Abstract Book:
D-DAYS 2015

Rotterdam
The Netherlands

DYSTONIA EUROPE

Dystonie vereniging

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

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Paola Bonsi, Italy
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Hans Koelman, The Netherlands
Marina de Koning-Tijssen, The Netherlands
Joachim Krauss, Germany
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Maja Relja, Croatia

Rotterdam 2 October 2015

Dear Participant,

On behalf of Dystonievereniging and Dystonia Europe, we are delighted to welcome you to Rotterdam, where the 22nd Dystonia Europe Annual Conference – D-Days 2015 will be held on the former royal cruiseship S.S. Rotterdam.

This year, we are very pleased also to join with the Dutch Dystonia Association (Dystonievereniging) in hosting their 30th anniversary events.

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.

We are delighted to be able to present the David Marsden Award during the conference, when you will also hear the winner present her paper.

An important part of any congress is the opportunity to meet old friends and connect with new ones, and we hope that you will have a pleasant stay on the S.S. Rotterdam.

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

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

Thank you all for joining us here on SS Rotterdam and we wish you an enjoyable, interactive and fruitful conference!

Warm regards

R. Scholten

Robert Scholten
President

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Analysis of movements and force control in focal dytonia for rehabilitation

The analysis of the characteristics of cervical head movements constitutes an essential prerequisite to identify the target muscles prior to a botulinum toxin treatment or tailored rehabilitation programme for cervical dystonia (CD). The high failure rate observed in antecollis and retrocollis treatments prompted us to analyse in greater detail dystonic activities in voluntary neck movements. Therefore, we are proposing to examine the biomechanics of 3-D voluntary neck movements for CD patients compared to control subjects, using compact, inertial sensors. These devices are designed to capture spatial movements of human segments and head. At this stage of the study, we are analyzing the data of the 30 CD patients and 30 healthy subjects. Only initial data on head movement characteristics in the sagittal plane are provided. Nevertheless, these preliminary observations serve as a basis for future analysis of the disorganization of the cervical movements in CD. In addition to this, comparative recordings with the inertial sensors have been performed before and after a 20 minutes of self-training of tailored exercises. The self-training programme consisted of constant repetition of the antagonist muscles activation, which acts to turn the head to the opposite side than the CD one. In the cases analyzed, practise of corrective exercises seems to improve movement and posture for CD.

If dystonia is clearly a motor problem, sensory aspects are also fundamental, especially those related to proprioception. A dysfunction in perception and integration of sensorimotor information is considered a key mechanism of dystonia. Also, we have assumed the assumptions that (i) force control deficit is affected in focal dystonia: writer's cramp (WC) and CD, and (ii) the deficits are greater in tasks requiring the use of proprioceptive feedback. Two groups of patients, one suffering from CD, the other from WC, in two different controlled studies, have performed isometric force control tasks with and without visual force feedback. The preliminary results show that voluntary force control is altered in tasks requiring use of proprioptive cues.

These different findings should have implications for the development of rehabilitation approaches in focal dystonia.

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Potential New Drugs for Dystonia

Paola Bonsi[1] and Antonio Pisani[1,2]

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. We therefore searched for alternative strategies aimed at normalizing D2 receptor function. Our experimental data indicate that striatal dysfunction can be rescued by modulating D2 receptor function at different levels, through either its regulatory protein RGS9-2, or its interacting receptors (mGlu5 and A2A). 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. approaches in focal dystonia.

David Marsden Award 2015:
MD Phd Cathérine C.S. Delnooz
The research has been performed at the Radboudumc, Nijmegen, The Netherlands
Currently at Movement Disorders at the University Medical Centre Groningen
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Task-free functional MRI in cervical dystonia revealsmulti-network changes that partially normalize with botulinum toxin

Cervical dystonia is characterized by involuntary, abnormal movements and postures of the head and neck. Current views on the pathophysiology of dystonia, such as faulty sensorimotor integration, abnormal sensory processing, and impaired motor planning, are largely based on studies of focal hand dystonia. Using resting state functional MRI, we explored whether cervical dystonia patients (n=23) have altered intrinsic functional brain connectivity compared to healthy controls (n=22), by investigating 10 resting state networks. Scans were repeated immediately before and some weeks after botulinum toxin injections to see whether connectivity abnormalities, if any, were restored.

