



A SUMMARY FOR THE DYSTONIA COMMUNITY

1st–3rd June 2023 • Croke Park, Dublin, Ireland



Samuel Belzberg 6th International Dystonia Symposium Summary

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DRIVING A DEEPER UNDERSTANDING OF DYSTONIA

The **Samuel Belzberg 6th International Dystonia Symposium (IDS6)** took place in Dublin, Ireland on June 1–3, 2023. IDS6 represents the latest chapter in a definitive series of international dystonia meetings organized by the Dystonia Medical Research Foundation (DMRF) since 1975. The first was a small event organized by the founders of the DMRF, Samuel and Frances Belzberg. Subsequent International Dystonia Symposia were held in 1986, 1996, 2002 and 2011.

Understanding of dystonia has increased significantly since the 5th International Dystonia Symposium held in Barcelona, Spain, in 2011. The goal of IDS6 was to extend knowledge beyond current boundaries, highlight important scientific advances in the field, stimulate discussion within and across disciplines, and push forward into a deeper understanding of the disorder and how to treat those who are affected.

A team of dystonia experts planned IDS6 to provide an overview of the clinical and research landscape through six key topics, highlighting where we are now, new thinking and research findings, topics of debate, and questions for future exploration. The program reflected the complexity and continuous development of dystonia research. In addition to oral presentations, more than 100 posters presented preliminary findings of research in progress.

The meeting was organized to promote discussion. Throughout the three days, sessions on *Breaking News and Highlights* provided a platform for young investigators to present on selected poster topics. *Point of View* sessions were incorporated into the program each day to present different perspectives on key issues.

Discussions at the end of each session consistently reflected the relevance of current research and clinical practice to dystonia patients' needs. This lay summary of the Symposium presents key findings of the latest dystonia research, breaking news in the scientific understanding of dystonia, and potential avenues for new discovery.

IDS6 was a joint organizational effort of the Dystonia Medical Research Foundation (www.dystonia-foundation.org) and Dystonia Europe (www.dystonia-europe.org). The Scientific Program Committee was co-chaired by H. A. (Buz) Jinnah, MD, PhD, and Antonio Pisani, MD, PhD, and included members from all over the world. The outstanding faculty and participants shared their expertise, and our sponsors provided their generous support, without which we would not be able to successfully organize this outstanding global event.



DMRF Founder Frances Belzberg addressed conference participants with this important reminder: *"People are waiting. People, like my daughter, are waiting for scientific breakthroughs and answers. So let's get to it!"*

Dystonia is a movement disorder that causes the muscles to contract and spasm involuntarily. Opposing muscles often contract simultaneously as if they are 'competing' for control of a body part. These involuntary contractions force the body into repetitive and twisting movements and irregular postures. There are multiple forms of dystonia, and the disorder affects children and adults of all ages and backgrounds.

Welcome to the Samuel Belzberg 6th International Dystonia Symposium

June 1st – 3rd, 2023
Dublin, Ireland



AN INTRODUCTION TO DYSTONIA

This section overviewed dystonia subtypes, how they are categorized, the successes and shortcomings of current treatments, and new topics in research.

WHERE ARE WE NOW?

How the definition & classification of dystonias has evolved

Anthony Lang, MD, FRCPC

University of Toronto, Toronto, Canada

Ever since the first description of dystonia in the late 19th century, there has been ongoing debate about the classification and descriptions of the various forms. It is important to have a classification system that guides diagnosis and also identifies dystonias by the cause, if known, to guide future research and treatment. In 2013 a group of experts updated the 1984 definition and classification of dystonia that secured dystonia's designation as a neurological movement disorder. Now, ten years later, experts in the field are working to integrate learnings from the past decade to update the definition and classification to more accurately describe dystonia and provide an improved framework for the medical and research community.

The 2013 definition and classification stated that "Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may resemble a tremor. Dystonia is often initiated or worsened by voluntary action and associated with overflow into adjacent or distant muscles." This seminal paper went on to classify dystonia using two points of reference: the clinical features including age of onset, body distribution, certain qualities about the symptoms, the presence of other movement disorders, and other neurological features and the cause. The second point of reference looked at other forms of the disorder, including genetic forms of the disease, acquired dystonia which develops because of external causes (for instance, trauma to the brain), and idiopathic dystonia which has no identifiable cause.

The current work examines the areas of the 2013 definition and classification that can be further strengthened by the experiences of the past decade in the clinic. The working group is looking at not only the age of onset, but the age of the motor dysfunction and the exact body regions affected by dystonia, separate from possible other possible symptoms. Additionally, it is expected that the

revised definition and classification will look at the rate of progression of symptoms, rapid or more gradual, and then whether there have been changes to the symptoms experienced over time. The variability of how symptoms are presented, the presence of a possible trigger such as a specific task. Finally, the new definition and classification may take into account presence of another movement disorder or other neurological features.

An updated definition and classification system is important as it guides diagnosis and treatment for the many forms of dystonia. It provides physicians with a check list of characteristics that, when applied to an individual, reveal a detailed description of that person's diagnosis utilizing the most up-to-date information available. This is important because to develop more effective, targeted treatment methods, physicians and researchers first need to identify the biological mechanisms that are altered in dystonia patients. To begin chipping away at this puzzle in a large population of patients with diverse clinical features and root causes, it is important to be able to categorize the patients into like groups. Identifying similarities in dystonia patients and how they respond to different therapeutic methods can provide hints towards their same or related altered biology—pointing research in the right direction for new drug targets and new drug development.

Defining the full dystonia syndrome can shape the therapeutic approach

Victor Fung, MBBS, PhD, FRACP

Westmead Hospital, Sydney, Australia

It is important that physicians and researchers use the same language to describe a dystonia patient's complete list of symptoms that consistently cluster together with dystonia, or their dystonia "syndrome". Identifying an individual's broader dystonia syndrome can be a useful method to identifying the best treatment plan for that individual. This will have increasing importance as more is learned about dystonia and more treatment options become available. Many forms of dystonia share clinical characteristics underscoring the importance of a comprehensive examination. When looking for additional clues to determine the cause of the symptoms, and to

develop a more tailored treatment plan, evaluating the features of the broader dystonia syndrome can be useful. This is particularly true when a patient does not have a known dystonia gene. In these cases, more advanced genetic testing may identify new genetic mutations that are associated with these new or existing dystonia syndromes, which is useful for ongoing diagnostic and treatment plan development purposes.

The link between dystonia and Parkinson's disease

Kailash Bhatia, FRCP, FAAN

University College London, London, UK

The links between dystonia and Parkinson's disease are important to understand to correctly diagnose a patient and identify the best treatment plan. However, there is still not enough known about the biological mechanisms underlying these different disorders to provide a clear and thorough description of the link between them. Yet, many clinical features, genetic variations, and adaptations in the brain that are shared between the two disorders have been identified. These points of overlap are useful areas of investigation to better understand the disordered biological processes that contribute to both disorders. More research is needed to identify possible links, including the biological mechanisms underlying dystonia and Parkinson's share motor circuits in the brain that give rise to both symptoms; altered dopamine signaling, a key component of cellular communication in motor circuits, can produce either or both disorders.

Dystonia treatments: Current successes? Where we improve?

Joseph Jankovic, MD

Baylor College of Medicine, Texas, USA

Dr. Jankovic presented successful treatment approaches that have been developed through meticulous clinical observations shared in published patient case reports across a large field of neurologists with movement disorder expertise. He then identified key steps to improving our treatment approach through specific needs in the areas of research and accessibility. Dr. Jankovic

laid out some guiding principles for the treatment process. These included:

- Identify any specific causes of the dystonia (i.e. lesions or abnormalities in the brain, metal accumulation, deficiencies in vitamins or dopamine, genetic mutations) which can indicate the best treatment approach, whether dietary changes, medication, or surgical intervention.
- Address comorbidities (i.e., pain, depression, and orthopedic complications) that can coincide with dystonia and impact a patient's quality of life.
- Explain that the current existing treatment options treat the symptoms of dystonia but do not alter the cause of the disease or provide a cure.
- Strategically select treatment methods that take into consideration the patient's age, type of dystonia, body distribution, and severity of symptoms.
- Reserve surgical intervention for patients with disabling dystonia that does not respond beneficially to medications or other therapeutic approaches (i.e., botulinum neurotoxin).

He also suggested ways researchers might be able to improve the treatment process. They included:

- Increasing our understanding of dystonia neurobiology, allowing us to develop disease-modifying treatment.
- Developing better outcome measurements for motor and non-motor aspects of dystonia, allowing us to expand our understanding of therapeutic success to include quality-of-life assessments.
- Conducting better, placebo controlled and longer-term clinical trials.
- Identifying better assays to determine whether a patient has neutralizing antibodies for botulinum neurotoxins, or better yet, investigate possible indicators that a patient is susceptible to develop neutralizing antibodies.
- Conducting better clinical trials that determine the value of rehabilitative interventions, such as vibrotactile stimulation and transcranial magnetic stimulation (TMS).
- Providing better access to safe, effective, and affordable treatments.

BREAKING NEWS & RESEARCH HIGHLIGHTS - DAY 1

New research made possible by fNIRS brain imaging

Renata Prôa

Hospital Israelita Albert Einstein, Sao Paulo, Brazil & Columbia University's Zuckerman Institute, New York, USA

Brain imaging like functional magnetic resonance imaging (or fMRI) or positron emission tomography (PET) are frequently used to evaluate dystonia and the effectiveness of different treatment methods. fMRI allows researchers to observe the blood flow within the brain of a patient, which is thought to correlate with brain activity, revealing differences in the reaction of brain circuit activation between patients with dystonia and those without. PET uses radioactively tagged compounds that can then be imaged as they travel through the brain, giving researchers more information on how different signaling or metabolic processes might be altered in individuals with different diseases. An example used in movement disorders are compounds that allow researchers to determine changes in dopamine movement across the brain (called a DaT scan). However, one big drawback to these imaging methods is that the patient has to be laying still in a dark room, positioning that does not for observing the majority of dystonia symptoms.

Functional near-infrared spectroscopy (fNIRS) is a brain imaging technique that allows data collection while patients are moving. Dr. Prôa shared preliminary findings using fNIRS in patients completing a writing task. This study showed that dystonia patients had even brain activation distributed more broadly across the motor regions of both sides of the brain, compared to controls that had a smaller area of activation almost exclusively on one side, with more defined areas of stronger activation. These findings demonstrate the value of fNIRS in dystonia research.

Early-onset dystonia patients use brain fuel differently

Stavros Tsagkaris, MD

Evelina London Children's Hospital, London, UK

Dr. Stavros Tsagkaris described his recent publication on glucose metabolism in children with early onset

dystonias. Glucose is a sugar that enters the bloodstream from the food we eat and then makes its way to the brain. Glucose metabolism provides the fuel for a wide range of fundamental brain functions. Using PET, the group found that children with early onset dystonias had many differences in glucose metabolism compared to the control group. The most common finding across the different early-onset dystonia patients was a reduction in glucose metabolism in brain regions associated with motor control. Many different types of dystonia exhibited distinct patterns of increased and decreased glucose metabolism, which Dr. Tsagkaris suggests could be valuable information for diagnostic purposes.

Cervical dystonia patients show altered immune system function

Laura Scorr, MD

Emory University School of Medicine, Atlanta, Georgia

Dr. Laura Scorr presented new data on the immunological mechanisms observed in cervical dystonia. There are many existing biological mechanisms that have shown that the immune system can affect neurological function. The specific cause of cervical dystonia is often unknown, but interestingly, there are many published anecdotal reports from patients suggesting that immune mechanisms may be linked to dystonia. In a clinical survey with 391 cervical dystonia patients and 300 controls found a significant association between cervical dystonia and thyroid disease.

The lab uses proteomics, or studies that investigate the structure and function of proteins and their interactions with cells in the brain and body, to investigate biological systems. Using proteomics with samples collected from cervical dystonia patients revealed increased indicators of immune system activity. During further analysis the lab found cervical dystonia patients had an increased levels of a specific inflammatory mediator called HLA DRB1*1503, which has been found in other studies to be associated with autoimmune diseases such as multiple sclerosis and lupus.

These preliminary findings illuminate a possible pathway to identifying biological mechanisms that cause cervical dystonia, allowing for the development of targeted,

disease-modifying treatment methods. It also provides a new avenue of immune research that might be relevant to other forms of dystonia.

Altered immune system biomarkers in adult-onset focal dystonias

Jigyasha Timsina, MS

Department of Psychiatry and Neurogenetics & Informatics Center, Washington University School of Medicine, St. Louis, Missouri

Jigyasha Timsina, a bioinformatics research analyst, presented her preliminary findings on a proteomics

study that analyzed proteins from 200 study participants. The participants selected for this study covered a range of dystonias, with 50 cervical dystonia patients, 50 laryngeal, 50 blepharospasm, and 50 non-dystonia controls. They found 15 different proteins were altered across all dystonia subtypes and specifically identified significant alterations to proteins associated with immune processes—aligning with findings seen by Dr. Scorr. Together these studies strongly emphasize the value of enhancing our understanding of the biological and neurobiological connections between dystonia and the immune system.



DEBATE INTRODUCTION: Differentiating Between Dystonia and Tremor

Essential Tremor (ET) is characterized by involuntary, rhythmic shaking. Confusingly, dystonic movements are often repeated and can be patterned or tremor-like in their presentation (i.e., myoclonus dystonia). Dystonic tremor (DT) is the term used when both features present in the same body regions or muscles. Tremor associated with dystonia (TAD) is when the two symptoms occur at separate sites or tremor and dystonia that coexist when the patient executes a specific voluntary movement.

Previously published papers reviewing the clinical landscape have stated that one in three patients are misdiagnosed with essential tremor, when the actual diagnosis is often Parkinson's or dystonia. If the numbers evaluated in this study are consistent across larger data sets of movement disorder patients, that would make essential tremor the most misdiagnosed movement disorder, which can limit the therapeutic potential for those patients until receiving the correct diagnosis.

POINT OF VIEW: DYSTONIA AND TREMOR

A continuum or separate entities?

