only source of information is a book, but now you as a student, you can go to PubMed and search and you can even challenge your professor and say, "No you are wrong. I read recently a new paper, saying that x, Y, or Z, are not similar to what you are saying." So this is the point. So why are you not dreaming very high?

For clinicians, I notice that recently many medical students or medical graduates are becoming fascinated by the model of working in lab or doing basic research. My advice is focus on your role as a clinician. There

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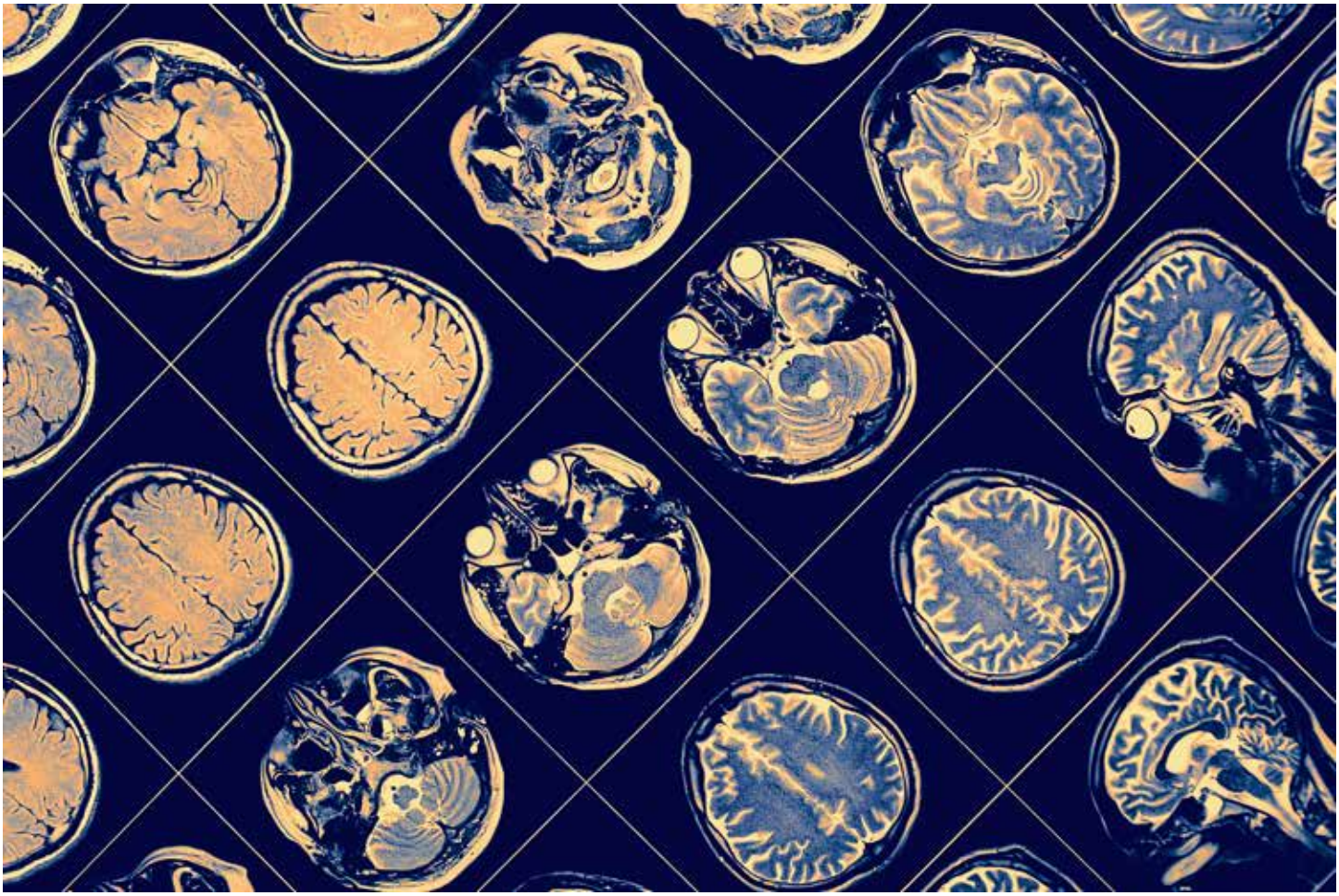
is no harm certainly to understand. There is no harm certainly to get training in labs and to even know how to do experiments. But never abandon your strengths. You are a clinician. You have good training. You have been investing a lot of time and money and effort for seven years, learning about disease and patients and so on, so do not lose this physician-patient relationship.

If you like to do research or basic research, you can adopt this MD-PhD model and you have some experience in the lab, but never to abandon your clinical support being a physician, a clinician. But for scientists, certainly you have to go outside Egypt for a while. Not forever, but at least you get training, you get in touch with the cutting edge knowledge and technology and then decide whether you want to return back and invest what you learned in your country or you continue your track.

It is very challenging and very difficult at least currently, to continue your research track as a scientist without going outside Egypt for a while. Never say "Okay we have everything." No, we don't have everything here. You have to be honest. You have to learn more. And we actually need those who are traveling abroad and learning more and then returning to their country. That's a brilliant model, you should have a chance to learn more and see the world. For basic scientists, certainly you have time to go to Europe, to America, to Japan, learn more, and then decide. For clinicians, never forget you are clinician, you are blessed being someone who have a physician-patient relationship. You know better about the needs of a patient, so never abandon this aspect of your career.

