Non-motor symptoms in patients with isolated idiopathic and inherited dystonia

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Non-motor symptoms in patients with isolated idiopathic and inherited dystonia

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To my beloved family
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**Manuscript I: Subtle sensory abnormalities in patients with isolated idiopathic and hereditary dystonia**

L. Paracka did the conception and design of the study, recruited subjects, collected data, performed statistical analysis, interpreted the data and wrote the manuscript. F. Wegner concepted and designed the study, recruited the patients, collected and interpreted data and contributed to the manuscript. C. Blahak, M. Karst and D. Dressler recruited the patients, collected data and approved the manuscript. J. Krauss supervised the research project, concepted and designed the study, recruited patients and contributed essentially to the manuscript.

**Manuscript II: Strategies to decrease injection site pain in botulinum toxin therapy**

L. Paracka concepted and designed the study, recruited the subjects, performed the testing, collected data, performed the statistical analysis, interpreted the data and wrote the manuscript. K. Kollewe and F. Wegner collected data and contributed to the manuscript. D. Dressler supervised the research project, interpreted the data, contributed essentially to the manuscript.
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Abbreviations list

BDI Beck depression inventory
BFM Burke-Fahn-Marsden Dystonia Rating Scale
BoNT botulinum neurotoxin
BP bodily pain
CDT cold detection threshold
CPT cold pain threshold
DBS deep brain stimulation
DMA dynamic mechanical allodynia
FI forearm ischemia
FKKS Frankfurt body concept scale
GH general health
GPe external globus pallidus
GPi internal globus pallidus
HDI Hamilton depression inventory
HDT hot detection threshold
HPT hot pain threshold
IS ice spray
LAC local anesthetic cream
MH mental health
MMT mini metal test
MPT mechanical pain threshold
MPTT mechanical pain threshold test
NOO nitrous oxide/oxygen mixture
PF physical functioning
PPT pressure pain threshold
PSP pain sensitivity for pinprick
QST quantitative sensory testing
RE role emotional
RP role physical
RPST repetitive pain stimulation test
SAKA acceptance of one’s body by the others
SASE aspects of outer appearance
SDIS dissimilatory body processes
SF social functioning
SGKB body concept towards the health
SIAS Social Interaction Anxiety Scale
SKEF bodily efficiency
SKKO body contact
SNpr substantia nigra pars reticularis
SPBF care towards the body and functionality to taking care about the body
SPIN Social Phobia Inventory
SSAK self-acceptance of the body
SSEX sexuality
STN nucleus subthalamicus
TDT tactile detection threshold
TSL thermal sensory limen
TWSTRS Toronto Western Spasmodic Torticollis Rating Scale
V vitality
VT vibration threshold
WUR wind-up ratio
1. Introduction

1.1 Definition

*Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation* (Albaneze et al. 2013b). This disease was first interpreted in 1911, when children of one family with evidence of involuntary movements (Oppenheim 1911) and "progressive torsion spasms" (Flatau 1911) were described. However, its clinical recognition was officially obtained in 1975 during the First International Symposium on Dystonia in New York, after which focal forms of dystonia such as blepharospasm, writer’s cramp and torticollis were acknowledged (Marsden 1976a,b,c).

1.2. Classification of dystonia

According to the new classification all dystonias are classified along two axes: clinical characteristics and etiology (Balint and Bhatia 2014; Albanese et al. 2013). Clinical characteristic represents the phenomenology of dystonia in a patient. It includes age of onset, body distribution, temporal pattern and association with other disorders. The second axis represents the etiology of dystonia and it covers anatomical changes (degeneration, structural change or neither) and pattern of inheritance (inherited, acquired and idiopathic). Primary dystonias include inherited dystonias and all idiopathic dystonias. Secondary dystonias are dystonias that manifest from other disease states or brain injury (Table 1).
### Axis 1. Clinical characteristic

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Infancy (birth-2 years)</th>
<th>Childhood (3-12 years)</th>
<th>Adolescence (13-20 years)</th>
<th>Early adulthood (21-40 years)</th>
<th>Late adulthood (&gt;40 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body distribution</td>
<td>Focal</td>
<td>Segmental</td>
<td>Multifocal</td>
<td>Generalized</td>
<td>Hemidystonia</td>
</tr>
<tr>
<td>Temporal pattern</td>
<td>Disease course</td>
<td>Static</td>
<td>Persistent</td>
<td>Action specific</td>
<td>Diurnal</td>
</tr>
<tr>
<td>Associated features</td>
<td>Isolated</td>
<td>Combined with other movement disorders</td>
<td>Associated with other neurological disorders and systemic diseases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Axis 2. Etiology

<table>
<thead>
<tr>
<th>Nervous system pathology</th>
<th>Structural lesion</th>
<th>Degeneration</th>
<th>No evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of inheritance</td>
<td>Inherited</td>
<td>Autosomal-dominant</td>
<td>Autosomal-recessive</td>
</tr>
<tr>
<td>Aquired</td>
<td>Perinatal brain trauma</td>
<td>Toxic</td>
<td>Infection</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Sporadic</td>
<td>Familial</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. New classification of dystonia (modified from Albanese et al. 2013b)
1.3. Pathophysiology of idiopathic and inherited dystonia

As already mentioned before dystonia has different causes and they do not share the same pathways of pathogenesis. Specific groups of dystonia have certain biological impairments in the molecular, cellular, physiological and anatomical levels, which at the end produce the final outcome (Prudente et al. 2014). It is believed that basal ganglia modulate the movements through direct and indirect pathway. Briefly, the direct striatomedial pallidonigral pathway is activated by glutaminergic projections from sensorimotor cortex and by dopaminergic nigral pars compacta (SNpc)-striatal projections. Activation of direct pathway inhibits internal globus pallidus (GPi) and substantia nigra pars reticularis (SNpr) by inhibitory gamma-amino butyric acid (GABA) neurotransmitter. The GPi’s and SNpr’s lower inhibitory activity to the motor part of the thalamus results in the increased activity of the thalamic projections to the cortex. Higher firing frequency of neuronal groups in the cortex leads to the amplified activity in the corticostriatal tract and in muscles, respectively. On the other side, in the indirect pathway, dopamine binds to the D2 receptors of the striatum, which causes declination of inhibition on the external globus pallidus (GPe) and nucleus subthalamicus (STN), which in the next step activates cells in the GPi. GPi inhibits the motor part of thalamus through GABA transmission, which decreases the excitatory drive to the cortex. In dystonic patients there is an imbalance of direct and indirect pathway (when direct pathway is overactive or indirect pathway is underactive) that produces excessive movement and overflow of activity in muscles (Hallett 2006).

The neuroimaging studies have contributed in understanding the anatomical basis of dystonia. The recent studies have shown the increasing association of cerebellar abnormalities in the physiology of dystonia as well (Prudende et al. 2014; Shakkottai 2014; Sadnicka et al. 2012). Abnormalities in the basal ganglia and their circuits and
also in cerebellum were found in different types of dystonia in functional imaging studies even when the lesions were not detected by ordinary imaging techniques (Lehericy et al. 2013; Zoons 2011; Neychev et al. 2011; Pantano et al. 2011; Colosimo et al. 2005; Argyelan 2009; Carbon and Eidelberg 2009). Another fact that supports the involvement of basal ganglia in pathophysiology of dystonia are neurosurgical studies that have shown an improvement of dystonia by deep brain stimulation of the GPi and pallidotomy (Moro et al. 2013; Vidailhet et al. 2012; Gross 2008).

In addition, dopaminergic dysfunction is a common cause of dystonia. Abnormal dopaminergic release, a high level of dopaminergic neurons, non-responsiveness to L-dopa, disorders of dopamine synthesis or transport can induce dystonias with various phenotypes (Kurian et al. 2011; Fogel 2013; Balcioglu et al. 2007; Zhao et al. 2008; Page et al. 2010; Song et al. 2012). This suggests that the levels of dopamine either too much or to less, can cause dystonia (Breakefield et al. 2008).

There are three abnormalities that underlie the pathophysiological substrate in dystonia: loss of inhibition, defects in the somatosensory integration and deranged plasticity (Quartarone and Hallett 2013). Briefly, the surround inhibition is a neural mechanism which can sharpen the desired movement by inhibiting the activity in adjunct muscles (Beck et al. 2008; Berardelli et al. 1998). Surround inhibition is reduced in focal hand dystonia and may contribute to the difficulties in focusing motor command and to the overflow phenomenon (Beck et al. 2009; Hallett 2011). Furthermore, defects in sensorimotor integration involve defects in sensory and perceptual function. Basal ganglia and cerebellum play a role of filtering or “sensory gaiting” of the information that is passed to the motor system (Pastor et al. 2004). Abnormalities in the perception of sensory information have been demonstrated in temporal and spatial domains in focal, as well as in the generalized and inherited
dystonias (Tinazzi et al. 2009; Neychev et al. 2011; Molloy et al. 2003; Bara-Jimenez et al. 2000; Kimmich et al. 2014). Moreover, functional imaging studies have revealed abnormal somatotopic representation in the sensory cortex (Elbert et al. 1998; Meunier et al. 2001). Additionally, plasticity mechanisms that help the brain to adapt to the environment as a part of the learning process are abnormal in dystonic patients (Quartarone et al. 2008). Abnormal plasticity has been reported in basal ganglia, cerebellum and in cortex of the patients with dystonia (Quartarone et al. 2008; Rothwell and Huang 2004; Thompson and Steinmetz 2009).

In summary, pathophysiology of dystonia is convoluted involving both basal ganglia-thalamo-cortical and cerebello-thalamo-cortical networks. The role of each level of those circuits and their implication in the subtypes of dystonia still remains unclear.

1.4. Clinical features and diagnosis of dystonias

According to the guidelines of the European Federation of Neurological Societies (Albanese et al. 2011), there are a few major recommendations for diagnostics of dystonia. Recognizing clinical features of dystonia is the first step of managing the patients with dystonia since the clinical phenomenology remains the main basis for the diagnosis and there is no specific diagnostic test. Albanese and Lalli (2012) have proposed criteria and a structuralized flowchart on recognizing the features of dystonia. Those criteria are:

1. Dystonic postures are twisted along its longitudinal axis and there is a sensation of rigidity on the dystonic part of the body. This does not comply for blepharospasm or laryngeal dystonia (Albanese and Lalli 2012).

2. Dystonic movements are involuntary and they may be twisting or a pull in a preferred direction with repetitive and patterned altitude and are often prone to
lessen when a given posture is identified (“null point”). They may be fast or slow and may appear as tremor, chorea, tic or myoclonus.

3. Geste antagoniste is a voluntary physical gesture or position which temporarily improves the dystonic posture (Poisson et al. 2012), especially early in the disease course (Kagi et al. 2013). These movements are never forceful and they do not push or pull the body part, but they represent a simple touch of the eyelid, an eyebrow, a neck etc. The alleviation of dystonia lasts as long as the trick lasts or reverses unconstrained slowly before its end.

