Diplomarbeit

Structural MRI of the cervical spine in patients with cervical dystonia

eingereicht von

Carmen Isabella Höllein

Geb.Dat.: 13.01.1987

zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde
(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Neurologie

unter der Anleitung von

Univ. Prof. Dr. med. univ. R. Schmidt
Ass.-Prof. Priv.-Doz. Dr. med. univ. P. Schwingenschuh
Sen. Scientist Dr. med. univ. MSc P. Katschnig-Winter

Graz, 13.12.2013 Carmen Isabella Höllein

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 13.12.2013 *Carmen Isabella Höllein*

Danksagungen

An dieser Stelle möchte ich mich bei meinem Erstbetreuer Univ. Prof. Dr. Reinhold Schmidt sehr herzlich bedanken.

Besonders bedanken möchte ich mich bei meinen beiden Betreuerinnen Ass.-Prof. PD Dr. Petra Schwingenschuh und Sen. Scientist Dr. MSc Petra Katschnig-Winter für die hervorragende Betreuung, die Ausdauer und die zahlreichen Ratschläge. Auch für die Hilfe bei der Auswertung der Studie sowie die schnelle und professionelle Englischkorrektur bedanke ich mich herzlich.

Ein weiterer Dank geht an Dr. Stephan Seiler, der mir in allen klinischen Fragestellungen und bei den klinischen Untersuchungen eine große Hilfe war.

Bedanken möchte ich mich auch bei Univ.-Ass. DI Dr. Edith Hofer, die mich bezüglich der statistischen Auswertung sehr unterstützt hat.

Desweiteren bedanke ich mich bei den drei Radiologen, OA Dr. Dennis Bohlsen, Assoz. Prof. PD Dr. Christian Enzinger und OA Dr. Marton Magyar, für die Beurteilung der MRT-Bilder.

Meinem Bruder Florian möchte ich herzlich für die Hilfe bei der Formatierung und die vielen guten Ratschläge danken.

Zu guter Letzt gebührt mein besonderer Dank meinen Eltern, die mir während meines gesamten Studiums nicht nur in finanzieller Hinsicht, sondern auch mit Rat und Tat zur Seite standen. Für ihre Hilfe und Motivation zu jeder Zeit möchte ich mich besonders herzlich bedanken.

Index

Zusammenfassung

Einleitung: Die zervikale Dystonie, die häufigste Form der fokalen Dystonien im Erwachsenenalter, ist eine seltene Erkrankung. Nur wenige Studien befassen sich mit diesem Krankheitsbild, vor allem in Verbindung mit Ursachenforschung und Botulinumtoxin Behandlung. Ziel dieser Studie war es zu untersuchen, ob strukturelle Veränderungen im MRT der Halswirbelsäule bei PatientInnen mit zervikaler Dystonie im Vergleich zur Normalbevölkerung häufiger auftreten und in welchem Zusammenhang verschiedene klinische Parameter mit solchen Veränderungen stehen. Weiters beschäftigte sich die Studie mit der Indikationsstellung für ein MRT der Halswirbelsäule bei PatientInnen mit zervikaler Dystonie.

Methodik: Wir rekrutierten 30 PatientInnen (8 Männer, 22 Frauen) mit zervikaler Dystonie. Im Abstand von drei Monaten erfolgten zwei identische Untersuchungsabläufe, die eine Anamnese, eine neurologische Untersuchung und die Beurteilung der zervikalen Dystonie mittels drei verschiedener klinischer Skalen (TSUI Skala, Toronto Western Spasmodic Torticollis Rating Scale, Burke-Fahn-Marsden Scale) beinhalteten. Im selben Zeitraum erfolgte die Kernspinuntersuchung der Halswirbelsäule, die von drei erfahrenen Neuroradiologen an Hand verschiedener MRT-Beurteilungsskalen (Kang, Matsumoto, Modic) ausgewertet wurde. Zum Vergleich wurde eine Kohorte mit 21 gesunden TeilnehmerInnen herangezogen, die die oben genannte Untersuchung einmal durchliefen und sich ebenfalls einem MRT der Halswirbelsäule unterzogen.

Ergebnisse: Es zeigte sich überwiegend eine gute Interrater Reliabilität der MRT-Beurteilungsskalen, die mit Hilfe des Intraklassen-Korrelationskoeffizienten und des Fleiss‘ Kappa ausgewertet wurde. Hinsichtlich struktureller Veränderungen der Halswirbelsäule konnten keine wesentlichen Unterschiede zwischen PatientInnen und den gesunden TeilnehmerInnen festgestellt werden. Bei PatientInnen waren HWS-Veränderungen mit einzelnen klinischen Parametern vor allem in den Segmenten C3/C4 und C4/C5 assoziiert, meist allerdings nur für einzelne Beurteilungsskalen. Bezüglich des klinischen Symptomes Schmerz konnte interessanterweise keine Assoziation zu Veränderungen im MRT festgestellt werden.

Schlussfolgerung: Aus unserer Studie konnten vier Kernaussagen getroffen werden. Die verwendeten MRT-Beurteilungsskalen waren zuverlässig. Zwischen PatientInnen und Kontrollen konnten keine wesentlichen strukturellen Unterschiede im Bereich der HWS festgestellt werden. Eine Assoziation zwischen klinischen Parametern und Veränderungen in der Bildgebung scheint vor allem in den Segmenten C3/C4 und C4/C5 aufzutreten, die klinische Relevanz dieser Assoziation ist jedoch umstritten. Basierend auf unseren Studienergebnissen ist eine Kernspinuntersuchung der Halswirbelsäule jedoch nur bei einer klinischen Verdachtsdiagnose mit therapeutischer Konsequenz indiziert, da strukturelle Veränderungen der HWS sowohl bei PatientInnen als auch in der Normalbevölkerung häufig sind und am ehesten auf degenerativen Veränderungen beruhen. Um genauere Aussagen treffen zu können, sind allerdings weitere Studien mit größerer Studienpopulation notwendig.

Schlagwörter: zervikale Dystonie, MRT, PatientInnen, Botulinum toxin, Veränderungen, Wirbelsäule

Abstract

Introduction: Cervical dystonia, which is the most common form of focal dystonia in the adulthood, is a rare disease. Only a few studies deal with this disease pattern especially with regard to the etiology and botulinum toxin therapy. In our study we investigated if structural changes of the cervical spine on MRI images are more frequent in patients with cervical dystonia than in the general population and which clinical parameters correlate with these abnormalities. Finally, we investigated whether there are any clinical parameters which strengthen the indication for an MRI of the cervical spine in patients with cervical dystonia.

Methods: We recruited 30 patients (8 men, 22 women) with cervical dystonia. Three months apart, two identical examinations were performed including medical history, a neurological examination and the evaluation of the cervical dystonia by means of three different rating scales (TSUI Score, Toronto Western Spasmodic Torticollis Rating Scale, Burke-Fahn-Marsden Scale). In the same period, MRI of the cervical spine was performed, which was analyzed by three experienced neuroradiologists with the help of different MRI rating scales (Kang, Matsumoto, Modic). For comparison 21 healthy participants were recruited who also underwent the above mentioned examination and the MRI examination of the cervical spine.

Results: The inter-rater reliability of each MRI rating scale which was evaluated with the intraclass correlation coefficient and Fleiss' kappa revealed good results in most of the cases. Concerning structural changes of the cervical spine, no major differences between patients and healthy participants were found. Cervical spine changes in patients were more prominent in segment C3/C4 and C4/C5 with regard to individual clinical parameters. Interestingly, the clinical symptom pain was not associated with imaging changes.

