

# Mezinárodní sympozium Dystonie a dystonické syndromy

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## Invited lectures

### Pathophysiology of dystonia

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Dystonia is a syndrome characterized by involuntary muscle spasms giving rise to abnormal postures. The pathophysiological mechanisms underlying dystonia are still uncertain. Most of the information was obtained in patients with adult onset focal dystonias; these forms are likely to share a common physiology, but this is not necessarily true for all types of dystonia [1]. Nevertheless, several studies demonstrated the occurrence of motor abnormalities also in non-dystonic segments of patients with focal dystonia [2]. A common mechanism has been identified in the loss of inhibitory functions operating at spinal, brainstem and cortical levels. In particular, many cortical circuits seem to be involved leading to the loss of surround inhibition and, consequently, to overflow and unwanted muscle spasms [3]. Converging data on focal dystonias also suggested a widespread disorder of somato-sensory processing that might be partially explained as well by a loss of inhibition [4]. Whether sensory abnormalities may be regarded as an endophenotypic trait of dystonia is still uncertain, although gray matter changes in the primary sensory cortex of patients with focal dystonia have been documented [5]. Reduced inhibition seems unlikely to be a causal factor in organic dystonia; it is more likely that the “genetic” loss of inhibitory functions represent the substrate on which other factors (such as abnormal plasticity with increased tendency to strengthen sensory-motor associations) should act to produce dystonia [6]. Recent studies on the effects of deep brain stimulation in dystonia have partially clarified the mutual relationship between excessive plasticity and lack of inhibition in dystonia [7].

Finally, primary dystonia has traditionally been viewed as the result of aberrant activity within the basal ganglia circuitry, but recent studies suggest that the cerebellum might play a crucial role in the disease. Abnormal cerebellar activity might trigger dystonia by altering the function of the basal ganglia. Primary dystonia, therefore, has been proposed as a neurodevelopmental circuit disorder, involving the cortico-striato-pallido-thalamo-cortical and the cerebello-thalamo-cortical pathways [8].

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### Rationale approach towards the treatment of Parkinson's disease

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Recently published data showed that non-motor symptoms – NMS (neuropsychiatric, sensory and gastrointestinal symptoms, sleep disorders, fatigue, nonmotor fluctuations, drug-induced symptoms, autonomic dysfunction and others) of Parkinson's di-

sease (PD) have a significant impact on quality of life of affected PD patients. There are several important studies showing the awareness of these symptoms among neurologists, intensity and combination of NMS (Priamo study, Recover study). Measures leading to better diagnosis and management of non-motor complications – f.i. using different questionnaires and scales (like WOQ-9, PDSS-2, PDQ-8) are highly appreciated. Continuous delivery of rotigotine via the transdermal system enabled better control of non-motor symptoms like sleep problems, fatigue, mood, cognition, and pain. Quality of life aspects could be improved as well. Adverse event profile is similar to other dopamine agonists. Intrajejunal delivery of L-DOPA is another option for severely disabled patients suffering from PD. Currently, we do not have disease modifying drug as originally proposed by ADAGIO study (clinical trial with rasagiline), so that our management of Parkinson's disease still remains symptomatic.

## Long-term treatment of cervical dystonia with botulinum toxin A

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Botulinum toxin A (BoNT-A) had been introduced into the treatment of cervical dystonia twenty years ago and reached widespread use in this chronic condition which also affects the quality of life of suffering patients and their sociological and employment status. Although nowadays there is no question about BoNT-A use as the first line treatment, its efficacy and safety; we are still missing the data about the long-term course of the illness under the BoNT-A treatment and related issues of quality of life and financial costs.

The goal of the presented study was to assess the long-term treatment of idiopathic cervical dystonia in patients treated with botulinum toxin A (BoNT-A), the impact on quality of life and financial costs.

**Selection criteria:** (i) Regular treatment with BoNT-A for at least ten years and (ii) continuous good clinical response to the BoNT-A injections. Group consisted of 69 patients. The efficacy of the treatment was assessed by Clinical Global Impression (CGI) Scale, Tsui scale, and patients' questionnaire. The cost of the BoNT-A treatment per year was compared to previous oral treatment (baclofen and clonazepam in most cases).