4. Mirror movements are dystonic movements of the less affected side with dystonia, which happen during the repetitive tasks of the affected side of the body (finger tapping, writing, painting etc).

5. Motor overflow is a muscle contraction which accompanies, but is anatomically distinct from the primary dystonic movement (Sitburana et al. 2009; Jedynak et al. 1991). It can be observed at peak dystonic movements, ipsilaterally or contralaterally, by inspection or EMG (Albanese et al. 2003).

The movement disorder society (MDS) Task Force on Rating Scales for Movement Disorders Steering Committee identified 7 out of 36 scales and questionnaires who meet the requirements to rate the motor symptoms of dystonia. The best identified scale to rate the generalized dystonia is Burke-Fahn-Marsden Dystonia Rating Scale (BFM). Cervical dystonia can be best rated with Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and cervical dystonia impact scale (CDIP-58). Blepharospasm Disability Index (BSDI) for blepharospasm and Craniocervical Dystonia Questionnaire (CDQ-24) for cervical dystonia and blepharospasm also meet the criteria of the task force (Albanese et al. 2013).

After the recognition of dystonia, it is important to identify the specific type of dystonia according to the classification scheme (Table 1) in order to provide the appropriate
management and treatment. When inherited dystonias are suspected genetic testing should be performed.

Neurophysiological studies are not recommended for clinical diagnostics of dystonia but may be used for clinical assessment by showing simultaneous activation of agonist and antagonist muscles.

Brain imaging is not necessary for diagnosis of classical idiopathic dystonia. Computerized tomography may reveal calcium and iron accumulation, magnetic resonance imaging may help to identify the acquired dystonias (Meunier et al. 2003; and pre-synaptic dopaminergic scan (DAT-SPECT or $^{18}$F-DOPA-PET) is useful to diagnose Parkinson’s disease with dystonia and L-dopa responsive dystonia. This may help to specify the tremor as well.

1.5. Treatment of dystonia

1.5.1. Botulinum toxin

Botulinum neurotoxin (BoNT) is considered the first line treatment for the focal dystonias. It has a well controllable paralyzing effect on muscles. There are three approved BoNT A medications: OnabotulinumtoxinA (onaBoNT-A), incobotulinumtoxinA (incoBoNT-A) and AbobotulinumtoxinA (aboBoNT-A). One approved BoNT type B medication (rimabotulinumtoxinB (rimaBoNT-B) is recommended when antibodies against BoNT-A occur. According to the American Academy of Neurology guidelines update summary (Simpson et al. 2016), BoNT is shown to be effective in cervical dystonia, blepharospasm and upper limb dystonia. In action specific dystonia (writer’s cramp) the effect of the treatment may not be optimal, since the therapeutic area is narrow in the forearm (Dressler et al. 2015a). Therefore, ultrasound and EMG guided injections are useful to enhance the accuracy of the treatment of musician’s dystonia (van Vugt et al. 2014; Schuele et al. 2005).
Apart from the focal dystonias, the high-dose therapy has been introduced to treat the more widespread dystonias (Dressler et al. 2015b). The disadvantage of BoNT treatment is that the injection site pain during the treatment may reduce the compliance especially after injections in the hand muscles and in children. Moreover, effect of the treatment lasts 8-12 weeks and the treatment has to be repeated regularly.

1.5.2. Deep brain stimulation (DBS)

Long-term electrical stimulation of the internal globus pallidus is considered an effective treatment for dystonias (Krauss et al. 2004). It is mostly indicated in the generalized dystonias or segmental forms, complex cervical dystonia, tardive dystonia and where botulinum toxin was refractive to relieve symptoms (Kupsch et al. 2006; Capelle and Krauss 2009). In generalized dystonias GPi DBS brings relief of symptoms in a range from 40-80 %. In a two year retrospective follow-up study of GPi DBS patients, excellent motor and functional outcome was found (Isaias et al. 2008, 2009; Cif et al. 2010). Young patients with primary dystonia and tardive dystonia, with shorter duration of the disease, have a better outcome of the pallidal DBS (Moro et al. 2013; Mehdorn 2016). However, in children with secondary dystonia the effect of the GPi DBS is controversial (Loher et al. 2001; Eltahawy et al. 2004;Krause et al. 2006; Alterman et al. 2007; Roubertie et al. 2012). GPi DBS in the secondary dystonia has shown a less positive effect, presumably because it is a more complex disorder and the DBS targets may be lesioned and dystonia is progressive (Welter et al. 2010; Vidailhet et al. 2012).

The mechanism of action of deep brain stimulation is not fully understood. It is believed that DBS influences the targeted structures and surrounding pathways, resulting in excitatory and inhibitory effects that modulate the basal ganglia-thalamo-
cortical pathway. This prevents oscillatory activity and bursts resulting in improved processing and reduction of disease symptoms (Huston et al. 2011; Hu and Stead 2014). Other targets for DBS in dystonia than GPi have also been suggested. Ostrem et al. (2011) have reported positive outcome of bilateral STN stimulation in 9 patients with cervical dystonia. The stimulation of ventral intermediate nucleus has also been suggested for the dystonias with tremor, when tremor is the more disabling part of the disease (Morishita et al. 2010).

1.6. Processing sensory information from skin to the cortex

Afferent inputs come from the specialized receptors that are located in the skin, subcutaneous tissue, muscle, joints and viscera. They include nerve endings in the skin associated with specializations that act as amplifiers or filters, and sensory terminals associated with specialized transducing cells that influence the ending by virtue of synapse-like contacts (Purves et al. 2001). Skin and subcutaneous receptors can be divided into three groups: mechanoreceptors, nociceptors and thermoreceptors depending on their selective sensitivity to respective stimuli (Light and Perl 1993, Sinclair 1981). Mechanoreceptors are specialized to sense mechanical forces from the skin and subcutaneous tissue. Thermoreceptors and nociceptors represent branching nerve endings of the unmyelinated Aδ and C sensory fiber system. They are located in the dermis and epidermis and have a role in transmitting pain and temperature sensations. Proprioreceptors are located in the skeletal muscles, tendons and fiber capsules of the joints. They provide information about the joint angle, muscle length, muscle tension and allow postural information about the limbs. Hence, different qualities of sensations are processed by different sensory fiber system. C sensory fiber system processes cold detection partly cold
and hot pain threshold and thermal sensory limen (ability to detect fast changes of the temperature). Aδ fibre system processes hot detection, hot and cold pain threshold, crude mechanical touch and thermal sensory limen. Aβ fibre system processes light touch, vibration, pressure and dynamic mechanical allodynia (Campbell et al. 1988, Beissner et al. 2010). After the receptors are irritated and the action potential is induced, sensory transduction through the peripheral nerve is triggered. The information is further carried on depending on the receptor system that has been triggering the action potential. There are two sensory pathways that convey information from the peripheral sensory nerve to the cortex. Fine touch, vibration, two-point discrimination, position sense of the joints are transmitted by the posterior column medial lemniscus pathway (PCML). Briefly, in PCML, the first order neurons carrying proprioceptive or touch information synapse at the gracile and cuneate nuclei of the medulla, axons from secondary order neurons decussate at this level and travel up the brainstem to the cells of ventral posterior lateral nucleus (VPL) of the thalamus (Davidoff 1989, Nathan et al. 1986). These cells as part of the third order neurons, project to the primary somatic sensory cortex (Fig. 1A).

![Fig. 1. Major pathways for sensation. (a) Spinothalamic tract. (b) Posterior column medial lemniscus pathway. (Adopted from © 2011 Pearson Education, Inc)](image_url)

The second pathway that carries sensory information is the spinothalamic tract (anterolateral tract). The anterior part of the tract carries information about crude touch and the lateral part conveys information for pain and temperature.
Neurons of the dorsal root ganglion after entering the spinal cord, ascend and descend one or two vertebral levels and they synapse in the substantia gelatinosa of Rolando or the nucleus proprius. The second order neuron decussates to the other side of the spinal cord and travels up to the different nuclei of the thalamus, where they ultimately synapse with third-order neurons. The neurons of third order project to the primary sensory cortex, cingulate cortex and insular cortex (Ropper and Samuels 2009). (Fig. 1B, adopted from © 2011 Pearson Education, Inc.).
2. Objectives

For a long time dystonia has been considered a pure motor disorder (Tamura et al. 2008). Recent evidence has postulated several non-motor features that accompany dystonia (Stamelou et al. 2012; Peall et al. 2015; Conte et al. 2016; Kuyper et al. 2011). Sensory tricks or “geste antagoniste”, the voluntary movements that temporarily improve dystonic posture or movement, indicate that afferent sensory inputs are affected in the patients with dystonia (Quartone and Hallett 2013; Muller et al. 2001; Schramm et al. 2007). Discomfort, pain and kinesthetic sensations can be observed weeks or months before the dystonia appears (Martino et al. 2005), although neurophysiological studies (neurographies and somatosensory evoked potentials) show no impairments also in the late stage of the disease (Abbruzzese et al. 2003). Basal ganglia and cerebellum have an influence in filtering or “sensory gaiting” the sensory information that is transmitted to the motor system (Kaji et al. 2001; Murase et al. 2000; Oulad Ben Taib et al. 2005). Since in dystonia there is a disruption in the striato-thalamo-cortical-pathway it is not surprising that there are impaired sensory and perceptual defects. Although there is a lot of evidence that there are sensory abnormalities, the relationship between dystonia and sensory abnormalities remains unclear. Moreover, the association of different qualities of sensations that are carried by C, Aδ and Aβ sensory systems with idiopathic and hereditary dystonia has not been revealed yet. Furthermore, it is uncertain if these sensory impairments are correlated to the age and to severity of motor symptoms.

The first line treatment of focal idiopathic dystonia is botulinum toxin. This treatment is sometimes very painful, especially in the hand palm and on the foot soles. Since this treatment is related to procedural pain and distress, this may reduce its compliance (Paracka et al. 2015). Different analgesic procedures have been proposed to reduce the Injection Site Pain during the treatment (ice-spray, nitrous...
oxide, anesthetic cream), but there are no studies that compare all those procedures intra-individually.

There is emerging evidence that psychiatric symptoms are present in a higher prevalence in patients with primary dystonia. Due to the involvement of fronto-striatal pathways in mood and behavioral regulations (Eldar and Niv 2015), it is not surprising that mood instability and anxiety might occur in the dystonic patients. Involuntary movements and twisted postures in dystonic patients cause slowness of voluntary movement and substantial disfigurement. This may cause disability in the patient’s everyday life and dissatisfaction with physical appearance. Embarrassment from the patient’s physical appearance may interfere with the social interaction and cause social avoidance and isolation (Jahanshahi et al. 2005; Page et al. 2007; Lewis et al. 2008). It has been postulated that there is a higher risk of depression and anxiety in patients with idiopathic and isolated inherited dystonias (Lewis 2008; Heiman et al. 2004; Moraru et al. 2002; Lauterbach et al. 2004, Müller et al. 2002; Gundel et al. 2003; Jahanshahi 1990a,b). However, different aspects of body concept not related only to the physical appearance, but also the self-perception of the body, efficiency and dissimilatory processes have not been thoroughly assessed in these patients. Moreover, the correlation between different aspects of body concepts and the severity of motor symptoms is still unknown.