We showed that cervical dystonia patients have reduced connectivity in selected regions of the prefrontal cortex, premotor cortex and superior parietal lobule within a distributed network that comprises the premotor cortex, supplementary motor area, primary sensorimotor cortex, and secondary somatosensory cortex (i.e., the sensorimotor network). With regard to a network originating from the occipital cortex (i.e., the primary visual network), selected regions in the prefrontal and premotor cortex, superior parietal lobule, and middle temporal gyrus areas have reduced connectivity. In contrast, increased connectivity in selected regions of the prefrontal, premotor, primary motor and early visual cortex was found within a network that comprises the prefrontal cortex including the anterior cingulate cortex and paracingulate cortex and parietal cortex (i.e., the executive control network). Botulinum toxin treatment resulted in a partial restoration of connectivity abnormalities in the sensorimotor and primary visual network. These findings demonstrate the involvement of multiple neural networks in cervical dystonia. The reduced connectivity, which is partly modifiable, within the sensorimotor and primary visual networks may provide the neural substrate to expect and explain defective motor planning and disturbed spatial cognition. Increased connectivity within the executive control network suggests excessive attentional control and while this may also be a primary trait, perhaps contributing to abnormal motor programming and execution, this may alternatively serve a compensatory function in order to reduce the consequences of the motor planning defect inflicted by the other network abnormalities.

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Rehabilitation in cervical dystonia

Cervical dystonia (CD) is a disabling movement disorderwhich is characterized by involuntary movements and abnormal postures of the neck and head. Treatment mainly aims at the relief of these symptoms and pain. During the last few decades tremendous progress has been made in the medical treatment of CD by botulinum toxin (BTX) injections. Although BTX injections reduce involuntary muscle contractions and pain, and correct abnormal posturing, many patients still experience difficulties with performing daily life activities. To overcome these problems many patients are referred for physical therapy in addition to medical treatment. However, evidence for the effects of physical therapy interventions is lacking (Delnooz et al. Mov Dis 2009, De Pauw et al. J Neurol 2014). Besides, many physiotherapists have no experience with the treatment of CD because it is a relatively rare disorder. Currently there is no consensus on the best treatment options for physical therapy in cervical dystonia.

Two reviews on the effectiveness of physical therapy in dystonia (Delnooz et al. Mov Dis 2009, De Pauw et al. J Neurol 2014) showed some promising studies of moderate methodological quality, which may have therapeutic implications. The interventions in these studies varied and included relaxation techniques, active exercise, muscular elongation and mobilizations of the spine (Tassorelli et al. Mov Dis 2006, Queiroz et al. Functional Neurology 2012, Boyce et al. Clin Rehabil 2013). The main similarity between these studies is that they all include specialized training programs aimed at motor (re)learning to reduce abnormal movement or postures in combination with BTX injections. All these studies, except Boyce et al., showed a decrease in disability and pain and a longer duration of the BTX effect in the combined BTX and training program group compared with BTX alone. Although promising, these are just a few studies with small numbers of participants and short intensive rehabilitation programs (4-12 weeks) which are not feasible in daily life.

Further research with large scale, well designed studies with clear descriptions of the applied interventions and valid and reliable outcome measures are needed. Furthermore feasibility, validity and cost-effectiveness of rehabilitation programs should be further investigated. In the ongoing DystonieNet trial towards the effectiveness of a standardized physical therapy program in cervical dystonia we try to overcome some of these problems to increase the evidence for rehabilitation methods in cervical dystonia. (Van den Dool et al. BMC Neurology 2013)

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Diagnostic strategies in young-onset dystonia

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Early aetiological diagnosis is of paramount importance for young-onset dystonia because some of the possible underlying conditions are treatable. Numerous genetic and non-genetic causes have been reported, and diagnostic workup is often challenging, time consuming and costly. Recently, a paradigm shift has occurred in molecular genetic diagnostics, with next-generation sequencing techniques now allowing us to analyse hundreds of genes simultaneously. To ensure that dystonia patients benefit from these new techniques, adaptation of current diagnostic strategies is needed. On the basis of a systematic literature review of young-onset dystonia, we present a diagnostic strategy with the aim of helping clinicians determine which patients may benefit by applying these new genetic techniques and which patients first require other investigations. While new genetic techniques are certainly not a panacea, possible advantages of our proposed strategy include earlier diagnosis and avoidance of unnecessary investigations. It will therefore shorten the time of uncertainty for patients and their families awaiting a definite diagnosis.