Mean number of BoNT-A injections per patient was 44.5, mean dose per treatment session was 490/140 units of Dysport®/Botox®. The mean period between two consecutive treatment sessions was 110 days. The mean Tsui score before the treatment was 11.5, after ten years the Tsui score declined to 8.0. CGI score was 1.9. Adverse events occurred in less than 1% of treatment sessions. There was a need to increase total dose of the BoNT-A approximately of 25%. Based on the patients' questionnaires, the most positive impact on their quality of life was in social communication. The cost of the BoNT-A treatment per patient and year was approximately 1,200 Euros; the cost of the commonly used oral treatment was 180 Euros.

Long-term treatment of cervical dystonia with BoNT-A is safe and improves their quality of life and social communication. The indirect costs have to be strongly considered when initiating the therapy of cervical dystonia.

## Dystonia in multiple system atrophy and progressive supranuclear palsy

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Dystonic features are common in multiple system atrophy (MSA) and they may involve the neck, larynx, limbs, and trunk (Pisa syndrome, camptocormia). In the cervical region, the presence of severe, fixed antecollis is highly suggestive of MSA; several observations suggest prominent antecollis may develop at some stage in up to 1/2 of sufferers, often becoming troublesome to the patients. Unfortunately, local injections of botulinum toxin, which are effective in orofacial as well as limb dystonia associated with MSA, may induce severe dysphagia with the necessity of nasogastric feeding after treatment of disproportionate antecollis. The classical clinical presentation of progressive supranuclear palsy (PSP) is characterized by marked axial rigidity. Severe neck rigidity influences the posture of these patients, which may appear characteristically erect like in the original cases published by Richardson and colleagues in 1963 (they described this clinical feature as "nuchal dystonia"). This form of neck dystonia is often painful and may further impair balance and vision of these unfortunate patients.

In some clinical reports of PSP ocular dystonic features, like blepharospasm and eyelid opening dystonia, are also frequently described. Even more typical is the occurrence of dystonia in the classical picture of corticobasal syndrome (CBS), in which one limb is typically found to be akinetic, rigid, apraxic, and dystonic (often with accompanying pain). Dystonia is present in 59–71% of CBS individuals in various series, mixing cases of clinical and pathological diagnoses. In a study of 36 patients with CBS, 33% had dystonia at the initial evaluation, but 83% had dystonia at their last follow-up (Rinne et al, 1994). Dystonia in

CBS is present often at rest rather than being purely action-induced. Typically, dystonia affects the involved arm and hand at onset, with 92% of CBS patients with dystonia exhibiting upper limb involvement. When symptoms begin in the leg, dystonic inversion of the foot can be seen, with 28% of CBS patients with dystonia developing leg involvement. Myoclonus has been commonly reported in association with dystonia, and the observation of dystonia and myoclonus in one upper limb strongly suggests the possibility of CBS.

## Botulinum toxin treatment of dystonia

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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. 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 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 1,000 MU have been used without clinically detectable systemic AE. BT can be used to treat focal dystonias including cranial, pharyngolaryngeal, cervical and limb dystonias. In segmental and generalised dystonias BT therapy has to be focused on the most relevant target muscles. Combinations with all other treatment options including deep brain stimulation are possible.

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.

## Pitfalls of deep brain stimulation for dystonia

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Deep brain stimulation of the internal globus pallidus (GPi DBS) has become an efficient tool for treatment of dystonia. Success heavily depends not only on accurate diagnosis and precise electrode placement in a particular region inside GPi but also on the way of effect assessment. A long-term follow-up of previously implanted patients helped to define several relevant predictive factors for pre-surgical identification of DBS responders. Potential non-responders include mainly those with secondary dystonia, e.g., after ischemic brain damage with more severe dystonic involvement, mostly fixed limb dystonia and a long history of the disorder. However, success is not guaranteed even in patients with DYT-1, otherwise seen as ideal candidates for GPi DBS. Many of them had deteriorated years after surgery despite their outstanding response in the first postoperative years. Reimplantation or an addition of another electrode bring improvement to only a few. On the other hand, excellent effects of DBS GPi were sporadically seen even in secondary dystonia. The DYT-1 patients who deteriorated the most after neurostimulation was switched off surprisingly exhibited lower long-term potentiation-like plasticity, and were chronically treated with a higher current drain. Hence, variable genetically-conditioned predisposition seems to be critical for patient's future response to GPi DBS. Response to changes in DBS parameters may occur after a delay of days or weeks, and it may often take months to reach an optimal setup even in responders. Besides checks on the precise electrode placement in the postero-ventral GPi and on the DBS system technical functionality, cases of long-term failure require frequent setup adjustments (markedly longer pulse duration, low or high frequency, use of several contacts, interleaved pattern, etc.). Frequent DBS GPi side effects include dysarthria, visual sensations, paresthesias and worsening of existing dystonia as well as dystonia spreading to unaffected segments. However, the main pitfall of GPi DBS remains the same: unrealistic expectations in the patient and sometimes even in his/her doctor.