Hence, objectives of this study are: 1. To analyze different sensory modalities in patients with idiopathic and inherited dystonia by using Quantitative Sensory Testing in the areas that are affected and not affected by the motor disorder. 2. To correlate the sensory symptoms with the age of patients and severity of the disease. 3. To analyze sensory symptoms intraindividually by comparing the sensory modalities between sides more affected and less affected with motor symptoms. 4. To find the most potent analgesic procedure for injection site pain reduction during botulinum
toxin treatment. 5. To evaluate the non-motor symptoms in patients with inherited and idiopathic dystonia including mood, anxiety, quality of life and body concept.
3. Manuscript I

Subtle sensory abnormalities in patients with isolated idiopathic and hereditary dystonia

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Abstract

Sensory abnormalities are increasingly being recognized as an accompanying symptom in patients with isolated idiopathic dystonia. The aim of this study was to investigate whether sensory abnormalities could be related to age or the distribution of motor symptoms in patients with primary dystonia. For this purpose we recruited 20 dystonic patients from which 8 had generalized dystonia, 7 cervical dystonia and 5 segmental dystonia with arm/hand involvement in dystonia. The patients with involvement of the arm/hand in dystonia were divided into two groups: younger than 40 years (6 patients) and older than 40 years (7 patients). All patients with cervical
dystonia were older than 40 years. We used Quantitative Sensory Testing (QST) at the back of the hand in all patients and at the shoulder in patients with cervical dystonia. The main finding was impaired dynamic mechanical allodynia (DMA) and thermal sensory limen (TSL). The other impairments were characteristic of the subgroups. In hands of dystonic patients there was a significant increase for DMA and thermal sensory limen in comparison to 19 matched healthy controls. Patients younger than 40 years with arm/hand involvement in dystonia had a higher cold pain threshold (CPT) and DMA, but decreased hot pain threshold (HPT) and wind-up ratio (WUR). Older patients displayed a diminished cold detection threshold (CDT) and WUR and higher TSL and DMA. The alterations were present on the clinically more and less affected side, with a higher pronunciations on the side more affected with dystonia. Patients with cervical dystonia showed a reduced hot detection threshold (HDT) and CDT, enhanced TSL and DMA at the back of the hand, whereas the shoulder QST only revealed increased CPT and DMA. Thus, in patients with primary dystonia QST clearly shows several significant sensory abnormalities which partly differed in age-groups and could also manifest in regions without motor symptoms.

Introduction

The dystonias are a heterogenous group of movement disorders that are defined by the nature of their abnormal movement (Jinnah et al. 2015). According to the modern definition, dystonia represent a movement disorder, which is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation (Albanese et al. 2013).
Idiopathic dystonia has been regarded as a basal ganglia disease and its circuits. The pathophysiology of dystonia still remains unclear, but several mechanisms, such as decreased inhibition, altered plasticity and dysfunction of oscillatory activity appear to be involved (Quartarone and Hallett 2013). In addition, there is evidence of involvement of sensory systems in the pathophysiology of dystonia. Imaging and electrophysiological studies have revealed abnormalities in sensorimotor networks (Carbon et al. 2008; Hallett 2006) and cerebello-thalamo-cortical pathways (Sako et al. 2015; Argyelan et al. 2009).

Dystonic patients often complain about pain, although the clinical examination and neurophysiological testing remains normal (Abbruzzese et al. 2003). They use certain maneuvers in order to temporarily improve the motor symptoms. This phenomenon has been recognized as sensory trick (e.g. geste antagoniste), suggesting an important role of the sensory system in the complex pathophysiology of primary dystonia (Berardelli et al. 1998).


Hence, we investigated the somatosensory integrity in patients with primary dystonia using quantitative sensory testing (Rolke et al. 2006a). This method allows the investigation of different sensory qualities such as heat, cold, paradox sensations (the ability to differentiate the warmth and cold), touch, pain, pressure and vibrations, which are transmitted by Aβ, Aδ and C fibers in the periphery. The aim of the study was to assess sensory processing in patients with isolated primary dystonia in relation to the patients’ age and motor symptoms.
Methods

Subjects

Twenty patients (10 men, mean age±SD 51.2±17.2 and 10 women mean age±SD 55.5±21.3) and 19 age and sex matched controls (10 men mean age±SD 49.3±18.7 and 9 women mean age±SD 48.1±19.0) were included in the study. Eight patients had generalized dystonia, five segmental dystonia with arm/hand involvement, and seven patients showed isolated cervical dystonia. Two of the patients had genetically proven DYT1 hereditary dystonia. The other patients were classified as idiopathic dystonia. According to the German Network for Neuropathic Pain sensory modalities are age dependant and the cut off age of 40 years has been proposed (Rolke et al. 2006b). Hence, the patients were divided in the subgroup older than 40 years and the subgroup younger than 40 years. Six patients with generalized dystonia were younger than 40 years, including the two patients with DYT1 dystonia. The other patients together with those with cervical dystonia and segmental dystonia were older than 40 years. Three of seven patients with cervical dystonia reported shoulder or neck pain, otherwise there were no pain symptoms or overt sensory deficit. Exclusion criteria were polyneuropathy, cognitive disturbances or any other neurological disease. Since the sensory perception may be influenced by botulinum toxin treatment, the patients who received botulinum toxin within six months prior to the testing were excluded from the study. All patients and controls signed written informed consent. The ethics committee of Hannover Medical School approved this study.

Neurophysiological and clinical assessment

In all patients standard nerve conduction velocity measurements to assess large myelinated fibers was performed. Neurographies and nerve conduction velocities
conducted from ulnar, radial and sural nerves were normal in all patients. Somatosensory evoked potentials were performed to exclude central sensory pathway disturbance. The Burke-Fahn-Marsden Dystonie Rating Scale (BFM) was used for all patients and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) in patients with cervical dystonia. Hand and arm dystonia was scored using the BFM motor subscore for arm (0-16); arm/hand with the higher score was characterized as clinically more affected side, the arm/hand with the lower score as clinically less affected. Because of the bilateral involvement in cervical dystonia, the shoulder was staged as one entity (the mean of both sides) for further analysis and compared to controls. BFM and TWSTRS scores are expressed as means±SD.

**Quantitative sensory testing**

In all patients the quantitative sensory testing (QST) battery was applied according to the protocol of the German Research Network of Neuropathic Pain (Rolke et al. 2006b). QST allows the assessment of specific myelinated Aδ- and unmyelinated C-fibers for temperature and pain, but also the evaluation of touch and vibration eliciting activity in large myelinated Aβ-fibers. It allows testing of sensory modalities not assessable by conventional neurophysiological methods. QST uses various stimuli to investigate the different sensory modalities such as the thermal test, mechanical stimuli (pinprick set), stimuli for touch (Fray Hair filaments, cotton wool, Q-tip, brush), vibration (tuning fork) and pressure (pressure pain algometer).

The testing of patients with arm/hand involvement in dystonia was compared to the side less affected by motor symptoms of dystonia and to the normal values of healthy controls. Since cervical dystonia most frequently involves bilateral contraction of neck muscles, the mean QST parameters of both shoulders were calculated and compared to age matched controls. In patients with cervical dystonia assessment
involved also QST of non-dystonic hands. In this case, the mean of both sides for all sensory profiles was compared to the values of healthy controls. Twelve tests were performed as previously described (Rolke et al. 2006a). Shortly, thermal thresholds were measured with the thermal sensory analyzer (MEDOC, Ramat Yishari, Israel). The cold detection threshold (CDT) and hot detection threshold (HDT) were registered with decreasing or increasing temperature stimuli, respectively, that were applied with a thermode of 3cm². The baseline temperature of the thermode was 32ºC, it increased and decreased the temperature by 1ºC/sec. For detection thresholds, subjects were asked to press the stop button in the moment they perceived the warm or cold stimuli. The same procedure was used for the thermal sensory limen (TSL), a test of paradoxical heat sensations, only that the changes of the temperature in the thermode was done consequently after the stop button was pressed and the patients had to indicate verbally if it was warm or cold. The TSL is designed to test paradoxical heat findings and the capability to detect fast changes of the temperature. The cold and hot pain thresholds (CPT, HPT) were measured by pressing the stop button when the sensation for cold or warm reached a painful sensation (range 0ºC to 50ºC).

The tactile detection threshold (TDT) was recorded with a set of Frey filaments (OptiHair MARSTOCKnervtest, Marburg, Germany) which exert forces of 0.25 to 512 mN. The patients had to indicate if they felt the stimuli with their eyes closed. The filaments with smaller forces were gradually introduced and the threshold was recorded where they lastly did not perceive any sensation. The final value was the geometrical mean of 5 series of ascending and descending stimuli.

The mechanical pain threshold (MPT) was registered with a set of weighted pinprick stimulators with a flat contact area of 0.25mm² diameter inducing pressure forces of 8, 16, 32, 64, 128, 256 and 512mN (MRC Systems, Heidelberg, Germany). Using this
set of stimulators and escalating the stimulation force from 8mN, subjects were asked to indicate the sharp sensation pain threshold. After determination of the sharp sensation pain threshold the stimulation force was gradually reduced to determine the dull sensation threshold. The ascending and descending stimuli were performed five times and limits for dull and sharp were registered. The MPT threshold was the geometrical mean of 5 series of ascending and descending stimuli (Baumgärtner et al. 2002).

The mechanical pain sensitivity to pin prick stimuli (PSP) and dynamic mechanical allodynia (DMA) was determined with a set of pinprick stimulators (MRC Systems, Heidelberg, Germany) and the following tactile stimulators: cotton wool (MEDIWOOD, megro GmbH, Wesel, Germany), a cotton Q-tip and a brush (Somedic, Hörby, Sweden). Sensitivity to sharp pin prick sensation and to tactile stimulators was determined. The subjects were asked to estimate the pain of the stimuli (pinprick and tactile stimulators) from 0 to 100, whereby 0 represents no pain (touch and no sharp sensation) and 100 represents the most unbearable intense pain. Every sharp sensation had to be evaluated with a value larger than 0. The final value was the arithmetical mean of the ratings across all stimuli (Baumgärtner et al. 2002).

The wind up ratio (WUR) was tested with the pinprick stimulator of 256 mN where single stimuli were compared to 10 pinprick stimuli repeated at a 1/sec rate. The testing was applied to five different skin sites (back of the hand or shoulder) and subjects were asked to rate the pain from 0-100. The final WUR value was the ratio between the 5 trains of 10 pinprick stimulations and 5 single stimuli.

