

Dystonia Europe 2012

with

COST Dystonia Training School

20 September 2012 – Bol Croatia

BOOK OF ABSTRACTS

Index

1. PRIMARY DYSTONIA

Joaquim Ferreira - *Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon*

2. DYSTONIA PLUS SYNDROMES

Marina AJ de Koning-Tijssen - *Head of movement disorders, Department of Neurology, University medical centre Groningen (UMCG), Groningen, The Netherlands.*

3. EARLY-ONSET DYSTONIA

Jean-Pierre Lin - *General Neurology & Complex Motor Disorders Service, Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, Lambeth Palace Road, London*

4. NEUROTRANSMITTER ALTERATIONS IN DYSTONIA

Antonio Pisani - *University of Rome "Tor Vergata", and Fondazione Santa Lucia I.R.C.C.S., Rome, Italy*

5. SECONDARY DYSTONIA – CLINICAL CLUES, SYNDROMIC ASSOCIATIONS & INVESTIGATIONS

Kailash P Bhatia - *Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London, U.K.*

6. WHAT IS NEW IN THE CELL BIOLOGY OF PRIMARY DYSTONIA AND DYSTONIA-PLUS SYNDROMES?

Tom Warner - *Department of Clinical Neurosciences, UCL Institute of Neurology, London, UK*

7. CURRENT CONCEPTS ON THE PATHOPHYSIOLOGY OF DYSTONIA

Mark Edwards - *Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK*

8. EPIDEMIOLOGY OF DYSTONIA

Justo García de Yébenes - *Department of Neurology, Hospital Ramon y Cajal, Madrid, Spain*

9. PSYCHOGENIC DYSTONIA SYNDROMES

Mark Edwards - *Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK*

10. GENETIC RISK FACTORS FOR DYSTONIAS

Thomas Gasser - *Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany*

11. GENERAL MANAGEMENT APPROACH TO DYSTONIA

Maja Relja - *University of Zagreb, School of Medicine and University Hospital Centre Zagreb, Department of Neurology, Zagreb, Croatia*

12. BOTULINUM TOXIN TREATMENT OF DYSTONIA

Dirk Dressler - *Movement Disorders Section, Department of Neurology, Hannover Medical School, Hannover, Germany*

13. SURGICAL APPROACHES FOR TREATMENT OF DYSTONIA

Joachim K. Krauss - *Department of Neurosurgery, Medical School Hannover, Hannover, Germany*

14. DBS FOR DYSTONIA-PRESENT AND FUTURE: DEEP BRAIN STIMULATION FOR DYSTONIA IN CHILDREN

Jean-Pierre Lin - *General Neurology & Complex Motor Disorders Service, Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, Lambeth Palace Road, London*

15. DBS FOR DYSTONIA-PRESENT AND FUTURE: NEUROPSYCHOLOGICAL, EUROPSYCHIATRIC AND QUALITY OF LIFE ISSUES

Marjan Jahanshahi - *Neuroscience Research Center, Department of Anatomy, Golestan University of Medical Sciences, Gorgan, Iran*

16. DBS FOR DYSTONIA-PRESENT AND FUTURE: HOW CAN WE INCREASE THE THERAPEUTIC OUTCOME OF DEEP BRAIN STIMULATION IN DYSTONIA?

Norbert Kovacs - *Department of Neurology, University of Pécs, Hungary*

17. TREATMENT-INDUCED CHANGE OF CORTICAL ACTIVATION: FMRI EVIDENCE OF THE CENTRAL EFFECT OF BOTULINUM TOXIN A IN IDIOPATHIC DYSTONIA AND POST-STROKE SPASTICITY

Petr Kanovsky, Petr Hlustik, Robert Opavsky, Tomas Veverka, Katerina Mensikova, Pavel Otruba, Alois Krobot - *Departments of Neurology and Rehabilitation Medicine, Palacky University Medical School, Olomouc, Czech Republic*

18. WRITER'S CRAMP

Zvezdan Pirtošek - *Department of Neurology, University Medical Centre, Ljubljana, Slovenia*

19. LIVING AND COPING WELL WITH DYSTONIA

Marjan Jahanshahi - *Neuroscience Research Center, Department of Anatomy, Golestan University of Medical Sciences, Gorgan, Iran*

20. PHYSIOTHERAPY IN DYSTONIA SYNDROMES

Jean-Pierre Bleton - *Neurology Department, Raymond Garcin Center, Saint Anne Hospital Paris, France*

1. PRIMARY DYSTONIA

Joaquim Ferreira - *Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon*

The classical concept of primary dystonia defines forms in which dystonia is the only clinical feature (apart from tremor) and without evidence of neurodegeneration or identifiable exogenous cause. In the pure forms, dystonia is the only clinical sign and these forms have been called "primary pure dystonia".

In the dystonia plus forms there are additional movement disorders (e.g., myoclonus or parkinsonism) and in the paroxysmal forms symptoms are intermittent and provoked by identifiable triggers (e.g., sudden movement, exercise induced or non-kinesigenic).

Primary dystonias include genetic forms and forms for which a cause is not usually found (such as most focal dystonias).

Two genes for primary pure dystonia have been identified: DYT1 and DYT6 Three other gene loci for autosomal dominant PPD (DYT4, DYT7, DYT13) and two forms of recessive PPD (DYT2, DYT17) have been also described.

In this lecture the definition and classification of primary dystonias will be discussed and the clinical features and recommendations for diagnosis will be summarized.