Alfonso Fasano, MD, PhD

University of Toronto, Toronto, Canada

Dr. Fasano explained that dystonia and tremor are neither a continuum nor separate entities. The same cause and adaptations to the brain can lead to both symptoms. As a result, we need to identify biomarkers, or shared biological features, from definitive cases and apply these to more complicated cases where there is less agreement to achieve more objective diagnoses. There are a few examples of biomarkers that could be useful when used alongside existing diagnostic features to enhance both the precision of the diagnosis and the treatment approach. Dr. Fasano also remarked on new technological advancements that may further enhance our ability to identify useful biomarkers.

Possible biomarkers for future use include symptom overflow and co-contracting muscles. The excess, involuntary movements that characterize dystonia are caused by a loss of inhibition in brain circuits that shape motor control. Loss of inhibition can produce co-contraction of opposing muscle groups that generally do not contract at the same time. These abnormalities can be easily observed in how an individual recovers from a blink reflex, for example.

Another potential biomarker might involve the time distinction limit. In these tests, patients are given two consecutive stimulating pulses with varied time in-between a specific muscle and then asked if they felt one or two pulses. Several published studies have shown that dystonia patients need more time in between the two pulses to be able to identify that two occurred, when compared to non-dystonia control groups or “essential tremor” patients.

Dr. Fasano also remarked on an exciting avenue of research using machine learning, which utilizes computer programming to integrate many clinical features in a similar way that a clinician would, while removing any unintended biases or human error. Often, these programs are uniquely capable of identifying unique patterns in the patient data that may not appear clearly to clinicians.

Two distinct but often overlapping entities

Sanjay Pandey, MD, DM

Amrita Hospital, Delhi, India

Many studies sampling different populations of dystonia and ET patients report greatly different percentages of overlapping symptoms. Some studies report next-to-no

overlap while others have reported up to 47%. More recently, an additional diagnosis has been added, termed ET+, for patients that fall in between the dystonia and ET umbrellas.

Dr. Pandey highlighted that dystonia and tremor have many shared genetic mutations. Furthermore, he showed one patient with both motor symptoms which were significantly reduced by levodopa treatment. Showing that these symptoms likely have similar brain abnormalities

that are modified with the same therapeutic interventions. This emphasizes the importance of harnessing the overlapping aspects of these disorders to further understand them.

Interestingly, published studies highlighting brain anatomy changes in dystonia and tremor have identified overlapping abnormalities across these two groups in both the cerebellum and basal ganglia, which are two brain regions that are important for movement.

HOT TOPIC: THE SCIENCE OF PHENOTYPING

Some forms of dystonic disorders may be considered borderline dystonia. For example, currently there is no agreement on the definition and clinical phenomenological description of pseudodystonia. Analogously, the paroxysmal dyskinesias have been considered a subtype of dystonia because dystonia is often the prevalent problem. However, it has been suggested that they are distinct disorders unrelated to dystonia. This Hot Topic session addressed the challenges in characterizing pseudodystonia and potential relationships between the paroxysmal dyskinesias with the dystonias.

How does pseudodystonia differ from “real” dystonia

Timothy Lynch, MRCP

University College Dublin, Dublin, Ireland

Pseudodystonias are conditions that may seem like dystonia but have different identifiable causes. They can have involuntary movements and postures like dystonia but are due to other factors. There are various types of pseudodystonias, some of which were listed in a 2013 classification paper on dystonia. Examples include tics, certain types of palsy causing postural issues, scoliosis, orthopedic and rheumatological conditions, and specific syndromes. Pseudodystonias can be divided into those with a neurological origin and those with a musculoskeletal origin. Neurological disorders involve problems with the brain, spinal cord, and nerves that control movement and other functions. There are certain clues that skilled clinicians look for to differentiate between dystonia and pseudodystonia.

If a patient experiences task-specific triggers, abnormal muscle activation, symptom reduction while asleep, and has effective sensory tricks, it is possible they have

dystonia. If a patient experiences muscle weakness or twitching, abnormal eye movements, upper respiratory infections, abnormal lumps, or experienced trauma that preceded symptoms, they may be experiencing pseudodystonia.

Paroxysmal dystonias: a subtype of dystonia or a different entity?

Serena Galosi, MD, PhD

Sapienza University, Rome, Italy

Paroxysmal dyskinesias (PKD) are characterized by episodic involuntary movements without loss of consciousness. PKD and dystonia are linked to dysfunction within the cellular networks in two distinct brain areas: the basal ganglia and the cerebellum. There are some shared biological features that have been observed in both PKD and dystonia, such as altered degrees of cellular activity. However, the specific cellular abnormalities that cause these features are different.

PKD can be linked to a failure of synapse homeostasis that leads to abnormal cellular excitability. Synapse homeostasis refers to balanced communication between

different parts of the brain. In synapse homeostasis the communication between brain cells is not too overwhelming or too weak. The cells are designed with specialized features that keep their signaling balanced, allowing for the brain to work properly.

Dystonia genes have been linked to the abnormal development of the cellular circuits in the brain that are responsible for motor control. The specific abnormalities vary widely and are linked to many different aspects of fundamental cell function and cell-to-cell signaling.





SPECIAL TOPICS IN DYSTONIA

This section covered interesting updates in the research phase that are shifting our understanding of dystonia and key topics of clinical debate.

UNDERSTANDING DYSTONIA MECHANISMS

What do task-specific dystonias tell us about the cause of dystonia?

Mark Hallett, MD

The National Institutes of Health, Maryland, USA

Task-specific dystonias are triggered by specific actions, like writer's cramp or musician's cramp. Generally, task specific dystonias are localized to the muscle group that is directly required in a task. However, the dystonia that occurs during this specialized action can overflow to neighboring areas during the specific task. The dystonia can also progress to be more broadly distributed and can occur when the area is at rest. Repetitive activity triggers the development of task specific dystonias. Generally, task specific dystonia is adult onset with no associated genetic mutation. However, task specific triggers have been observed in patients with DYT1, DYT6, DYT7, and DYT13. Ongoing research into focal and task specific dystonias has revealed interesting abnormalities in the brain that can inform our understanding of the cause of dystonia.

The cells within different brain regions connect to one another to create many different, distinct circuits that dictate how the body functions. Brain imaging techniques allow scientists to compare the circuits in dystonia patients compared to non-dystonia volunteers. Brain imaging studies in dystonia patients with focal, task-specific dystonias identified several different abnormalities in brain circuits associated with movement planning, action monitoring, and body awareness.

Paired Associative Stimulation (PAS) is often used to explore how different brain regions communicate and how their connections might be strengthened or modified. It is a method that pairs electrical or magnetic pulses with specific actions or sensations. Synchronizing the pulses with specific actions or sensations aims to enhance communication between different parts of the brain, somewhat like coordinating traffic signals to keep traffic flowing smoothly at intersections.

This technique can then be used in dystonia patients and non-dystonia volunteers, to identify any differences in brain plasticity between the two groups. Several studies using PAS have revealed that dystonia patients experience

excessive plasticity that is likely allowing for the repetitive actions to impair brain circuits, leading to the development of task specific dystonia.

Beginning to identify sex-dependent biological mechanisms in dystonia

Ellen Hess, PhD

Emory School of Medicine, Georgia, USA

Dystonia can affect males and females differently due to genetic factors. While some types of dystonia are equally prevalent in both genders, others show variations. For instance, dystonias caused by specific genetic mutations like THAPI, TH, and TORIA appear in similar numbers among males and females. However, mutations in GCH1, GNAL, and ANO3 lead to dystonias that are around 15-20% more common in females. Within the large Dystonia Coalition research data base of 3,216 dystonia patients, there are significantly more females affected by focal dystonias than males. For example, laryngeal dystonia affects four times as many females than males and cervical and blepharospasm affects nearly three times more females.

When investigating the reasons behind these sex differences, it's essential to start by closely observing patients with dystonia. Notably, clinical reports indicate that changes in ovarian hormones like estrogen, triggered by events like pregnancy, menstrual cycles, or polycystic ovary disease, can influence the onset or severity of dystonia in females.

Surprisingly, studies in mice with DOPA-responsive dystonia have revealed that higher estrogen levels correspond to more severe dystonic symptoms, paralleling the experiences of around 40% of women with dystonia. The clues from the literature suggest that the specialized proteins on the surface of brain cells that detect estrogen may contribute to the function of brain cells within motor centers. However, the specific mechanisms are not well understood. So far, researchers have shown a certain subtype of cell that sends signals to the globus pallidus internum (GPi) has 5 times the number of estrogen receptors. The GPi is a brain region that facilitates movement and is a key DBS target for

dystonia patients. Importantly, these findings were seen in both male and female animal models.

Genetic studies have shown that there are 9,000 genes within the motor centers of the brain that can be altered uniquely between males and females. While these genes produce similar results in healthy brains of both sexes, the processes governing protein production can be influenced by factors like aging, diseases, and treatments. This divergence can lead to differences in proteins contributing to gender-related disparities in dystonia development and progression.

What do autoimmune mechanisms tell us about the cause of dystonia?

Bettina Balint, MD

University of Zurich, Zurich, Switzerland

Dr. Balint started discussing stiff person spectrum disorders (SPSDs), outlining the varied features that can indicate an accompanying dystonia diagnosis or pseudodystonia. Patients with SPSP and dystonia experience sustained muscle contractions that cause abnormal movements or posture, movements that can occur in a patterned presentation, contractions that become worse with action, and symptoms that may overflow into neighboring muscle groups. She compared this to individuals with SPSP and pseudodystonia.

Patients experience constant stiffness with additional contractions, different movement patterns than dystonia patients, no sensory tricks, no task specific or mirror dystonia, and less overall movements than dystonia.

Next, she described rare autoimmune disorders that cause dystonia and are often debated to be pseudodystonias (i.e., paroxysmal dyskinesia, faciobrachial dystonic seizures spectrum). Autoimmune disorders occur when the body's immune system mistakenly attacks its own cells and tissues. An autoimmune disorder can trigger brain inflammation or encephalitis. These autoimmune disorders have been found to have different types of antibodies that target proteins in the brain that are important for brain function. In some people, more indirect immune system dysfunction, such as brain tissue damage caused by a stroke, is the source of their dystonia.

Overall, Dr. Balint concluded that true dystonia in autoimmune disease is rare and pseudodystonia is probably more frequent. In cases of dystonia with autoimmune disease, symptoms are generally not isolated to one part of the body, which can provide a hint to investigate immune features during the diagnostic process. Furthermore, the varied antibodies with different brain targets, suggest the significant network-wide interaction of specialized proteins in dystonia biology.



DEBATE INTRODUCTION: Is Psychogenic Dystonia a Neurological Disorder?

In 1976, Dr. David Marsden strongly argued that focal dystonias are “a physical illness, not manifestation of a psychiatric disorder”. Many pioneers in the fields of neurology and psychiatry had long argued that some forms of dystonia were psychiatric in nature. Dr. David Marsden published the reasons why focal dystonias were thought to be psychogenic:

- The bizarre nature of dyskinesias
- The task specificity, where other motor acts with the same muscles can be unaffected
- The relief by sensory tricks
- The “exquisite” sensitivity to social and mental stress
- The failure so far to identify any biological cause
- Accompanying psychiatric disorders

Are the biological differences observed in individuals with psychogenic or functional dystonias the cause of the disorders themselves or are they consequences of the symptoms? Drs. Aybek and Carson discussed the different points of view.

POINT OF VIEW: FUNCTIONAL (PSYCHOGENIC) DYSTONIA

A manifestation of a neurological disease?

Selma Aybek, MD

Inselspital, Bern, Switzerland

Dr. Aybeck provided evidence that suggests functional dystonia is a neurological disease.

Stress exacerbates many different neurological disorders. Stress can make disorder symptoms worse, and this phenomenon has been linked to many understood biological mechanisms, though many have not yet been discovered.

Typical brain imaging allows us to identify changes in the number of connections between different areas of the brain, giving some indication of how information flows between brain regions. A recently developed method for analyzing brain imaging data allows us to observe the connections between brain regions in much greater detail. This method revealed unique differences in the brain circuits of people with functional neurological disorders, reinforcing Charcot’s early thoughts that “there is without a doubt, a lesion” in the brain but it “escapes our present means of anatomical investigation.”

In addition to brain circuit changes, many published studies from Dr. Aybek and other dystonia researchers have found genetic and epigenetic changes in patients with functional dystonia. Genetic changes are changes to the code which can result in deformed proteins that have less to no function or are not made at all. The long genetic code is packaged in a specific way that allows the proteins to be made by cellular machinery and epigenetic changes impact the packaging that can also result in aberrant protein production.

Published studies have found psychiatric disorders (i.e. major depression, anxiety, phobia, panic disorders, etc.) are equally prevalent in individuals diagnosed with psychogenic dystonia and focal hand dystonia. Another study found that 77% of dystonia patients did not have a traumatic life event that they associate with the onset of their dystonia, suggesting that these events may be risk factors for some patients but are not the cause.

Dr. Aybek noted that the consensus on the classification of dystonia from 2013 did not place psychogenic dystonias under the pseudodystonia category. Instead, psychogenic

dystonia can be found under acquired dystonia, which is a category that includes dystonias caused by brain injury, infection, drug exposure, etc. This categorization reinforces the current leading opinion, that psychogenic dystonias are true dystonias with a distinct biological origin.

A manifestation of psychiatric illness?

Alan Carson, MBCHB, MPHIL, MD, FRCPSYCH, FRCP

University of Edinburgh, Edinburgh, United Kingdom

Within this debate, there are two perspectives that are worth understanding. First is that functional dystonia (FD) arises from altered features in an individual's biology which allows psychiatric symptoms to be tethered to neurological symptoms. The alternative perspective is that FD is fundamentally psychiatric and that any biological differences that can be observed exist because of the FD.

Brain imaging studies have identified many changes in the circuitry that connects different brain regions in those with FD. The specific circuits include those in charge of emotional and cognitive processing and the connections between the two, as well as our sense of agency or self-awareness (i.e., initiating movement, our perception of our body in space, etc.). However, we also know that experiencing dystonia symptoms alone can contribute to brain adaptations. To understand how, it helps to think a bit more about how the brain controls actions.