The vibration detection threshold (VT) was determined with a Rydel Seiffer fork (c64 Hz, 8/8 scale) placed at processus styloideus ulnae or the acromion. The testing was repeated 3 times and the final value was the arithmetical mean of 3 sensations.
The pressure pain threshold (PPT) represents the tenderness resistance of the muscles. PPT was recorded by pressure pain algometry (Somedic Algometer, Hörby, Sweden). This device has the ability to quantify the tenderness of muscles. It contains a rubber disc with an area of $1\text{cm}^2$ that displays the pressure on a specific part of the body. The assessment was performed on M. abductor pollicis brevis and M. trapezius.

**Neuropsychological examination**

The patients and the controls underwent neuropsychological testing for cognition (Mini Mental Score) and attention (Trail Making Test) as such impairment may interfere with the results of the QST testing.

**Statistical analysis**

To determine the data distribution the Shapiro-Wilk test and visualisation assessment were performed. Normally distributed data were analysed as raw data and with 95% confidence interval. Non-normally distributed data were $\log_{10}$ transformed in order to reach the normalization. Test for normality was carried out in each sequence of the analysis and if $\log_{10}$ transformation was performed. To compare both sides to the normal values throughout different QST parameters, $z$-transformation was used for each subject according to the formula $z\text{-score}=(X_{\text{single patient}} - \text{Mean}_{\text{controls}})/\text{SD}_{\text{controls}}$. QST parameters for hand were first analysed for all patients ($n=20$), including patients with isolated cervical dystonia ($n=7$). The mean of both sides of the hands was compared to the mean of both hands of controls. Next, 13 patients with arm/hand involvement in dystonia were compared with controls in relation to the clinically more or less affected side and age. Additionally, the subgroups of patients older ($n=7$) and younger the 40 years ($n=6$) with arm/hand involvement in dystonia
were compared with controls in association with the clinically more or less affected side and age. The mean of both sides of the shoulder QST in patients with cervical dystonia was compared to the mean of the shoulder QST of the age matched controls. The same procedure was done in the hand QST for patients with cervical dystonia. Z-scores greater than 2 were reported as gain of sensory function and values below 2 were reported as loss of sensory function.

Correlation analysis between BFM and QST values of the hand and TWSTRS and QST values of the shoulder was performed with Spearman-Rho test. For statistical analyses and visualisation of data we used SPSS (IBM Deutschland, Ehningen, Germany). Two-sided p-values <0.05 were considered statistically significant.

Results

The mean BFM motor score for all patients was 16.4±9.3, (generalised 28.3±5.7, segmental 11.3±4.1, cervical dystonia 6.0±2.2). A significant difference (p=0.023) in the arm BFM subscore was registered comparing the more affected dystonic arm/hand (7.5±3.8) against the less affected arm/hand (3.7±2.8) in patients with involvement of arm/hand dystonia (n=13). The mean in TWSTRS motor score for patients with cervical dystonia was 8.6±2.5 (n=7).

There was no significant correlation between BFM and any QST score (Table 1). The correlation of TWSTRS with QST of the shoulder was insignificant as well (Table 1).

The hand QST was first analysed for all dystonic patients, including the patients with isolated cervical dystonia. As indicated above, in patients with cervical dystonia the mean of both sides was calculated and compared to the normal values.

The hands of dystonic patients showed a sensory gain for dynamic mechanic allodynia and thermal sensory limen in comparison to the matched controls (n=20, Fig. 1A, Table 2).
In order to analyse more homogenously the effect of dystonia in sensory functions, the patients with cervical dystonia were excluded during the next calculations. Compared to healthy controls the QST detected sensory loss for cold detection threshold on the clinically more affected side, as well as sensory gain for dynamic mechanical allodynia bilaterally (n=13, Fig. 1B, Suppl. Table 1).

In the patients older than 40 (n=7, Fig. 1C, Suppl. Table 2) there was a sensory loss for cold detection threshold and wind up ratio, but increased sensitivity for thermal sensory limen and for dynamic mechanical allodynia. The QST in patients younger than 40 (n=6, Fig. 1D, Suppl. Table 3) showed increased sensitivity for cold pain threshold and dynamic mechanical allodynia whereas hot pain threshold and wind up ratio were reduced. There was no significant difference between clinically more or less affected sides in both age-groups.

In the hand QST of the 7 patients with isolated cervical dystonia a sensory decrease for cold and hot detection thresholds was found as well as increased sensation for allodynia and thermal sensory limen compared to controls (Fig. 1E, Suppl. Table 4).

In the shoulder QST of 7 patients with cervical dystonia a higher score for cold pain threshold and dynamic mechanical allodynia was detected in comparison to controls (Fig. 1F, Suppl. Table 5).

Z-scores of the clinically more affected arm/hand showed a higher shift from normal than the clinically less affected arm/hand in all instances compared to controls (Fig. 1B-D). In the older dystonic patients the shift of the more affected arm/hand from healthy control level was much more apparent than of the less affected arm/hand (Fig. 1C). In younger patients the differences of z-scores between sides tended to be lower (Fig. 1D).
Fig 1. Means of z-scores of QST: A. Hand QST in all dystonic patients (n=20); B. Hand QST in patients with dystonic arm/hand involvement (n=13) after exclusion of cervical dystonia patients; C. Hand QST in patients older than 40 (n=7); D. Hand QST in patients younger than 40 (n=6); in all groups (B-D) there is no significant sensory difference between clinically more and less affected sides; E. Hand QST in patients with cervical dystonia (n=7); F. Shoulder QST in patients with cervical dystonia (n=7).

QST parameters: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), mechanical pain sensitivity for pinprick (PSP), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT). Z-scores higher than 2 are considered as sensory gain and z-scores below 2 are considered as sensory loss.
Discussion

Our study shows that QST may detect subtle sensory abnormalities in dystonic patients in absence of overt sensory symptoms. The alteration of sensory function was registered on modalities that are transmitted by C fibre (cold detection, partly cold and hot pain threshold and thermal sensory limen), Aδ fibre (hot detection, hot and cold pain threshold, thermal sensory limen) sensory systems (Beissner et al. 2010) and predominantly by the Aβ fibre (dynamic mechanical allodynia) sensory system (Campbell et al. 1988).

The main findings in the hand QST of all investigated patients was increased dynamic mechanical allodynia and thermal sensory limen. Some other sensory modalities (cold and hot detection, cold and hot pain threshold, thermal sensory limen and wind up ratio) were relevant for subgroups. Decreased sensations for cold and hot detection threshold confirm the abnormalities that were found in a previous QST study (Suttrup et al. 2011), although in our study there was no abnormality for mechanical pain threshold and pain sensitivity for pinprick in our patients. Moreover, our patients showed increased dynamic mechanical allodynia in comparison to controls, in contrary to the study by Suttrup et al. (2011), where none of the patients showed this impairment. In that study only patients with writer’s cramp were assessed and only the affected side with dystonic motor symptoms showed sensory abnormalities. In our study we have assessed patients with generalized, segmental and cervical dystonia. We have found sensory alterations on both sides at the back of the hand with a more accentuated distribution on the clinically more affected side, although there was no significant difference between sides. However, the findings were diverse in age-groups, the younger patients showed increased cold pain and decreased hot pain threshold, whereas we found reduced cold detection and enhanced thermal sensory limen in the older patients.
Interestingly, we detected subtle sensory impairments on hands of patients with isolated cervical dystonia. These findings suggest that sensory impairment in these patients is present regardless of the motor distribution of the disease contrary to the study from Suttrup et al. (2011), where only the clinically affected dystonic region showed deterioration of QST modalities. To our knowledge, for the first time the shoulder QST was done in patients with cervical dystonia. Our results showed increased dynamic mechanical allodynia and cold pain threshold compared to matched healthy controls suggesting that this localization is also suitable for further sensory examinations in patients with dystonia.

Dynamic mechanical allodynia enhancement was the most consistent finding in our investigated patients. It is a stimulus evoked pain (Sandkühler 2009) that is induced by light touch (brush, cotton wool and Q tip). However, our patients perceived those light stimuli as sharp, not as painful. They had only altered perception of the quality of the stimuli, not touch induced pain or hyperalgesia. Moreover, allodynia for punctuate stimuli (pain sensitivity for pinprick) was not found in our dystonic patients. Therefore, pathophysiological mechanisms that have been proposed for DMA in peripheral and central neuropathic pain or in post stroke pain cannot explain the impairment of this sensory modality in dystonic patients.

In addition, although we have demonstrated that the somatosensory processing is also impaired in clinically distant areas, the z-scores of the arm/hand more affected with dystonia showed a higher shift from the values of the controls than the arm/hand less affected by dystonia in all its domains. These findings were more expressed in the older patients, although they were not statistically significant. Interestingly, in younger patients the differences of z-scores between sides tended to be lower, which may suggest a slight enhancement of sensory subtle abnormalities with increasing age of dystonic patients.
There was no significant correlation between the motor score of the disease (BFM scale, TWSTRS) with QST parameters. This may indicate that there is a generalized subtle sensory deficit in dystonic patients independent from motor symptoms. Loss of sensitivity in temporal and spatial discrimination in patients with primary dystonia has been demonstrated in previous studies (Bara-Jimenez et al. 2000; Scontrini et al. 2009; Bradley et al. 2012, Hutchinson et al. 2013) and in the non-affected body regions as well (Molloy et al. 2003; Putzki et al. 2006; Fiorio et al. 2008). Abnormal spatial discrimination thresholds were found even in unaffected relatives (siblings and children) of patients with sporadic adult onset dystonia (Walsh et al. 2007, 2009). However, deficits in spatial discrimination threshold are not detected in DYT1 and DYT6 dystonic patients, which means that there is an endophenotypic trait of sensory abnormalities in patients with hereditary dystonia (Deik et al. 2012; Molloy et al. 2003). Moreover, the abnormalities in temporal perception of consecutive stimuli have been shown in unaffected DYT1 carriers, which implies that sensory deficits in dystonia are not a mere consequence of abnormal movements, but may occur before overt motor manifestations (Fiorio et al 2007). Additionally, botulinum toxin and GPi-DBS did not appear to normalise temporal discrimination threshold in patients with cervical dystonia, which means that this finding is likely to be causal in the genesis, rather than epiphenomena secondary to abnormal motor activity (Sadnicka et al. 2013, Scontrini et al 2011).

The mechanism of occurrence of these QST impairments is uncertain. Pathogenesis of dystonia could help understand the appearance of QST impairments in these patients. It is known that the defect in sensorimotor integration plays a major role in pathophysiology of dystonia (Quartarone et Hallett 2013). Basal ganglia have an important role in the modulation of sensory stimuli and a direct influence in the somatosensory integration (Kaji 2001; Graybiel 2004; Ding et al. 2010). Furthermore,
cerebellum receives input from the spinal cord and influences the somatosensory system (Oulad Ben Taib et al 2005; Daskalakis et al. 2004). Functional imaging studies have revealed abnormalities in basal ganglia, pathways to and from basal ganglia and also in cerebellum in dystonic patients, even when lesions were not evident by ordinary clinical imaging methods (Lehericy et al. 2013; Zoons et al 2011, Neychev et al. 2011; Argyelan et al 2009; Niethammer et al 2011; Carbon et al. 2010).