Conclusion: Based on our results, we can make four statements. MRI rating scales we used were reliable. No major structural differences were found between patients and controls. Structural changes in patients with cervical dystonia seem to be associated with clinical parameters predominantly in segment C3/C4 and C4/C5. However, the clinical relevance of these associations is debatable. Based

on our study results, magnetic resonance imaging of the cervical spine in patients with cervical dystonia should only be considered if on clinical basis a morphological correlate is suspected, since structural changes are very common in patients and in the general population, most likely due to degenerative changes. In order to make any further statements, studies with larger study population are needed.

Keywords: cervical dystonia, MRI, patients, botulinum toxin, changes, spine

1 Introduction

The term “dystonia” was first coined by Oppenheim in 1911. He described the so-called dystonia musculorum deformans which is known as primary generalized torsion dystonia today (1).

Cervical dystonia, the most common form of focal dystonia, is a rare disease (2). However, patients, who suffer from it, often have a high level of psychological strain. They often have to cope with neck pain as well as head tremor and abnormal posture. Frequently, patients feel ashamed in public and retire from work.

Only a few studies explore this disease in more detail, predominantly with regard to the etiology, which is still unknown, as well as to treatment with botulinum toxin and its effect.

Until now, no study exists focusing on patients with cervical dystonia and magnetic resonance imaging (MRI) of the cervical spine. Therefore, the aim of our consecutive case-control study was to explore whether differences in structural changes of the cervical spine exist between patients and healthy controls. Additionally, we tried to correlate these imaging changes with clinical parameters to delineate recommendations about MRI examination of the cervical spine in patients with cervical dystonia.

1.1 Classification of dystonia

Dystonia is part of the hyperkinetic movement disorders. The term “movement disorders” was defined by Stanley Fahn in 1968 and means the representation of several neurologic dysfunctions which focus on clinical expression rather than on an anatomic location (3).

Dystonia is a heterogeneous group with a lot of different characteristics and manifestations. Over the last decades, a set of classifications of this clinical picture has been developed. They have been advanced due to the scientific progress in research and the new acquired knowledge.

The current available classification of dystonia was published by Fahn, Jankovic and Hallett in the year 2011 (4). This hyperkinetic movement disorder is divided into three equal aspects. These are the age at onset, the distribution of the involved body parts and the etiology. The first two points primarily serve the clinical consideration and have an influence on the treatment as well as on the prognosis. It concerns especially the primary or idiopathic dystonia. Yet, the most frequent and common classification is the etiological one which contains all forms of the disease pattern (5).

Classification by age at onset differs from the beginning of the disease before the age of 26 and after the age of 26 (4). The type which starts already in the childhood is mostly based on a gene mutation in the DYT1 gene (6). It is called early-onset dystonia (4). The progression of the disease normally starts in one limb and spreads afterwards to other body parts. However, the face and the bulbar muscles are not involved. The second possibility is called late-onset dystonia and starts in the adulthood. It became evident that patients between the age of 30 and 40, having focal dystonia, are more likely to suffer from a writer's cramp. In contrast to that, people over 40 years mostly get a dystonia which attacks the craniocervical muscles (7). In general, the disease can start at every age. Though, it has been observed that the progression of the illness is much more severe the earlier the indisposition begins (8).

The classification by distribution applies to specific body parts which are affected by dystonic movements. The focal dystonia for example attacks only one region of the body. The cervical dystonia (CD, spasmodic torticollis) belongs to this variant, which will be explained later on in more detail. Another type is called segmental dystonia with a characteristic distribution on contiguous body parts. In addition to that, there is the multifocal dystonia. The patient has few affected body parts but they are not next to each other. Generalized dystonia complies with the affection of the legs, the trunk and other areas. In contrast to that, the hemidystonia involves only one half of the body (5).

The third and most relevant classification is the one by etiology. It has been changed and improved over the last years and includes clinical and pathological characteristics as well as the existence or absence of genetic features (5). Primary dystonia belongs to this classification. It is defined as follows: there has to be just the dystonia with or without tremor in the absence of other neurological symptoms or signs. Furthermore, no secondary cause is found. The absence of neurodegeneration is typical and imaging is without pathological findings (5,7). In contrast to this kind of dystonia, there are the so-called dystonia-plus syndromes.

These are characterized by the absence of neurodegeneration, however other symptoms and signs can be found. This term includes dopa-responsive dystonia (DRD), myoclonus dystonia and rapid-onset dystonia parkinsonism. Secondary dystonia is defined through its verifiable cause as for example trauma and drugs. There is a wide range of substances which can induce an acute dystonic reaction. Furthermore, dopamine-receptor antagonists can on one hand trigger an acute dystonic reaction but can on the other hand initiate a chronic progressive movement disorder (7). Also brain lesions, especially in the putamen, can indicate this disease (9). Rarely, dystonia is the consequence of an infection like the Japanese B encephalitis. Another group represents the so-called heredodegenerative dystonia. It is defined through its "syndromic associations" meaning that the appearance of the disease is in context of other degenerative disease patterns like Parkinson's disease (PD) or ataxia (7,10). In the last group, dystonia is a feature of another neurologic disease such as dystonic tics, paroxysmal dyskinesias, Parkinson's disease, progressive supranuclear palsy (PSP) and cortical-basal ganglionic degeneration (CBGD) (4).

Obviously, the classification of dystonia is difficult due to its variability of the manifestation and etiology of the disease.

In the following table the classification of dystonia by Fahn, Jankovic and Hallett is listed (Table 1) (4).

I. Age at onset	**II. Distribution**	**III. Etiology**
A. Early ≤ 26 years	A. Focal	A. Primary
B. Late > 26 years	B. Segmental	B. Dystonia-plus
	C. Multifocal	C. Secondary
	D. Generalized	D. Heredodegenerative
	E. Hemidystonia	E. Others (Dystonic tics, Paroxysmal dyskinesias, PD, PSP, CBGD)

Table 1: Classification of dystonia (adopted from Fahn et al. Principles and Practice of Movement Disorders, Elsevier 2011)

1.2 Cervical dystonia

The next section presents more details about cervical dystonia, which is the most common form of focal dystonia. Since cervical dystonia is the main topic of this diploma project, it is important to get more information about its epidemiology, etiology and anatomy. But also knowledge about the clinical presentation and symptoms, diagnostic investigations and treatment of the disease is necessary.

1.2.1 Epidemiology

The epidemiology of cervical dystonia is not exactly identifiable due to insufficient studies. Because of that, the incidence (the number of new affections in the population per year) and prevalence (the number of the disease cases in the population) can just be estimated. Some studies focus on the data collection of the prevalence of primary dystonia. Indeed, there are some differences in study design, study groups referring to quantity, age and ethnicity, case-finding procedures and diagnostic criteria (11). Thereby, study comparisons are not possible. The incidence of dystonia is often not considered in studies.

There are only two epidemiological studies identifying the cases of cervical dystonia. The first one has been conducted in China. The prevalence estimates of the late-onset dystonia devoted 30 people per million in this study. In contrast, the Egyptian study estimates the prevalence at 100 cases per million (12,13). Altogether, dystonia is a rare disease (2).

Basically, cervical dystonia is the most frequent type of late-onset focal dystonia. The prevalence is estimated at 5.9 per 100.000 (2). The incidence of cervical dystonia is 11 per million per year (14).

As already mentioned, cervical dystonia belongs to the late-onset dystonias meaning the beginning is in adulthood. It shows its frequency peak in the fifth decade (15). However, the disease can break out at any age and has a late tendency to spread and progress (16).

Furthermore, some studies proved differences in the sex distribution. Women are concerned 1.6 times as often as men suffering from a dystonia in the craniocervical region (17).