The brain is a series of complex, interlocking circuits that send signals to the body to dictate many diverse functions. The body then sends signals back to the brain about ongoing sensory inputs, information about the actions being executed, where we are in space, etc. Through these processes, repeated exposure to a certain stimulus will produce changes in the brain. For example, when babies learn to pick up a cup and take a drink, it takes many coordinated skills that the brain learns through repeated exposure and gradual brain changes. It makes sense that there would be changes in the brain in response to dystonic movements. These changes



extend beyond the brain regions specifically responsible for directing motor movements because experiencing symptoms can be painful, stressful, anxiety-inducing, or otherwise emotionally and cognitively challenging.

Dr. Carson outlined the ways in which the diagnosis and treatment of FD require psychiatric and neurologic expertise. First, understanding the risk factors associated with the development of FD requires a depth of psychiatric knowledge. However, the examination used to gather the relevant clinical information on an individual's disorder requires neurologic expertise. After the diagnostic interview and tests are completed, the clinician must synthesize this information together to formulate the diagnosis, which will then require the psychiatric knowledge base to understand how the risk factors and examination results fit together. Lastly, developing the best treatment approach requires an understanding of both, and often predominantly psychiatric.

Neurologists and psychiatrists should work together "because we are better together than apart." Dr. Carson emphasized that there is a large opportunity for psychiatrists to expand their understanding of how the brain influences mental and emotional health and the impact this has on the body by investigating FD with neurologists.

POINT OF VIEW: NON-MOTOR FEATURES

The main goal of this session was to focus on scientific relevance and biological basis of non-motor symptoms of dystonia. Some evidence suggests that non-motor features reflect shared biological mechanisms with dystonia, while other evidence implies it is a reaction to a chronic stigmatizing disorder. These presentations covered both perspectives.

Shared biology with motor features

Kathryn Peall, BMBCh, FRCP, PhD

Cardiff University, Cardiff, United Kingdom

Dystonia is thought to be a network disorder, characterized by abnormal signaling within and between multiple brain regions in the motor networks. Several non-motor symptoms can accompany dystonia, such as psychiatric symptoms (i.e., anxiety, depression), cognitive impairments, pain, and difficulty with sleep. With dystonia, there is a high amount of variability in the motor symptoms across the large patient population and the non-motor symptoms are similarly variable. Dr. Peall focused on psychiatric disorders, observed to occur in more similar frequency across different dystonia subtypes compared to the other non-motor symptoms.

Data published in 2022 showed that dystonia patients experience a significant peak in their psychiatric symptoms around the time of receiving their dystonia diagnosis. Another research study found links between genes associated with dystonia and genes that can influence anxiety and other psychiatric disorders. A study published from Dr. Peall's lab found that cultured cells engineered to have the DYT11 mutation associated with myoclonus dystonia were hyperactive as a result of a loss of a protein that helps maintain synaptic connections. This same protein has been implicated in anxiety disorders and autism spectrum disorders in other research studies.

An expected side effect of chronic disorder

Davide Martino, MD, PhD

University of Calgary, Calgary, Canada

In a study published in 2021, 43 individuals with cervical dystonia were surveyed about their motor and non-motor features experienced with dystonia. Fourteen of the participants had increased anxiety, depression, pain catastrophizing, and sleep disturbances. Most importantly, this subgroup did not differ in terms of age, disease length, or motor symptom severity. This data prompts the question: is this enough to suggest that the motor and non-motor features are linked to distinct biological changes in the brain?

Dr. Martino emphasized the impact of the social stigma that many dystonia patients experience while navigating a world with limited familiarity of movement disorders. Many research studies have shown that stigma strongly impacts a patient's quality of life. One study showed non-dystonia participants viewed videos of generalized dystonia patients and found indications of stigma could be significantly reduced if the participants were provided information about the individual in the video—highlighting the importance of educational or awareness campaigns.

The next area for important research is to move beyond dystonia patient accounts of their experience with motor and non-motor features to identify direct links between symptoms and stigma. For example, a paper published in 2021 used an experiment showing that stigma experienced during an online job interview increased an individual's pain perception. Although the mechanisms of pain in dystonia are highly complex and not fully understood, replicating this work would improve our understanding of how stigma impacts dystonia patients with altered biology.



DYSTONIA ANATOMY

A wide range of topics including brain regions implicated in dystonia, how cells within the brain form abnormally wired circuits, and genetics.

AREAS OF THE NERVOUS SYSTEM RESPONSIBLE FOR DYSTONIA

Organization of normal movement: cortex, basal ganglia and cerebellum

John Rothwell, PhD

University of College London, London, United Kingdom

To understand dystonia, we must understand the anatomy of movement circuits in the brain and how cell-to-cell signaling within the circuits produces normal movements. This understanding allows researchers to identify locations where dystonia disrupts the system, which results in abnormal movements.

The three key brain regions responsible for movement are the cortex, the basal ganglia, and the cerebellum.

The cortex, takes ongoing sensory inputs, movement history, and other information like motivation into consideration to decide what and when to do something. The cortex sends this information to the basal ganglia.

The basal ganglia is situated deeper within the brain and houses many of the deep brain stimulation targets. It allows appropriate movements and inhibits others. For example, it may allow you to walk and chew at the same time, while choosing not to run or jump. The basal ganglia then sends this information to the brainstem.

The brain stem is a cluster of brain regions that connects to the spinal cord. Through the spinal cord, the brain stem sends messages to muscle fibers, where they directly control muscle contraction. The diverse types of movements that can be executed by the body are a result of various patterns of cell signaling within the cells of the brainstem and spinal cord.

The cerebellum, which sits below the very back of the brain, takes the basal ganglia's movement plans and adapts it to fit an often-changing environment. The cerebellum does this by comparing how accurately the predicted movement matches the actual movement being executed and makes any necessary adjustments to the timing and amount of muscle contraction to align with the intended plan. The cerebellum sends information both to the cortex and to the pattern generators within the brainstem and spinal cord.

The organization of the movement circuits in the brain are also highly complex. For example, there are a handful of brain cell clusters within the basal ganglia that are defined by their unique function and circuit wiring.

The circuits, or connections between cells in these different brain regions, are highly intricate, creating different patterns of cellular activation that allow for diversity and precision in motor movements. Separate patterns are responsible for movement in each limb. The specific chain reaction in cellular activation is important in dictating the timing for muscles to flex and extend in a coordinated fashion that produces the simple-seeming movements.

The patterns for individual limbs must then also coordinate with the patterns for other limbs because most movements are coordinated across multiple limbs.

Structural imaging of dystonia: modern lesion network mapping

Michael Fox, MD, PhD

Brigham and Women's Hospital, Massachusetts, USA

It can be difficult to definitively identify which region of the brain causes neurological symptoms. A good indicator can be the study of brain lesions. When someone experiences targeted damage to a brain region, often through a stroke in that region, the resulting symptoms from the damage can provide insight into the responsibilities of that part of the brain. The case of Phineas Gage is a famous historical example that shows how brain lesions can reveal critical information about the brain's functions. When a metal rod went through his brain in an accident, it damaged a specific area, drastically changing his personality and behavior. This helped scientists understand that the frontal lobes play a crucial role in regulating our emotions and decision-making. This demonstrates how brain lesions give us clues about how different brain regions control different aspects of our behavior.

Brain lesions can be broadly categorized into two types: acquired and congenital. Acquired lesions can result

from traumatic brain injury, infections, tumors, or vascular issues, and they are associated with conditions such as epilepsy, stroke, or brain tumors. Congenital lesions, on the other hand, are present from birth and are often linked to many different genetic disorders. Many published case reports have identified brain lesions in dystonia patients, with ~53% of lesion-induced dystonia patients having focal dystonia.

The same links between brain region and symptoms can be made when a brain region is stimulated with DBS or with non-invasive transcranial magnetic stimulation (TMS). If targeted stimulation of a brain region alleviates symptoms, that brain can be directly implicated in causing those symptoms.

A common approach to understanding neuroanatomy associated with different neurological disorders like dystonia has been brain imaging which is often referred to as “functional imaging”. One type of functional imaging is to use an MRI to image the brain while a patient is experiencing symptoms, allowing researchers to observe activity patterns across many brain regions that coincide with the symptoms. There are many studies that have done exactly this for dystonia and found many brain regions with significant changes compared to study participants that do not have dystonia.

However, this research approach has inherent flaws. First, these changes in brain activity during symptoms may reveal the cause of dystonia, but they may also be showing us how the brain circuits are trying to compensate for abnormalities that cause dystonia. The variability in how we can interpret this neuroimaging data doesn’t make it less valuable, but it does mean that we have to find additional ways to identify the locations that cause dystonia because those are the best targets to reduce symptoms or, better yet, modify the disease.

Research published from the Fox Lab and others observed 359 brain lesions in patients with many different types of dystonia. They found that the location of the lesion within the brain was associated with the body part where the patient experienced dystonia. For example, cervical dystonia patients have significantly more brain lesions in the cerebellum and brainstem compared to patients with dystonias that affect their limbs. However, when

they looked at all cervical dystonia patients, they found the brain lesions distributed widely across 25 brain regions. They tried looking at the parts that overlapped across patients with the same symptoms and often found their lesions did not even border one another. When the Fox Lab further examined the data on cervical dystonia patients, they found that the widely distributed lesions all fell within a specific circuit between the cerebellum, a movement center, and the somatosensory cortex, a part of the brain that detects sensory inputs.

This research suggests that DBS may be more successful when targets are within the cervical dystonia connectome, an exciting development for the patient community.

Functional imaging of dystonia: common themes or too much heterogeneity?

Jon Stoessl, MD

University of British Columbia, Vancouver, Canada

Heterogeneity in research means the data being described has too much variability to be interpreted. In the context of functional brain imaging data, the variability may refer to both the dystonia subjects themselves or the resulting data.

Specifically, dystonia subjects participating in studies can have many different dystonia subtypes and within each individual subtype they can vary in the associated clinical features, progression patterns, non-motor features, response to medication, other unrelated health conditions, stress levels, sleep quality, and many other details. All these variables can influence the way the brain signals to the rest of the body. Even the data itself can vary widely. For instance, many patients with the same type of dystonia may have brain lesions in different locations.

In research studies, scientists start with a question, design an experiment to test it, and then analyze the data to get an answer. In clinical dystonia research, the analysis often compares a feature in dystonia patient to that same feature in non-dystonia participants. Variability within participants introduces a high amount of variability in the features being observed. This can conceal important differences between the two groups.

Because dystonia can be so diverse, affecting different parts of the body with different levels of severity caused by different things, it makes sense that brain anatomy would differ from case to case. Additionally, the brain abnormalities that cause disorders like dystonia can also prompt the brain to try and compensate for the abnormalities to regain normal function. The data collected from functional imaging may tell us about the cause of dystonia but may also tell us about the changes in the brain due to this kind of compensation. Isolating the cause is necessary to develop new effective therapies. To better understand the way dystonia affects the brain, it's important to keep variability to a minimum.

Anatomical basis of dystonia: what can we learn from animal studies?

Roy Sillitoe, PhD

Baylor College of Medicine, Texas, USA

Developing animal models for disease research is invaluable because it allows scientists to study diseases in controlled settings that are difficult to replicate in humans. These models enable researchers to explore the causes of diseases and test potential treatments and provide a crucial bridge between basic laboratory discoveries and potential clinical application of diagnostic tools and therapies.

Animal models can be engineered to have the same genetic mutation observed in humans with dystonia, allowing scientists to evaluate abnormalities at the level of the brain circuits and individual cells. Currently, there are many dystonia animal models using rats, mice, monkeys, hamsters, fruit flies, flat worms, and even a duck model of torticollis. Different animal models have different research value. For example, fruit flies and the flat worm are the most robust tools for investigating the cellular and molecular impact of genetic mutations.

Rodents are commonly used as animal models because they allow researchers to investigate the impact of genetic mutations. They also exhibit complex behaviors that have been thoroughly characterized. Finally, there are many methods to look at the cellular circuits in the rodent brain and how it functions.

The same functional imaging methods used in humans can be used in animal models to observe brain circuit changes. This work reinforces the clinical hypothesis that dystonia is a brain network disorder, affecting several brain regions and how they signal to one another.

Instead of using genetic mutations currently linked to dystonia in humans, the Sillitoe Lab uses a genetics-based tool to block the cell-to-cell communication at an isolated point within the rodents' dystonia brain circuit. The resulting mouse model has severe dystonia and provides the perfect tool to observe how repetitive voluntary movements trigger involuntary movements.

Using a small metal electrode to record cellular activity within the cerebellum of these mice, the group can observe that these cells have bursts of activity with intermittent pauses compared to the normal mice where the cells show constant, even activity. When they used DBS to electrically activate the cells within the cerebellum, likely improving the cellular activity to be more constant like is seen in non-dystonic mice, the mouse had reduced the dystonia. Ongoing work in the Sillitoe Lab is also using this mouse model to optimize DBS stimulation procedures for enhanced symptom relief.

New imaging methods: how can they be applied to dystonia?

Joel Perlmutter, MD

Washington University, Missouri, USA

There are many different kinds of imaging methods currently explored, most of them have been applied to dystonia.