2. DYSTONIA PLUS SYNDROMES

Marina AJ de Koning-Tijssen - *Head of movement disorders, Department of Neurology, University medical centre Groningen (UMCG), Groningen, The Netherlands.*

The dystonias can be classified based on etiology. Until recently, four groups could be recognized: 1. primary dystonias, 2. Dystonia-plus or primary 'plus' syndromes (including the paroxysmal dystonias), 3. Secondary dystonia, and 4. Dystonia in heredo-degenerative disorders. A newly suggested classification proposes to make the paroxysmal dystonia a separate entity resulting in 5 groups with different etiology. In this lecture we will discuss the phenotype and genotype of the dystonia-plus and paroxysmal dystonias.

The 'plus' in dystonia plus stands for *myoclonus* (myoclonus dystonia, DYT11 or 15) or *parkinsonism* (dopamine responsive dystonia, DYT5, or rapid onset dystonia parkinsonism, DYT 12 or 16). The clinical features of each of these dystonia plus syndromes will be discussed and illustrated on a video. Not only motor features will be discussed but also co-morbid psychiatric features. For each of the dystonia plus forms the mode of inheritance and possibilities for genetic screening will be presented. In which patient should we screen a specific gene? In paroxysmal dystonias additional clinical features include *chorea and ballism*. Three types can be recognized. This will be illustrated and both the clinical and genetic features of the paroxysmal dyskinesia will be discussed.

3. EARLY-ONSET DYSTONIA

**Jean-Pierre Lin - General Neurology & Complex Motor Disorders Service,
Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust,
Lambeth Palace Road, London**

Dystonia is defined as a neurological syndrome characterized by involuntary, sustained, patterned and often repetitive muscle contraction of opposite muscles, causing twisting movements or abnormal postures during motor tasks. Dystonia is increasingly recognized as a cause of **disability, dysarthria, dysphagia, deformity** and sudden **dystonic death** in children with cerebral palsy and other disorders. However the onset of dystonia, athetosis, chorea, myoclonus or tremor in the previously well infant, child or young person is often regarded as perplexing, difficult to explain, individually rare and puzzling. Since there are many individual causes of primary dystonias, dystonia plus syndromes and secondary dystonias, there may be common mechanisms shared by all human beings that select out these pathological motor patterns.

Dystonia is thought to arise from an excess of cerebral plasticity and reduced inhibition. A very distinct form of dystonia arises in certain occupations that require intense, repetitive training such as musician's dystonia: in such cases, often only the performance of the musical task elicits the dystonia, whereas other actions may be executed without difficulty. The processing of sensory input appears integral to developing dystonia, and, in some cases may modify the expression of the dystonia by the use of the characteristic '*geste antagoniste*' (touching or applying pressure to a particular part of the body) that is helpful in reducing dystonia in many people. Dystonia may be seen as an activity-dependent phenomenon. Although there are now many genes that predispose to dystonias and other movement disorders, the genetic mutation alone is not enough. For instance in idiopathic torsion dystonia, due to the autosomal dominant DYT1 mutation altering the protein Torsin A, there is only an approximately 30% '*penetrance*'. Manifest DYT1 carriers appear to have a single nucleotide polymorphism (snp) **val66met** in the Brain Derived Nerve Growth Factor (BDNF) which is only found in one third of the population. Non-dystonic healthy individuals with the **val66met** snp also have smaller hippocampi and reduced episodic memory. Non-manifest DYT1 carriers have a **val66val** BDNF snp shared with 65% of the general population. BDNF is essential for glutaminergic receptor activity-dependent synaptic plasticity. Rapid repetitive pre-synaptic stimulation produces release of BDNF from electrically active neurones and enlargement of dendritic spines leading to **Long Term Potentiation** (LTP). LTP is enhanced in **immature** compared to adult brain. By contrast, inactivity, immobility and slowly repetitive pre-synaptic stimulation may lead to reduction in AMPA receptors in post-synaptic membranes stimulating type I metabotropic glutamate receptors that activate phosphoinositide turnover in dendritic spines leading to **Long Term Depression** (LTD) associated with reduced BDNF production. Primary dystonias can now be seen as utilizing fundamental mechanisms for neuronal sensori-motor organization, though the balance between LTP and LDP may underpin many other functions including memory. Repetitive transcranial magnetic or direct current stimulation may reduce cortical plasticity and increase inhibition by altering the balance of LTP and LTD in the neurons of people with focal dystonias, giving benefits that may last several weeks. Deep brain stimulation may operate by similar mechanisms in the short and long-

term, but as the stimulation is continuous, the effect may be sustained over many years. These examples suggest that potent environmental inputs may initiate a subtle re-organization of the sensori-motor plasticity essential for normal human function and development.

This dystonic expression of disordered motor control may not be accidental but may share characteristics with the early developing motor brain function of babies and infants. The human brain has adapted from a long evolutionary process harking back to vertebrate life under water. In a watery environment, slow wavy movements are economical but rapid movements difficult because of viscous drag: the occasional flick is possible to dart away but cannot be sustained. Water exerts a constant pressure on all surfaces of the body. Gravity is partly counter-balanced by the even thrust of buoyancy all around. In air, buoyancy and viscous drag are lost, gravity bears down. The movements of the newborn are slow and ponderous, but within months become frankly fast, rhythmic or fragmented, though undirected. In infancy (4-9 months) bizarre limb postures and attitudes flow effortlessly one into another in a constant rehearsal of future purposeful movements, often to the delight of admiring parents and family. The hands may be purposefully active while the legs kick or vice-versa. When the operational criteria of co-contraction of agonist and antagonist muscles is used, infantile motor patterns are quite clearly dystonic in character. An explanation for this is the necessity for the infant brain to express abundant plasticity and little inhibition at birth. This plasticity offers the immature motor system plentiful opportunities to adapt to the constraints of the physical environment. The complete reverse of this is the immobile embryo, newborn or infant for whom survival and developmental prognosis are extremely bleak because such infants are not able to generate exploratory motor behaviour or to gain rewards for their actions.