Additionally, the ethnic origin seems to have influence on the appearance of torticollis spasmodicus. In an incidence study it became evident, that the white

population is more frequently affected by this disease than the black population (14). Equally, according to a Norwegian study, Europeans suffer more often from dystonia than the first generation of immigrants of Asian and African origin. The prevalence differed from 283 to 34 per million (18).
A positive family history is an important risk factor for getting a primary dystonia (11,19,20). Defazio et al. summarized some studies which have proved the cumulative presence of dystonia in families (21).
Apparently, there are only a few studies focusing on the epidemiology of dystonia because dystonia seems to be rare, have low morbidity and be generally non-fatal (2). Nevertheless, diagnostic investigation is often difficult and the treatment of the disease is inadequate because of the insufficient or missing diagnostic process.

1.2.2 Etiology

The etiology and pathogenesis of cervical dystonia is still unclear. The disease is characterized by contractions of agonists and antagonists of the neck muscles (7). Basically, cervical dystonia can be classified as primary cervical dystonia or secondary cervical dystonia. The first-mentioned one is also called idiopathic cervical dystonia (ICD) and is the most frequent one. There is no recognizable cause. Primary torsion dystonia is defined as a syndrome with following characteristics: dystonia and/ or tremor of the arms or head and neck but without presence of neurodegeneration (5). Furthermore, it is not allowed to find any evidence of a secondary cause in the case history, in the physical examination, in laboratory tests and in diagnostic imaging (7). In medical research some gene mutations associated with the development of dystonia have been discovered. However, cervical dystonia is rarely due to these genetic changes. In a large German family with seven CD patients, the mapping of the DYT7 locus to chromosome 18 could be shown. All of them suffered from adult-onset torticollis (22). Another gene alteration is the polymorphism in the dopamine D5 receptor (DRD5) gene. This mutation is also associated with adult-onset cervical dystonia (23,24). In some studies, SNPs (single nucleotide polymorphism) in TOR1A and THAP1 gene have been found. These SNPs seem to be involved in the development of cervical dystonia (25-27). The above mentioned gene mutations might be associated with the appearance of primary cervical dystonia. The

combination with different environmental risk factors finally results in cervical dystonia (21).
In contrast to primary cervical dystonia, there is secondary cervical dystonia. Proving is always the presence of a cause. Patients developing a cervical dystonia during their lives sometimes indicate in their case history an abnormal birth or developmental history (28). This is one reason to get this disease. Another cause is a multiplicity of drugs that have to be considered. There are some substances which can trigger an acute dystonic reaction representing a neurological emergency. The term "acute dystonic reaction" is defined as a reaction to this drug within 48 hours (7). Neuroleptics and antiemetics like metoclopramide belong to this group of drugs (29). Cervical dystonia can also arise as the consequence of the long-term taking of different medication. However, there are just a few cases reported. In principle, every region of the body can be affected; but the head and neck are the most common parts. Dystonia is then called tardive dystonia (30). Primarily, substances influencing the dopamine level are an important cause. The dopamine-receptor antagonists belong to this group. These are for example trifluoperazine or chlorpromazine (31). The so-called stimulants, also affecting the dopamine system, have a stimulating effect on the central nervous system (CNS). Sometimes an antiemetic drug like metoclopramide induces dystonia. Rarely, a range of other drugs such as antiepileptics, anti-histamines, or antidepressants may be causative. However, since it is very unusual getting a dystonia triggered by these drugs, they are not described in detail (32).
Furthermore, other neurological diseases may be accompanied by a cervical dystonia. A dystonia for example can appear in the context of a dementia. Different types of dystonia, including focal dystonias and torticollis, might be first symptoms of spinocerebellar ataxia (SCA) 3, 7 and 17 (33-35). Evidence of early presence of ataxia is important for the correct diagnosis (36). A few cases of patients who developed dystonia after an infection with Japanese B encephalitis or Sydenham's chorea have been described (7). Lastly, trauma and injury should be mentioned as a cause for dystonia. 5 to 21% of patients with cervical dystonia have a positive history of a head or neck trauma. Sometimes, it might be the trigger for a patient's dystonia (37-40). The dystonia can appear instantly or with a delay up to 12 months (41). Although the type of the injury is not known until now, the localization has to be in specific areas in the brain. They can be damaged for

example by tumor, stroke or brain inflammation. Dystonia is a disorder of controlling head posture. Therefore, the extrapyramidal system has to be affected. The so-called basal ganglia belong to it. The exact mechanism of the development is still unknown (42). Obviously, there are some known causes which are probably responsible for the appearance of cervical dystonia. However, the exact processes are not explored in total until now. Table 2 gives an overview of the different causes of CD.

I. Primary CD	Gene mutation: • DYT7 locus to chromosome 18 • Polymorphism in the DRD5 gene • SNPs in TOR1A and THAP1

II. Secondary CD	Abnormal birth
	Abnormal developmental history
	Drugs:
	• Acute dystonic reaction:
	  ▪ Neuroleptics
	  ▪ Antiemetics
	• Long-term medication:
	  ▪ Dopamine-receptor antagonists
	  ▪ Stimulants
	  ▪ Antiemetics
	  ▪ Antiepileptics
	  ▪ Antihistamines
	  ▪ Antidepressants
	  ▪ Benzodiazepines
	  ▪ Steroids
	  ▪ Contraceptive pill

III. CD and ataxia or dementia	Japanese B encephalitis Sydenham's chorea
IV. Trauma and injury	Tumor Stroke Brain inflammation Trauma Vascular malformation

Table 2: Etiology of cervical dystonia

1.2.3 Anatomy

Cervical dystonia can affect different muscles (Figures 1-5). These are the platysma, the sternocleidomastoid muscle, the three scalene muscles, the longus colli muscle, the trapezius muscle, the levator scapulae muscle, the splenius capitis muscle and the semispinalis capitis muscle (43).