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## Secondary dystonia

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Dystonia, defined by the involuntary sustained muscle contractions resulting in the twisting movements or abnormal posturing of body parts, is always a diagnostic challenge. Probably the most important diagnostic issue is the differentiation between primary and secondary dystonia, or dystonia-plus syndrome. Secondary dystonia causes are numerous: brain lesions of various origins (but mainly ischemic), neurodegenerative diseases, exposure to drugs, metabolic diseases and many others. Incidence and prevalence data are rather limited. There were several large cohorts studied and published, in which the prevalence of secondary dystonia varied between 30–60%. This broad spectrum of prevalence rate jeopardises the epidemiological studies in primary dystonia, and undoubtedly makes the differential diagnosis of dystonia a difficult task. However, there are some published and confirmed clues which may help in the diagnostic process.

Dystonia, which manifests with prominent involvement of the oro-mandibulobuccal area, is usually caused by the drug intoxication or PKAN or neuroacanthocytosis. Dystonia, which accompanies Parkinsonism, should be considered as a dopa-responsive dystonia, or Wilson's disease, or young-onset Parkinson's disease, or parkinson-plus syndrome, e.g. PSP. Dystonia, accompanied by the disorder of ocular motility, is suspect from Nieman-Pick disease, Huntington's disease, Louis-Bar disease or some of the spinocerebellar ataxias. Huntington's disease may be a cause of dystonia accompanied by the progressive dementia, as well as gangliosidoses GM1 and GM2. Several different diseases can cause the dystonia-deafness syndrome. Friedreich's ataxia can manifest with dystonia and peripheral neuropathy. Dystonia with retinitis pigmentosa should be caused by the PKAN. Many other rare causes have been described in case reports, and this number is constantly increasing. So, to appropriately diagnose the secondary dystonia require not only the perfect knowledge of any described causes, but also the creativity in debunking the new ones.

## Franz Xaver Messerschmidt (1736–1783) – on the border between the creation and illness

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The author poses a hypothesis which tries to interpret the bizarre late work of the Austrian sculptor F. X. Messerschmidt. After a promising career at the court of the Empress Maria Theresia his life took a dramatic downturn in his 33<sup>rd</sup> year. He settled down in Pressburg (Bratislava) where he lived until his death at the age of 47 (1783). Most of his time there he dedicated to creation of the busts with grotesque expressions, whose sense has remained a puzzle for art – historians up to today. The author calls attention to a probable occurrence of psychiatric and neurological disease. Contemporary records describe hallucinations and persecution delusions; higher epigenetic risk of schizophrenia development can be presumed (extremely advanced age of the father at the time of the artist's conception). The late Messerschmidt's style bears traces of schizophrenic stereotypes. Besides this, the expressions of the statues resemble facial dystonia. The occurrence of dystonia was recently confirmed in patients in later stages of schizophrenia even if they had never used antipsychotics. The author at the same time draws attention to a conviction proven by documentation to have been held by Messerschmidt that it is possible to have control of somebody by imposing certain features upon his or her face. The author coins a hypothesis that Messerschmidt himself suffered from dystonia as a symptom of his schizophrenia. The involuntary movements of his face he interpreted as being caused by ghosts who tried to get control over him by imposing upon him the same face features as they themselves possessed. The exact record of his own dystonia on the faces of the "ghosts" represented the sculptor's defence against them. Messerschmidt's work thus would not have been only an artistic act but also a way of fighting his own hallucinations and delusions. These extrapyramidal manifestations featuring in the work would explain why all attempts to adequately interpret the expressions he gave to his sculptures have so far failed.

## Gait compensation strategies in Parkinson's disease

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Disorders of gait, postural instability and falls seriously impair self-sufficiency and quality of life of patients with advanced Parkinson's disease (PD). While in early disease pharmacotherapy can satisfactorily improve motor function including gait, advanced PD is marked with motor fluctuations and other problems that interfere with locomotion, often resisting to medical treat-

ments. For example, freezing of gait (FOG) may occur even in the “ON” state with otherwise fair mobility following a dose of dopaminergic treatment.

