Abstract Book
D-DAYS 2017

DYSTONIA EUROPE

ARD

Dystonia Europe would like to thank the following people for their involvement in making this conference possible:

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Dear Participant,

Welcome to Rome and the Annual European Dystonia Days – D-DAYS 2017.

On behalf of Dystonia Europe and in collaboration with ARD – The Italian Dystonia Association, we are delighted to welcome you to Rome, the capital city of Italy.

During these D(ystonia)-DAYS you will hear presentations about Dystonia and learn about what is going on in the field of treatment, research and rehabilitation. We are very grateful to all the speakers and chairs who have joined us to share their expertise within Dystonia.

As well as learning more about Dystonia we also hope that you will enjoy meeting old friends, and connect with new ones, and above all, have a pleasant weekend here in Rome.

If you have any questions about anything do not hesitate to ask us and we will try and help as best as we can.

We also take the opportunity to thank our sponsors for making this meeting possible. Dystonia Europe is very grateful for your support and we are glad that so many of you are showing direct interest in our work by being represented here.

We thank you all for joining us here in Rome and we wish you an enjoyable, interactive and fruitful conference!

Warm regards

Merete Avery
President
Dystonia Europe

Flavia Cogliati
President
ARD – Italian Dystonia Association

Secretariat: Square de Meeus 37 - 4th Floor, B-1000 Brussels, Belgium
E-mail: sec@Dystonia-europe.org
Website: www.Dystonia-europe.org
Facebook: www.facebook.com/Dystonia.europe

Professor Alberto Albanese

Responsabile Neurologia
Istituto Clinico Humanitas
Milan, Italy

What is Dystonia?

New Classification and Definition of Dystonia

Dystonia is a movement disorders that remains underdiagnosed. In cases with mild phenomenology often Dystonia remains undiagnosed, because patients or caretakers do not seek medical advice and doctors do not have criteria for asserting diagnosis when phenomenology is too mild. However, also when phenomenology is overt, Dystonia may remain underdiagnosed. Patients with Dystonia are likely to receive a diagnosis of essential tremor or Parkinson disease instead.

A better knowledge of Dystonia depends on improved definition, classification and diagnostic criteria. Definition and classification have been recently updated. Dystonia is a movement disorders combining dystonic postures and movement; the latter may have the appearance of tremor. Dystonic tremor is specifically underdiagnosed and many cases of dystonic tremor are classified as essential tremor. The recent classification of Dystonia distinguishes two axes.

Axis I describes phenomenology, while Axis II describes etiology. The recent classification systematizes many previously unsettled issues and provides an innovative service to doctors and patients.

What remains missing is a set of solid criteria for the different Dystonia syndromes. The Dystonia Task Force of the International Parkinson's disease and Movement Disorders Society has defined the definition of Dystonia diagnostic criteria as the next priority.

Professor Alfredo Berardelli

Department of Neurology and Psychiatry, Sapienza Università of Rome and NEUROMED Institute (IRCCS)
Rome, Italy

Causes and pathophysiological mechanisms in Dystonia

Dystonia is characterized by involuntary and sustained muscle contractions causing abnormal postures; Dystonias affecting a single body part is the most frequent form in adult subjects. Dystonia is etiologically and phenomenologically heterogenous.

In idiopathic Dystonia no obvious neuronal degeneration is detected. In secondary cases the site of the lesions may provide some insight into the neural structures involved in the pathophysiology of Dystonia. Dystonia has also a variable body distribution of the motor symptoms of Dystonia (from focal forms to generalized involvement of several body regions). Basal ganglia structures and their connections with cortical areas have been implicated in the pathophysiology of Dystonia. Structural lesions of the brainstem and cerebellum - as evidenced by clinical, neuroimaging and pathologic investigations- are also present in secondary forms of focal Dystonia. Dystonia was previously considered a pure basal ganglia disorder, but several studies have now suggested that Dystonia should be considered a disorder of sensorimotor network.

Studies using transcranial magnetic stimulation have demonstrated an increased excitability and increased plasticity of primary motor cortex and sensorimotor cortices. Other studies have demonstrated a lack or a reduction of inhibition at multiple central nervous system levels. An abnormal sensory-motor and sensory integration is also present in Dystonia, as demonstrated by studies testing tactile sensory mechanisms. Neurophysiological studies support the concept that a combination of an (i) abnormally reduced inhibition, (ii) maladaptive plasticity, (iii) sensory abnormalities and (iv) cerebellar abnormalities play a role in the pathophysiology of primary Dystonia. Although the various forms of Dystonia share common pathophysiological mechanisms the role played by each mechanism may differ in the various types of Dystonia.