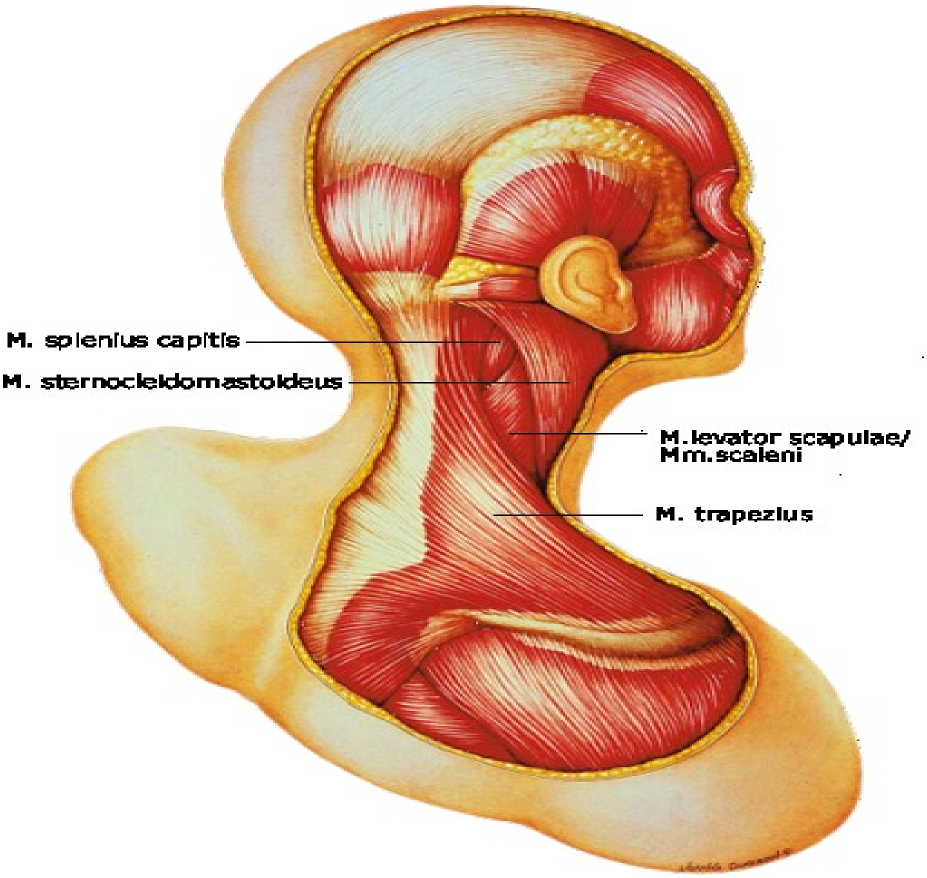


Figure 1: Affected muscles in cervical dystonia 1 (adopted from Dippon C. Zervikale Dystonien- Beschreibung der Symptomatik, Diagnostik, Therapie und Nebenwirkungen, 2005)

Depending on the affected neck muscles, the manifestation of the disease can be very different. The above mentioned muscles will be explained in more detail with respect to the nerval innervation, the muscle origin, the muscle insertion and the function.

The platysma belongs to the group of the facial muscles. It is innervated by the facial nerve. The origin is located on the mandibular base as well as on the parotid fascia. The insertion is formed by the skin below the clavicle and the pectoral fascia. The platysma is responsible for the skin tension of the neck and the formation of longitudinal folds (44).

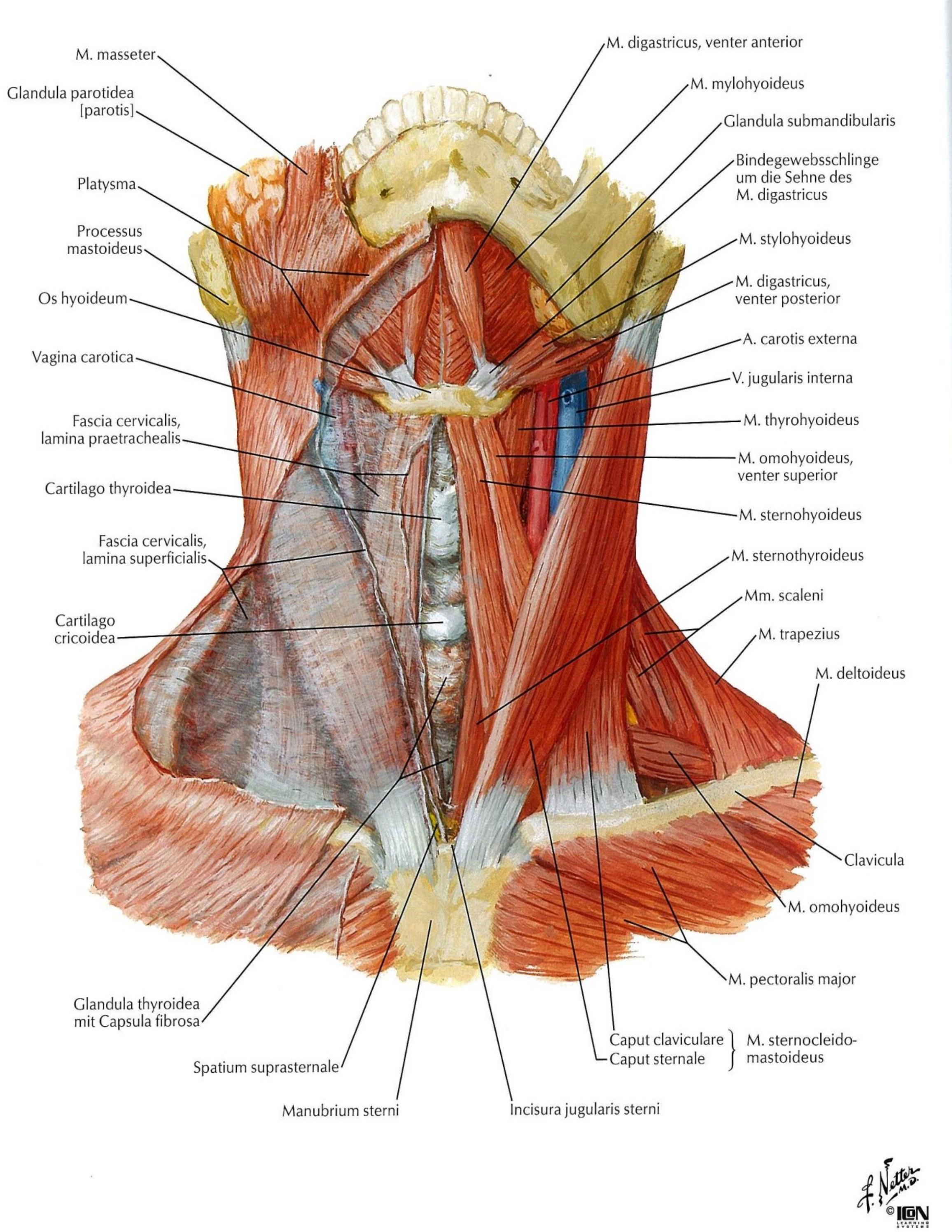


Figure 2: Affected muscles in cervical dystonia 2 (adopted from Netter et al. Atlas der Anatomie des Menschen, Elsevier 2003)

Another affected muscle in cervical dystonia is called the sternocleidomastoid muscle. It is part of the lateral neck muscles. It is innervated by the accessory nerve and also some parts of the cervical plexus. The sternocleidomastoid muscle's origin has two caputs. On the one hand there is the caput sternale which raises on the ventral side of the sternum, on the other hand the caput claviculare which starts as a short tendon at the medial third of the collarbone. The muscle is mounted at the mastoid process and also laterally at the superior nuchal line. This neck muscle has different functions. It can twist the head to the opposite side if the activity is unilateral. If there is a bilateral muscular activity, the head is raised and pulled forwards. Furthermore, the caudal cervical vertebras can be bended and the cranial neck vertebras can be stretched (44).

The scalene muscles consist of three parts. These are the scalenus anterior muscle, the scalenus medius muscle and finally the scalenus posterior muscle. The neural supply of this muscle plate is made by direct nerve branches of the cervical plexus and also the brachial plexus. The scalenus anterior muscle origins are the anterior tubercles of the transverse processes of the third to sixth neck vertebras. The insertion as a short tendon is the tuberculum musculi scaleni anterioris of the first rib. Next to it is the origin of the scalenus medius muscle. It is also the tubercles of the transverse processes but in this case from the third to the seventh cervical vertebras. As mentioned above, the first rib behind the sulcus arteriae subclaviae acts as muscle attachment. Finally, the scalenus posterior muscle origins at the posterior tubercles of the transverse processes of the fifth and sixth neck vertebras. The second and the third rib serve as insertion. The three muscles have the same function. On the one hand they induce a lateral flexion of the cervical spine and on the other hand they are involved in the respiration raising the thorax (44).

Furthermore, the longus colli muscle can be affected in cervical dystonia. It belongs to the prevertebral muscles. The innervation is directly through nerval branches which are part of the cervical plexus. The origin ranges from the fifth cervical vertebral body to the third thoracic vertebral body. Additionally, it origins on the anterior tubercles of the transverse processes of the second to fifth neck vertebras. The muscle has three insertions: first, the transverse processes of the fifth to seventh cervical vertebras, second, the second to fourth cervical vertebral bodies and third, the anterior tuberculum of the atlas. The longus colli muscle function is the ventral head flexion as well as the torsion to the ipsilateral side (44).