Furthermore, alterations in the somatosensory cortex related to deranged somatotopic representation, such as abnormal cortical finger representation and disordered homuncular arrangement were found in patients with focal dystonia (Catalan et al. 2012, Elbert et al. 1998, Bara-Jimenez et al 1998) and have been seen in both hemispheres as well (Meunier et al. 2001). Additionally, abnormal plasticity has been demonstrated in several types of dystonia (Quartarone et al 2008). Although plasticity is a normal property of the nervous system, maladaptive plasticity could occur as a result of intrinsic defects in plasticity mechanism or breakdown of these mechanisms (Neychev et al. 2011). Abnormal plasticity leads to changes in the connectivity of the sensory and motor networks resulting in abnormal sensory and motor functions.

These complex structural and functional changes of the brain of dystonic patients may contribute to the sensory alterations that we have detected with QST. Our findings may suggest that the deranged somatosensory integration and plastic changes can lead to the less reliable differentiation of somatosensory stimuli (dynamic mechanical allodynia, temperature thresholds) and slower detection of the sensation (thermal sensory limen), and that these abnormalities may partly increase with age of the patient. Whether these impairments are a consequence of a deficit of
global sensorimotor integration or of the specific levels of the loop, or even a process of maladaptive plasticity, remains unclear. Moreover, it is speculative if these QST changes represent a primary sensory lesion or a reaction to maladjusted central changes in the patients with dystonia. The further analysis of the separate subtypes of dystonia may elucidate the understanding of sensory impairment in these patients and the possible endophenotypic trait of sensory changes in the subgroups. Finally, future studies should be addressed to the clarification of the role of specific parts of the thalamo-striato-cortical and cerebello-thalamo-cortical pathways in the development of sensory changes in dystonic patients.

Conclusion
Subtle sensory abnormalities can be detected by QST testing in patients with primary dystonia. These impairments are partly age dependent and are not correlated with the severity of motor symptoms. Moreover, these findings can be detected regardless of the distribution of motor symptoms and are likely a characteristic of the disease.

References


Table 1. Correlation of Burke-Fahn-Marsden Dystonia Rating Scale (BFM) and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). P value is considered significant when \(p<0.05\). Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), mechanical pain sensitivity for pinprick (PSP), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).
Table 2. Hand QST of all dystonic patients (n=20) compared to matched healthy controls (n=19) showing the raw data and log transformed parameters of non-normally distributed data. QST parameters are given as means±SD. P values are related to raw data when the data are normally distributed and to log transformed data when they are non-normally distributed. Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), mechanical pain sensitivity for pinprick (PSP), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).

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<th>QST parameters</th>
<th>Dystonic patients raw</th>
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<th>Dystonic patients log</th>
<th>Controls log</th>
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Suppl. Table 1. Hand QST of patients with hand involvement in dystonia (n=13), after exclusion of patients with cervical dystonia only, compared to matched healthy controls (n=19). There is no significant sensory difference between patients’ clinically more affected and less affected arm/hand. QST parameters are shown as means ± SD. P values are related to raw data when the data are normally distributed and to log transformed data when they are non-normally distributed.

Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), mechanical pain sensitivity for pinprick (PSP), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).
Suppl. Table 2. Hand QST of patients older than 40 with hand involvement in dystonia (n=7) compared to age matched healthy controls (n=10). There is no significant sensory difference between patients’ clinically more affected and less affected arm/hand. QST parameters are shown as means ± SD. P values are related to raw data when the data are normally distributed and to log transformed data when they are non-normally distributed.

Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), pain sensitivity for pinprick (PSP) dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).

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<td>1.57±0.09</td>
<td>1.99±1.01</td>
<td>1.91±1.98</td>
<td>0.17±0.17</td>
<td>0.25±0.22</td>
<td>0.27±0.04</td>
</tr>
<tr>
<td>VDT(8)</td>
<td>7.11±0.58</td>
<td>7.39±0.68</td>
<td>7.58±0.61</td>
<td>0.25±0.15</td>
<td>0.15±0.17</td>
<td>0.12±0.16</td>
</tr>
<tr>
<td>PPT(kPa)</td>
<td>342.8±70.57</td>
<td>368.2±131.15</td>
<td>327.87±139.38</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
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</tbody>
</table>
Suppl. Table 3. Hand QST of patients younger than 40 with hand involvement in dystonia (n=7) compared to age matched healthy controls (n=10). There is no significant sensory difference between patients’ clinically more affected and less affected arm/hand. QST parameters are shown as means ± SD. P values are related to raw data when the data are normally distributed and to log transformed data when they are non-normally distributed.

Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), pain sensitivity for pinprick (PSP) dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).
<table>
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<th>QST parameter</th>
<th>Cervical dystonia</th>
<th>Controls</th>
<th>Cervical dystonia</th>
<th>Controls</th>
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<td>raw</td>
<td>raw</td>
<td>log</td>
<td>log</td>
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<tr>
<td>CDT(°C)</td>
<td>-2.03±1.08</td>
<td>-1.13±0.33</td>
<td>0.44±0.18</td>
<td>0.58±0.03</td>
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<tr>
<td>HDT(°C)</td>
<td>4.17±1.77</td>
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<td>0.58±0.21</td>
<td>0.28±0.148</td>
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<tr>
<td>TSL(°C)</td>
<td>5.65±2.21</td>
<td>2.89±0.99</td>
<td>0.44±0.18</td>
<td>0.58±0.03</td>
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<td>CPT(°C)</td>
<td>17.48±10.61</td>
<td>17.91±8.97</td>
<td>n.s.</td>
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<td>HPT(°C)</td>
<td>42.29±4.02</td>
<td>43.33±3.14</td>
<td>n.s.</td>
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<td>TDT(mN)</td>
<td>4.13±7.61</td>
<td>2.76±1.41</td>
<td>0.44±0.43</td>
<td>0.23±0.11</td>
<td>n.s.</td>
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<td>MPT(mN)</td>
<td>77.49±57.35</td>
<td>44.77±35.21</td>
<td>1.78±0.36</td>
<td>1.51±0.39</td>
<td>n.s.</td>
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<td>MPS</td>
<td>1.58±1.83</td>
<td>1.24±1.08</td>
<td>0.344±0.261</td>
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<tr>
<td>DMA</td>
<td>0.13±0.07</td>
<td>0.024±0.052</td>
<td>0.052±0.026</td>
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<td>WUR(ratio)</td>
<td>2.21±0.91</td>
<td>1.91±0.19</td>
<td>0.49±0.12</td>
<td>0.46±0.02</td>
<td>n.s.</td>
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<td>VDT(°8)</td>
<td>7.13±0.29</td>
<td>758±0.61</td>
<td>n.s.</td>
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<td>PPT(kPa)</td>
<td>330±86.38</td>
<td>327.87±139.38</td>
<td>n.s.</td>
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Suppl. Table 4. Hand QST in patients with cervical dystonia (n=7) compared to age matched healthy controls (n=9). The QST values represent the mean of both sides of the hands. QST parameters are given as means ± SD. P values are related to raw data when the data are normally distributed and to log transformed data when they are non-normally distributed. Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), mechanical pain sensitivity for pinprick (PSP), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).
Suppl. Table 5. Shoulder QST in patients with cervical dystonia (n=7) compared to age matched healthy controls (n=9). The QST values represent the mean of both sides of the shoulder. QST parameters are given as means ± SD. P values are related to raw data when the data are normally distributed and to log transformed data when they are non-normally distributed. Abbreviations: Cold detection threshold (CDT), hot detection threshold (HDT), thermal sensory limen (TSL), cold pain threshold (CPT), hot pain threshold (HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), mechanical pain sensitivity for pinprick (PSP), dynamic mechanical allodynia (DMA), wind up ratio (WUR), vibration threshold (VT), pressure pain threshold (PPT).
Strategies to decrease injection site pain in botulinum toxin therapy

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Key Words: Botulinum Toxin, Therapy, Injection Site Pain, Reduction

Abstract

Botulinum toxin (BT) is now used for numerous indications including dystonias, spasticity, cerebral palsy, hyperhidrosis, cosmetics and chronic migraine. It has to be injected into its target tissues thus causing injection site pain (ISP). We wanted to compare the efficacy of various analgesic interventions suggested for ISP reduction.

In 13 healthy controls pain thresholds in the fingertips II and III bilaterally were determined in the Mechanical Pain Threshold Test (MPTT) and the Repetitive Pain Stimulation Test (RPST) at baseline and under nitrous oxide/oxygen (NOO), ice spray (IS), local anaesthetic cream (LAC) and forearm ischaemia (FI).

All analgesic interventions studied produce statistically significant and robust analgesic effects in the MPTT and the RPST. NOO had stronger analgesic effects than the other interventions, although this superiority was statistically significant only in the RPST and not against IS.

Additionally considering duration, localisation and penetration depth of the analgesic effect, hyperhidrosis treatment may benefit from NOO, IS and LAC. In palmar hyperhidrosis FI is possible and also reduces BT washout. Cosmetic indications may
also benefit from NOO and LAC. For BT therapy of spasticity, dystonia and tremor
only NOO may offer intramuscular analgesic effect. Its systemic and prolonged effect
is also an advantage in wide-spread injections in several body parts.

Future studies are necessary to test the influence of penetration depth and
combinations of analgesic interventions.

Introduction

Therapeutic use of botulinum toxin (BT) has expanded into many medical specialties
where it is used for numerous indications including dystonias, spasticity, cerebral
palsy but also hyperhidrosis, cosmetics and chronic migraine. Due to its mode of
action and its biological properties BT has to be injected into its target tissues.
Depending on the particular target tissue, this can be unpleasant for the patient. Over
the years several methods have been proposed to reduce this injection site pain
(ISP). We wanted to compare the analgesic efficacy of some of them.

Methods

Design: The pain sensitivity of the index and third fingertip was investigated without
and with four analgesic interventions.

Subjects: 13 healthy controls (7 males aged 36.3±8.3y, 6 females aged 36.0±10.2y)
gave informed consent and were included in the study. All of them underwent
neurological examination, electroneurography and somatosensory evoked potential
testing to exclude sensory pathway abnormalities.
**Study parameters:** Pain sensitivity was the study parameter. It was measured as the pain threshold determined by the Mechanical Pain Threshold Test (MPTT) and by the Repetitive Pain Stimulation Test (RPST).

For the MPTT (Greenspan & McGillis 1991) the pain threshold was determined by a set of weighted pinprick stimulators with a flat contact area of 0.25mm in diameter producing pressure forces of 8, 16, 32, 64, 128, 256 and 512mN (MRC Systems, Heidelberg, Germany) on the fingertip. Escalating the pressure force subjects were asked to indicate when the sensation started to feel sharp (sharp threshold, given in mN). After determination of the sharp threshold the pressure force was then gradually reduced and the subjects were asked to indicate when the sensation started to feel dull (dull threshold, given in mN). This ascending and descending stimulation scheme was performed five times and all sharp and dull thresholds were registered. The MPTT pain threshold for each finger tip was the geometric mean of five ascending and descending stimulation schemes (Baumgärtner et al. 2002) calculated according to the formula: \[ GM_{y} = \sqrt[5]{y_1 \times y_2 \times \ldots \times y_n} \, . \]

MPTT pain thresholds were determined for fingertips II and fingertips III of both hands. The final MPTT pain threshold (given in mN) was the mean value of the MPTT pain thresholds for fingertip II and fingertip III on the right side and fingertip II and fingertip III on the left side. Final MPTT pain thresholds were calculated for the baseline, i.e. without analgesic intervention, and for each analgesic intervention. The analgesic intervention 'forearm ischemia' could not be tested with the MPTT, because of the duration of the testing procedure.