In line with historical descriptions of paradoxical kinesia as an enigmatic feature observed in the pre-levodopa era, till this time PD patients use various cues, tricks and aids to improve their mobility. In particular, these strategies compensate for the deficit to execute motor sequences such as gait. Analyzing common traits of patient’ self-invented strategies may contribute to understanding their mechanisms and to developing focused rehabilitation techniques.

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## Psychogenic dystonia

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According to current definitions, psychogenic movement disorders (PMD) cannot be explained by organic damage to the nervous system and are thought to have a psychological origin, but in contrast to factitious disorder or malingering, the symptoms are not intentionally produced. From a neurophysiological point of view, PMD are hypothesized to have a basis in faulty inhibitory circuits of motor control.

PMD are estimated to account for 2–3% of patients in common neurological practice and are even more prevalent in specialized movement disorders clinics. Psychogenic dystonia represents one of the most common PMD, usually afflicting young adults, more often women than men. Suggestive features include sudden onset, paroxysmal course, spontaneous remissions and inconsistent character in time. Co-occurrence of other PMD and multiple somatizations are common. More specifically for psychogenic dystonia, fixed dystonic postures and legs involvement is often present. Bizarre gait with high energetic expenditure is then almost a rule, presenting as extreme slowing or complex acrobatic-like movements. Abnormal postures and movements may not correspond to typical patterns of organic movement disorders (e.g., isolated facial hemidystonia). Neurological examination should look for psychogenic signs such as false weakness, sensory disorders, and effects of distraction. However, organic dystonias also involve features that may appear bizarre, such as task-specific occurrence and geste antagoniste in idiopathic focal dystonias or complex movement patterns in paroxysmal dyskinesias. The diagnosis and especially the therapy of psychogenic dystonia thus remain a challenge.

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## Dystonia: indications – models – mechanisms

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Dystonia is generally considered a basal ganglia (BG) disorder with models of dystonia incorporating changes of function in the basal ganglia thalamo-cortical “motor” circuit (BGTC) to explain its development. Although largely refractory to medical therapy, deep brain stimulation (DBS) in the internal segment of the globus pallidus (GPi) and more recently the subthalamic nucleus (STN) have proven effective in improving dystonic movements. Indications for surgery are patients with primary dystonia in whom medical therapy is not effective or is associated with intolerable side effects. Patients with primary generalized dystonia were treated with DBS soon after its development since medical therapy is often ineffective for these patients or they develop intolerable side effects and the extent of involvement of the body with dystonia is too large to warrant treatment with botulinum toxin. Patients with primary dystonia involving segments of the body, i.e. segmental dystonia, as well as many focal dystonias including cervical dystonia have also benefited from DBS, particularly those in whom botulinum toxin therapy is not adequate or no longer effective. DBS has been much less effective, however, for those with secondary dystonia; results vary greatly across patients. This is likely due to the varied and often broadly distributed pathological basis for these dystonias. The exception to this rule is tardive dystonia. Patients with tardive dystonia respond to DBS to an extent that is similar for that reported for patients with primary dystonia. Although generally very effective, there can be significant variability in the beneficial effects of DBS across patients and centers performing the surgery. This variability likely lies in our lack of understanding of the pathophysiological basis for its development, variability in technical expertise at each center and lack of understanding of DBS mechanisms. Some variability in the response of patients to DBS may lie in the select somatotopically segregated involvement of neuronal populations within the targeted structure. Within key nodal points we hypothesize that similar physiological changes occurring over widespread regions of each structure result in involvement of multiple body parts and produce generalized dystonia, while more restricted changes likely lead to segmental and focal dystonia. Based on the location of the