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Dystonia and Complex Regional Pain Syndrome

Complex Regional Pain Syndrome (CRPS) is characterized by pain and accompanied by sensory, autonomic, trophic, and motor abnormalities and generally follows a trauma of a limb. Reported motor impairments include weakness, problems with initiation and execution of movements, and prominent abnormal posturing which is commonly designated as dystonia. Several pathophysiological mechanisms have been postulated to underlie the motor abnormalities in CRPS, ranging from structural and functional alterations in skeletal muscle tissue to psychological factors. In this presentation the phenomenology and current concepts on motor abnormalities in CRPS will be discussed.

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What are the faces of dystonia?

Over the last 40 years, the appreciation of dystonia has changed dramatically. Although dystonia had been diagnosed before in patients with generalised dystonia, the large majority of patients with dystonia went by unrecognised, and the disorders they suffered from were mostly seen as manifestations of a psychological disease. Thanks to the works of Dr. David Marsden, who identified different forms of focal dystonia, and of Dr. Alan Scott, thanks to whom botulinumtoxin became available for treatment of patients, the face of the problem changed and the movement disorders, patients suffered from, were recognised. With that lots of energy has been fuelled to unravel this still mysterious disorder. Patients with dystonia may suffer from a generalised form which mag leave these patients hardly any possibility for focussed intentional movements at all, while at the other end of the spectrum patients may suffer from dystonia only when performing highly complex movements such as playing a musical instrument, which however may also have detrimental consequences in ruining musical careers. Although in the last 40 years a lot has been changed for the good of patients with dystonia, dystonia is still a burden for many patients. All these patients represent the many different faces of dystonia.

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Non-motor symptoms in dystonia

The term dystonia is used to describe a motor phenomenology. It is currently defined as a movement disorder characterized by sustained or intermittent muscle contractions resulting in abnormal movements and postures. (Albanese 2013) In addition to these well-defined motor symptoms, the presence of non-motor symptoms is increasingly recognized. Moreover, non-motor symptoms seem to be an important determinant of quality of life and disability in movement disorders. (Zurowski 2013, Peall 2015) Non-motor symptoms include psychiatric symptoms, cognition, sleep disorders, sensory abnormalities and pain. In this presentation, evidence for non-motor symptoms in dystonia will be discussed and the issue whether non-motor symptoms are secondary to the motor symptoms or if they are intrinsic to the neurobiology of dystonia.

Psychiatric symptoms are most frequently investigated with anxiety, depression and obsessive-compulsive disorder being most common. Cognitive impairment is limited and involves either global deficits or isolated difficulties in specific domains. Disturbances to sleep were most common in the dopa-responsive dystonias. Sensory testing in DYT1 cases identified an intermediate subclinical phenotype. Clues like onset of non-motor symptoms before the onset of motor symptoms, the fact that different forms of dystonia have different prevalence rates for psychiatric disorders, or sleep disorders that does not improve after botulinum toxin treatment all suggests that the non-motor symptoms are part of the phenotype of dystonia and represents a shared neurobiology.

Non-motor symptoms form an integral component of the dystonia phenotype. However, future studies should involve a complete assessment of all symptom subtypes in order to understand the frequency and gene-specificity of these symptoms. This will enable early symptom identification, appropriate clinical management, and provide additional outcome measures in future clinical trials.