Activity-dependent neuronal plasticity may modulate LTP to lay down functions and LDP to suppress functions. As babies grow and develop, motor plasticity is 'tuned' by task-specific inhibition leading to the acquisition of the typical motor milestones of infancy such as rolling, sitting, standing and walking, skilled manual function and speech. Early human motor development can be viewed as arising from an adaptive balance between akinesia when asleep and a wakeful continuous exploratory kinesia, the fine tuning of which may be easily disrupted by a variety of endogenous and exogenous influences to produce maladaptive dystonia-dyskinesia. In activities where motor skills must remain broad and innovative, a heightened cerebral plasticity is essential though this may culminate in occupational dystonias. In primary and secondary dystonias, plasticity may reign unchecked with an apparent loss of the usual inhibitory controls to motor performance: effectively returning our motor systems to a helpless primordial state.

It is a dilemma for some children with cerebral palsy that they should spend their whole lives in a state of 'excessive motor plasticity', unable to lay down even the most rudimentary functional motor patterns and movements. It is a challenge to applied functional neurophysiology, medical neurology and neurosurgery, to find effective strategies for timely recognition and management of these early dystonias of childhood to re-focus the brain's capacity for plasticity and essential inhibitory mechanisms towards positive goals.

Some classical infantile dystonias will be presented along with 'grey cases' that present a diagnostic challenge on the border between normal development, developmental delay and pathological dystonia of infancy.

4. NEUROTRANSMITTER ALTERATIONS IN DYSTONIA

Antonio Pisani - *University of Rome "Tor Vergata", and Fondazione Santa Lucia I.R.C.C.S., Rome, Italy*

Clinical and experimental evidence converge to suggest that changes in the balance of neurotransmitters in specific brain regions is a cardinal feature in the pathogenesis of dystonia. The lack of clear evidence for neural degeneration in human post-mortem cases reported in the literature led to hypothesize that dystonia may be generated through an abnormal neuronal signaling occurring within specific brain regions, especially the basal ganglia, and in particular the striatum, and the cerebellum (Breakefield et al., 2008; Neychev et al., 2010). After reviewing evidence implicating the striatum in dystonia, we focus on the influence of two neuromodulatory systems: dopamine and acetylcholine. Numerous lines of evidence link dopaminergic dysfunction to the occurrence of different forms of dystonia (Augood et al., 2002, 2004; Perlmutter and Mink, 2004). An altered dopaminergic neurotransmission at striatal level has been found specifically in DYT1 dystonia. In a PET study, a significant reduction in D2 receptor binding has been described in patients with the DYT1 mutation (Asanuma et al., 2005). Accordingly, an altered ratio of dopamine metabolites was reported in brain samples from genetically confirmed cases of DYT1 dystonia, suggestive of an increased dopamine turnover (Augood et al., 2002). Moreover, a reduction of dopamine levels was found in the striatum of DYT1 patients (Furukawa et al., 2000). Recently (Wakabayashi-Ito et al. 2011) it was found that the torsin, the *Drosophila* ortholog of the early-onset dystonia TOR1A (DYT1), plays a role in a dopamine metabolism, by acting as a positive-regulator of GTP cyclohydrolase protein. The study of animal models of DYT1 dystonia also showed a significant alterations of dopamine metabolism. In mice overexpressing mutant torsinA (hMT1 mice) (Sharma et al., 2005), basal striatal dopamine levels and binding of D1 and D2 receptors were unchanged (Balcioglu et al., 2007; Zhao et al., 2008), whereas amphetamine-induced dopamine release was reduced. Dopamine metabolite ratios were found either increased (Zhao et al., 2008), or unchanged (Balcioglu et al., 2007). In this mouse model we described a striking abnormality in the response of striatal cholinergic interneurons to D2R activation (Pisani et al., 2006; Sciamanna et al., 2011), consisting in a paradoxical excitatory response, rather than the physiological inhibition. Accordingly, an increase of acetylcholinesterase expression was found in the striatum of these mice. As a consequence of such "hypercholinergic" state, a bidirectional impairment of corticostriatal synaptic plasticity occurs in mice with mutant torsinA, in accordance with the notion that cholinergic signalling exerts a profound influence on striatal plasticity.

Together, these results support the existence of a profound imbalance between striatal dopamine and acetylcholine signalling, which is responsible for the impairment of the striatal output. Collectively, the evidence suggests that many different forms of dystonia may involve abnormal plasticity in the striatum and may well justify the utilization of anticholinergic drugs in the treatment of dystonic symptoms. An improved understanding of how neurochemical alterations influence altered plastic processes would improve our understanding of the pathophysiology of dystonia.

5. SECONDARY DYSTONIA – CLINICAL CLUES, SYNDROMIC ASSOCIATIONS & INVESTIGATIONS

Kailash P Bhatia - *Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London, U.K.*

Background: Dystonia is a hyperkinetic movement disorder defined by involuntary sustained muscle spasms and unusual postures. Etiologically, dystonic syndromes can be broadly divided into primary and secondary forms, dystonia-plus syndromes and hereditary degenerative forms. In particular, diagnosis of secondary dystonic syndromes can be challenging in view of the variety of causes.