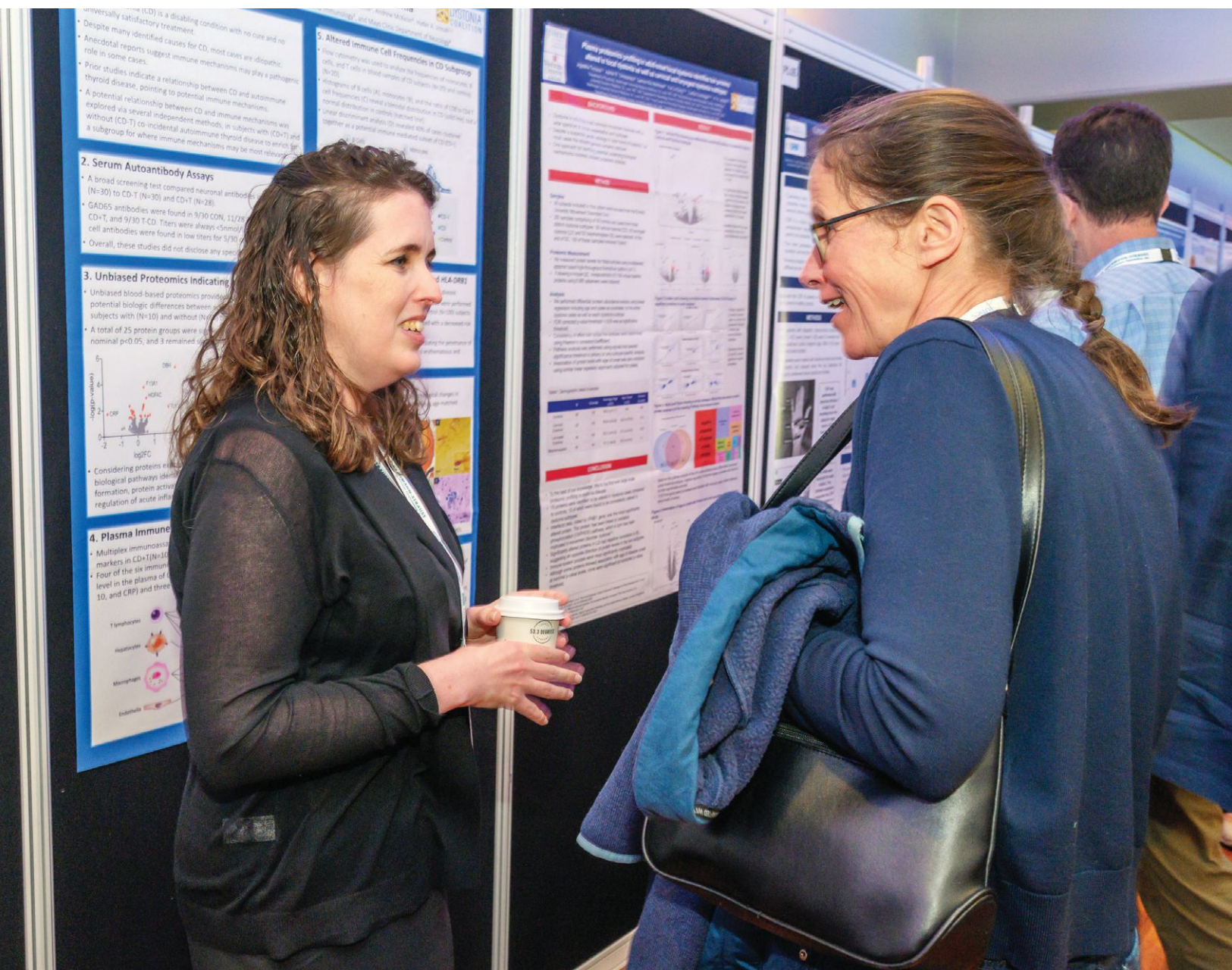
One type of functional imaging is Positron Emission Tomography (PET) scans. PET scans allow researchers to observe different features of brain activity. They do this by injecting specialized compounds into the body that illuminate certain brain signaling components, like dopamine production. Dr. Perlmutter outlined several PET compounds and additional imaging methods and corresponding research findings that are applicable to dystonia.

Another of such useful methods in Magnetic Resonance Imaging (MRI) that, for example, can directly examine iron levels method the living brain. Iron plays a crucial role in brain health, and abnormal iron levels can indicate various neurological conditions. Researchers can combine this method with Diffusion Tensor Imaging (DTI), a sophisticated imaging technique, to observe any indications of damage or alterations to brain circuits.

Finally, the powerful 7T functional MRI (fMRI), uses a higher magnetic field strength to observe much more

detailed and precise imaging of brain function. However, it's worth noting that 7T fMRI is not typically used for routine clinical purposes and is primarily a tool for advanced clinical research due to its higher cost and limited availability.

All these methods allow researchers to observe and record changes in the brain of live patients providing unprecedented insight not the inner workings of the brain and its abnormalities.



BREAKING NEWS & RESEARCH HIGHLIGHTS - DAY 2

Genetic features in monogenic forms of dystonia and parkinsonism

Lara Lange, MD

University of Luebeck, Luebeck, Germany

Whole genome sequencing is a powerful technology that reads all the genetic information in a person's DNA. In dystonia disease research, it can help scientists identify genetic variations that might be linked to the development or progression of dystonia, paving the way for more targeted and personalized treatments based on an individual's unique genetic makeup.

Dr. Lange described two extensive global collections of genetic samples from individuals with dystonia and Parkinson's disease: the ProMoveGene and the Global Parkinson's Genetic Programs, consisting of 12,000 and 962 participant samples, respectively. These large genetic datasets make it easier to identify subtle genetic abnormalities that might otherwise appear random in smaller datasets where they occur only once or twice.

These datasets include individuals with known genetic mutations who exhibit dystonia symptoms, as well as those with the same genetic mutations but no symptoms. This allows researchers to enhance our understanding of genetic penetrance, which determines the likelihood or degree to which a specific genetic mutation or variant will lead to a particular condition in an individual who carries that mutation. Having extensive genetic databases enables us to investigate the variability in symptom presentation, progression rates, and other clinical features potentially linked to unidentified genetic variations and precise diagnosis of dystonia.

Cellular abnormalities reveal a mechanism contributing to dystonia

Christian Schlieker, PhD

Yale University, Connecticut, USA

Dr. Schlieker's lab studies the impact of TorsinA mutations on brain cell function. TorsinA mutations, which cause DYT1 dystonia, have been shown to cause abnormalities in the nuclear envelope of many different animal models

of this disease (mouse, fruit flies, and flatworms). The nuclear envelope is the protective barrier around the nucleus, the control center of our cells. It's made up of two membranes and has tiny openings called nuclear pores that act like gates, allowing cellular molecules to move in and out of the nucleus, helping the cell function properly.

TorsinA creates atypical pockets, called blebs, in the nuclear envelope which impair the cell function. Inside these blebs, certain proteins start to clump together, making it hard for the cell to get rid of old or damaged proteins. Dr. Schlieker's lab developed unique ways to observe bleb formation and the accumulation of damaged proteins over time. Using this method, they found that proteins critical for essential cellular function are also getting stuck in the blebs.

The lab attempts to determine the cellular processes that are impacted by the protein accumulation in blebs and whether this abnormal biology is the primary cause of dystonia or a secondary insult to the cellular machinery that can influence severity and progression of the disease.

Genetic study suggests possible therapy for X-linked dystonia-Parkinsonism

Aloysius Domingo, MD, PhD

Harvard Medical School, Massachusetts, USA

Dr. Domingo presented a large collaborative research project that applies genetic methodologies to identify possible genetic therapies for X-linked dystonia Parkinsonism (XDP). The lab developed a process of turning skin cells from patients with the TAF1 mutations that cause XDP into neurons cultured in a dish. Comparing these cells to those created from non-dystonia participants, they found numerous genetic differences across a range of brain regions including the cerebellum.

To learn if these changes are significant, they used specialized molecular tools that allow to correct genetic problems in cells. These corrections rectify genetic and protein abnormalities and hold the potential for a disease-modifying treatment. This method fixed the

genetic abnormalities in the TAFI patients samples showing the potential value of these genetic tools as a personalized medicine option to treat XDP in the future.

Cellular activity in the cerebellum is linked to dystonia symptoms

Meike van der Heijden, PhD

Virginia Tech School of Neuroscience, Virginia, USA

Dr. van der Heijden elaborated on the dystonia mouse model described by Dr. Sillitoe in his talk earlier in the day. In this model researchers disconnected the cerebellum from a brain region involved in movement control and found that this change caused dystonia, ataxia, and tremor. Cell-to-cell communication is essential for the brain function, including movement control. This research study asked the question of whether this mouse model displays different patterns in electrical spikes in the cerebellum when the animal is experiencing ataxia, dystonia, or tremor.

Using specialized electrodes implanted into the brain, they observed three distinct spike patterns that were consistently associated with the three different movement disorders. This finding does not prove that the different activity patterns cause the different symptoms; it simply tells us that they are correlated. To determine whether these activity patterns are causing the symptoms, they used another technique that allows researchers to control the cellular activity in a specific brain region. With this method they were able to replicate the patterns of activity observed before in the dystonia mouse model, which triggered the same symptoms in a non-dystonia mouse. As a result, they were able to determine that specific activity patterns of cells in the cerebellum can cause dystonia, ataxia, and tremor movements. The study deepens our understanding of the role the cerebellum plays in affecting normal and abnormal movements.



POINT OF VIEW: DEVELOPMENTAL OR DEGENERATIVE?

Many researchers claim that dystonia, or at least some of its genetic forms, is a developmental disorder. Others imply dystonia is a neurodegenerative disorder. The goal of these presentations was to present both perspectives, each of which may apply in different circumstances.

Dystonia is a developmental disorder

William Dauer, MD

University of Texas Southwestern, Dallas, Texas, USA

Historically, disorders have been labeled as neurodevelopmental if their symptoms emerge in childhood. However, research has shown that these disorders can also result from underlying biological abnormalities that affect brain development but don't manifest symptoms until later in life. Dr. Dauer focused on generalized dystonia caused by the DYT1 mutation in the TorsinA protein. Typically, DYT1 dystonia begins in the preteen or teen years, progresses briefly, and then remains constant throughout an individual's life. Some individuals, known as asymptomatic carriers, carry the DYT1 mutation but never develop dystonia symptoms. Interestingly, if someone with the mutation makes it through adolescence without symptoms, they are likely to become asymptomatic carriers. This pattern suggests that genetic mutation can affect brain development in a long lasting way that becomes apparent during adolescence, leading to symptom onset.

Experiments have supported this concept by linking neurodevelopmental abnormalities to delayed symptom onset. In these studies, researchers introduced the DYT1 mutation in the embryos of one group of mice and in adult mice in another group. Only the mice with the mutation present during embryonic development showed symptoms later in life. Moreover, when TorsinA

function was restored to a normal level during adolescence in mice with the DYT1 mutation, motor symptoms were significantly reduced, which was not observed when TorsinA function was restored in adult mice.

Dr. Dauer likened neurodevelopmental disorders to buildings lacking earthquake-resistant features. In this analogy, the brain represents the building, and development is the earthquake. Without essential design features, a significant earthquake during development can impact the brain's structural integrity and function. This evidence provided by his experiments suggests that DYT1 dystonia is indeed a developmental disorder.

Dystonia can be a degenerative disorder

Ryuji Kaji, MD, PhD

Tokushima University, Tokushima, Japan

Neurodegenerative disorders are characterized by a progressive loss or death of brain cells. MRI images of the brain as well as post-mortem brain assessment have shown neurodegeneration within a key movement center in individuals with X-linked dystonia Parkinsonism. Brain cells have specific systems in place to protect them from damage. Published research has found defects in the brain region where neurodegeneration occurs. Additionally, brain lesions in the basal ganglia or cerebellum can produce dystonia symptoms.

POINT OF VIEW: CELL CIRCUIT MODELS

Early studies of cervical dystonia emphasized a basal ganglia origin, while more recent studies have emphasized the cerebellum. Presentations in this session emphasized the network model of dystonia, focusing on different anatomical and functional networks.

Cervical dystonia is caused by a defect in the neural integrator for head control

Aasef Shaikh, MD, PhD

Case Western Reserve University, Ohio, USA

The term neural integrator refers to the circuits in the brain responsible for receiving and processing complex information about the body's position in space during ongoing movement. This includes the brain's ability to run the calculations necessary to send the correct movement signals and body position from the brain to the muscles. Dr. Shaikh hypothesized that the head neural integrator circuit receives feedback from the neck position, the cerebellum, and the basal ganglia and found a connection between the neural integrator and dystonia.

Researchers first found that disrupting the information the brain is receiving about head position in non-dystonic individuals could induce cervical dystonic tremor movements by. They also examined the activity of brain cells that respond to head movement in patients with cervical dystonia. The specific patterns of activity observed in these cells indicated that the problem in the neural integrator is not the processing of information by the cell circuit itself, but the very information being received by the circuit. These abnormal activity patterns were observed in key regions within the basal ganglia that are important targets for deep brain stimulation making studies of the neural integrator critical for therapeutic improvements.

Cervical dystonia is caused by a defect in the network for attention orienting

Conor Fearon, BE, MB, PhD

*Mater Misericordiae University Hospital &
St. Vincent's University Hospital, Dublin, Ireland*

Attention orienting is the way our bodies move towards the focus of our attention. Dr. Fearon discussed a specific brain circuit model responsible for attention orienting that may be linked to cervical dystonia (CD). We know that CD patients have a loss of inhibitory signaling in many different circuits. Signals in the attention orienting circuit, that is affected in CD, are sent to the neck muscles to turn the head. Studies have found that reducing inhibitory signaling within this circuit hyperactivates cells that respond to sensory stimuli for longer periods of time. This can ultimately lead to increased signals being sent to the neck muscles, resulting in dystonia symptoms.

The possible link between the dysfunction in the attention orienting circuit and dystonia is reinforced by many other behaviors that are also abnormal in dystonia patients. For example, an increasing number of research studies have found that dystonia patients have diminished ability to accurately perceive and distinguish the timing of two separate events or sensations in time—termed temporal discrimination. Another relevant mechanism is sensorimotor integration, which combines sensory information, like touch or sight, with motor functions facilitating coordinated and purposeful movements that are compromised in CD. Understanding these functional mechanisms will be critical to successful treatment of CD.



PHYSIOLOGICAL BASIS OF DYSTONIA

Identifying the connection between cellular abnormalities and symptoms through research animal models and successful treatment methods.

Physiological changes in human dystonia: where are we now?

Robert Chen, MA, MBBChir, MSc, FRCPC

University of Toronto, Toronto, Canada

Understanding physiological abnormalities in the nervous system is important to better understand dystonia.

The brain and spinal cord are the two key components of the nervous system. Nerves extend from the spinal cord to diverse tissues in the body including skin, muscles, and organs to collect sensory information about the world and the body's movement within it. Then they send that information to be processed by the brain.

There are several abnormalities in the nervous system that are often observed in dystonia. In addition to the loss of inhibitory signals being sent from the spine to the muscles, there is a known loss of inhibitory signals throughout cell circuits in the brain that are linked to movement. Abnormalities have also been observed in hyperactive cells in these same circuits.