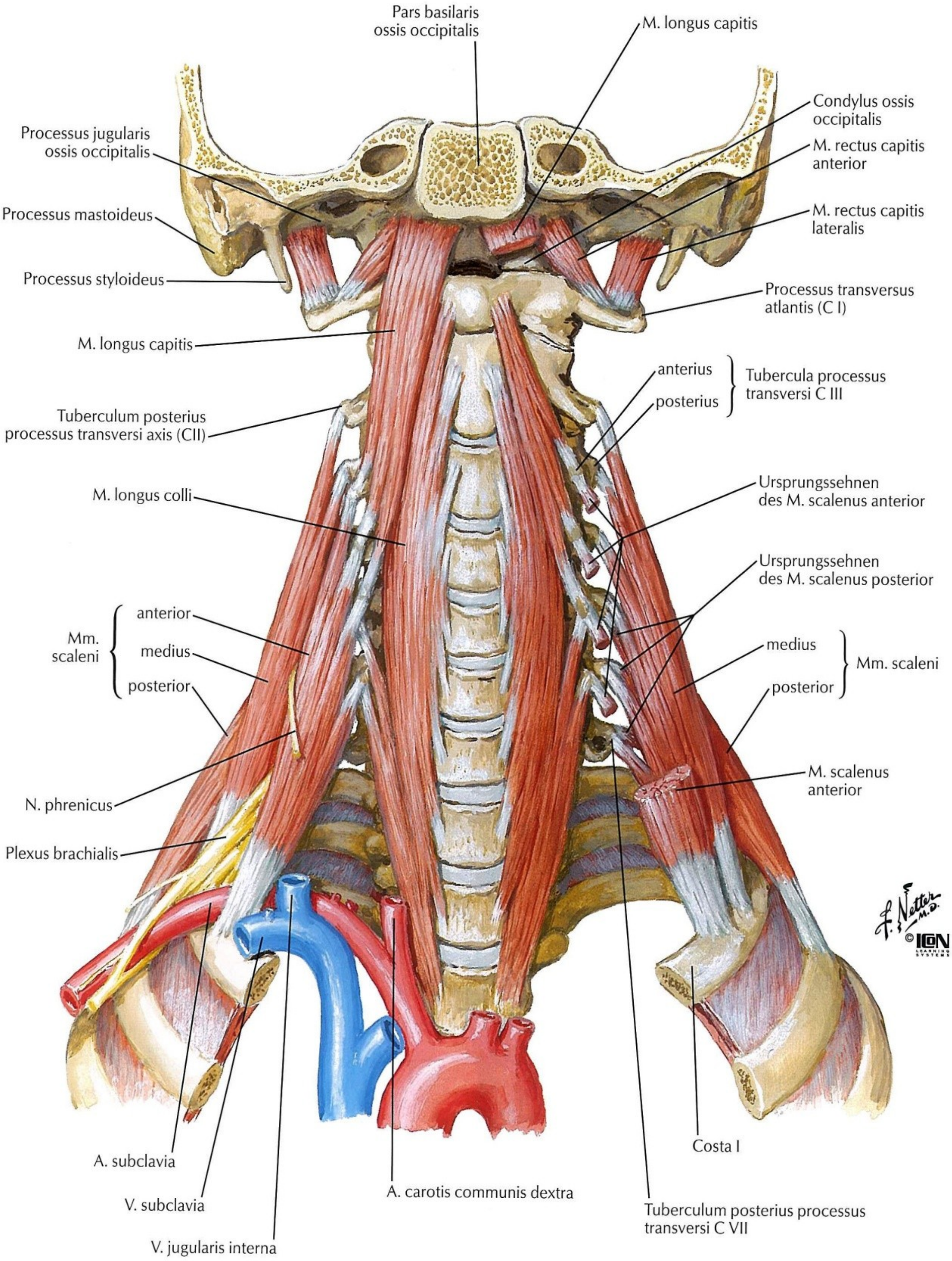


Figure 3: Affected muscles in cervical dystonia 3 (adopted from Netter et al. Atlas der Anatomie des Menschen, Elsevier 2003)

Two muscles belonging to the trunk and shoulder musculature are the trapezius muscle and the levator scapulae muscle. In cervical dystonia just the pars ascendens of the trapezius muscle is involved. The accessory nerve and branches of the cervical plexus are responsible for the innervation. The muscle origins at the occipital squama between the highest nuchal line and the superior nuchal line and the spinous processes of the upper neck vertebras above the nuchal ligament. The pars ascendens inserts at the acromial third of the clavicle and has the following function: if the shoulders are immovable, the head is turned to the contralateral side and the cervical spine can be stretched. The levator scapulae muscle is also innervated by branches of the cervical plexus but additively of the dorsal scapular nerve. The posterior tubercles of the transverse processes of the first to fourth neck vertebras represent the origin. The insertion is the superior angle of the scapula as well as the contiguous margins. The levator scapulae muscle is responsible for the stretching of the cervical spine (44).