I will highlight some clinical clues and syndromic associations as well as investigational findings which may be helpful in the approach to a patient with suspected secondary dystonia.

I will outline characteristic clinical and neuroimaging findings which may be directive in the diagnostic process of dystonia patients and facilitate making the correct diagnosis, thus allowing initiating the best treatment.

Secondary causes of dystonia include, among others, strategic brain lesions of various origins, metabolic disease, neurodegenerative conditions, and previous exposure to drugs or toxins. Presence of clinical signs including prominent oromandibular involvement, eye movement disorders, retinitis pigmentosa, deafness, peripheral neuropathy, parkinsonism or progressive dementia should alert the clinician to consider a secondary cause. Strategic lesions within the basal ganglia, but also within the brainstem, cerebellum or cortical areas may underlie dystonia and should thus be excluded.

Conclusions: When thorough clinical examination reveals features atypical of primary dystonia, syndromic associations may help the clinician to narrow down the list of differential diagnosis. Directive investigations like neuroimaging may confirm the clinical suspicion.

6. WHAT IS NEW IN THE CELL BIOLOGY OF PRIMARY DYSTONIA AND DYSTONIA-PLUS SYNDROMES?

Tom Warner - *Department of Clinical Neurosciences, UCL Institute of Neurology, London, UK*

In the last 15 years there has been a great increase in our understanding of the genetics and cellular pathogenesis of a number of forms of primary dystonia and dystonia-plus syndrome. This has come particularly from the study of DYT1 and 6 primary dystonia and dopa-responsive dystonia (DRD), myoclonus dystonia syndrome (MDS) and rapid-onset dystonia parkinsonism (RDP).

The cell biology of DYT1 dystonia has been best described. The *DYT1* gene encodes the AAA protein torsinA. Cell and transgenic models have provided evidence to support a role for torsinA in endoplasmic reticulum, nuclear envelope and synaptic function, which may be disrupted by the loss of glutamate residue in the mutant form of the protein. DYT6 dystonia is caused by mutations in the *THAP1* gene, whose protein appears to be involved in regulation of transcription. Study of the genes for *GCH1*, *SGCE* and *ATP1A3* cause DRD, MDS and RDP respectively, and have been shown to be involved in various cellular processes including dopaminergic neurotransmission, ER trafficking and maintenance of the neuronal membrane potential.

Despite the numerous pathways and cellular functions that have been implicated in these genetic forms of dystonia, a number of central themes have been identified and these will be explored in the lecture.

7. CURRENT CONCEPTS ON THE PATHOPHYSIOLOGY OF DYSTONIA

Mark Edwards - *Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK*

Dystonia, in common with most movement disorders, is generally characterised as a basal ganglia disorder. This is in keeping with the ability of basal ganglia lesions and degeneration to cause dystonia and the ability of deep brain stimulation surgery of the basal ganglia to alleviate dystonia. Some forms of dystonia (for example focal hand dystonia in musicians), are characterised by onset after excessive practice of a fine motor task, and this suggests that there may be a key role for abnormal motor learning, or more widely, abnormal motor system plasticity in the generation of dystonia.

However, pathophysiological research in dystonia has revealed abnormalities that go beyond the basal ganglia and involve more than just the motor system. There is a clear role for dysfunction in other brain structures, for example the cerebellum, in some patients with dystonia. The sensory system is also abnormal in many patients with dystonia. In this talk I will briefly summarise this large field of evidence and discuss a "network" approach to understanding dystonia pathophysiology.

8. EPIDEMIOLOGY OF DYSTONIA

Justo García de Yébenes - *Department of Neurology, Hospital Ramon y Cajal, Madrid, Spain*

The epidemiology of dystonia has been investigated in several studies with different methodology, including service based studies, such as treatment settings or record linked platforms, or population based studies, using as the end points of these studies epidemiological variables such as the prevalence, incidence, incapacity and mortality. Results obtained in the service based studies provide data suggesting that dystonia accounts for a large number of subjects, having a prevalence as the fourth most frequent movement disorder, after tremor, restless legs and Parkinson's disease. The absolute prevalence greatly varies from one study to another owing to the differences in accessibility to specialized neurological care in different communities and health care systems. Results from population studies are limited by subjectivity of the research teams since there is no objective diagnostic criteria nor biomarkers for dystonia.

With all these limitations taken in consideration it could be established that the crude prevalence of primary dystonia in most studies ranges from slightly over one hundred to several hundreds of patients per million. Generalized dystonia accounts for a small proportion, less than 10% cases of the total. The most frequent focal form of dystonia is torticollis, with the exception of the countries South of Europe where blepharospasm takes the lead. In general it is considered that there is a gradient North to South for blepharospasm, strongly suggesting that the risk of blepharospasm could be increased by sun light exposure. But that risk factor has not been substantiated by measuring subjects with occupational differences in sun light exposure, for instance, like comparing the prevalence of blepharospasm in miners and sailors of the same community and with similar access to specialized neurological care.

Regional trauma, both episodic and repetitive microtrauma, have been considered to increase the risk of focal or segmental dystonia. There is a high prevalence of occupational dystonia in music performers and it has been proposed that this is related to repetitive, at times painful, exercise. There are also occasional reports of laryngeal dystonia in subjects forcing their voice, such as singers, teachers and others, but a well designed study is still needed.