DBS lead and its encompassing volume of tissue activation, the beneficial effect of these therapies may encompass several or only a few body segments and result in varying degrees of improvement in dystonic symptoms. Few models of dystonia have taken the somatotopic organization of the GPI into account and only recently have new models moved away from the classic “rate” theory. New models are incorporating changes in discharge patterns, receptive fields, and synchronization of neurons within and across key nodal points in the BGTC motor circuit. More recently it has been appreciated that brain circuits outside of the basal ganglia may be involved and not affected by stimulation in GPI or STN. The cerebellum has become intimately linked to the pathophysiology of dystonia and may play a greater or lesser role based on the “type” of dystonia. As such we now view dystonia as a more system wide dysfunction of multiple brain circuits. Although cerebellar (CB) and BG motor circuits are often considered in isolation in both normal and dysfunctional motor control, we are becoming more aware of the interaction within and across these pallidothalamocortical and cerebellothalamocortical circuits. The extent to which either substrate is involved, or whether it is a deficiency in the integration between overlapping BG and CB circuits that leads to dystonia, remains unclear. What is clear, however, is that if we are to improve the effectiveness of DBS therapies, we will require a sound scientific rationale for the patients we select, the DBS parameters we choose and the brain sites we target.

## Surgical treatment of dystonia

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Most procedures applied in the past for neurosurgical treatment of dystonia such as peripheral denervation, myotomie or myectomy as well as ablative stereotactic operations (radiofrequency lesions; thalamotomy or pallidotomy) or implantation of pump systems for intrathecal baclofen infusion are meanwhile in large parts replaced by deep brain stimulation (DBS). Besides DBS only extradural selective sectioning of nerves with terminals ending in dystonic muscles (selective peripheral denervation), a procedure reserved for the treatment of cervical dystonia, has still some importance. Except for the application of pallidal DBS in primary generalized or segmental dystonia in adult patients – here clinical studies meet the criteria of evidence level – the efficacy of this treatment modality in other types of primary dystonia (e.g. cervical dystonia, Meige syndrom) is documented by small case series or uncontrolled studies only. In the group of secondary dystonias the improvement of motor symptoms in patients treated with DBS for tardive dystonia is as good as in primary dystonia. Secondary dystonia caused by brain trauma or other reasons leading to damage or dysfunction of brain tissue respond to a lower degree and with comparably greater interindividual variability. Despite its lower efficacy and poor data record, DBS should also be considered in these patients as an individual treatment option applied with the aim to improve the most disabling symptoms consecutively increasing the quality of life. The mode of action underlying the clinical efficacy of DBS is not unraveled in detail. Probably and comparable to Parkinson's disease highfrequency stimulation overrides pathological oscillation patterns within basal ganglia neural networks also in dystonia.

## Genetics of dystonia

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In recent years, the identification of several new dystonia genes has improved our understanding of the etiology of the rare monogenic forms and of dystonia in general, and has provided important insights into the nature of this clinically and genetically heterogeneous disorder. In the current dystonia genetics nomenclature, 19 different chromosomal regions are termed DYT (to denote their putative link to dystonia), and numbered in chronological order of their identification (DYT1-20; with DYT5a/DYT14; DYT9/DYT18 being identical, and DYT5b being a separate locus). Thus the monogenic dystonia forms are clinico-genetically grouped as i) ‘pure dystonias’ (DYT1, DYT2, DYT4, DYT6, DYT7, DYT13, DYT16 and DYT17), ii) ‘dystonia-plus syndromes’ (dystonia combined with parkinsonism – DYT3, DYT5 and DYT12, or myoclonus – DYT11 and DYT15) and iii) ‘paroxysmal dystonias/dyskinesias’ (with episodic manifestations of dystonia as seen in DYT8-10 and DYT18-20). For 10 of these forms causative genes are identified and thus, the mechanism of disease pathology is partially explained. In addition to the single gene mutations, genetic modifiers and risk factors also seem to play an important role in etiology of dystonia. In this talk I will summarize the current knowledge and understanding of the molecular genetics of dystonia and review proposed molecular mechanism leading to the familial forms of the disease.

## Free communications

### Interdisciplinary special interest groups (ISIG) for optimizing multimodal therapy of movement disorders

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**Objective:** To develop an interdisciplinary special interest group (ISIG) as a communication platform for optimization of interdisciplinary therapies of movement disorders.

**Background:** Increasing complexity of therapeutic strategies for movement disorders requires interdisciplinary therapies involving several medical and nonmedical therapists. Coordinating all different involved professions is difficult.

**Methods:** Since October 2006, 20–35 physiotherapists, occupational therapists, speech therapists, nurses and physicians and invited guests are meeting each third Wednesday of each quarter 7–10:30 p.m. as a semi-open group.