Abnormal patterns in muscle contractions are foundational abnormalities observed in patients with dystonia, which are often used to determine a diagnosis. One example of this is the co-contraction of opposing muscles. To bend the arm, for example, we need our biceps on the front to contract while our triceps on the back extend. The instructions for the opposite actions occurring in coordination are delivered from the brain, down the spinal cord, and to the muscles through different nerves. A classic physiological abnormality in dystonia is the co-contraction of these opposing muscles in the body. This is a result from the reduction in the inhibitory or "stop" signals coming from the spinal cord to the muscle that needs to relax.

Overall, it is important to note that these symptoms are not limited to dystonia and also appear in other neurological or neuropsychiatric disorders. Additionally, the data on the specific causes of these symptoms are a work in progress and much of the existing data has a lot of variability.

DBS in humans: what can we learn about the cause of dystonia?

Marie Vidailhet, MD

Hôpital de la Salpêtrière, Paris, France

Researchers hope that by expanding our understanding of genetic mutations and the cellular processes that they disrupt, we will better understand the cause of dystonia. However, it is important to be aware that genetics does not currently provide explanations for all patients with dystonia.

Specifically, a large study surveyed 764 individuals with dystonia and showed that those with a known, identifiable genetic mutation for dystonia make up only 20% of those with combined dystonia and 4% of those with isolated dystonia. This is important because although some genetically confirmed forms of dystonia respond well to DBS, such as myoclonus dystonia patients with the DYT11 or epsilon-sarcoglycan mutation, genetics alone does not allow us to determine whether DBS is going to be a successful treatment method.

The reality is that DBS outcomes are difficult to predict. Researchers are curious to learn how DBS influences dystonias with unknown causes. Dystonia experts have learned that the symptoms associated with generalized and cervical dystonia can be lessened by DBS targeted to the pallidum, a brain region within the movement circuits. In research studies that show the results from groups of patients with similar symptoms and the location being targeted by DBS, the outcomes and success of the treatment method can vary, and the cause of this variability can be difficult to pinpoint.

Unfortunately, the variability in DBS outcomes can make it difficult to predict which patients will benefit most from this invasive therapeutic procedure. Researchers have worked to find other factors that could help aid in this prediction, such as age of the patient, disease duration, severity of symptoms, amongst many others. These details can suggest that a positive outcome is more likely but there are no clear patterns that indicate future DBS success.

It is important to continue to collect data on new cases of DBS and revisiting previously published cases as we

learn more. Reanalyzing data on DBS outcomes on an increasingly large group of patients may help us identify additional features shared by patients that experience significant improvements.

Physiological basis for dystonia: what can we learn from animal studies?

Antonio Pisani, MD, PhD

IRCCS Mondino Foundation, Pavia, Italy

Animal models have greatly informed our current understanding of how the brain and body work together. In dystonia research, the use of animal models has expanded exponentially, with more and more important research findings being published each year. As the research findings from animal models accumulate, we can begin to identify parts of the picture more clearly and ultimately will see how the different parts fit together to create the full picture.

One clear part of the dystonia picture that has been revealed through many important studies is that the loss of inhibition in the brain produces hyperactivity of the cells in the circuits responsible for movement. This creates an overflow of movement information being sent from the brain to the muscles.

Another part of the picture that we can see is that the abnormalities in cell-to-cell signaling that hijack normal motor learning in the brain can cause task-specific dystonia. Learning and memory in the brain is possible due to neuronal changes that allow them to more easily pass signals that produce a behavior or action, a process that is often called “plasticity”.

When an individual learns to play the violin, they are combining a precise motor action that is necessary to create different notes with their cognitive ability to read the sheet music instructions for a song. Learning to play a song is a clear example of how repetition is important. In the brain, this repetition is activating the motor movement circuits that send signals to the muscles and the cognitive circuits for music-reading. Repeated activation of these cell circuits in the brain induces changes in the cells themselves and the type of signals they send

between one-another, which ultimately improves our ability to execute that specific action. This is the cellular basis of learning, with the “memories” existing in the brain as those adaptations to the cells and their signaling machinery.

In individuals with dystonia, researchers have found many differences in how our cell circuits adapt during learning, that have implications in the resulting motor signals being sent to the body. Task-specific dystonia is a great example of this, where repetitive movements can increase the likelihood that those movements trigger dystonia. Interestingly, the same abnormal cell learning and memory features are also observed in other types of dystonia, including individuals with DYT1 that have dystonia symptoms and even those with the mutation that do not have the associated symptoms.

As we gained insight into these processes from studying various animal models of dystonia, the changes observed in their cells have also been seen in humans with dystonia. These changes alone often do not present a big enough problem to the brain-body systems to produce dystonia right away. Instead, the hyperactivity and changes during learning and memory accumulate throughout stages of development or maturation (i.e., adolescence), eventually reaching the threshold that triggers dystonia symptoms—which has also been observed in both animal models and humans. Overall, this validates the use of animal models in studying dystonia, providing invaluable tools to analyze its symptoms and cellular mechanisms.

Cerebellar stimulation for dystonia?

Andres Lozano, OC, MD, PhD, FRCSC, FRSC, FCAHS

University of Toronto, Toronto, Canada

The cerebellum is a brain region that has been thoroughly discussed throughout the meeting. It is both an important part of many circuits linked to movement and the site for several cell and circuit-based changes observed in dystonia. Many dystonia experts have published work on how dysfunction of cell signaling in the cerebellum is strongly linked to dystonia. As researchers work to better understand the role of the cerebellum in dystonia, interest in the cerebellum as a DBS target is growing.

Currently, 60-70% symptom reduction is a successful outcome for dystonia patients undergoing DBS. Although this is clearly beneficial, it prompts experts to continue searching for methods that enhance this therapeutic value even further. One current limitation with including the cerebellum as a potential target for DBS is deciding which specific location to target. The cerebellum is very large and how different areas connect to the movement circuits throughout the rest of the brain are not fully understood.

There are several case studies that highlight patients that have received cerebellar stimulation for dystonia, epilepsy, ataxia, tremor, and stroke. The most common method to deliver stimulation to this brain region has been through stimulating electrodes that curve around the surface of the cerebellum. DBS has also been used to provide electrical stimulation to deeper regions within the cerebellum. In a population of 600 patients with cerebral palsy, two-thirds experienced significant symptom improvement from cerebellar DBS. Despite success with cerebellar DBS, the best target location has not been identified. Furthermore, it is unclear when the cerebellum may be a better DBS target compared to the currently most common targets.

New technology allows neurosurgeons to implant a sensor on the surface of different brain regions at the same time as the DBS implant. The sensor allows clinicians to observe how changes in brain activity coincide with dystonia symptoms, informing future stimulation programs for the DBS that automatically turn up during symptoms and down when they subside. Sensor implants during cerebellar DBS showed clear indications of brain activity associated with dystonia symptoms, suggesting a path forward to enhancing the value of cerebellar DBS.

To implement this DBS target more confidently in the future, researchers need to answer a few key questions. First, which specific region within the cerebellum is best for stimulation? Second, which dystonia syndromes respond best to stimulation in this brain region compared to other common DBS targets? Third, should the cerebellum be reserved for patients where other DBS targets have not improved their symptoms? And last, can sensors that show cell activity in the cerebellum help indicate whether this is the best target for DBS and provide a better stimulation program to enhance symptom relief?



POINT OF VIEW: SENSORIMOTOR INTEGRATION

Sensory abnormalities and abnormal sensory thresholds have been extensively studied across many types of dystonia. These presentations addressed the significance of these findings for the biology of dystonia. The speakers argued whether such processes are specific and fundamental to or rather non-specific consequences of dystonia.

Abnormal sensory processes are a fundamental defect underlying dystonia

Michele Tinazzi, MD, PhD

University of Verona, Verona, Italy

The sensorimotor system receives information from the senses and uses it to coordinate movements and actions. Brain circuits are all interconnected and their abnormal function in dystonia, potentially reinforces the undesired outcomes.

DYT1 dystonia patients have a lessened ability to accurately distinguish the timing of two separate sensations, termed “temporal discrimination”. Similarly, dystonia patients with focal hand or cervical dystonia have been found to have difficulty distinguishing between two pinpoint touch sensations as they get closer together, called “spatial discrimination”. Moreover, a part of the brain called the somatosensory cortex, which processes sensory information from the body, has abnormalities in individuals with focal dystonias. Dystonia patients also have deficits in proprioceptive processing, which is the brain’s way of understanding where your body parts are without having to look at them, helping you coordinate movements and maintain balance.

Individuals with dystonia have a loss of inhibition in brain circuits responsible for processing sensory information and producing movements. When you no longer limit the volume of cell signals flooding into a brain region, you alter the resulting instructions sent from the movement circuits to the muscles. The signal overload can significantly alter how cells in each brain region function. One example

of this is abnormal plasticity. As discussed in Dr. Pisani’s presentation, brain plasticity refers to the changes that occur in cell circuits that allow them to more easily pass signals that produce a behavior or action.

Abnormal sensory processes are a non-specific consequence of the disorder

Antonella Conte, MD, PhD

Sapienza, University of Rome, Rome, Italy

Dr. Conte provided evidence that these abnormalities are present in movement disorders other than dystonia. Spatial discrimination is abnormal in dystonia patients but also in individuals with Parkinson’s and multiple system atrophy, confirming that they are not unique to dystonia.

How is sensory processing impacted when dystonia symptoms are alleviated? Interestingly, the hindered spatial discrimination observed in individuals with cervical dystonia improves with botulinum neurotoxin treatment and similar improvements are seen in individuals with Parkinson’s after symptom management. These findings suggest that sensory processing abnormalities are a consequence of the motor symptoms because they dissipate when treatments reduce the symptoms. However, another study contradicts this, as spatial discrimination abnormalities were observed in individuals with the genetic mutations for dystonia but without motor symptoms—diminishing the possibility that the abnormalities in sensory information processing in such cases are result of motor symptoms.

POINT OF VIEW: MALADAPTIVE PLASTICITY

The role of brain plasticity in dystonia has been the subject of both human and animal studies. Its causal role in dystonia has never been established. The reported findings may be a fundamental defect underlying dystonia, or simply a consequence of dystonia. The goal of these presentations was to present both perspectives.

Abnormal plasticity is the fundamental defect underlying dystonia

Angelo Quartarone, MD

University of Messina, Messina, Italy

Dr. Quartarone argued that abnormal plasticity, or signaling-dependent changes in the brain, is a fundamental feature of dystonia. Studies using experimentally applied non-invasive brain stimulation showed that individuals with dystonia exhibit a greater amount of brain plasticity than non-dystonia participants. These studies also found that changes in the brain areas with increased plasticity were less specific than in non-dystonia participants.

Another point that supports this perspective is that it takes three to six months for the symptom relief associated with DBS to take effect. Though this may seem like a long time for patients seeking relief, this finding suggests that the stimulation reverses the plasticity that was causing dystonia symptoms. The specific mechanisms by which DBS reorganizes cell signaling in these circuits is not yet fully understood.

Another clue that abnormal brain plasticity is a fundamental cause of dystonia is the presence of sleep disturbances before dystonia symptom onset. During sleep, the brain cells undergo a specialized process that helps clean up the circuits used during the day. Dystonia may appear when this process fails to happen.

Abnormal plasticity is a non-specific consequence of many movement disorders

Anna Sadnicka, MD, PhD

St. George's University of London, London, UK

Dr. Sadnicka presented an opposing perspective, suggesting that abnormal plasticity might not be the underlying cause of dystonia. A significant part of this argument revolves around the limitations of non-invasive brain stimulation (NIBS) methods used to assess brain plasticity in humans.

One issue highlighted is the variability in how people respond to NIBS. Some individuals exhibit plasticity in response to NIBS while others do not. For instance, in a study involving 56 participants, less than 50% displayed plasticity, making it challenging to draw conclusions about the role of plasticity in all dystonia patients. Furthermore, the same NIBS experiment conducted a week apart on the same individuals often yielded dissimilar responses. Plasticity itself can be inhibitory or facilitatory, meaning it can either reduce or enhance circuit activation. The same individuals that showed circuit enhancement one week could show no response or even an inhibition of the circuit the next week and vice versa.

Another aspect of the argument points out that abnormal degrees of plasticity have also been observed in other patient populations, such as Alzheimer's and autism. Additionally, limitations in current NIBS methods restrict researchers to gathering information from the surface of the brain, while many important brain regions contributing to dystonia are located deeper within the brain.



UNDERLYING MOLECULAR MECHANISMS

What is known about the abnormal cellular processes in different types of dystonia and what questions are key to address next to get closer to new treatments

Overview of dystonia genetics

Michael Zech, MD

Technical University of Munich, Munich, Germany

Dr. Zech reviewed the timeline of new genetic methodologies that have impacted dystonia gene discovery.

The first three dystonia genes discovered were GCH1 in 1994, linked to L-dopa responsive childhood-onset dystonia, TOR1A in 1997 for early-onset generalized dystonia, and THAPI in 2009, which causes early-onset dystonia in muscles of the head and neck. These mutations were discovered through two types of genetic analysis called linkage analysis and candidate gene analysis. With linkage analysis, scientists examine the genetic makeup of families affected by dystonia to identify patterns of inheritance and locate specific genes associated with the condition. Candidate genes are genes that researchers suspect might be involved in dystonia based on existing knowledge. They examine these genes in affected individuals looking for any mutations.

In 2009, a new genetic analysis method called Whole Exome Sequencing (WES) was invented. WES allowed researchers to look at the entire set of genes that code for every protein in the body. As a result, dystonia researchers found ANO3 in 2012 and GNAL in 2013, both linked to dystonias of the head or neck. They also discovered TUBB4A in 2013, which is linked to early onset generalized dystonia, dysphonia, and other more complicated types of dystonia. More extensive use of WES that included dystonia patients and their family members allowed researchers to identify a long list of additional genes associated with dystonia.