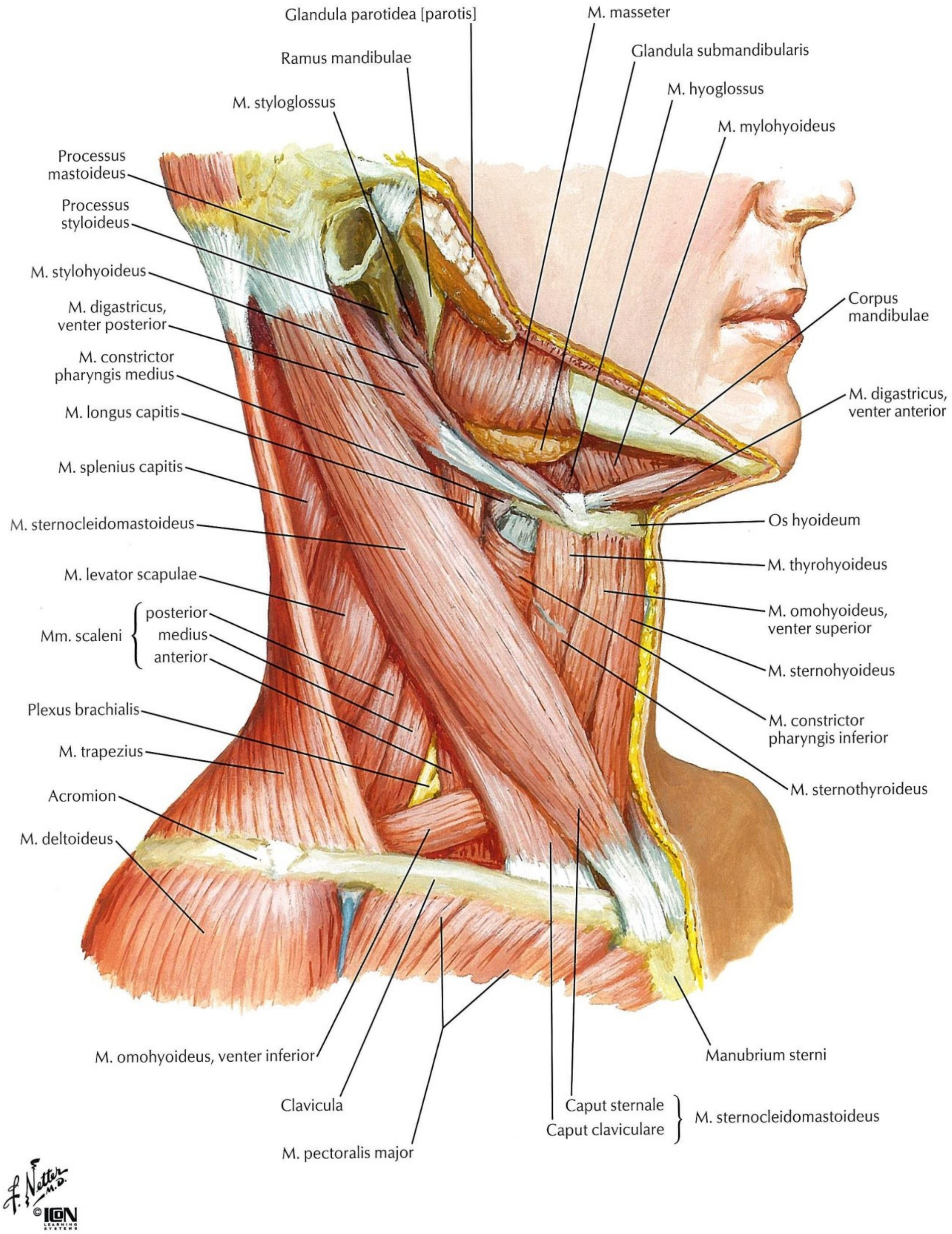


Figure 4: Affected muscles in cervical dystonia 4 (adopted from Netter et al. Atlas der Anatomie des Menschen, Elsevier 2003)

Finally, there can be two muscles affected which belong to the autochthonus back muscles. They are called the splenius capitis muscle and the semispinalis capitis muscle. Both are innervated by the rami posteriores of the cervical nerves. The splenius capitis muscle origins at the nuchal ligament and also at the spinous process of the third to seventh neck vertebras. The insertion is located on the mastoid process. The muscular function is various. Within unilateral involvement the lateral flexion and the rotation of the cervical spine and the head is to the ipsilateral side. If there is bilateral activation the cervical spine will be extended. The semispinalis capitis muscle has its origin at the transverse process of the seventh thoracic vertebra to the third neck vertebra. The occipital squama between the highest nuchal line and the superior nuchal line serves as insertion. If there is an unilateral innervation, the vertebral spine as well as the head will turn to the contralateral side and an inclination happens. Bilateral activity initiates an extension of the vertebral spine (44).

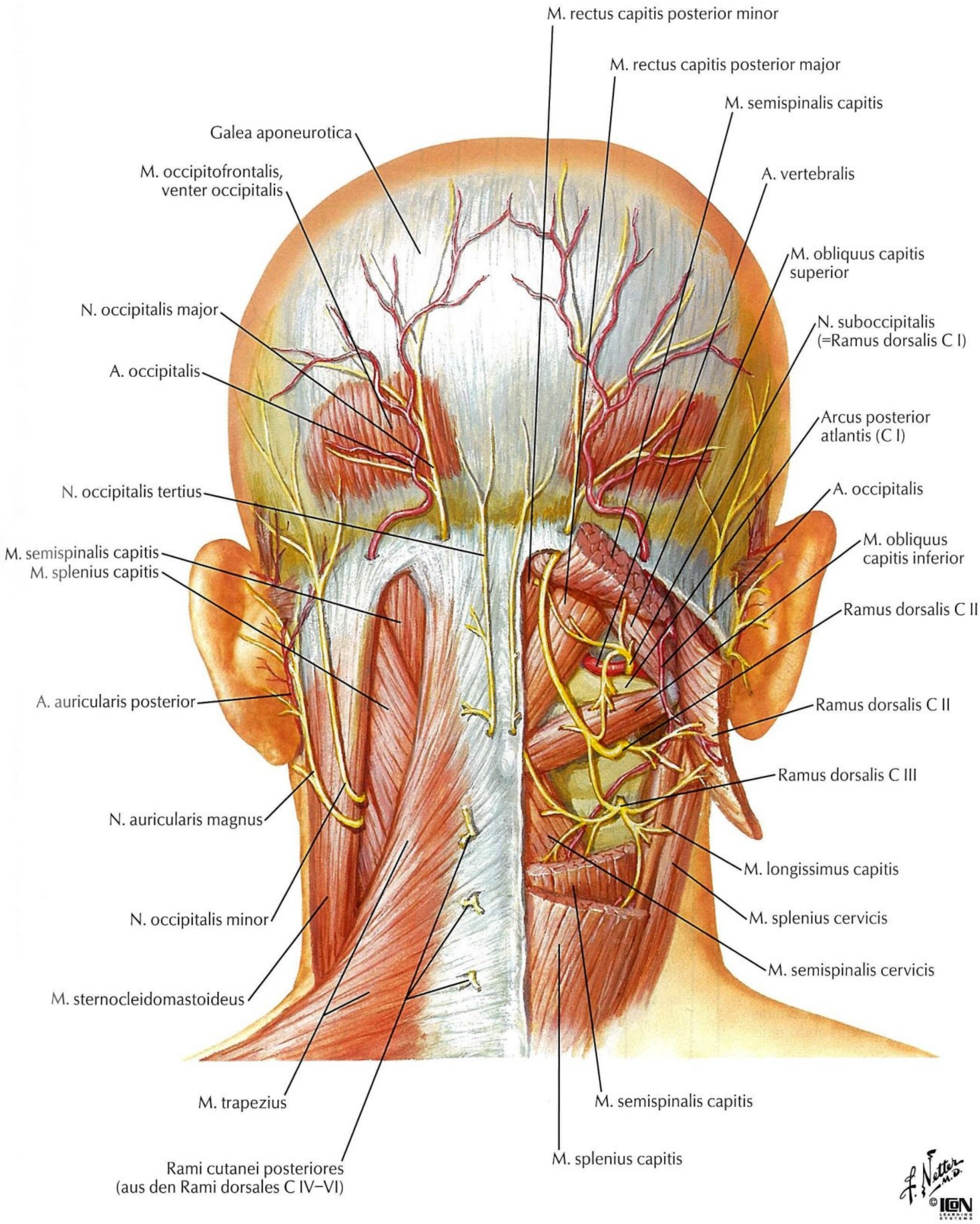


Figure 5: Affected muscles in cervical dystonia 5 (adopted from Netter et al. Atlas der Anatomie des Menschen, Elsevier 2003)

Knowledge about the anatomy is fundamental for the therapy with botulinumtoxin and the right implementation. Table 3-5 gives an overview of all affected muscles.