The RPST was also performed with the above described weighted pinprick stimulator set (MRC Systems, Heidelberg, Germany). Repetitive stimuli (2Hz for five seconds)
with increasing pressure forces of 8, 16, 32, 64, 128, 256 and 512mN were applied to the fingertip and subjects were asked to indicate at what pressure force pain was felt (pain threshold, given in mN). The final RPST pain threshold (given in mN) was the mean value of the RPST pain thresholds for fingertip II and fingertip III on the right side and fingertip II and fingertip III on the left side. Final RPST pain thresholds were calculated for the baseline and for each analgesic intervention.

**Analgesic interventions:** All subjects underwent a series of analgesic interventions after their baseline pain sensitivity was assessed. First analgesic intervention was application of an equiproportional fixed mixture of nitrous oxide and oxygen (NOO, Livopan®, Linde Gas Therapeutics, Unterschleißheim, Germany). NOO was inhaled by the subjects for 5 minutes before and throughout the testing procedure. Total inhalation time was usually 15-20min. Second analgesic intervention was ice spray (IS, Eisspray-ratiopharm 150ml). IS was applied 5s before testing and it was re-applied every 30s onto the fingertip. Third analgesic intervention was forearm ischemia (FI). For this the blood pressure cuff of a sphygmomanometer was positioned on the upper extremity over the biceps brachii muscle, set to a pressure of 20mm Hg over the systolic pressure and held for 5min. Fourth analgesic intervention was the application of a lidocaine 2.5%/prilocaine 2.5% local anaesthetic cream (LAC, Emla®, AstraZeneca, Wedel, Germany). LAC was applied 40min prior to the testing. During this period, subjects were instructed not to wash their hands and not to touch anything.

**Statistical Analysis:** To determine the data distribution the Shapiro-Wilk test and visualisation assessment were used. Normally distributed data were analysed by applying the One-way ANOVA test. For statistical analyses and visualisation of data, SPSS (IBM Deutschland, Ehningen, Germany) was used. Two-sided p values <0.05
were considered statistically significant. Comparisons were calculated between each analgesic intervention and the baseline and in between all analgesic interventions.

Results

The effects of the analgesic interventions on pain sensitivity as tested in the MPTT are shown in Figure 1. In the MPTT all patients responded to all analgesic interventions performed. NOO reduced the pain sensation from the baseline of 39±36.9mN to 190.14±96.6mN (p<0.001), LAC to 177.7±108.5mN (p<0.001) and IS to 173.4±111.3mN (p=0.001). There was no statistically significant difference between the analgesic effects of these analgesic interventions.

Fig. 1. Pain threshold in the Mechanical Pain Threshold Test (MPTT) under various analgesic interventions. All analgesic interventions tested produce a statistically significant reduction of the pain threshold. There was no statistically significant difference between the different analgesic interventions. Abbreviations: LAC (local anaesthetic cream), NOO (equiproportional fixed mixture of nitrous oxide and oxygen), IS (Ice spray). Median ± 95% confidence interval. *=p<0.05
The effects of the analgesic interventions on pain sensitivity as tested in the RPST are shown in Figure 2. In the RPST, again, all patients responded to all analgesic interventions. NOO reduced the pain sensation from the baseline of 96±39.25mN to 512±236.7mN (p<0.001), LAC to 256±92.32mN (p=0.008) and IS to 256±148.3mN (p=0.009). The FI reduction to 192±71.8mN (p=0.08) was statistically not significant. NOO showed statistically significant superiority over LAC (p=0.03) and FI (p<0.001) and a tendency against IS (p=0.08). No adverse effects were registered during the analgesic procedures.

Discussion

Several analgesic interventions have been proposed for ISP reduction during BT therapy including dermal application of local anaesthetic creams (Carruthers & Carruthers 2005) or ice spray (Elibol et al. 2007), forearm ischemia (Dressler 2000) and inhalation of nitrous oxide/oxygen mixtures (Paracka et al 2015). Our study is the
first comparing various analgesic interventions including NOO against each other. Our data show that all analgesic interventions studied produce statistically significant and robust analgesic effects in the MPTT and the RPST. Analgesic effects are similar. NOO, however, had stronger analgesic effects than the other interventions tested, although this superiority was statistically significant only in the RPST and not against IS.

A previously published study compared local anaesthetic cream, ice and vapocoolant spray and found comparable effects of ice and EMLA cream. However, spray did not offer pain relief (Fung et al. 2012).

Choosing an appropriate analgesic intervention for a specific procedure starts with a comparison of analgesic potency. Our study shows superior analgesic effects of NOO against LAC and FI and - as a trend only - against IS.

Other aspects shown in Table 1, however, also need to be discussed when choosing an appropriate analgesic intervention. Considering the duration of the analgesic effect, NOO and LAC produce continuous and long-lasting effects, whereas the effects of FI and IS are short-lasting. Concerning the localisation of the analgesic effect, NOO offers wide-spread systemic effects, whereas the effects of LAC, IS and FI are local. For anatomic reasons, FI can only be used in the forearm. Considering the penetration depth, NOO and FI may also reach deeper muscular tissues, whereas analgesic effects of LAC and IS seem to be more restricted to superficial tissues. NOO and LAC consume moderate costs and time, whereas cost and time consumption are low for IS and FI.
<table>
<thead>
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<th>Analgesic intervention</th>
<th>Duration of effect</th>
<th>Localisation of effect</th>
<th>Penetration depth</th>
<th>Costs</th>
<th>Time consumption</th>
<th>Use for botulinum toxin therapy</th>
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</thead>
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<td>NOO</td>
<td>long expandable</td>
<td>systemic</td>
<td>probably high</td>
<td>moderate</td>
<td>moderate</td>
<td>dermal applications, muscular applications</td>
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<tr>
<td>FI</td>
<td>short</td>
<td>regional forearm only</td>
<td>probably high</td>
<td>low</td>
<td>low</td>
<td>dermal applications, muscular applications</td>
</tr>
<tr>
<td>LAC</td>
<td>long</td>
<td>local</td>
<td>probably low</td>
<td>moderate</td>
<td>moderate</td>
<td>dermal applications</td>
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<tr>
<td>IS</td>
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<td>local</td>
<td>probably low</td>
<td>low</td>
<td>low</td>
<td>dermal applications</td>
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</table>

Table 1. Suitability of various analgesic interventions for botulinum toxin therapy. Abbreviations: LAC (local anaesthetic cream), NOO (equiproportional fixed mixture of nitrous oxide and oxygen), IS (Ice spray), FI (forearm ischaemia).

BT therapy of hyperhidrosis may benefit from NOO, IS and LAC. In palmar hyperhidrosis FI is possible and at the same time also reduces the BT washout at the injection site. BT therapy for cosmetic indications may also benefit from NOO and LAC as the targeted muscle tissue is very superficial and can easily be reached. Application of IS in facial cosmetic procedures may be difficult because of eye protection. For BT therapy of spasticity, dystonia and tremor, where skeletal muscles are targeted, NOO, LAC and IS may reduce the pain arising from the skin penetration, but only NOO may offer an additional intramuscular analgesic effect. NOO’s systemic effect also is an advantage when dystonia and spasticity requires wide-spread injections in several body parts.

For multiple dermal injections in pain sensitive areas such as the face, the palms and the feet and in children, use of appropriate analgesia is frequently required and - if offered - will increase the patient’s compliance to undergo BT therapy.

NOO shows superior analgesic effects and it also reaches deeper structures in comparison to the other analgesics giving it an advantage in muscular BT injections.
Additional analgesic strategies such as pH reduction of the reconstituted BT drugs may also be used (Dressler et al 2016).

Future studies are necessary to test the influence of penetration depth and combinations of analgesic interventions to further improve analgesic effects.

**Conflict of Interest:** The authors report no conflict of interest.

**References**


Psychiatric symptoms in patients with isolated idiopathic and inherited dystonia

Methods
Patients: The study was comprised of twenty patients (10 males aged 51.2±17.2 and 10 females aged 55.5±21.3 years) with the average disease duration of 11.47±16.27 years. Eight patients had generalized dystonia, five segmental dystonia, and seven patients showed isolated cervical dystonia. Two of the patients were diagnosed with DYT1 hereditary dystonia. All other subjects were classified as idiopathic dystonia. Exclusion criteria were dystonias related to other diseases. Patients were evaluated by Burke-Fahn-Marsden Dystonia Rating Scale (BFM) and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) motor examination to stage the disease severity. Informed consent to participate was obtained after the approval by the ethics committee of Hannover Medical School. Mini mental state test was done in all patients to evaluate cognitive impairment. Patients were asked to perform the standardized scales SF36 (quality of life), Beck depression inventory, social phobia scale, social phobia anxiety scale and Frankfurter body concept scale. The structural interview for Hamilton depression inventory was also used to objectively measure the mood.

Materials
SF36
The short form health survey is designed to survey the quality of life in medical outcome research (Ware et al 1992). SF36 is a multi-item scale that assesses physical and mental well-being including eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions (Ware et al. 1992). The values of dystonic patients were then compared to the normal values from the surveys that correspond to German population (Ellert et al. 1999, 2004; Ware et al. 1998).

Beck depression inventory (BDI)

BDI is a questionnaire, a self-rating depression inventory, consisting of 21 items that cover affective and somatic symptoms of depression (Beck et al. 1961). Scores between 0-9 represent no depression, 10-18 mild depression, 19-29 moderate to severe depression, and scores from 30-63 indicate severe depression (Beck et al. 1988). The test is designed in a way that the patients have to define how they felt in the past week.

Hamilton depression inventory (HDI)

HDI is a semi structured diagnostic interview, which is performed by a healthcare professional. It consists of 21 items and it contains somatic symptoms and relatively few affective and cognitive symptoms (Hamilton 1960; Williams et al. 2001, Shafter et al. 2006). Score of 0-7 indicates no depression, 8-16 mild depression, 17-23 moderate depression and 24 or higher severe depression (Zimmerman et al 2013).
Social phobia inventory (SPIN)

The SPIN is a 17-item self-rating scale for social anxiety disorder (social phobia). It includes 17 items assessing symptoms of social anxiety disorder (fear, avoidance, physiological arousal) (Connor et al. 2000). Scores less than 20 represent no social phobia, 21-30 mild, 31-40 moderate, 41-50 severe, 51 and above very severe social phobia.