With regards to secondary dystonia it is interesting to notice that their prevalence changes over time with relation to many environmental agents. A careful review of some Middle Age and early Renaissance paintings suggest that during these centuries dystonia related to epidemic ergotism was not uncommon. Likewise, drug induced dystonia was very common in psychiatric patients treated with neuroleptics in the late fifties and early sixties. Similarly, a transient increased number of cases of dystonia secondary to cerebral palsy was detected when the extension of the neonatal intensive care unit increased survival of children with cerebral palsy.

9. PSYCHOGENIC DYSTONIA SYNDROMES

Mark Edwards - *Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK*

As with many other movement disorders, patients with what we now recognise as organic dystonia, were diagnosed with hysteria. The process of reversing this diagnosis continued into the 1980s and beyond. However, as with all other neurological symptoms, abnormal postures can occur as part of psychogenic neurological disorders. In this lecture I will show examples of psychogenic dystonia, describe the ways in which they can be positively differentiated from organic dystonia, and discuss briefly modern ways of understanding “psychogenic” neurological disorders. This discussion has a direct influence on treatment of these disorders and our attitudes towards patients who suffer from them.

10. GENETIC RISK FACTORS FOR DYSTONIAS

Thomas Gasser - *Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany*

The dystonias are a heterogeneous group of hyperkinetic movement disorders, characterized by involuntary sustained muscle contractions that lead to abnormal postures and repetitive movements. Many forms of dystonia have an underlying genetic basis with clear monogenic inheritance in more severe forms, and potential genetic susceptibility factors for primary focal dystonia.

A growing number of causative genes for monogenic forms of primary dystonia and a number of dystonia-plus syndromes is being discovered, which help to define molecular pathways which may play a role in the etiology of the disorder. However, the relationship between genotype and phenotype is not always straightforward. Reduced penetrance and variable expressivity seems to be the rule, rather than the exception, so that additional genetic or non-genetic modifiers have to be postulated.

So far, the different molecular pathways identified in the various forms of dystonia do not converge in a common pathway, which would explain the common feature of a dystonic movement disorder. However further insight is expected through the development of animal models and improved imaging techniques, so that this research will hopefully result in better diagnosis and treatment of patients.

11. GENERAL MANAGEMENT APPROACH TO DYSTONIA

Maja Relja - University of Zagreb, School of Medicine and University Hospital Centre Zagreb, Department of Neurology, Zagreb, Croatia

Dystonia is a hyperkinetic movement disorder, characterized by sustained muscle contractions causing mainly repetitive twisting and abnormal posture.

The first step in treatment is attempting to determine the cause of the dystonia.

For secondary dystonias, treating the underlying cause may improve the dystonia, while specific etiological treatments are available for only a few forms of disease (e.g. Wilson's disease and dopa-responsive dystonia-DRD).

Patients with (DRD) improve significantly with small doses of levodopa. Neurologists should try a course of levodopa therapy for all patients with an early onset dystonia, particularly with limb-onset dystonia in order to determine if DRD is the cause.

There are currently no known treatments that can reverse the course of primary dystonia. However, symptoms may usually be managed with a combination of treatments: oral medications, injections of botulinum toxin (BTX) into dystonic muscle, and surgery.

Oral medication has been milestone in dystonia therapy until BTX treatment was introduced in clinical practice 20 years ago, especially for the focal subtypes. BTX is today treatment of choice for cervical and craniofacial dystonia supported by several double-blind studies. Oral medications are still widely used (anticholinergic, benzodiazepines, baclofen, tetrabenazine as first-line drugs) particularly in generalized dystonia. Many others drugs have been tested in small uncontrolled clinical trials and there is a lack of evidence to give recommendations for good practice point.

Deep brain stimulation (DBS) is increasingly used in the treatment of medically refractory dystonias, including primary generalized dystonia.

Supportive and physical therapy may play a role for some patients, most often as a supplement to other therapies.

In this lecture oral medication and supportive therapy for dystonia will be discussed.

12. BOTULINUM TOXIN TREATMENT OF DYSTONIA

Dirk Dressler - *Movement Disorders Section, Department of Neurology, Hannover Medical School, Hannover, Germany*

Botulinum Toxin (BT) is used in various medical specialties. Dystonia, however, is still one of the most important indications for BT therapy.

BT drugs consist of botulinum neurotoxin, complexing proteins and excipients. Botox[®], Dysport[®] and Xeomin[®] are BT type A drugs and produce similar therapeutic and adverse effects (AE). Neurobloc[®]/MyoBloc[®] is based upon BT type B. Its use is limited by substantial systemic anticholinergic AE and an increased antigenicity. The potency of BT drugs may be compared as follows: Botox[®] : Xeomin[®] : Dysport[®] : Neurobloc[®]/MyoBloc[®] = 1 : 1 : 3 : 40. BT selectively blocks the cholinergic innervation of striate and smooth muscles and exocrine glands. It can produce obligate, local and systemic AE. Its overall AE profile including long term safety, however, is excellent. BT can be blocked by antibodies. Risk factors include single doses, interinjection intervals and the immunological quality of the BT drug applied. Planning of BT therapy is based upon target muscle identification and estimation of the degree of their dystonic involvement. For planning of BT therapy and BT placement electromyography and imaging techniques may be used additionally. So far, total Xeomin[®] and Botox[®] doses of up to 1000MU have been used without clinically detectable systemic AE.

BT can best be used to treat focal dystonias. In segmental and generalised dystonias BT therapy has to be focussed on the most relevant target muscles. Combinations with all other treatment options including deep brain stimulation are possible.