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Genetics and new patient registry

The dystonias comprise a heterogeneous group of movement disorders with variable age of onset, body distribution, and genetic background sharing the core clinical features of twisting, repetitive movements or abnormal postures. DysTract, a consortium of German research institutions supported by the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung; BMBF), focuses on the aetiology and pathophysiology of isolated (dystonia as the only sign) and combined forms of dystonia, where dystonia may be combined with other movement disorders, such as parkinsonism. The cause of isolated and combined dystonias is either unknown or genetic. While a total of nine genes have been unequivocally identified to cause isolated (TOR1A [DYT1], THAP1 [DYT6], and GNAL [DYT25] or combined forms of dystonia (TUBB4 [DYT4], GCHI1 [DYT5a], TH [DYT5b], SGCE [DYT11], ATP1A3 [DYT12], PRKRA [DYT16]), two genes await independent confirmation (CIZ1 [DYT23], ANO3 [DYT24]. Many of these genes show markedly reduced penetrance and have (i) raised general concerns about genetic versus environmental factors in the manifestation of dystonia syndromes, (ii) proven the molecular pathogenetic heterogeneity of isolated and combined dystonias, (iii) triggered the search for common final pathophysiological disease pathways of dystonia causing clinically similar symptom manifestations in genetically divergent disorders.

The field of dystonia has witnessed major advances at many different levels including a revised definition and classification, identification of new causative dystonia genes by next generation sequencing and of first candidate genetic risk factors by genome-wide association studies, new pathophysiological insights into monogenic forms, and first systematic evaluation(s) of treatment outcomes. Yet, important questions currently remain unanswered including the prevalence of mutations in known dystonia genes, elucidation of the underlying aetiology in the about 25% of all dystonia patients who are negative for known mutations but display a positive family history, environmental risk factors and triggers of dystonia.

Most of these questions can only be addressed in a multidisciplinary and multi-centre effort and hinge on the availability of a carefully selected, prospectively followed, sizable clinical cohort.

Creative and novel concepts are then required to make optimal use of this cohort, which will be examined in a multimodal fashion in the DysTract consortium and serve as a national resource not only of clinical data but also as a biorepository for DNA, fibroblasts, and induced pluripotent stem cell lines. By enrolling a total of 3,000 patients with isolated and combined forms of dystonia into the registry, DysTract will cover almost a quarter of the expected ~13,000 dystonia patients in Germany.

The DysTract consortium aims to 1) explore phenotypic variability and frequency of mutations in known dystonia genes in a large national cohort of dystonia patients; 2) define endophenotypes using neuroimaging or electrophysiology; 3) identify novel disease genes; 4) elucidate disease mechanisms and to identify read-out parameters for possible biomarkers and drug targets in iPSC-derived neurons from patients with monogenic and non-genetic dystonia; 5) better understand environmental factors; 6) better understand mechanisms of compensation in non-manifesting mutation carriers; 7) identify common final pathophysiological pathways of dystonic motor symptoms, 8) compare the efficacy of different treatments.

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Botulinum toxin – where we are now?

Since its introduction in the 1980s, botulinum toxin type A (BoNT-A) has become the accepted standard of treatment for patients with most types of focal dystonia, including cervical dystonia (CD). Injector expertise and skill level to identification of muscles involved my affect treatment outcome. However, there are few published recommendations or guidelines for its practical use in these conditions.

Several formulations of botulinum toxin are available. Widely investigated and widely used preparations of BoNT A are: onabotulinum toxin A (Botox®, Allergan); abobotulinum toxin A (Dysport®, Ipsen) and incobotulinumtoxin A (Xeomin®, Merz). There is only one formulation of toxin B as rimabotulinum toxin B (Neurobloc®, Solstice).
All BoNT-A formulations have similar indications and studies have demonstrated similar efficacy and safety profiles. However, different BoNT-A formulations and products are not interchangeable and units cannot be compared or directly converted.

Despite widespread therapeutic use of BoNT over more than three decades, there is a remarkable paucity of published data on the mechanisms of action and its effects on clinical outcomes. It is widely accepted that injections of BoNT-A into the affected muscles inhibit acetylcholine release from the synaptic vesicle and inhibits neuromuscular transmission producing muscle relaxation. But today antinociceptive effects of BoNT-A is also established. Thus, the involvement of the CNS in the mechanism of action is also suggested.

The beneficial effects of BoNT in dystonia lasts for several months and repeated injections are needed. But, there is a striking difference between the injection intervals given in everyday clinical practice and the injection intervals preferred by patients. Recent data have indicated that different injection intervals may improve overall patient satisfaction. Finally, the development of novel neurotoxins with different therapeutic properties which may extend the therapeutic benefit to a greater range of disease and patient populations.

Notes

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