Anna Castagna, MD

Neurologist
Physical Medicine and Rehabilitation Unit
Head Movement Analysis Laboratory and
Botulinum Toxin Clinic
IRCCS Santa Maria Nascente, Fondazione Don Gnocchi
Milan, Italy

Rehabilitation in Dystonia

Dystonia is an hyperkinetic movement disorder characterized by abnormal posture and movements involving different body parts and with different etiology. The pathophysiology of Dystonia is still unclear but abnormal sensory- motor mechanisms of integration at cortical and subcortical level associated with maladaptive plasticity determining impaired motor control and planning, have been demonstrated. The involvement of multiple neural networks (cortexes, cerebellum and basal ganglia) is under study also with neuroimaging techniques. Whereas efficacy of Botulinum toxin (BoNT) treatment has been approved in Dystonia, there is no strong evidence of the effectiveness of physical therapy and no consensus on the validity of the different rehabilitative approaches in clinical practice has been reached. Certainly a tailored multidisciplinary team approach is necessary to define the different strategies and interventions for every specific type of Dystonia and every single patient. Nevertheless there are some encouraging data from two systematic reviews [1,2] which described the effects of different rehabilitation strategies in various forms of idiopathic Dystonia and cervical Dystonia alone, suggesting that multimodal rehabilitation programs (stretching, active exercises, retraining bio-feedback approach and muscle relaxation techniques), added to BoNT injection, further improve disability and pain with good interfence on quality of life. It is, therefore, difficult to identify the most effective intervention or combination of interventions.

Protocols focused on sensory perception and motor re-learning processes associated with bio-feedback and spatial rehabilitation are currently studied. A special emphasis on self-management of symptoms and the ability of patients to improve their performance of daily life tasks should be focused on.

1. Delnooz C, MWIM H, MA T, van de Warrenburg BP.. Paramedical treatment in primary Dystonia: a systematic review. Movement Disorders (2009) 24:2187–98.10.1002/mds.22608

2. De Pauw J, Van der Velden K, Meirte J, Van Daele U, Truijen S, Cras P, et al. The effectiveness of physiotherapy for cervical Dystonia: a systematic literature review. J Neurol (2014) 261:1857–65.10.1007/s00415-013-7220-8

Professor Carlo Colosimo

Department of Neurology
Santa Maria University Hospital
Terni, Italy

Botulinum toxin therapy for Dystonia

Botulinum neurotoxins have been shown to be a safe and effective therapeutic option for most forms of focal Dystonia, and are now considered to provide the best symptomatic treatment in these disorders. However, only a few papers addressed the long-term efficacy and safety of repeated treatments with this drug. We have recently reviewed the data from all clinical trials that have assessed the long-term results of botulinum neurotoxins A (BoNT-A) and B in the treatment of the different forms of focal craniocervical Dystonia, including cervical Dystonia (CD), blepharospasm, oromandibular, and laryngeal Dystonia.

These long-term studies have demonstrated that the majority of patients comply with this repeated treatment because they experience a positive and stable effect over time. In spite of the wide spectrum of side effects reported to be associated with BoNT-A treatment, there is no evidence of specific side effects due exclusively to the long-term use of such drugs.

The only exception to these positive long-term findings is the occurrence of a subgroup of patients with CD who fail to maintain a sustained response after the first or second effective treatment (the so-called secondary non-responders), only partly owing to the development of neutralizing antibodies against the toxin. Longitudinal studies aimed at defining the risk factors for this abnormal pattern of response to botulinum toxin treatment are currently being conducted.

Hortensia Gimeno

Occupational Therapist
NIHR Clinical Research Fellow
Complex Motor Disorders Team
Evelina Childrens Hospital
London, United Kingdom

Occupational Therapy in Dystonia

Children with Dystonia including dyskinetic cerebral palsy (CP), have significant problems carrying out everyday activities. Childhood Dystonia is often refractory to pharmacological interventions and other currently medical strategies. At best, drugs usually focus on symptom management (1), and at worst lack empirical evidence of effectiveness. The therapeutic goals of drug and surgical treatments are typically aimed at what may be important biomedical goals – e.g., to reduce Dystonia – but evaluation in terms of activity and participation in real life functioning contexts is still lacking (5). Arguably this should be at the core of all our efforts to fully understand the outcomes of potentially expensive and invasive intervention such as deep brain stimulation (DBS). In childhood-onset Dystonia, newly developed International guidelines for dystonic CP report OT, PT and SLP as the cornerstones of rehabilitation (AACPDM, Clinical guidelines). Thus, the recommendations must be interpreted and applied to clinical practice with caution.

Currently, there is onlyone rehabilitation study, led by the presenter in childhood-Dystonia that has been registered and the results will be presented in this meeting. This rehabilitation trial uses and Occupational Therapy Intervention, the Cognitive Orientation to daily Occupational Performance (CO-OP)) (11) to augment the results of DBS.