Typical target muscles for BT therapy of cranial dystonia include the frontalis, procerus, corrugator supercilii, orbicularis oculi, nasalis, levator anguli oris, orbicularis oris, risorius, depressor anguli oris, mentalis, masseter and pterygoidei muscles; for cervical dystonia the sternocleidomastoideus, scalenii, splenius capitis, semispinalis capitis, trapezius, levator scapulae and the short neck muscles and for laryngopharyngeal dystonia the throat muscles and the thyroarytenoid, lateral cricoarytenoid, posterior cricoarytenoid muscles. Other typical target muscles include the arm, leg and truncal muscles.

Recent safety data and availability of immunologically improved BT drugs are now allowing higher BT doses thus expanding BT's use into more wide-spread dystonias.

13. SURGICAL APPROACHES FOR TREATMENT OF DYSTONIA

Joachim K. Krauss - *Department of Neurosurgery, Medical School Hannover, Hannover, Germany*

In the past, a variety of surgical methods has been applied to treat severe and disabling dystonia, in particular selective peripheral denervation and thalamic radiofrequency lesioning were shown to be efficient. The advent of DBS, however, revolutionized the surgical treatment of dystonia.

The benefit of pallidal DBS has been well appreciated in primary dystonias, both in generalized dystonia and in segmental or complex cervical dystonia. Predictors for good outcome are younger age, shorter disease duration and a positive DYT1 status. More has to be learned about the various issues associated with secondary dystonia.

Only recently, side effects of chronic pallidal DBS such as bradykinesia and freezing of gait have been acknowledged. Nevertheless, although these might be disabling in individual patients, usually a compromise between optimal effect of stimulation and avoidance of such side effects can be made. On the other hand, observation of such side effects prompted the re-evaluation of alternative targets such as the thalamus or the subthalamic nucleus. Multifocal DBS is a new concept that might be useful also in selected patients with dystonia.

14. DBS FOR DYSTONIA-PRESENT AND FUTURE: DEEP BRAIN STIMULATION FOR DYSTONIA IN CHILDREN

Jean-Pierre Lin - General Neurology & Complex Motor Disorders Service, Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, Lambeth Palace Road, London

The term dystonia refers to a heterogeneous group of disorders characterised by "*involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both*"¹. In primary dystonia the dystonic movements are the only feature of neurological disease. Primary dystonias of childhood generalise early, 60% being recognised by 10 years and 80% by 15 years of age². Secondary dystonias are symptomatic disorders, with the abnormal movements secondary to a disease process of injury affecting the brain². In childhood secondary dystonia is more common than primary dystonia³. Heredodegenerative dystonia is the term given to dystonia caused by neurodegenerative disorders⁴, of which neurodegeneration with brain iron accumulation (NBIA) is a relatively common form⁵.

Childhood dystonia exerts an adverse influence on growth, development, education, activity and participation. Unchecked by effective management the progressive natural history of dystonia is one of disability, deformity and, rarely, sudden dystonic death. Despite its profound consequences, dystonia as a principal disorder of movement in childhood is likely to be under-recognised^{6; 7}. Childhood dystonia is frequently refractory to pharmacological management, and even when effective, medication use is often limited by unwanted adverse affects, e.g. sedation and respiratory distress⁸.

The Globus Pallidus internus (GPI) was originally the target of the ablative stereotactic technique of pallidotomy used in the treatment of dyskinesia⁹. GPI Deep Brain Stimulation (DBS) is an established management for medically refractory primary dystonia, with benefits maintained several years after electrode implantation¹⁰⁻¹². It remains unclear which patients will benefit from DBS, or the optimal timing of surgery. In patients with primary dystonia a longer duration of dystonic symptoms prior to DBS surgery is related to poorer outcome¹³⁻¹⁵.

Secondary dystonias appear less responsive to DBS than primary dystonia^{16; 14; 15}. Timing of DBS surgery for the management of dystonia is an important issue, particularly as dystonia duration adversely affects outcome¹³. In childhood the timing of surgery is even more critical, as successful intervention could lead to increased participation and access to schooling, in addition to the direct gains of a reduction in unwanted movements.

Clinical examples of early and late DBS surgery for primary and secondary dystonias in the paediatric age-group will be presented with a specific focus on diagnostic aetiology, ***Duration of Dystonia at Age of Surgery*** (DD:AS) ratio (representing the proportion of life lived with dystonia), appropriate outcome measures,^{29, 30, 32, 37} battery life³⁴ and rechargeable stimulators,^{35, 36} in children and young people²²⁻³⁷.

15. DBS FOR DYSTONIA-PRESENT AND FUTURE: NEUROPSYCHOLOGICAL, NEUROPSYCHIATRIC AND QUALITY OF LIFE ISSUES

Marjan Jahanshahi - Neuroscience Research Center, Department of Anatomy, Golestan University of Medical Sciences, Gorgan, Iran

Deep brain stimulation (DBS) is an effective treatment for dystonia. To optimize surgical outcome, careful selection of patients is important.

The relevant evidence on the effect of dystonia and the impact of its treatment with DBS on cognition, mood and behaviour and quality of life, as considered in the report for the Movement Disorders Society Task Force for DBS for Dystonia (Jahanshahi et al, 2011) will be reviewed.

Based on this evidence, recommendations for the cognitive and psychiatric assessment of patients prior to and after surgery will also be outlined.

16. DBS FOR DYSTONIA-PRESENT AND FUTURE: HOW CAN WE INCREASE THE THERAPEUTIC OUTCOME OF DEEP BRAIN STIMULATION IN DYSTONIA?