It is important to note that while WES is an effective analytical tool, it has not been able to identify 55% of individuals with complex dystonias, 80% of individuals with combined dystonias, and 95% of those with isolated dystonias—leaving plenty of room for genetic research to expand and improve on how we diagnose and treat the disease. Novel methods have the capacity to do exactly that once they become more cost-effective for patients and improve our methods to interpret the resulting data. One example of such methods Whole-Genome Sequencing (WGS). WGS focuses on the areas of the genetic code that are known to provide the instructions for making the

proteins in our bodies. WGS is more comprehensive and covers the coding and non-coding regions, giving a full picture of an individual's genetic code. Dr. Zech provided one example where a myoclonus dystonia patient in whom WES analysis did not detect the common SGCE mutation, however, WGS identified so far unknown abnormal copies of the SGCE gene.

While genetic research has uncovered a lot about different forms of dystonia, there is still work to be done to unravel the complex mystery that surrounds complex, combined, and isolated dystonias. New technology and research methods are tackling this important issue with the hope to diagnose and treat the disease more effectively.

What are the biological mechanisms of dystonias with partial penetrance?

Chi Wang Ip, MD

University Hospital Würzburg, Würzburg, Germany

New research links the genetic mutations associated with the disease to the development of the motor symptoms, suggesting interesting avenues for further research with animal models and in the clinic.

Genetic penetrance refers to the likelihood that a person with a specific genetic mutation will develop the associated condition. For the DYT1/TOR1A mutation, only around 30% of people with this mutation develop generalized dystonia. Because so many people with the mutation do not develop dystonia, the genetic mutation must not be the full story.

One possibility that researchers think could explain why some individuals develop motor symptoms is the two-hit hypothesis. It is a theory that suggests two separate events or factors are needed to cause a particular condition or disease. In the context of dystonia, it proposes that the genetic predisposition provides the first hit to the biological systems and an environmental or additional genetic trigger can serve as the second hit that is required for manifestation of the symptoms of the disorder.

Examples of the first-hits to the brain include changes in cell-to-cell signaling within motor circuits, abnormalities in plasticity, and abnormal sensorimotor processing.

Examples of the second-hit include the adverse events experienced during fetal development, childhood infections, taxing process of adolescent development, exposure to general anesthesia, or physical trauma.

The interaction between genetics and the environment has been strongly supported in many other instances of neurological disorders. However, the current clinical data on the two-hit hypothesis in dystonia remains highly variable, making it difficult to identify whether this is consistently a biological process where a genetic mutation predisposes an individual and the environment triggers the onset of the disorder.

Overall, Dr. Ip explained the difficulty in integrating what we know from highly variable patient data and many different types of animal models. Particularly, he noted that differentiating between abnormal biology that is causing dystonia and the abnormalities that are a result of biological systems compensating for dystonia.

Stem cells: new technologies and application to dystonia

Cristopher Bragg, PhD

Massachusetts General Hospital, Massachusetts, USA

Induced pluripotent stem cells (iPSCs) are an important tool in disease research, especially when developed from patients' own cells. These cells, derived from skin or blood samples, retain the genetic information responsible for diseases. Scientists are now able to convert them into specific, affected cell types, for example different brain cells. iPSCs enable scientists to closely examine disease effects, test potential treatments, and gain insights into disease mechanisms, all of which are unattainable with clinical skin or blood samples alone.

Dr. Bragg described research that utilized iPSCs with a revolutionary research tool called CRISPR, which is a genetic editing tool that works like molecular scissors and glue that can cut out or replace specific parts of our genes. Using iPSCs and CRISPR, researchers can create different cell types that carry disease-causing mutations allowing them to better understand the cellular cause of disease. By examining cells taken from dystonia and non-dystonia patients, researchers can identify the key

features of the disease by studying the composition and behavior of these cells. New drug therapies can be tested using the dystonia cells to determine if their characteristics can be reverted to those seen in the non-dystonia cells.

Importantly, the same genetic mutations can be monitored in different types of brain cells. The inhibitory, excitatory, and dopamine neurons that are crucial in movement circuits can all be studied using these methods. Introducing these genetic mutations into different cell types allows researchers to characterize how the mutations exert unique impact on specific cell populations.

Shared biological pathways in dystonia: one or many paths to new therapies

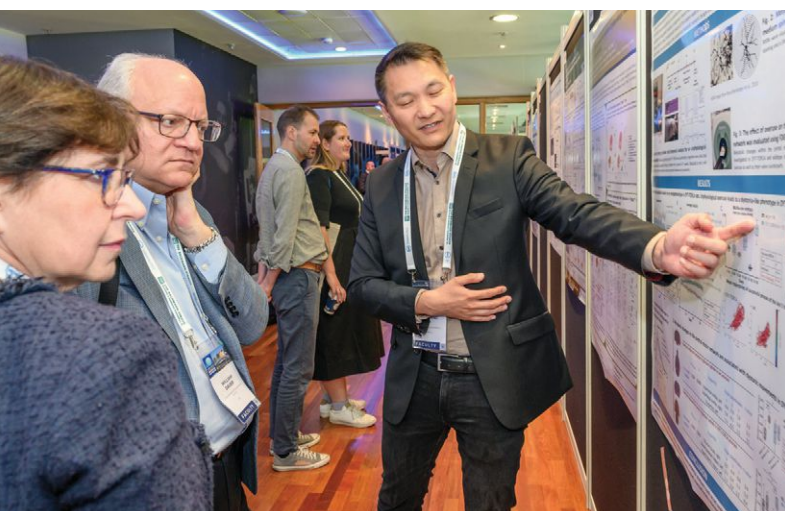
Niccolò Mencacci, MD, PhD

Northwestern University, Illinois, USA

More and more evidence suggests that different dystonia genes are linked through shared biological processes in the brain. Many of these genes contribute to cell signaling in movement circuits in the brain. The passage of chemical signals from the brain requires many different steps. The cell sending the chemical signal needs to synthesize the transmitter molecule, store and release it at the appropriate time. The cell receiving the signal has specialized proteins that intercept the signal molecule and trigger a specific series of events within the cell that are ultimately converted into the electrical signal. There are many dystonia-associated genetic mutations that may hinder each of these steps, so it is critical to understand these processes and mechanisms to design treatment strategies that target and correct them.

There are also dystonia gene mutations that have been found to affect myelin in brain cells. Myelin is a specialized insulation that wraps around neurons facilitating them to send the electrical signals faster and farther within the circuits important for movement. Other genetic mutations have been linked to dysfunction of lysosomes, which are the recyclers of the cell, breaking down waste materials and old cellular components to keep the cell clean and functional. Interestingly, lysosome dysfunction is thought to be linked to the development of healthy myelin.

All these shared dystonia genes and pathways offer an exciting opportunity to understand the molecular basis of dystonia and develop rational therapies targeting the core mechanism of this disease.



New ways to exploit existing resources

Jan Teller, MA, PhD

Dystonia Medical Research Foundation

Dystonia researchers have access to many different tools and data repositories to continue their exploration of dystonia. Collaboration and communication between different research teams is essential to learning more about the mechanisms of the disease, developing new treatment methods, and finding a cure.

The most critical resource available to researchers are biobanks. Biobanks are collections of biological samples, which scientists carefully collect, store, and catalog. These samples include blood, tissue, or DNA from humans and animals. This biological library helps researchers study diseases and find new treatments by allowing them to compare samples from different individuals. There are several biobanks that store dystonia samples.

One of them has been set up by the Dystonia Coalition, a group made up of 40+ dystonia centers all over the world

to enhance their individual research efforts by having much larger data sets. The biobank established by the Dystonia Coalition has collected DNA samples from more than 3,600 individuals supplemented by their dystonia course and progression. and 3000+. The Coalition has contributed to over 200 research publications, many of which used the biobank as a research resource, highlighting the importance of these repositories. Additional biobanks are housed across the world. In Germany, a biorepository called DysTract, contains a systematic collection of data about the course of the disease, genetic screening for known dystonia mutations, stores blood samples and other biomaterials, videos of symptoms, and clinical data that could be useful for research projects. The DMRF created an online platform called The Global Dystonia Registry, where individuals could take surveys, upload medical records, track health outcomes, and learn about the latest research and clinical trials. Currently, there have been 6,582 registered participants that collectively have provided 177,773 survey question responses. Finally, Dystonia Europe developed a tool called MyBrainNet that provides many valuable features for patients, physicians, organizations, and researchers. Patients can create electronic diaries to improve their quality of life. This tool also benefits physicians by facilitating communication and providing important information about patients.

In addition to providing blood samples or DNA and completing surveys, important neurological disease research is accomplished using post-mortem brain tissue. In one of such efforts, DMRF has partnered with Harvard's Brain Tissue Resource Center establishing a collection of dystonia brains.

By establishing these data and material banks, researchers are able to use the dystonia patients shared experiences and clinical data along with their biological samples to find answers to important questions about the nature of the disease.

BREAKING NEWS & RESEARCH HIGHLIGHTS - DAY 3

TOR1A dystonia can be linked to spinal cord dysfunction

Amanda Pocratsky, PhD

University of College London, London, UK

Cells within the spinal cord have specialized circuit patterns of activation that send specific movement instructions to the muscles to trigger many distinct movement patterns (i.e., walking versus skipping). The commonly held belief in dystonia field indicates that dysfunction occurs within the many different brain regions that send problematic signals to the muscles. Dr. Pocratsky described her recently published research findings on the defects observed in the spinal cord in mouse models with TOR1A mutations.

Researchers exclusively mutated TOR1A in the cells within the mouse spinal cord, leaving the TOR1A fully functional in cells within the brain. By targeting the spinal cord, they were able to show that TOR1A deficits are sufficient to produce dystonia symptoms in their mouse model. The motor symptoms progressed gradually mirroring what is observed in humans with TOR1A mutations. When they recorded muscle activity of muscle groups that activate in a coordinated way in non-dystonia mice, excessive and disorganized muscle activity in the TOR1A model was recorded, similar to what is observed in humans. This mouse model will continue to be a useful tool for future studies evaluating the abnormalities in the spinal cord, how they contribute to dystonia symptoms, and what treatments may best target this location of dysfunction.

TOR1A dystonia genetics and the role of the brain's immune system

Lisa Rauschenberger, MD

University Hospital Würzburg, Würzburg, Germany

Dr. Rauschenberger presented research on the two-hit hypothesis in dystonia. The genetic mutations associated with dystonia have low penetrance, causing the disorder only in a subset of individuals with the mutation. The reason for this is not known. The two-hit hypothesis proposes that the genetic mutation is the first cause of damage to the cell circuits and that a second hit is necessary to induce the symptoms. Some examples may

include a viral infection or trauma. This talk specifically discussed the data suggesting that one possible second-hit is abnormal immune system activity within the brain pointing to microglia—specialized immune cells of the brain. These cells are very important in early brain development and are known to contribute significantly to plasticity. Microglia also play a role in maintaining cellular homeostasis. The research from Dr. Rauschenberger showed that blocking microglia function in rodents with the TOR1A mutation causes dystonia symptoms—emphasizing the importance of further studies on the relationship between dystonia and the immune system.

Dopamine and acetylcholine send key movement signals in DYT1

Giuseppe Sciamanna, PhD

UniCamillus International Medical University of Rome, Santa Lucia Foundation, IRCCS Rome

The cellular activity within the external portion of a brain region called the globus pallidus (GPe) has been shown to be abnormal in dystonic patients and animal models of dystonia. The GPe is situated with the motor circuits of the brain, sending signals to the basal ganglia. If the cellular activity is abnormal, so are those signals. To better understand the cellular abnormalities that contribute to the increased cell activity, Dr. Sciamanna characterized many cellular differences in the GPe. In non-dystonia mice, a drug called quinpirole, which increases locomotion in mice, inhibited cellular activity in a specific cell population. In the mice with the TOR1A mutation, this inhibition went away. Specific proteins important for transporting dopamine, a key signaling molecule in movement circuits, were significantly reduced in the mice with the TOR1A mutation. Dr. Sciamanna looked at the downstream brain regions that the GPe sends signals to. In the TOR1A mice, he found that the GPe sends more activating signals to the downstream targets, which in-turn increased the cell activity in those brain regions as well. Overall, this data reveals cell signaling mechanisms for the enhanced activity observed in the rodent models of dystonia and dystonia patients. It also suggests possible points to target when developing new therapeutic methods.

Serotonin: a key signaling molecule in stress-induced dystonia onset

DaSeo Kim, PhD, KAIST

Daejeon, Korea

Stress is a key factor that can worsen dystonia symptoms, but we still do not know much about the biological origins of this relationship. We know that chronic stress can alter signaling within cell circuits by changing levels of serotonin, a signaling molecule. We also know that the circuits impacted by chronic stress overlap with the movement circuits. The likelihood of this connection is reinforced by published data from humans with medication-induced changes in serotonin signaling that develop movement disorders, 20% of which exhibit dystonia.

Using a method that allows researchers to turn off the signaling from a certain cell type, the Kim Lab turned off

serotonin signals reaching the cerebellum. When they did this in a mouse model for dystonia, they significantly reduced the dystonia symptoms. There are drugs that can be used to block serotonin signals in the brain and the Kim Lab found that these drugs block the onset of dystonia in the mouse models of dystonia.

The group further researched the connection between serotonin, stress, and dystonia. They found that stress increases serotonin release in the cerebellum, triggering dystonia. The sequence between stress and dystonia could be blocked with the same drug that blocks the serotonin signals in the brain—suggesting a possible therapeutic option to research further. It is important to note that serotonin is important for many different aspects of brain function, so it is necessary to thoroughly research the impact of this drug before using it as a therapeutic option.



POINT OF VIEW: WHAT IS A “DYSTONIA GENE”?

Nomenclature, or the way names are chosen for things, is used in the dystonia field to refer to specific genetic mutations associated with specific dystonia diagnoses. For example, in the existing naming scheme, generalized dystonia with mutations in the TOR1A gene is called DYT1. Other dystonia genes are also called DYT, followed by a different number. Some argue this nomenclature has become overly complicated by our expanding genetic data.

The talks covered the work being done by the Movement Disorder Society Task Force on Genetic Nomenclature to develop a new naming scheme that more clearly and comprehensively refers to complex genetic disorders. As the new naming scheme is used more by researchers, having some familiarity with the scheme will be useful in understanding published research.