The presentation will use a series of videos to demonstrate the results of the intervention and the key concepts of the intervention will be outlined.

H. A. Jinnah, MD, PhD

Professor, Departments of Neurology,
Human Genetics, & Pediatrics
Emory University School of Medicine
Atlanta, USA

Dystonia Research Around the Word

In the past decade, research being conducted for all types of Dystonia has increased dramatically in many parts of the world.

In general, this research falls into two broad categories; Basic Sciences Research and Clinical Research. The Basic Science Research focuses on the biological processes that cause Dystonia. These processes include changes in genes and the biochemical pathways they control, the brain areas that are responsible for Dystonia, what the neurons are doing in these regions. This type of research is aimed at better understanding the causes of Dystonia. The Clinical Research focuses on people with Dystonia.

Clinical Research may include studies that address how Dystonia affects patients, how existing treatments can be optimized, and finding new treatments. This type of research is aimed at improving how patients may be treated. Both types of research are essential for finding better treatments, and ultimately a cure. The support and engagement of people with Dystonia is important for both types of research, whether it is finding a new gene, understanding what part of the brain is affected, or helping to test a new approach for treatment.

Antonio Pisani, MD, PhD

Department Systems Medicine
University of Rome Tor Vergata
Neurophysiology and Plasticity Lab
IRCCS Fondazione Santa Lucia, Rome, Italy

Drugs for Dystonia?

Despite knowledge on Dystonia has greatly improved in recent years, yet to date there is no pathogenesis-targeted therapy for most Dystonias. Dopa-responsive Dystonia is the only syndrome in which a disease-specific treatment is available, since biochemical and molecular genetic studies suggested that the primary abnormality was a defect in dopamine synthesis. Therefore, treatment for most Dystonias is aimed at providing symptomatic relief and is still based mainly on empirical experience rather than scientific rationale (Albanese et al., 2015). Different drug classes have been used, such as anticholinergics (Jankovic, 2013). However, the therapy must be tailored to the specific needs of patients, and often requires a combination of several medications.

The identification of a common pathogenic mechanism in distinct Dystonia forms would provide a common target and facilitate therapeutic intervention.

Genetic, clinical and experimental evidence indicate that multiple Dystonia-causing mutations, either directly involved in DA metabolism and signalling (e.g. GCH1, TH, SPR, GNAL), or indirectly (DYT1, SGCE), converge to affect striatal dopamine responses, that therefore may be central to isolated Dystonia, even when symptoms do not benefit from dopaminergic therapies (Goodchild et al., 2013). In particular, robust experimental evidence show a significant alteration of striatal dopamine D2 receptor function in several DYT1 Dystonia rodent models (Eskow Jaunarajs et al., 2015). Unfortunately, direct intervention on D2 receptor is ineffective. It is thertefore mandatory to search for alternative strategies aimed at normalizing D2 receptor function.

Experimental data indicate that striatal dysfunction can be, at least in part, rescued by modulating D2 receptor function at different levels, either through its regulatory protein RGS9-2, or its interacting receptors. In particular evidence converges to indicate both glutamate mGlu5 and A2A adenosine receptors as potential targets for pharmacological intervention. Of note, these targets have been evaluated for parkinsonism in clinical trials and pharmacological tools are available for repositioning further supporting the view that an effort for developing pathogenesis-targeted therapies is possible and timely.

Professor Maja Relja

Movement Disorders and Neurodegeneration Center
Department of Neurology, Medical School,
University of Zagreb
Zagreb, Croatia

Non-Motor Symptoms in Dystonia

Dystonia is characterized by involuntary sustained or intermittent muscular contractions that cause repetitive movements and abnormal postures. Contrary to common views the non-motor symptoms are present in Dystonia patients. For long time most of the researches were focused on motor symptoms of Dystonia while accompanied non-motor disorders were often being unrecognized or disregarded. The nonmotor symptoms may complicate motor presentation in Dystonia. Evidence is emerging that non-motor sympoms such as neuropsychiatric, cognitive, sleep, sensory and pain play an important role in Dystonia. Non-motor symptoms may occur in dystonic patients releted to the primary pathophysiology of Dystonia and/or as a secondary consequence of Dystonia.

It is well known that non-motor symptoms in different movement disorders is stronger determinants of Quality of Life (QoL) than the motor symptoms. Non-motor symptoms in patients with Dystonia can also be a key determinant of health related QoL. Thus, routine clinical examination in patients with dytonia should include motor as well as nonmotor status examination Conequentlly, higher awareness of non-motor symptoms in dystonic patients needs to be raise.

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