Norbert Kovacs - Department of Neurology, University of Pécs, Hungary

For the treatment of medication-refractory dystonia, bilateral pallidal deep brain stimulation (**GPI-DBS**) is proven to be an efficient option. On average, 40-55% improvement on dystonia rating scales (**DRS**) could be achieved according to the results of multicenter trials¹⁻³ lasting for years⁴. However, a considerable portion (10-25%)¹⁻³ of the patients experience minimal alleviation despite of good electrode placement. These patients can be regarded as non-responders to GPI-DBS defined as having either limited improvement (<25% on DRS) or worsening.

Utilizing different stimulation modes, the efficacy of GPI-DBS in dystonia can be improved. Besides adjusting the amplitude, frequency or pulse-width of stimulation, one can change the electrode configuration from the commonly applied **single monopolar stimulation** mode (one contact on the electrode is negative) to either **double monopolar stimulation** (two –usually adjacent- negative contacts on the electrode are stimulated with same amplitude and pulse-width values) or **bipolar stimulation** mode (one contact on the electrode is positive) in case of unsatisfactory outcome⁵. Although these techniques had been utilized in multicenter trials, non-responsiveness to GPI-DBS did occur².

Most GPI-DBS trials applied Kinetra generator (Medtronic, Minneapolis, MN) enabling double monopolar stimulation, where both negative contacts were stimulated with the same pulse-width and amplitude values. In these cases, the lowest threshold for eliciting side-effects limited the amplitude of the common stimulation of both negative contacts.

However, the newer devices utilizing the recently introduced interleaving mode allow the independent stimulation of two contacts with different pulse-width and amplitude values. Therefore, presumably larger and more conical electrical spreading and tissue activation can also be achieved. Recent case studies suggest that this might be accompanied by increased efficacy.

17. TREATMENT-INDUCED CHANGE OF CORTICAL ACTIVATION: FMRI EVIDENCE OF THE CENTRAL EFFECT OF BOTULINUM TOXIN A IN IDIOPATHIC DYSTONIA AND POST-STROKE SPASTICITY

Petr Kanovsky, Petr Hlustik, Robert Opavsky, Tomas Veverka, Katerina Mensikova, Pavel Otruba, Alois Krobot - *Departments of Neurology and Rehabilitation Medicine, Palacky University Medical School, Olomouc, Czech Republic*

The central mechanism of idiopathic dystonia is presumed within the brain albeit no direct evidence of any brain structures involvement in the development of dystonic dyskinesia exists. Similarly, the exact cerebral mechanism of post-stroke spasticity is unknown. We have consecutively done a series of experiments in which we aimed to describe the potential central mechanisms more precisely.

There were four fMRI studies performed in which we used botulinum toxin A (BoNT-A) injections in previously untreated patients to study the processes at different levels of central nervous system. In the first three studies we recorded the changes in the cortical activation in patients with post-stroke spasticity who performed either the sequential finger movements or the mental simulation of the movement. fMRI showed increased activation of the classical "non-motor" structures (posterior cingulum, precuneus, DLPFC), which has been decreased or "normalised" following the BoNT-A treatment. In the fourth study, the impact of BoNT-A treatment on the cortex activation pattern in cervical dystonia has been studied; the significant decrease of the activation of premotor cortex has occurred.

We have concluded that the successful treatment with BoNT-A can change the characteristics of both spasticity and dystonia by the affection of its generating structures. It seems that these are formed not only by the classical "motor" structures, but also by the "non-motor" ones.

18. WRITER'S CRAMP

Zvezdan Pirtošek - *Department of Neurology, University Medical Centre, Ljubljana, Slovenia*

Dystonia is an involuntary, sustained muscle contraction causing twisting movements and abnormal postures. It may be classified as focal, multifocal, segmental, hemidystonia and generalized dystonia. Focal dystonia affects only one body part of the body. Writer's cramp is a form of task-specific focal dystonia. The estimated prevalence is considered to be 69 cases per 100,000 population; possibly an underestimation, because many patients never seek medical assistance.

Clinically, dystonic posturing becomes evident with attempts to perform a specific task, such as writing.

The hand may assume semiflexed or hyperextended position of the fingers with possible ulnar or radial deviation of the wrist, supination or pronation or elbow and shoulder elevation.

Prevalence is slightly higher in men with the male-to-female ratio about 1.3:1. However, in women this disorder usually presents earlier than in men. It is thought to be most prevalent between the ages of 30 and 50.

Most cases are idiopathic. Known causes and risks include repetitive hand movements such as typing and writing, in 5-10% injury to the hand or arm immediately preceding the onset of symptoms, and, in 5-20 % of patients a positive family history of a similar condition. Very rarely, individuals with primary, typically generalized DYT1 dystonia may present with writer's cramp as the only symptom.

The most important part of examination is observation of the limb during writing with, either mild spontaneous or typical action-induced dystonic posturing and, occasionally, reduced arm swing. However, a large-amplitude writing-induced tremor may be found in patients affected with primary writing tremor, believed by some to be a variant of writer's cramp.

On examination, either spontaneous or action-induced mild dystonic postures may be observed and, occasionally, reduced arm swing. One third of patients have a tremor in the affected limb while writing and cerebellar abnormalities of unclear significance have been detected.

This dystonic syndrome may be assessed with functional scales such as the Arm Dystonia Disability Scale (ADDS) or Writer's Cramp Rating Scale (WCRS), with kinematic analysis of handwriting movements and with electromyography which may detect simultaneous contraction of agonists and antagonists. Occasionally, nerve conduction studies or MRI scan may be required to exclude a trapped nerve or a structural lesion, respectively. Although there was a report on structural abnormalities in the cerebellum in writer's cramp, the significance of this finding remains unclear.