**Results:** ISIG meetings covered the followings topics: 1. Development of a communication form (referral sheet) to facilitate flow of information about treated patients amongst different therapists. 2. Development and training of classificatory systems to harmonize communication. 3. Introduction and training of quantification systems to measure treatment effects. 4. Discussion of case studies to optimize treatment strategies. 5. Presentations of specific movement disorders to improve and harmonize general knowledge of movement disorders. 6. Development of a webpage and a data base of ISIG therapists to facilitate internal and external communications. 7. Two further groups started at other locations in Germany their work with the same concept.

**Conclusions:** ISIG stability over more than 5 years and its expansion to other locations documents its demand. ISIG promote interdisciplinary therapies for movement disorders; facilitate internal communication amongst involved therapists as well as external communication with patients and referring physicians. They may also play an important role in continuing medical education. ISIG should also be incorporated in emerging treatment guidelines.

### Long-term treatment of writer's cramp with botulinum toxin A – retrospective assessment of the clinical impact

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**Objective:** The goal of the study was to assess the long-term treatment of writer's cramp in patients treated with botulinum toxin.

**Introduction:** Botulinum toxin A proved to be successful treatment for the patients suffering from writer's cramp but its long-term application needs to be clarified in the motor domain and quality of life domain (like social activities).

**Patients and methods:** Selection criteria were treatment with botulinum toxin for at least 5 years and continuous good clinical response to injections. Group consisted of 12 patients (10 females, 2 males, mean age 48 years (SD = 10.3), mean disease duration 18.3 years (SD = 7.8), mean age at disease onset 38.4 years (SD = 10.2)). The efficacy of the treatment was assessed by a clinical exam, patients' self-assessment, patients' questionnaire, and CGI-S scale.

**Results:** Mean follow-up of the patients was 5.5 years (range 5–9 years). Mean number of botulinum toxin injections per patient was 11.5 (range 4–25); mean dose per treatment session was 176 units of Dysport (SD = 79) and 45 units of Botox (SD = 5). The mean period between two treatment sessions was 19 weeks (SD = 61.8). The mean CGI-S score before the treatment was 5.25 (SD = 0.7), after five years the score declined to 2.25 (SD = 0.4). We did not observe the need to change the botulinum toxin dose. Adverse events were mild, occurring in less than 30% of treatment sessions (finger weakness, local pain). Based on the patients' questionnaires, the quality of life was improved.

**Conclusions:** Long-term treatment of writer's cramp with botulinum toxin A is safe and efficacious.

### Deep brain stimulation in hyperkinetic disorders

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**Introduction:** Deep brain stimulation (DBS) is used clinically and/or experimentally in treatment of several subtypes of hyperkinesia. These include not only tremor, but also choreatic dyskinesia related to Parkinson's disease and dystonia. DBS effect and target in tics in myoclonus is not clear yet.

**Methods:** We review major hyperkinetic disorders that can be treated by DBS. We also sum up our own results of DBS in various dystonic syndromes in a group of 15 patients.

**Results:** DBS of globus pallidum internum (GPI) shows important clinical benefit in several dystonic syndromes, especially if axial signs, mobile dyskinesia and genetic forms of DYT 1 or 11 are present. Setting of optimal DBS parameters is time-consuming process that takes several months before optimal settings are found.

**Conclusion:** DBS is a neurostimulation method with long-term clinical effect in dystonia and with partial effect on tics. Indication of suitable patients for DBS GPI requires multidisciplinary team and cooperation.

### The mechanisms of movement control and time estimation in cervical dystonia patients – behavioral study

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The pathophysiology of cervical dystonia is still relatively unknown. The functional imbalance of respective muscle groups is thought to be caused by neurochemical abnormalities in the basal ganglia and recently, there has been emerging substantial evidence of considerable cerebellar involvement. This project aims to affirm the function of the above mentioned structures in precise movement timing. The participants were asked to perform a series of simple computer tasks where the parameters of a moving object (speed, acceleration, partially the movement direction) were randomly generated by the software. As the object moved from left to right on the computer screen, the participant had to press a button in an optimal time window to launch a "fireball" from the bottom of the screen that was supposed to hit the moving target. The "fireball" travelled with a constant speed and with a constant trajectory. However, as the speed was not sufficient to ignore the launch-interception time, anticipatory reaction according to changing parameters of the object was essential. We evaluated the hit ratio and percentage of early and late errors. The results were compared to the healthy subjects' data. The overall hit ratio in the healthy subjects was significantly higher than in the cervical dystonia group (42.07%  $\pm$  9.18% versus 34.91%  $\pm$  8.23%). The reaction time in cervical dystonia patients was significantly longer as well. Our data suggest that cervical dystonia patients have a substantial problem with predictive motor timing. The results imply that cerebellum and basal ganglia participate in the integration of visual information with motor output.