Muscle	Innervation	Origin	Insertion	Function
Platysma	-Facial nerve	-Mandibula base -Parotid fascia	-Skin below the clavicle and the pectoral fascia	-Skin tension of the neck -Formation of longitudinal folds
Sterno-cleidomastoid Muscle	-Accessory nerve -Cervical plexus	-Caput sternale -Caput claviculare	-Mastoid process -Laterally at the superior nuchal line	-Twist head to the opposite side -Head raising and pulling forwards -Bending of the caudal cervical vertebras -Stretching the cranial neck vertebras
Scalenus anterior Muscle	-Direct nerve branches of the cervical and brachial plexus	-Anterior tubercles of the transverse processes of the 3rd to 6th neck vertebras	-Tuberculum musculi scaleni anterioris of the first rib	-Lateral flexion of the cervical spine -Raising the thorax during respiration
Scalenus medius Muscle	-Direct nerve branches of the cervical and brachial plexus	-Tubercles of the transverse processes of the 3rd to 7th neck vertebras	-1st rib behind the sulcus arteriae subclaviae	-Lateral flexion of the cervical spine -Raising the thorax during respiration

Table 3: Affected muscles in cervical dystonia 1 (adopted from Putz et al. Sobotta- Atlas der Anatomie des Menschen; Tabellen zu Muskeln, Gelenken, Nerven, Elsevier 2006)

Muscle	Innervation	Origin	Insertion	Function
Scalenus posterior Muscle	-Direct nerve branches of the cervical and brachial plexus	-Posterior tubercles of the transverse processes of the 5th and 6th neck vertebras	-2nd and 3rd rib	-Lateral flexion of the cervical spine -Raising the thorax during respiration
Longus colli Muscle	-Direct nerve branches of the cervical plexus	-Bodies of the 5th neck to the 3rd thoracic vertebras -Anterior tubercles of the transverse processes of the 2nd to 5th neck vertebras	-Transverse processes of the 5th to 7th cervical vertebras -Bodies of the 2nd to 4th cervical vertebras -Anterior tuberculum of the atlas	-Ventral head flexion -Torsion to the ipsilateral side
Trapezius Muscle (Pars ascendens)	-Accessory nerve -Branches of the cervical plexus	-Occipital squama between the highest nuchal line and the superior nuchal line -Spinous processes of the upper neck vertebras above the nuchal ligament	-Acromial third of the clavicle	-Torsion to the contralateral side -Stretching of the cervical spine

Table 4: Affected muscles in cervical dystonia 2 (adopted from Putz et al. Sobotta- Atlas der Anatomie des Menschen; Tabellen zu Muskeln, Gelenken, Nerven, Elsevier 2006)

Muscle	Innervation	Origin	Insertion	Function
Levator scapulae Muscle	-Direct branches of the cervical plexus -Dorsal scapular nerve	-Posterior tubercles of the transverse processes of the 1st to 4th neck vertebras	-Superior angle of scapula and contiguous margins	-Cervical spine stretching
Splenius capitis Muscle	-Rami posteriores of the cervical nerves	-Nuchal ligament -Spinous processes of the 3rd to 7th neck vertebras	-Mastoid process	-Lateral flexion and rotation of the cervical spine -Head moving to the ipsilateral side -Cervical spine extension
Semispinalis capitis Muscle	-Rami posteriores of the cervical nerves	-Transverse processes of the 7th thoracic to the 3rd neck vertebras	-Occipital squama between the highest nuchal line and the superior nuchal line	-Vertebral spine as well as the head turn to the contralateral side -Inclination -Extension

Table 5: Affected muscles in cervical dystonia 3 (adopted from Putz et al. Sobotta- Atlas der Anatomie des Menschen; Tabellen zu Muskeln, Gelenken, Nerven, Elsevier 2006)

1.2.4 Clinical presentation

Dystonia is characterized by prolonged muscle contraction. This is followed by twisting, repetitive movements or abnormal posture (45). Another term for cervical dystonia is torticollis spasmodicus but it does not detect the dystonic feature of this disease. Torticollis reflects the twisted neck as a physical sign and may result from different non-dystonic diseases (46). Cervical dystonia is based on contractions of agonists and antagonists in the neck musculature. These muscle groups are innervated at the same time due to the wrong muscle coordination. This results in an abnormal head posture (42).

Furthermore, cervical dystonia can be classified in four types referring to the neck deviation: torticollis, laterocollis, anterocollis and retrocollis (Figure 6) (47). The first one is defined as a rotational movement of the chin around the longitudinal axis of the shoulder. If the head turns in the coronal axis and simultaneously the ear moves in the direction of the shoulder, it is called laterocollis. According to the sagittal plane, we know anterocollis and retrocollis. Typical for anterocollis is the chin moving toward the breast. In contrast, a neck deviation to the back is called retrocollis (46). Each of these movement abnormalities can appear individually or in combination. However, the occurrence of a single neck deviation is rare with less than 30% of patients having an isolated abnormality. Torticollis is with roughly 80% the most frequent single change. In contrast to this, the sole presence of an anterocollis virtually does not exist (37,39,48). About 60% of patients show a combination of the above mentioned possibilities. The most common types appearing together are torticollis and retrocollis (49).

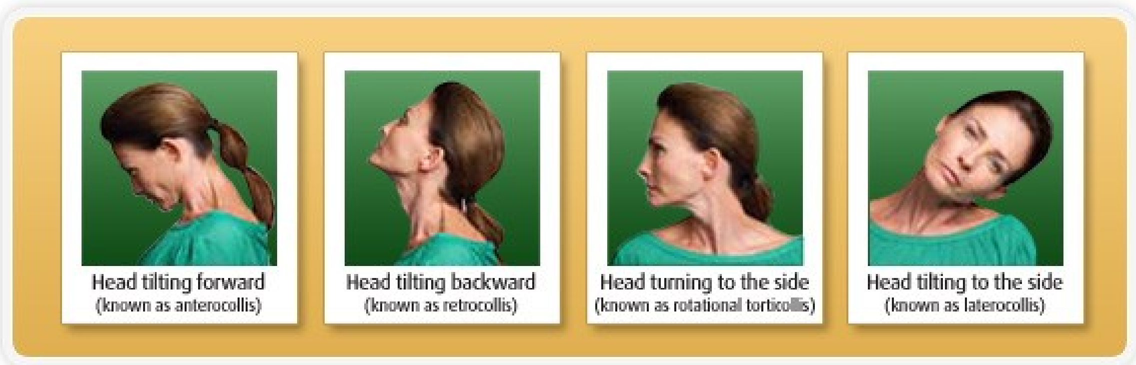


Figure 6: Different types of cervical dystonia (adopted from Ipsen Biopharmaceuticals Inc, Medicis Aesthetics Inc. Types of cervical dystonia- Are there different kinds of cervical dystonia?)

Sometimes, a shoulder elevation can be recognized additionally. Furthermore, cervical dystonia can be associated with tremor. Head tremor as well as hand tremor may coexist with an abnormal head posture. A study showed that almost 40% of patients with cervical dystonia suffer from a head tremor and almost 25% of them additionally have a postural tremor of the hand (50). It is not clear so far if this tremor in the head or the hand is an additional appearance of the primary dystonic disorder or if it is a separate movement disorder like essential tremor for example (46). Additionally, the presence of pain in cervical dystonia is common.

75% of the patients suffer from neck pain which is responsible for a significant proportion of their disability (37,38,48,51). According to the study by Rondot et al., in 99% of the patients disability was found and the severity of the disability varies from mild to severe (39). In many patients a so-called geste antagoniste can be observed (Figures 7-8). This is a sensory trick to reduce the dystonic movement. There are several mechanisms: the most common ones include touching the chin, the face or the head. Sometimes the leaning against a headrest is helpful as well as to put something in the mouth or to pull the hair. At the beginning of the disease, these tricks seem to help but with further disease progression the effect wears off. Also, there are some less common possibilities to improve the symptoms, such as relaxation and alcohol consumption. On the other hand, cervical dystonia can be aggravated by activity, fatigue, or stress (52,53).

Figure 7: Geste antagoniste 1 (adopted from Scott B. Evaluation and Treatment of Dystonia)

Figure 8: Geste antagoniste 2 (adopted from the personal teaching collections of Simon, et al.)

Basically, cervical dystonia can arise as an isolated focal dystonia or as a part of a segmental or generalized dystonia. Normally, the disease starts slowly with unspecific symptoms. At the beginning, patients describe symptoms like pulling or drawing in the neck or an unwanted twisting or jerking of the head (46). Therefore, it often takes very long until the right diagnosis is made. The progress of cervical dystonia varies in individual patients. There is usually a worsening of the cervical dystonia symptoms during the first five years. Mostly, after this period of disease exacerbation, the symptoms remain static. Only between 10 and 20% of patients show a symptom reduction or remission. Usually, this also happens within the first five years (51,54).