Shaimaa: Thank you for reviewing the current situation, challenges, and opportunities for the future. Thank you for your advice to the younger generation, your advice for teamwork and establishing concepts, and for your hard efforts to do all these researches and to establish these newly growing concepts. It was a pleasure to focus on these efforts in Egypt and in Africa. Thank you very much.

Mohamed Salama: Thank you. The pleasure is mine.



Moving Toward Target-Specific Therapies: What's New in Parkinson's Disease and Huntington's Disease

— *Tatyana Simuni, MD, Northwestern University, Chicago, IL, USA*
— *Tiago Mestre, MD, MSc, University of Ottawa, Ottawa, ON, USA*

Tatyana Simuni, MD

Tiago Mestre, MD, MSc

While a cure is a pinnacle in therapeutics of neurodegenerative disorders, the field is not there yet. Disease-modifying therapeutics (DMTs) to slow disease progression and delay onset of advanced disease manifestations are urgently needed. Parkinson's disease (PD), the second most common neurodegenerative disorder with complex multifactorial pathophysiology of recognized heterogeneity, has a significant societal impact more than any other movement disorders. On the other hand, Huntington's disease is a rare neurodegenerative disorder associated with a fully penetrant autosomal dominant genetic mutation in the huntingtin (HTT) gene and provides a unique model for developing target-specific interventions.

Fortunately, the pipeline is richer than ever in both PD and HD. A comprehensive review of PD experimental therapeutics (1) cited 145 active clinical trials including symptomatic and disease-modifying interventions and spanning Phase I (35%), Phase II (46%) and Phase III (19%) trials.

The current generation of DMTs in PD is much more grounded in disease biology, informed by recent discoveries in PD genetics and molecular biology and enhanced with an armamentarium of novel biomarkers (2). These attributes instill tremendous hope, though challenges remain. The two most active categories of development include alpha-synuclein and genetically targeted therapeutics. Multiple lines of data support the pivotal role of alpha-synuclein in PD pathogenesis, being the main constituent of Lewy bodies, the hallmark of PD pathology (3). The most advanced in clinical trial development are alpha-synuclein monoclonal antibodies targeting the extracellular protein. Results of the first two Phase II studies, PASADENA (NCT03100149) and SPARK (NCT03318523) were recently announced. Both studies did not meet the respective primary outcome(s). Contrary to SPARK trial, PASADENA 52 week results (4) document signals of efficacy in the secondary and exploratory digital outcomes.

Other efforts are ongoing in PD, including other monoclonal antibodies in earlier phases of development and targeting alpha-synuclein misfolding (UCB 0599, NCT04658186). Nilotinib postulated to increase alpha-synuclein clearance via stimulating autophagy, was evaluated in Phase 2 studies that did not confirm initial enthusiasm from a small open label study (5). Genetically-targeted therapeutics are very appealing as a DMT strategy, as it is applicable to PD subgroup sharing mutations in a causative or risk gene that are easily identified. Several GBA targeting therapeutics are in clinical development. MOVES-PD study testing the substrate-reducing drug venglustat (NCT02906020), is the most advanced trial and has not met primary or secondary outcomes. Other therapeutic approaches to rescue a dysfunctional GBA pathway are underway.

LRRK2-targeted therapeutics is perhaps of greatest impact in PD, as LRRK2-related PD is responsible for 3% of sporadic cases and up to 30% of familial cases in certain ethnic groups(6). There are two LRRK2 targeting therapeutic programs currently in clinical development. Small molecules LRRK2 inhibitors (DNL151 and DNL201) have completed Phase Ib studies (NCT04056689 and NCT03710707) and have advanced to a phase II/III study (7). An alternative approach is the use of antisense oligonucleotide (ASO) designed to bind to LRRK2 mRNA and thus reduce LRRK2 protein levels (NCT03976349).

HD has experienced a dramatic advance in the therapeutic development of DMTs in the last 5 years, mostly driven by genetically validated targets of the HTT gene (HTT-lowering therapies). More recently, somatic instability of HTT CAG repeat at an individual level started to be evaluated as a therapeutic target (SHIELD-HD, NCT04406636). HTT-lowering therapies represent a wide array of therapeutic strategies that target the biosynthesis of the mutated HTT protein at its different stages including transcription repression, splicing modification, pre-mRNA clearance or translation inhibition. The two most advanced clinical programs include ASOs targeting the nuclear pre-mRNA of both mutated (mHTT) and wild-type HTT (GENERATION HD1; NCT03761849) or specifically the mHTT (PRECISION-HD1; NCT03225833 and PRECISION-HD2; NCT03225846). Both programs have recently reported negative results. The PRECISION-HD1/HD2 programs failed to report a robust target engagement with marginal reductions of CSF mHTT protein. The phase III trial GENERATION HD1 followed a positive IONIS-HTTRx first-in-human trial(8), and dosing has been terminated prematurely due to a worse progression in the group more frequently administered the active treatment(9). Further insights into these negative results are eagerly awaited to better understand its meaning and scope.

We have entered a new phase of DMT development, grounded in target-specific strategies. While recent results are disappointing, the field is poised to succeed. The road is challenging but better understanding of the disease biology will pave the way to success.

In the interim, clinicians may question whether we should focus on symptomatic therapies or DMT. To a large extent the dividing line is artificial. Until the time we develop DMT, any intervention that improves quality of life and/or reduces disability will have a meaningful impact on people living with these devastating diseases. The field is making progress, but the challenges remain.

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