### Changes in sensorimotor network activations after botulinum toxin type A injections in patients with cervical dystonia – a functional MRI study

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**Background:** Patients suffering from cervical dystonia (CD) are very often notably limited in working and social activities. Botulinum toxin type A (BoNT-A) is currently considered to be one of the most effective therapeutic options. The pathophysiology of CD and other focal dystonias has not been fully explained to date. Results from neurophysiological and morphological studies suggest the significant involvement not only of the basal ganglia and thalamus, but also functional abnormalities in premotor and primary sensorimotor cortical areas are considered to be a crucial factor in the development of focal dystonias.

**Methods:** Ten BoNT-A naive patients suffering from cervical dystonia were examined with functional MRI during skilled hand motor task and also during electric stimulation of peripheral nerve; the examination was repeated four weeks after the first BoNT-A injection to dystonic neck muscles.

**Results:** First BoNT-A injection, although it had a good clinical effect, did not lead to any significant changes in activation of cortex or basal ganglia in our group of CD patients. In contrast, the previous work of our group (Opavsky et al. J Neur Sci 2011) showed in long-term BoNT-A reduced activation of the ipsilateral supplementary motor area and dorsal premotor cortex.

**Conclusion:** The results of the study do not manifest clear BoNT-A effects at the central nervous system level. However, our study examined just patients after a single BoNT-A application. Many other studies, such as the study presented above, used long-term BoNT-A treated patients. From this perspective, these results considered together would suggest the hypothesis



that robust central changes develop after long-term regular BoNT-A treatment, although even the first BoNT-A application is clinically effective.

### **Sensorimotor network in cervical dystonia and the effect of botulinum toxin treatment – a functional MRI study**

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Cervical dystonia is the most frequent type of focal dystonia. Converging evidence suggests that primary dystonia at least partly originates from dysfunctional basal ganglia and cortico-striato-thalamo-cortical motor circuits.

Seven patients suffering from cervical dystonia and nine healthy controls were examined with functional magnetic resonance imaging in order to localize and compare the activation patterns during a skilled hand motor task, as well as to determine task-related activation changes induced by botulinum toxin type A treatment.

Clinically, botulinum toxin treatment induced significant lowering of Tsui scores. Functional magnetic resonance imaging data demonstrated overall reduced extent of hand movement-related cortical activation but greater magnitude of blood oxygenation level dependent signal change in the contralateral secondary somatosensory cortex in patients compared to controls. Botulinum toxin treatment led to reduced activation of the ipsilateral supplementary motor area and dorsal premotor cortex in patients following effective botulinum toxin treatment of dystonic muscles. The patients' post-treatment sensorimotor maps showed significantly smaller basal ganglia activation compared to controls.

These results provide imaging evidence that abnormalities in sensorimotor integration extend beyond circuits controlling the affected body parts in cervical dystonia. The study also supports observations that botulinum toxin type A effect has a correlate at central nervous system level, and such effect may not be limited to cortical and subcortical representations of the treated muscles.

### **Abnormal somatosensory cortical activation in cervical dystonia and its modulation with botulinum toxin – a fMRI study**

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Converging data on focal dystonias suggest a widespread disorder of somatosensory processing. The aims of our study were, first, to assess somatosensory activation patterns in cervical dystonia beyond the representation of the affected body parts and, second, to search for task-related activation changes induced by botulinum toxin type-A (BoNT-A) therapy. Functional MRI during electrical median nerve stimulation was employed in seven cervical dystonia patients and nine controls; the examination was repeated five weeks after BoNT-A application to dystonic neck muscles. The pre-treatment activation map of patients showed activation in the contralateral primary somatosensory cortex, but missing activation in the secondary somatosensory cortex and insula, in contrast to controls and patients after treatment. Clinically significant effect of BoNT-A therapy was associated with a significant increase of BOLD response in the contralateral secondary somatosensory, insular and inferior parietal cortices. The post-treatment somatosensory maps of patients did not significantly differ from controls. This study has provided evidence of widespread disruption of somatosensory processing in cervical dystonia and its modification with BoNT-A therapy.