The list of DYT genes

Connie Marras, MD, PhD University of Toronto
Toronto, Canada

The Movement Disorder Society Task Force on Genetic Nomenclature adopted several rules in establishing the nomenclature for dystonia genes. If dystonia is the main clinical feature, the disorder will get the “DYT” prefix.

If dystonia co-exists with another movement disorder, such as Parkinsons or myoclonus, there will be a combined prefix, like DYT/PARK or MYC/DYT.

If dystonia is present but not predominant or there are more than two movement disorders the prefix will be MxMD, which stands for mixed movement disorders.

Instead of being numbered in ascending order, the suffix will now directly refer to the mutated gene. For example, DYT1 dystonia, which is a mutation in the TOR1A gene, will now be referred to as DYT-TOR1A.

The list of “other” genes

Katja Lohmann, PhD

University of Luebeck Luebeck, Germany

Dr. Lohmann focused on the combined dystonias, where dystonia is a key clinical feature alongside other prominent clinical features (i.e., Parkinsons, ataxia, etc.). Dr. Lohmann highlighted many remaining examples of variability within the clinical population that make any naming scheme far from perfect. There are many different genetic mutations that are found in individuals with dystonia symptoms, Parkinson’s symptoms, or combination of the two. The same can be seen with dystonia and ataxia. The variability in patients with the mutations that can but do not always produce dystonia makes it difficult to determine whether DYT designation should be in the naming scheme. Currently, these decisions are made by the consensus amongst expert, requiring open discussion on how to clearly categorize and reference these varied disorders.

POINT OF VIEW: RARE MONOGENIC DYSTONIAS VS COMMON IDIOPATHIC DYSTONIAS

Finding new dystonia-causing genes offers opportunities to understand more common adult-onset focal dystonias, both biologically and clinically. One of the major reasons that many clinicians do not follow genetic discoveries is because they are not relevant to the vast majority of the more common dystonias they see, and their biology seems different. The goal of these presentations was to summarize both perspectives.

Monogenic dystonias: shared mechanisms with common idiopathic dystonias

Nicole Calakos, MD, PhD

Duke University Medical Center, North Carolina, USA

We know very little about the biological mechanisms underlying idiopathic dystonia. Data shows that genetic dystonias and non-genetic dystonias can cause abnormalities in the same or related signaling circuits within the brain. For instance, brain lesions observed in cervical dystonia patients were distributed across many different locations throughout the connected motor circuit. The same motor circuit is linked to cell signaling dysfunction observed in genetic forms of dystonia.

One interesting example of how altered biology across different forms of dystonia converge in specific cellular processes is the integrative stress response (ISR). The ISR functions as a cellular alarm system that activated during stress. It helps cells adapt to stressful conditions by slowing down processes that are not immediately necessary and redirecting resources to deal with the stress, ultimately promoting cell survival. The ISR plays a crucial role in maintaining cellular homeostasis by ensuring that cells can effectively respond to and recover from stressful situations, helping to keep the internal cellular environment stable.

Dr. Calakos noted her scientific excitement as more and more dystonia mutations have been related to this fundamental cellular process studied in her lab. Currently, the group is working to take their findings connecting dystonia and the ISR from isolated cells to humans. The goal is to determine whether similar abnormalities can be

observed—opening the door for testing new therapeutic approaches to restore normal ISR, which might be the shared mechanism for many dystonias

Monogenic dystonias: distinct mechanisms from common idiopathic dystonias

Roberto Erro, MD, PhD

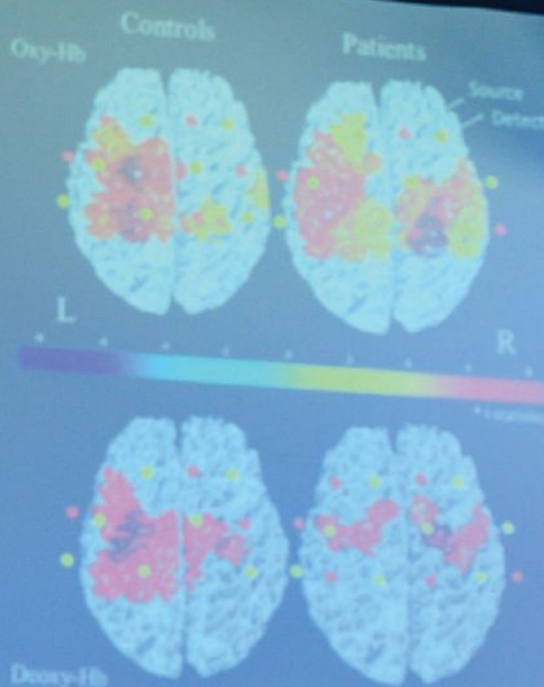
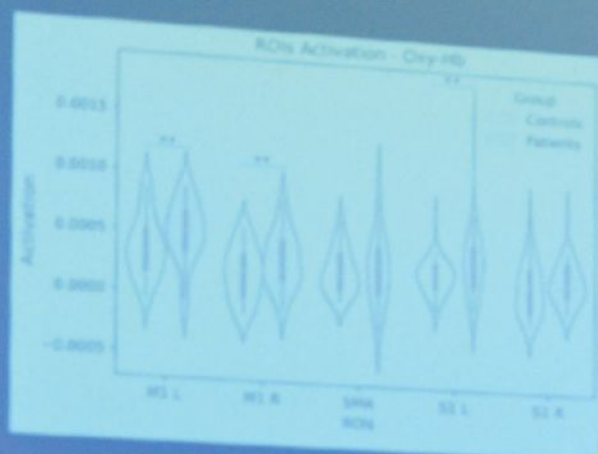
University of Salerno Salerno, Italy

This talk presented the opposing opinion, that monogenic and idiopathic dystonias are linked to distinctly different mechanisms. First, both monogenic and idiopathic dystonias are highly heterogeneous or varied in their clinical features and in what is known about their associated cellular dysfunction. The variability may suggest that there are several different underlying causes that converge on a few specific cellular processes or circuit signaling.

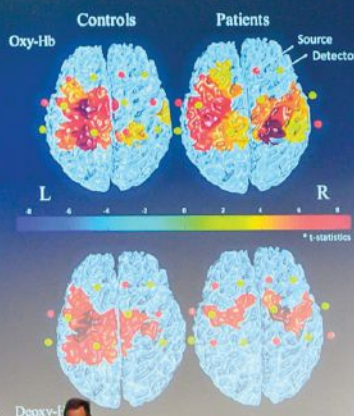
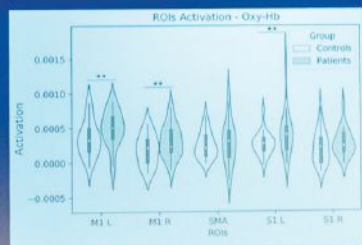
Second, the genetic causes of early-onset dystonias barely overlap with the genetic causes of late-onset dystonias. Genes are instructions for proteins that serve specific functions in our cells, so if there is minimal overlap in the genetic mutations driving these differently timed disorders, the defective cell mechanisms are also perhaps less likely to overlap.

Finally, different types of dystonia respond very differently to treatments that alter the dopamine signaling in the brain. Some dystonias respond to such treatments very well, others do not respond at all, and some respond on a case-by-case basis, makes it difficult to envision the specific shared biology.

What do we see?



What do we see?



EXPERIMENTAL THERAPEUTIC OPTIONS

Current research on new therapeutic approaches that are being researched as possible methods for more regular use

What are the biological targets of new experimental oral medications?

H.A. Jinnah, MD, PhD

Emory School of Medicine, Georgia, USA

New discoveries in dystonia enhance the possibilities of new disease-modifying drugs. The path to developing improved options with enhanced symptom relief or reduced side effects is important for patients and the research community.

The motor circuits of the brain are currently known to be altered in several ways in individuals with dystonia. Key features, such as the reduction in the inhibitory signals that leads to enhanced activity in certain brain areas, can be potentially targeted by existing drugs or drugs being developed. Two existing medications, benzodiazepines and baclofen, work to target this problematic circuit feature in dystonia by artificially reinserting inhibitory signals, quieting the hyperactivity. However, we have an extremely limited capacity to target specific brain areas with medications that tend to be distributed across the entire brain, which means inhibiting circuits not involved in dystonia, producing undesirable side-effects.

New drugs on the market do not necessarily lead to improved outcomes. Parampanel could decrease the excitability observed within movement circuits of dystonia patients, because it blocks excitatory signals from being passed from one brain cell to the next. This could possibly stop the hyperactivity across brain regions. Unfortunately, the drug had worse negative side effects in the older CD population than it does when used for epilepsy in children.

Dipraglurant works similarly to Parampanel except instead of completely blocking the excitatory signals causing hyperactivity in the circuit, it reduces the volume of signals being sent at each step, causing a gradual reduction in the overall cell-to-cell activation. Unlike Parampanel, this drug was well tolerated with minimal side effects, but the signal volume reduction was not substantial enough to reduce symptoms.

Other medications impact serotonin signals. Overall, these drugs do not improve dystonia symptoms. However, some individual patients see improvements while on these medications, suggesting the value for

future studies that identify which patients would benefit from these drugs. Specifically, the role of serotonin in stress-induced dystonia may be impacted by these medications.

Although the first impression of these clinical trial results may be that they failed to produce the desired results for patients, meaningful information is still gained from these studies. First, it is useful to confirm whether possible medications already on the market can benefit dystonia patients. In the process of ruling these options out, we learn more about dystonia biology and how it differs from the other disorders utilizing these medications. Additionally, these studies refine the clinical trial process, highlighting which tools for symptom evaluation work best for testing new drugs and which tests are robust enough to produce meaningful data in studies with fewer participants, which is very useful with a highly diverse dystonia population.

A few drugs have had more success in preliminary clinical research. A new drug, Sodium Oxybate, was shown to improve laryngeal dystonia symptoms by reducing hyperactivity within the cerebellum that coincided with symptoms. Interestingly, stimulants or amphetamines work well in suppressing paroxysmal dyskinesia attacks in a very specific subtype with the KCNMA1 mutation. Similarly, patients ADCY5-related dyskinesia experience symptom relief from caffeine. These findings motivate further evaluation of different types of dystonia with similar mutations that might also benefit. Currently, there are several drugs developed by pharmaceutical companies that are being tested but due to confidentiality agreements this data cannot be shared until after publication.

Botulinum neurotoxin therapy: what are the new trends?

Cynthia Comella, MD, FAAN, FASM, FANA

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Botulinum neurotoxic therapy (BoNT) is a critically important treatment for dystonia patients. BoNT works by interacting with the dystonic muscle. When movement signals are sent from the brain, down the spinal cord, and to the muscles, they reach their final stop at the neuromuscular junction. At this signaling intersection, the specialized cell sent from the spinal cord (called a motor neuron) releases a specific chemical signal onto

the muscle fiber. The muscle fiber has receptors that detect the chemical signal, triggering muscle contractions. BoNT injected into the dystonic muscles navigates to these intersections and disrupts the release of the chemical signal, blocking the muscle contraction message from being relayed from the brain in that specific location. Unfortunately, some individuals develop an immune response in the form of neutralizing antibodies (NABs) to BoNT, which makes further injections ineffective. It is known that the total toxin volume and frequency can affect the development of NABs, requiring clinicians make an effort to reduce both of these aspects.

There are specific parts of the BoNT molecule that allow for these different functions. One part, called the heavy chain, helps the toxin get into the cell and block the release of the chemical signal. The light chain is the part that actually disrupts the signal release. Currently, there are seven different types of BoNT that differ based on the shape of the heavy chain and light chain. These differences can affect how potent a toxin is, with a more potent toxin requiring less amount to achieve the same therapeutic benefit. Currently, there are four BoNTs that are clinically available: Botox (from Allergan Inc.), Xeomin (Merz Pharma), Dysport (Ipsen Pharma), and Myobloc/Neurobloc (US-World Meds).

There are many questions that fuel ongoing research on BoNTs. Are certain types of BoNT less likely to trigger an immune response, allowing for shorter intervals between injections? Does switching to a different type after developing NABs restore the therapeutic benefit? Do the effects of certain BoNTs last longer, allowing for longer intervals in between injections?

BoNT is the primary treatment used for focal dystonia. It is also used to treat specific locations in generalized dystonias. Despite its popularity as a treatment for dystonia, many patients discontinue treatment for various reasons. Many patients lose up to 80% of the therapeutic benefit in 12-18 weeks, with 88% noting symptom re-emergence starting at 74 days. Generally, the peak benefit occurs around two weeks post-injection. This onset and offset of the benefit produce a cyclical process of symptom relief, often called the yo-yo effect. There are additional features that can impact a patient pursuing this treatment method long-term such as negative side effects, lose

benefit due to NABs, the cost associated with regular injections, the inconvenience of routinely traveling for injections, and unrealistic expectations for therapeutic benefit that produce disappointment.

One BoNT that has yet to receive FDA approval, called DaxibotulinumtoxinA (or DAXI), has been shown in clinical trials done by Dr. Jankovic to be effective for up to 25.7 weeks post-injection. Another new type of BoNT, which is a category E type, has been shown to reach the maximal effect much faster than the currently clinically available BoNTs, suggesting possible use to reduce the yo-yo effect by using this toxin as a booster. However, the research on whether that could increase the risk of developing NABs still needs to be done.

There are many aspects of BoNT therapy that could be addressed to improve the overall patient experience. First, training and targeting procedures used for injections could enhance patient outcomes. Currently, some clinicians use EMG, ultrasound, or other imaging to optimally target areas of the muscle that are overactive, but this is not a consistent practice. Second, it is important to continue to improve the toxins themselves by developing forms with a more rapid onset and longer duration of symptom relief, fewer side effects, and a reduced risk of developing an immune response.

Surgical therapies: what's next?

Elena Moro, MD, PhD

Grenoble Alpes University, Grenoble, France

A handful of therapeutic procedures work by altering the brain either structurally, by creating small, targeted lesions, or by altering circuit activity through different types of applied stimulation. Dr. Moro, an expert in deep brain stimulation (DBS) for movement disorders, started her talk by thoroughly explaining what we currently know about DBS and what needs to be investigated to enhance the therapeutic success of this procedure. Currently, there is a large amount of variability in the therapeutic success of DBS—highlighting the importance of DBS research.