Social interaction Anxiety Scale (SIAS)

SIAS measures social interaction anxiety and assesses anxiety during the interaction with others (friends, opposite sex, strangers). This includes fears of being inarticulate, sounding boring, sounding stupid, not knowing what to respond, and being ignored (Mattick and Clark 1998). It includes 20 items and scores higher than 43 represent probable social anxiety.

Frankfurt body concept scale (FKKS)

This scale evaluates the perception of the body image and self-concept, how the body and inner and outer appearance is perceived by the subject. It consists of 64 items, divided in 8 subscales: body concept towards the health (SGKB), care towards the body and functionality to taking care about the body (SPBF), bodily efficiency (SKEF), body contact (SKKO), sexuality (SSEX), self-acceptance of the body (SSAK), acceptance of one's body by the others (SAKA), aspects of outer appearance (SASE) and dissimilatory body processes (SDIS). Values for each subscore were compared with the mean score of the German population survey (Deusinger 1998).
**Statistical analysis**

Cut-offs for BDI, HDI, SIAS, SPIN classification were used to compare depression, social phobia and social interaction anxiety. An ANOVA test was used to compare the SF36 and FKKS subscores with the normal values. The correlation between motor scores (BFM and TWSTRS) and non-motor scales (BDI, HDI, SIAS, SPIN) and all subscores for SF36 and FKKS was done with Spearman-Rho bivariate correlation test. For statistical analyses and visualisation of data we used SPSS (IBM Deutschland, Ehningen, Germany). Two-sided p-values <0.05 were considered statistically significant.

**Results**

The mean age (±SD) of male patients with dystonia was 51.2±17.2 and of females was 55.5±21.3 years. Disease duration was 11.5±16.3 years. The mean BFM score of all patients and all subscores was 19.4±10.7. According to the mini mental state test, our patients did not show the signs of dementia (28.2±1.4).

Based on the evaluation of self-reported BDI and structuralized interview HDI, patients with idiopathic dystonia show signs of mild depression (12.0±7.2 and 8.1±5.1, respectively).

According to our results, a mild phobia (21.5±12.6) but no social interaction anxiety (21.3±16.9) was observed.

Compared to the general population, dystonic patients reported lower scores of quality of life in all areas (Fig. 1). The poorest score was registered for physical role (p=0.002), general health (p=0.005), social functioning (p=0.03), emotional role (p=0.025) and mental health (p=0.03) (Fig. 1). The physical summary score of quality of life (PCS) was 41.2±5.9, whereas mental score of quality of life (MCS) was 39.7±9.3.
Fig. 1. Quality of life in patients with dystonia in comparison to healthy controls presented as mean±SD. Abbreviations: Physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), role emotional (RE), mental health (MH). *p<0.05.

Body concept perceived by the patients was significantly impaired in seven of its domains in comparison to controls (Fig. 2): The lowest scores were registered for functionality of bodily care (p=0.006), body contact (p=0.002), sexuality (p=0.001), self-acceptance of the body (p=0.001), aspects of bodily appearance (p=0.0001) and dissimilatory processes (p=0.04).
Fig. 2. Frankfurt body concept scale in comparison to the healthy controls presented as mean±SD.

Abbreviations: Body concept towards the health (SGKB), care towards the body and functionality to taking care about the body (SPBF), bodily efficiency (SKEF), body contact (SKKO), sexuality (SSEX), self-acceptance of the body (SSAK), acceptance of ones body by the others (SAKA), aspects of outer appearance (SASE) and dissimilatory body processes (SDIS).*p<0.05

Table 1 summarises Pearsons correlations between BFM and depression, social phobia and social interaction anxiety, all subscales for SF36 and FKKS. The severity of motor symptoms had a significant effect on depression scores. There was a positive correlation of motor scores and HDI (p=0.04) and BDI (p=0.008). There was no significant correlation observed between motor scores and anxiety scores, subscores for SF36 and FKKS.
Table 1. Correlation of motor score BFM (Burke-Fahn-Marsden Dystonia Rating Scale) with mood scales, anxiety scales, body concept and quality of life.

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<td>Role emotional</td>
<td>0.43</td>
<td>0.08</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.39</td>
<td>0.66</td>
</tr>
</tbody>
</table>

In the next step, we wanted to determine how depression in dystonic patients is related to anxiety, body concept and quality of life, depression scores were correlated with the social phobia scores and subscores of quality of life and Frankfurt body concept scales. Depression scores showed significant correlations (p<0.01) with
social phobia inventory (p=0.01, r=0.52), subscores of SF36 (physical role p=0.003, r=-0.34; social functioning p=0.001, r =-0.24 and mental health p=0.002, r=-0.67) and subscores for FKKS (sexuality 0.0001, r=-0.57, aspects of physical appearance p=0.0003, r=-0.76 and dissimilatory processes p=0.007, r=-0.43).

In order to determine how body concept can affect the quality of life, different areas of body concepts were correlated with physical summary score of quality of life (PCS 41.2±5.9) and mental score of quality of life (MCS 39.7±9.3). In our patients, lower physical summary score was determined by lower ability to take care of the body (p=0.002, r=0.53), lower body contact (p=0.0001, r=0.63) and dissimilatory processes (p=0.0004, r=0.23). The decreased ability to accept the body (p=0.01, r=0.32), reduced self-perceived sexuality (p=0.0029, r=0.54) and physical appearance (p=0.007, r=0.43) affect the mental score of the quality of life. These results show how strong the psychological symptoms influence the quality of life in dystonic patients.

Finally, there was no correlation between anxiety scores and SF36 and FKKS.
6. General discussion

Several studies have revealed that primary dystonia apart from being a movement disorder is related to many non-motor features (Peall et al. 2015; Stamelou et al. 2012; Fabbrini et al. 2010; Kuyper et al. 2011). In this study we investigated the sensory symptoms by using the Quantitative Sensory Testing to assess sensory processing in patients with isolated primary dystonia in relation to the patients’ age and motor symptoms. Moreover, since the treatment with botulinum toxin in dystonic patients is sometimes associated with pain in the injected region, we compared the analgesic potency of several methods such as ice spray, nitrous oxide/oxygen mixture, anesthetic cream and forearm ischemia to reduce injection site pain. Finally, we examined psychiatric symptoms in dystonic patients such as mood, anxiety, body concept and also their impact for the quality of life.

In the first part of the thesis, we demonstrated several subtle sensory abnormalities in patients with isolated idiopathic and hereditary dystonia which we detected using the Quantitative Sensory Testing (QST). We focused more on the specific qualities of sensations which require higher differentiation of the stimuli and these findings were analyzed in relation to the disease severity and age-dependency. The tested areas were the back of the hand for all patients and shoulder for patients with cervical dystonia. We investigated twelve sensory modalities, such as: Cold and hot detection threshold (CDT and HDT), thermal sensory limen (TSL), cold and hot pain threshold (CPT and HPT), tactile detection threshold (TDT), mechanical pain threshold (MPT), dynamic mechanical alldynia (DMA), pain sensitivity for pinprick (PSP), wind-up ratio (WUR), vibration threshold (VT) and pressure pain threshold (PPT). The main finding was impaired DMA and TSL, whereas the other modalities were relevant for subgroups (CDT, HDT, CPT, HPT, WUR). The impairments were found at the back of the hand and at the shoulder.
DMA is pain in response to a non-nociceptive stimulus (Sandkühler 2009). Although our patients did not perceive the light stimuli (brush, Q-tip, cotton wool) as painful, they perceived them as sharp, suggesting that there is an impairment of sensory perception in dystonic patients. Nevertheless, hyperalgesia for mechanical stimuli (pain sensitivity for pinprick) was not registered in our patients.

The patients older than 40 years showed impaired CDT, TSL, DMA and WUR, whereas the patients younger than 40 years showed abnormal sensitivity for CPT, HPT, DMA and WUR. The abnormalities were found on the side more affected and less affected with dystonia with the prevalent distribution on the clinically more affected side. Additionally, our study shows not only impairments on the shoulder QST, but also in the hand QST of the patients with isolated cervical dystonia, which suggests that the presence of the sensory abnormalities is independent from the dissemination of motor symptoms. This opposes the findings from Suttrup and al. (2011), who found impairments only on the affected side of their patients with writer’s cramp. We believe that these findings are different because the writer’s cramp as a task specific dystonia can hardly be compared with our sample of patients (generalised, segmental and isolated cervical dystonia) as they are heterogeneous in aetiology.

Although both sides in our dystonia patients displayed impairments in the QST values, the z-scores of the clinically more affected side showed a higher discrepancy from normal values than of the clinically less affected side. This was revealed mostly in patients older the 40 years. In the patients younger than 40 years the z-scores of the QST values tended to be similar on both sides. In addition, we tested the correlation of disease severity with the sensory symptoms in primary dystonia patients. For this purpose we compared the Burke-Fahn-Marsden Dystonia Rating Scale (BFM) and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
with QST values of the dystonic patients. Our results show no dependency of motor severity with the QST abnormalities which again indicates the overall impairment of the sensory processing in patients with primary dystonia.

Behavioural studies have shown that temporal and spatial discrimination are compromised in patients with various types of dystonia (Hutchinson et al. 2013; Bradley et al. 2012; Bara-Jimenez et al. 2000; Scontrini et al. 2009). These findings were confirmed in the clinically distant areas as well suggesting that abnormal sensory processing is a fundamental disturbance in patients with primary dystonia (Molloy et al. 2003; Putzki et al. 2006; Fiorio et al. 2008). The absence of impairment for spatial discrimination in patients with DYT1 and DYT6 dystonia indicates that specific sensory impairments may have an endophenotypic trait of the disease. Moreover, abnormal temporal discrimination thresholds in non-manifesting relatives of patients with DYT1 (Fiorio et al. 2007) and adult onset sporadic primary dystonia demonstrate that sensory abnormalities may be a surrogate marker of the disease (Walsh et al. 2007).

Defects in the sensorimotor integration and abnormal plasticity have been proposed as pathophysiological mechanisms for dystonia and may explain the impairments in sensory perception in these patients (Perruchoud et al. 2014, Quartarone et al. 2008). Disability to coherently organize bodily sensations and motor responses might contribute to the alterations that we have detected with QST.

Our findings may suggest that the altered somatosensory integration and abnormal plastic changes can lead to the less reliable distinction of somatosensory stimuli (dynamic mechanical allodynia, temperature thresholds) and slower detection of the sensation (thermal sensory limen) and are partly age dependent. However, these changes are not correlated to the disease severity and to the distribution of motor symptoms.
In the second part of the thesis we compared the potency of different analgesic methods for reduction of injection site pain during treatment with botulinum toxin in dystonic patients. We wanted to find the most suitable method to achieve short-term modulation of pain which would facilitate the treatments that involve the areas that are known to be more sensitive such as palm of the hand and sole of the foot. For this purpose we compared the efficacy of ice-spray (IS), local anesthetic cream (LAC), nitrous oxide/oxygen mixture (NOO) and forearm ischemia (FI) with the mechanical pain threshold test (MPTT) test and repetitive pain stimulation test (RPST). Our data show that all analgesic interventions studied, produce statistically significant effects in the MPTT and the RPST. Analgesic effects in MPTT show similar potency of NOO, IS and LAC to reduce the injection site pain (ISP). However, in RPST, the stronger analgesic effects in comparison to LAC and FI was registered for NOO. This effect was not observed for IS. Although different analgesic methods have been proposed for ISP by using local anaesthetic cream (Carruthers & Carruthers 2005), nitrous oxide (Paracka et al. 2015), forearm ischaemia (Dressler 2000) and ice spray (Elibol et al. 2007), their limitation was that they did not compare the potency of different methods intraindividually. In our study we tested MPTT and RPST under different analgesic methods in healthy controls.