Pathophysiologically, there is evidence for abnormalities in the basal ganglia in all patients with dystonia leading to the abnormal sensory processing in patients with dystonia with (consequent?) increased motor cortex excitability which - along with decreased cortical inhibition - causes abnormal motor output with sustained muscle contraction causing twisting movements and abnormal postures.

Similar to some other dystonias, about 5% of patients report spontaneous remission, usually in the first 5 years, but with a relapse after some years later in most cases.

Non-medical managements include starting to write with the contralateral hand, altering the grip of the pen, increasing the diameter of the pen or using differently shaped and more bulky writing devices or other means of transcription, such as typing or dictation. Immobilization of the affected hand was not beneficial, but transcutaneous electrical nerve stimulation (TENS) is reported to be superior to placebo. Surgical treatment (deep brain stimulation, stereotactic nucleus ventrooralis thalamotomy) may be of value in selected patients.

Treatment with Botulinum toxin injections seem to have the best results. This substance blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. injected intramuscularly, botulinum produces a localized chemical denervation muscle paralysis in overactive muscles, reducing dystonia.

In one of the pioneering studies confirmed by later reports we (Turjanski, Pirtosek et al 1996) reported forty-four patients with disabling writer's cramp and one with a musician's cramp who were treated with botulinum toxin injections for a mean period of 12 (range, 3-48) months. The forearm muscles causing the dystonic position were identified by inspection while writing; botulinum toxin was then administered under electromyographic (EMG) guidance. The degree of improvement in writing and amelioration of pain were rated with self-assessment scales. Patients reported significant improvement in writing after 56% treatment sessions (TS) and in pain after 62% treatment sessions. Mild weakness occurred after 32% treatment sessions. Twenty-nine patients discontinued treatment, generally after the initial botulinum toxin injection. In 16 patients who remained on treatment with a mean follow-up of 21 (range, 3-48) months, the improvement in writing and pain was present after 76 and 79% of the treatment sessions, respectively. We conclude that botulinum toxin injections offered a worthwhile and sustained functional improvement to 36% of our patients with writer's cramp.

19. LIVING AND COPING WELL WITH DYSTONIA

Marjan Jahanshahi - Neuroscience Research Center, Department of Anatomy, Golestan University of Medical Sciences, Gorgan, Iran

Dystonia is a chronic disorder that can have an impact on the daily activities and quality of life of people with the illness.

I will first review some of the factors that research studies have shown to be important in determining how people adjust to a chronic illness such as dystonia.

Based on this research evidence, I will go on to suggest some common sense approaches that people with dystonia can adopt to live better with dystonia.

20. PHYSIOTHERAPY IN DYSTONIA SYNDROMES

Jean-Pierre Bleton - Neurology Department, Raymond Garcin Center, Saint Anne Hospital Paris, France

Physiotherapy is recognised as a useful associated treatment of dystonia syndromes since the 1970s. The introduction of botulinum toxin has not put into question its interest. Physiotherapy retains its indications and the two treatments mutually interact in order to reduce the abnormal postures. Although physiotherapy seems to play an important role, physiotherapists have few reliable scientific studies upon which to choose appropriate methods of rehabilitation. Usually, the different physiotherapy programs for focal dystonia are based on pathophysiology and case studies. This means that their content and modalities need to be defined more precisely.

The most widespread method is the behaviourist approach designed as a re-learning process. In this approach, the physiotherapy programs are established to eliminate the abnormal postures, sensory disturbances and undesirable gestures. Although the muscular dysfunction has been highlighted by many pathophysiological studies, few programs focus on function of the muscles involved. The lack of inhibition of the dystonic muscles and the weakness of their antagonistic muscles seems to be essential parts of the physiotherapy.

These two options (re-learning posture and muscular strength control) are proposed in the two main indications of the physiotherapy for dystonia syndromes: writer's cramp and cervical dystonia.

In the re-learning approach for writer's cramp, the aim of rehabilitation is not to treat a specific group of muscles but to correct the abnormal pattern. Writing exercises with pencil are used to regain fluidity and comfort of penhold. Exercises, that do not trigger the dystonic movements are selected.

Sensory control is trained, focusing on perception of pressure of the fingers on the pen. During writing practice, the patient concentrates on keeping his/her hand and upper limb relaxed.

The muscular strength control programs for writer's cramp focus on the correction of muscular disorder by exercise programs of dexterity: independence of the fingers, precision of digital force control and timing of the movement.

In the re-learning protocols for cervical dystonia, the exercises are performed in order to stop, and then replace involuntary and inappropriate head movements by conscious and co-ordinated movements. The patient must learn to recognise his/her spasms in order to better control them. He/she strives to remain immobile for progressively increasing amounts of time, without causing excessive fatigue. Controlled immobility and natural head posture are repeated several times a day. This requires calm attention, muscle relaxation control and a certain degree of vigilance on behalf of the patient.

Cervical dystonia is recognized as a functional inability to activate the muscles required to carrying out corrective movements. In the muscular strength control program, the muscles recognised as responsible for pathological posture are the focus. Strengthening of weak muscles allows a better functional balance between dystonic and corrective muscles. The choice of muscles to reinforce is therefore a fundamental step influencing the results of rehabilitation.

These different options need to be validated and compared by controlled studies in order to be performed in standard physiotherapy.