DBS alters activity patterns in parts of the brain that are important for movement. Published research has shown that DBS can alter patterns in plasticity, the cellular and

cell circuit changes that are observed in dystonia patients. Functional brain imaging studies have revealed significant changes in brain activation in individuals with dystonia. Furthermore, functional imaging has shown that the circuit activation patterns in dystonia patients are shifted much closer to the patterns observed in non-dystonia research participants. Interestingly, DBS has been shown to reduce the same brain activity that is reduced in response to sensory tricks—reinforcing the same shared therapeutic mechanisms.

We have also learned which genetic forms of dystonia respond well to DBS. Beneficial effects are often observed in individuals with TOR1A, TAFI, SGCE, GNAL, KMT28, or PANK2 mutations. A limited number of cases have also shown a beneficial effect for individuals with GNAO1, GN81, or VPS16 mutations. Less benefit is seen in individuals with THAP1 or ATP1A3 mutations.

Continued research into DBS could improve patient outcomes. DBS has been used to treat dystonia for more than 25 years. However, much of the clinical data on the success of DBS follows patients for a maximum of 8.5 years. The therapeutic value and any changes over time cannot be sufficiently captured within this timeframe, especially for pediatric patients. Increasing clinician access to long-term data will not only enhance understanding of the longevity of this therapeutic method, but it will also give us more data on how DBS impacts brain circuits and plasticity over time along with the relationship between DBS success and genetics as new genetic discoveries occur.

As our understanding of the genetics underlying different dystonias expands, we will gain further insights into which genetic mutations may serve as a biomarker for responding well to DBS. Better yet, we may gain a stronger understanding of which individuals respond best to specific stimulation target sites, which is of particular value as researchers increase the number of possible DBS targets.

Adaptive DBS (aDBS) utilizes the implant of sensors that sit on the surface of the brain to detect brain activity that coincides with dystonia symptoms that then trigger the stimulation through the regular DBS electrodes that target deeper brain structures. Existing DBS methods

are simpler; the stimulation settings are set and updated periodically by neurologists to deliver constant stimulation at a level that offers the most benefit. As a result, the a DBS approach reduces unnecessary stimulation, simplifies and personalizes stimulation programming, and has been shown to improve symptom relief. However, the existing clinical research studies are small, and more data is needed to thoroughly understand the value of these new methods.

Prior to targeted stimulation with DBS, the primary surgical approach for movement disorders was creating targeted lesions in different brain regions. This localized tissue damage creates a dead end in the portion of the brain circuit that passes through that region. Many of the brain regions that are currently targeted by DBS were key target areas for these lesion approaches. Because the brain is symmetrical, with most brain regions existing on either side of the brain, DBS generally involves symmetrical electrode placements to stimulate the same structure on either side. Currently we have enough research to show that bilateral lesions to the pallidum do not produce favorable results, with unilateral lesions producing better outcomes.

Recently, the use of focused ultrasound to create targeted lesions in the brain has been returning to the clinical space for a few reasons. First and foremost, this procedure is non-invasive, an appealing feature to patients unwilling to undergo brain surgery. Additionally, focused ultrasound is being coupled with brain imaging techniques such as MRI to study how well new brain imaging can enhance the therapeutic outcomes of the classical lesion approach. The research on these approaches is relatively new and although there are some favorable results, the variability in patient response observed in these clinical studies emphasizes the need for more research to understand the possible value.

Overall, Dr. Moro highlighted the maintained and expanding value of DBS for treating dystonia and as a valuable tool to better understand the impact that dystonia has on brain circuits, further enhancing all therapeutic methods. Furthermore, new methods of adaptive DBS are being researched to enhance the therapeutic value of DBS moving forward. Separate technological advancements have resurrected the use of therapeutic lesions and ongoing research studies

will assess the value of this non-invasive approach compared to DBS, identifying which dystonia subpopulations are best suited for this method. As researchers better define how dystonia impacts brain circuits and how DBS alters circuits, they will be able to more closely determine optimal target regions—emphasizing the synergy between basic science research and clinical research to enhance therapeutic outcomes for patients.

Clinical trials: what are the obstacles to testing new options?

Sarah Pirio Richardson, MD, FAAN

University of New Mexico, New Mexico, USA

There are four main obstacles to creating effective clinical trials. Researchers need to answer important questions before moving to a clinical trial. Do we need new options and therapies? What is the effect of the drug or treatment? Are we measuring the symptoms patients care about? Do we have the tools needed to conduct clinical trials?

Most dystonia experts would agree that there need to be better treatment options for dystonia patients.

Unfortunately, the processes to complete preclinical and clinical research require extensive funding. From the perspective of outside funders, it may seem as if there are plenty of sufficient treatment options, making this research funding harder to come.

A published study surveying 1,528 patients showed that ~25% of patients (focal, generalized, hemidystonia, multifocal, and segmental all represented) are not using current therapeutic options for a variety of reasons. Another 25-35% are using botulinum neurotoxin (BoNT), which can produce variable outcomes for patients. That variability leads to many patients suspending injections. Another study surveyed 1,071 patients with cervical dystonia. Only 56% reported being fairly or completely satisfied with their BoNT treatment. These studies show a significant therapeutic gap in clinicians' ability to treat dystonia patients.

Dr. Pirio Richardson reiterated the yo-yo effect that is often experienced by dystonia patients using BoNT

therapies, indicating additional possibilities that impact the patient experience. For example, some patients might experience a short duration of therapeutic response, leaving them without any benefit in-between injections. Other patients may experience dose failures on occasion and develop a neutralizing immune response. This means they have to wait through the full cycle before receiving the next injection. Another possibility is that patients receive a decreasing benefit with subsequent injections. These are all possibilities that need to be looked at further in large populations of patients.

Several studies have shown that patients with CD tend to rate their therapeutic outcomes less favorably than their physicians. This suggests that the threshold for therapeutic success is dictated by statistical measurements in clinical research studies and may not align with the degree of symptom relief that is necessary to feel beneficial to a patient. Specifically, a treatment that improves symptoms by 25% is considered a success in a research study, but this bar could be too low for a patient who may feel similarly disabled or impacted in their daily lives.

A recent publication from Dr. Pirio Richardson shows that on average patients report a ~35% improvement in most symptoms associated with their dystonia is the lowest amount of improvement that they would find meaningful. The one exception to this was anxiety and depression where a 26% improvement would be beneficial. This suggests that there are likely different thresholds for therapeutic benefit for different symptoms that collectively contribute to a patient's quality of life, which need to be thoroughly evaluated in future studies.

Dr. Pirio Richardson highlighted a particular tool that her team is developing to enhance clinical research studies. They created a survey that more effectively evaluates a patient-centered outcome for a treatment method. They also developed a phone application that allows users to take the survey weekly. The intention is to use this to more thoroughly evaluate the patient experience during treatment for cervical dystonia, blepharospasm, and laryngeal dystonia.

POINT OF VIEW: SOME RECENT SUCCESSSES

Physical and occupational therapy in dystonia

Marina de Koning-Tijssen, MD, PhD

University Groningen, Groningen, The Netherlands

Physical therapy (PT) focuses on improving physical function and mobility through exercises, stretches, and other techniques. Occupational therapy (OT) helps individuals regain the skills needed for daily activities and improve their quality of life after injury or illness. In this talk Dr. Tijssen described the challenges to improve the use of these therapeutic options for dystonia.

The motor and non-motor symptoms of dystonia collectively contribute to patients having significant, complex disabilities. As a result, many individuals with dystonia have reduced participation in activities that are key in daily life. This loss of self-confidence and independence, social withdrawal, and employment problems, can be just as debilitating as the disease. Medication or medical procedures can provide some symptom relief, but often the therapeutic benefit varies and there are many quality-of-life factors that are not directly addressed with these methods.

Expanding the treatment approach beyond the primary treatments to include PT and OT could provide significant benefit. However, currently rehabilitative services for dystonia are rarely available for patients, emphasizing the demand for robust research that supports the value of these additional therapies to provide a more comprehensive approach to treating dystonia.

It is difficult to combine the few PT/OT studies to draw overarching conclusions because the specific interventions varied substantially, including exercise, massage, biofeedback, the use of kinesiology tape, and more. Unfortunately, the variability in the studies resulted in the collective therapeutic impact of these interventions being low. However, they do pave the way for future studies with more precise designs and larger patient cohorts, by showing preliminary data that there could be meaningful benefit.

Published studies have shown Cognitive Orientation to Daily Occupational Performance (CO-OP) is a strategy

that uses a long list of possible cognitive strategies to help an individual attain a specific functional goal. For instance, before CO-OP therapy, a boy with a hyperkinetic movement disorder could not pick up a glass of water without spilling. After training, he could hold the glass without spilling, even while walking around. The list of possible strategies included distraction from overly focusing on the task or the bodies movements, using visualization to reduce anxiety, tension, or other emotions, imagining the successful motor movement, visualizing people/places/things that support task performance, redirecting attention to an object or location related to the task that is outside of the body, directing attention to the body part involved in the task. These varied options allow for a personalized treatment approach.

Inherited dystonias with targeted therapies

Aurélie Méneret, MD, PhD

Pitié-Salpêtrière Hospital Paris, France

Dr. Méneret described seven different genetically inherited disorders that often include dystonia symptoms and that have targeted treatment approaches. The talk highlighted the importance of enhancing our understanding of dystonia genetics allowing us to identify targeted therapies when the associated cellular mechanisms are known. Several examples were presented.

Dopa-responsive dystonia is caused by mutations that disrupt dopamine production, a key signaling molecule important for movement. As a result, this disorder can be effectively treated with dopamine replacement therapies like Levodopa.

Wilson's Disease is caused by copper accumulation in the body and as a result these patients can take medications that bind to the copper and help the body discard it as waste.

Cerebrotendinous xanthomatosis is a rare genetic disorder where the body can't break down cholesterol properly. This causes cholesterol to build up in the brain and tendons, leading to problems with movement and thinking. Treatment with a medication called

chenodeoxycholic acid can help lower cholesterol levels and prevent these issues from getting worse, especially when started early.

Ataxia with Vitamin E Deficiency is a rare condition that affects the nervous system. It happens when the body can't properly use vitamin E, which is crucial for keeping the cells in our nervous system healthy. Taking supplemental vitamin E can improve symptoms like trouble with balance and coordination.

The cellular activity that allows cells in the brain to pass signals within circuits is largely supported by sodium channels. Specific cellular events trigger the opening and closing of these channels and close regulation of these triggers keep cells from being hyperactive. Paroxysmal kinesigenic dyskinesia is caused by sodium channels that are more easily opened. As a result, drugs that block these channels are a very successful therapeutic option.

Niemann-Pick Disease Type C is a rare genetic disorder characterized by fat buildup in the body. Miglustat is a medication used to reduce fat accumulation, helping to slow the disease progression and alleviate some symptoms.

Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS) is a rare genetic disorder that affects the brain's ability to use glucose for energy. A ketogenic diet, which is high in fats and low in carbohydrates, is often used as a treatment because it provides an alternative energy source for the brain.

More recently, caffeine has been shown to greatly alleviate symptoms of ADCY5-related dyskinesia, however, the specific cellular mechanism is not yet known. Ongoing studies on genetic therapies are being conducted to create targeted treatments.

PKAN: one enzyme defect, multiple targets

Belen Pérez Dueñas, MD

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Pantothenate kinase-associated neurodegeneration (PKAN) is a rare genetic disorder caused by mutations in a gene called PANK2. This gene provides instructions for making a protein that plays a crucial role in producing

a molecule called coenzyme A, which is essential for various cellular processes. When the PANK2 gene is mutated, it disrupts coenzyme A production, leading to a buildup of iron in certain parts of the brain and causing the characteristic symptoms of PKAN that include movement problems and neurological deterioration.

Typical PKAN symptoms start before the age of six, and are characterized by rapid progression of dystonia, Parkinsonism, diminished movement, and blindness. Atypical PKAN has a wide range of onset beyond 6 years with highly variable symptoms (i.e., task specific dystonia, tics, gait issues, OCD) and progression rates. Many PKAN patients have oromandibular dystonia and experience dystonia relief from sensory tricks.

PKAN has a unique biomarker called the “eye of the tiger” which is a unique pattern seen on brain MRI scans. It appears as a bright central region surrounded by a darker ring in the globus pallidus of the brain. This distinctive pattern is caused by the abnormal accumulation of iron and serves as a key diagnostic marker for PKAN, helping doctors confirm the presence of this rare neurodegenerative disorder. Unfortunately, the “eye of the tiger” feature is a late sign of PKAN, that indicates advanced neurodegeneration. Ideally, therapeutic methods that researchers are trying to develop now, are applied earlier on to avoid late-stage progression.

The metabolic pathway associated with coenzyme A is well understood. As a result, there are many known possible points in the pathway to intervene and hopefully block the iron accumulation that produces neurodegeneration. Dr. Pérez Dueñas outlined several examples of preclinical studies and clinical trials that focused on different drugs that target different parts of the pathway. Clinical trials that have already been completed have not produced a useful treatment option. However, a couple of preclinical studies have shown exciting results that are not being taken into clinical trials to be tested in the patient population.

These clinical trials are complicated by two issues that are difficult to work around. First, typical and atypical PKAN vary significantly from one another and atypical PKAN is highly variable as a group. In a clinical research study, it is difficult to draw meaningful conclusions about

the effect of a medication if the population taking that medication is variable. Second, patients recruited for these studies tend to be in mid- or late-stage progression of PKAN, due to the often-used diagnostic criterion, the

“eye of the tiger”, being visible only at later stages of progression. It is likely that some treatments would work well for earlier stages of the disorder, but we do not currently have a reliable biomarker for early-stage PKAN.



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Thank you to the organizing committee, speakers, and attendees for sharing their work and facilitating meaningful discussion. Collectively, these efforts bring the research community one big step closer to new treatment methods and the eventual cure.

Kylie McPherson, PhD

Neuroscientist | Dystonia Patient & Advocate

The scientific and clinical research shared at the Samuel Belzberg 6th International Dystonia Symposium was translated for the patient audience by Dr. McPherson. As a neuroscientist with dystonia, she has a unique interest in meaningful scientific and medical communication that shares key research discoveries and actionable advice to the patient community.