The choice of the appropriate analgesic during the botulinum toxin treatment should be made in relation to the region that is being injected and the properties of the analgesic method. IS and FI have a short lasting effect, in contrary to NOO and LAC that have long lasting effects. Furthermore, IS, FI and LAC have a local effect, whereas NOO shows systemic effects. However, considering penetration depth during the botulinum toxin treatment, NOO would be more effective for injection in the deeper structures such as skeletal muscles in dystonia, spasticity and tremor, because of its systemic effect, in contrast to LAC and IS which have superficial
effects. Additionally, LAC and NOO can be used for injections in the face. IS cannot be used in this region, because of the eye protection. Moreover, FI could be used only for injections in the hand and lower arm, because of anatomical reasons. Injection site pain should be considered in patients who are treated with botulinum toxin. A proper analgesic method could offer a better acceptance of the patient to undergo the treatment.

Psychiatric symptoms related to patients with idiopathic and inherited dystonia represent the third part of the thesis. Based on our results we confirm the previous reports that dystonic patients have increased risk of depression and that the severity of depression is not related to the disease duration (Fabbrini et al 2010). In our sample of patients, most of the patients were in the range of mild depression. There are different reports about the association of depression with the severity of dystonia. In a previous study (Lewis et al. 2008) the correlation between depression and the extent of dystonia was demonstrated, whereby patients with focal dystonia have lower depression scores than those with hemi-dystonia, segmental or multi-focal dystonia. Scheidt et al. (1996) have found a correlation between Tsui score for cervical dystonia and depression. On the other hand, several publications have not found a correlation between the depression and the severity of the disease (Gundel et al 2003, Fabbrini et al 2010). In the present study we correlated the depression scores with the overall dystonia motor score, regardless of the body part affected with dystonia. We have found that depression is correlated to the total BFM score according to both self-reported depression scale (BDI) and structuralized interview (HDI).

Moreover, our patients have reported higher prevalence of social phobia, which overlaps with the strong evidence of an increased rate of anxiety personality disorder including obsessive compulsive disorder and avoidant personality disorder in patients
with dystonia (Moraru et al, 2002, Cavallaro et al 2002, Gündel et al 2001). Increased prevalence rate of obsessive compulsive disorder in patients with dystonia was registered also in comparison to the healthy controls (Lencer et al 2009, Lehn et al 2014). In the present study the patients reported a mild social phobia, which is ranged in the lower level of the mild scale. In addition, the prevalence of social phobia is correlated to mood, but not to the severity of dystonia. Furthermore, in our sample of patients there was no reported social interaction anxiety and no extensive fear or embarrassment in common social interactions, in contrary to the other studies where a high prevalence of comorbidity of lower social coping in patients with dystonia was revealed (Gündel et al 2001). In a more recent study no higher prevalence of anxiety in patients with focal dystonia than in the general population was found (Fabbrini et al 2010). In contrary to these findings, in a study by Voon et al. (2010), a higher rate of anxiety disorder was registered in musicians with dystonia than in non-dystonic musicians. This can be explained by the greater psychiatric burden that the musicians with dystonia carry in contrary to the non-dystonic musicians (Conte et al 2016).

To our knowledge different qualities of body concepts have not been investigated thoroughly in patients with dystonia. In the previous studies body concept in dystonic patients was analyzed only in one of its components, e.g. the effect of the disfigurement in the other psychiatric symptoms (Lewis et al 2008, Gündel et al 2001). In our study we have assessed the overall body concept including cognitive and affective attitudes of body image. Self-evaluation of body image and the components of the body concepts in dystonia patients were impaired in our study. The attitude towards their bodily wellbeing is decreased. In addition, our patients perceive themselves unable to take care of their body and to improve its functionality suggesting a lack of attention and consideration of the body. Apart from the impaired
cognitive components of the body concept, there is the reduced affective dimension of the body image. Dystonic patients find the physical contact with others uncomfortable. Furthermore, their attitude towards their own attractiveness and sexuality is very low. Moreover, aesthetic aspects of their appearance and body processes make their body unacceptable to them.

Mood and body concept in dystonic patients seem to have an impact on each other, since patients with decreased self-evaluation of affective components of body concept have higher BDI and HDI scores. This means that the self-perceived dissatisfaction with the body image in dystonic patients may lead to depression. Interestingly, an impaired body concept does not necessarily lead to anxiety disorder, since there was no correlation between body concept dimensions and anxiety scores.

There is evidence that the extent of dystonia is correlated with lower quality of life. In a study done by Skogseid et al (2007), there was a correlation between TWSTRS and lower quality of life in patients with cervical dystonia. Page et al. (2007) revealed that the patients with generalized dystonia have lower quality of life than patients with focal dystonia. In the present study we had a mixed group of the dystonic patients, where BFM was the marker of severity of dystonia. Quality of life in our patients was not determined by the severity of dystonia, as there was no correlation between BFM score and areas of quality of life. The main impairments of the quality of life were observed in the physical role (functionality), concepts of general health, social functioning, emotions and mental health. Although in the previous studies depression and anxiety appear to have a significant negative effect on quality of life (Page et al 2007, Pekmezovic et al 2009, Ben-Shlomo et al 2002), we have found negative correlations of quality of life with depression only and not with the anxiety scores. Social phobia scale was not correlated to any of the quality of life domains. However, there is an increasing psychosomatic component which interferes with the quality of
life of the patients with dystonia. Disability to taking care of the body, discomfort and impaired body contact and also dissimilatory processes are correlated with the physical part of the quality of life scale. Lower self-acceptance of the body, lower self-esteem towards sexuality and lower physical appearance determine the psychological part of the quality of life. This means that quality of life in dystonic patients is aggravated by these internal conflicts.

Although we have reported the increased prevalence of non-motor symptoms such as depression, anxiety, decreased body concept and their effect on the quality of life, little is known about the management of these symptoms in dystonic patients. Therefore, it is important to recognize these non-motor symptoms early in the disease course, since with adequate therapeutical management the quality of life in these patients may increase again.
7. Summary

Lejla Paracka

Non-motor symptoms in patients with idiopathic and inherited dystonia

Dystonias represent a movement disorder which is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflowing muscle activation. Idiopathic dystonia has been regarded as a basal ganglia disease and its circuits. The pathophysiology of dystonia still remains unclear, but several mechanisms, such as decreased inhibition, altered plasticity and dysfunction of oscillatory activity appear to be involved. Apart from being known as a motor disorder, there is a growing evidence of occurrence of non-motor symptoms in patients with primary dystonia. This is not surprising due to the involvement of the cortico-striato-thalamo and cerebello-thalamo-cortical pathways in the pathophysiology of dystonia.

In the first part of the study, we detected several sensory abnormalities by using quantitative sensory testing (QST) in twenty patients with primary dystonia (8 general, 5 segmental and 7 isolated cervical dystonia). The QST was performed at the back of the hand in all patients and at the shoulder in patients with cervical dystonia. The main findings were increased dynamic mechanical allodynia (DMA) and thermal sensory limen (TSL). DMA is a stimulus evoked pain, which is elicited by light touch, whereas TSL represents the ability to detect fast changes of the temperature. Our results show that younger patients with hand dystonia had a higher cold pain threshold (CPT) and DMA, but decreased hot pain threshold (HPT) and wind-up ratio (WUR), which represents pain threshold after repetitive stimuli. Older patients displayed a diminished cold detection threshold (CDT) and WUR as well as
higher TSL and DMA. The alterations were present on the clinically more and less affected side, with a higher pronunciation on the side more affected by dystonia. Patients with cervical dystonia showed a reduced hot detection threshold (HDT) and CDT, enhanced TSL and DMA on the back of the hand, whereas the shoulder QST only revealed increased CPT and DMA. Thus, in patients with primary dystonia QST clearly shows several subtle sensory abnormalities which partly differed in age-groups and could also manifest in regions without motor symptoms (manuscript submitted).

In the second part of the study, we tested the potency of different analgesic methods for reduction of injection site pain during treatment with botulinum toxin in dystonic patients. For this purpose we compared the efficacy of ice-spray (IS), local anesthetic cream (LAC), nitrous oxide/oxygen mixture (NOO) and forearm ischemia (FI) with the mechanical pain threshold test (MPTT) and repetitive pain stimulation test (RPST). Our data show that all analgesic interventions studied, produce statistically significant effects in the MPTT and the RPST. Most analgesic effects were similar, NOO, however, had stronger analgesic effects than the other interventions tested, although this superiority was statistically significant only in the RPST and not against IS. The choice of the appropriate analgesic method during the botulinum toxin treatment should be made depending on the region that is being injected and the properties of the analgesic method (manuscript submitted).

In the third part of the study, psychiatric symptoms such as mood, anxiety and body concept were examined in relation to the severity of the disease and quality of life in dystonic patients. Our results show that patients with dystonia have higher prevalence for mood instability and anxiety, but not for social interaction anxiety. Moreover, the depression was correlated to the severity of motor symptoms and to social phobia. Furthermore, we found impairments of the body concept in both
cognitive and affective subscores. In addition, there is an increasing psychosomatic component which interferes with the quality of life of the patients with dystonia. Mood and body concept have an impact on each other and negatively influence the physical and psychological part of the quality of life scale (manuscript in preparation).
8. Zusammenfassung

Lejla Paracka

Nicht-motorische Symptome in Patienten mit idiopathischer und hereditärer Dystonie


Im ersten Teil der Studie wiesen wir verschiedene sensorische Auffälligkeiten durch die Quantitative Sensorische Testung (QST) in 20 Patienten mit primärer Dystonie (8 generalisierte, 5 segmentale und 7 isolierte cervicale Dystonie) nach. Die QST wurde auf dem Handrücken in allen Patienten durchgeführt, in Patienten mit cervicaler Dystonie auch an der Schulter. Die Hauptergebnisse sind erhöhte Parameter für dynamic mechanical allodynia (DMA) und thermal sensory limen (TSL). DMA ist ein stimulusabhängiger Schmerz, der durch nur leichte Berührung induziert wird, TSL ist

der Botulinumtoxin-Therapie sollte von der zu behandelnden Region und den speziellen Eigenschaften der analgetischen Methode abhängig gemacht werden (Veröffentlichung eingereicht).

9. References:


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