Apparently, the clinical picture of cervical dystonia is heterogeneous. There is also large symptom variability with regard to the presence of pain or the association with tremor. An early correct diagnosis is mandatory to initiate appropriate treatment and improve patients' quality of life.

1.2.5 Diagnostic investigation

Cervical dystonia is the most common form of adult-onset focal dystonia. However, it is difficult to make the right diagnosis of this disease. In a group of 300 patients with idiopathic cervical dystonia about 25% of them were initially misdiagnosed (48). A fast and exact diagnosis is necessary to initiate an adequate therapy. There are several possibilities of diagnostic investigations. The investigations should be carried out in the following order: taking the medical history, a physical examination, the disease classification evaluated by different dystonia rating scales, laboratory testing, investigation with electromyography and finally different imaging procedures. Following, each step of the diagnostic process will be explained in detail.

1.2.5.1 Medical history and physical examination

At the beginning, a detailed medical history is taken. It should focus on other neurological symptoms, head or neck injuries, exposure to drugs influencing dopamine receptors, symptoms prior to onset of dystonia, and family history of dystonia (46). Based on this information, a differentiation between primary and secondary cervical dystonia is possible in most of the cases. Primary or idiopathic cervical dystonia is characterized by the presence of dystonia with or without a tremor of head or arms, in the absence of other neurological symptoms and signs (5). In idiopathic dystonia there is no underlying cause in contrast to symptomatic cases. The age at onset, the mode of onset, the distribution, and also other clinical characteristics need to be delineated (55). Typical for secondary dystonia is the presence of a specific cause. Information about a previous head or neck trauma or a detailed medication history is therefore crucial. In this regard, past or present intake of neuroleptic drugs has to be considered. Tardive dystonia can also be triggered by the intake of antiemetics such as metoclopramide (30).

Next to a routine neurological examination, the physical examination includes the palpation of the muscles as well as an inspection of the abnormal posture. Thereby, the increased muscle activity can be observed. Additionally, the presence of a geste antagoniste should be detected. Also, the active and passive range of mobility is tested before and after the use of this sensory trick. In some cases, the additional examination by a physical therapist may be useful. In doing so, length and strength (force-generating capacity) of the muscles as well as the favorite patterns of movement of the shoulder girdle and thoracic and lumbar spine are captured. Therefore, different home exercises can be developed for the patient (56).

Obviously, a precise medical history and physical examination can be helpful to make the right diagnosis.

1.2.5.2 Rating scales

Different rating scales are used for the evaluation of cervical dystonia. Amongst the most important are the TSUI Score, the Toronto Western Spasmodic Torticollis Rating Scale, and the Burke-Fahn-Marsden Scale, which will be explained in more detail.

The **TSUI** Score has been developed by Tsui et al. (57) and is a clinical evaluation tool. In this scale, divided into four scores, different information is recorded. Firstly, abnormalities of head posture are rated. Depending on the severity of the abnormal head posture, points are ranked. The next subscale estimates the duration of the pathological movements being intermittently or constant. The presence of a shoulder elevation is part of the third division of the TSUI Score. The last part assesses the presence of a head tremor, which may be horizontal, vertical, or mixed (58). Additionally, the patient indicates the presence of pain which is also included in the score. The TSUI Score is a frequently used scale to evaluate cervical dystonia (see Appendix 1).

Next, the **Toronto Western Spasmodic Torticollis Rating Scale**, shortly TWSTRS, is described (53). The TWSTRS is proposed by Cano et al. as the current clinician-based outcome measure of choice (58). At the beginning, the position of the head, neck, and shoulders is evaluated as well as the efficiency of an existing geste antagoniste. Furthermore, the period of time to hold the head straight and the extent of movements of the head and neck muscles are evaluated (56). It also includes three subdivisions referring to severity (clinician-related), disability and pain (58). A higher score indicates a higher disability (56) (see Appendix 2).

Furthermore, the **Burke-Fahn-Marsden Scale** (BFM) is used to rate dystonia (59). This scale consists of the movement scale, which is clinician-rated, and of the disability scale (58). Thereby, dystonia is evaluated in all body parts (in contrast to the two aforementioned scales, which only rate cervical dystonia), and similar to the other rating scales a sum score indicates the severity of dystonia (see Appendix 3).

For the sake of completeness, some other rating scales such as the Cervical Dystonia Impact Profile (CDIP-58) (60), the Medical Outcomes 36-Item Health Survey Questionnaire, and the Functional Disability Questionnaire should be mentioned (56,61).

Hence, there are several rating scales to evaluate cervical dystonia. However, it is difficult with the existing rating scales to contain all the important outcome domains which are relevant to patients (58). None of the scales contains all aspects of this complex disease.

1.2.5.3 Laboratory tests

Laboratory tests, namely routine blood and urine analyses, may be used for diagnostic purposes (62). In the study of Risvoll and Kerty, no single laboratory test shows any pathology. They determined that the cause for idiopathic cervical dystonia cannot be found by doing laboratory tests. The detection rate of laboratory findings in CD patients is similar to the normal population (63).

In patients who develop dystonia before the age of 50, Wilson's disease has to be ruled out. Therefore, serum ceruloplasmin is measured (63). In some cases, especially those with a positive family history for dystonia, a gene mutation may be detected (see 1.2.2 Etiology).

1.2.5.4 Electromyography

Electromyography (EMG) is the most frequent used diagnostic method for cervical dystonia, especially for the idiopathic one (64). By using electromyography, a dystonic pattern can be recognized as needle EMG can show the pathological firing of the motor unit action potentials of muscles which are affected (65,66). However, there are some neck muscles which cannot be identified in the conventional 37-mm needle EMG because they are not accessible (67). Another problem is the invasiveness of the procedure, which may be painful, and there is a risk for infections and bleedings (68,69). Therefore, a non-invasive alternative to identify dystonic neck muscles is needed.

1.2.5.5 Imaging procedures

Different imaging methods may be useful in the diagnostic work-up of dystonia patients.

An X-ray of the cervical spine is frequently performed if a person develops an abnormal head posture. Degenerative changes can be found in a high percentage (63.1%) of performed cervical spine X-rays. But this method is not very sensitive because it is not proven yet if the dystonia is responsible for the development of the degenerative changes. People suffering from an adult-onset dystonia are often 50 years and older. Therefore, the abnormalities in the spinal column could appear due to older age (63).

Computed tomography (CT) and magnetic resonance imaging of the brain and the spine are imaging methods frequently used in patients with dystonia with the aim to detect structural abnormalities and therefore distinguish secondary from primary dystonia. However, most patients with cervical dystonia do not have specific imaging abnormalities (63). Nevertheless, in the literature it is recommended that all patients should undergo a MRI of the brain and also of the cervical spine (46).
Furthermore, an 18-F-FDG PET/CT can be performed. In this imaging method 18-F-FDG is applied. Normally, this substance is absorbed by contracting muscles. Because of the increased uptake and the enhanced glucose metabolism the localization of dystonic muscles can be evaluated. Severity of primary cervical dystonia and the level of 18-F-FDG uptake are associated with each other. Therefore, it might be useful performing 18-F-FDG PET/CT for localizing dystonic cervical muscles in patients with cervical dystonia (64). However, this method is not performed in routine clinical practice.
Sonography does not have a leading role diagnosing cervical dystonia. In one study using transcranial sonography (TCS) the authors reported hyperechogenic abnormalities of the medial segment of the lenticular nucleus (LN) in up to 75% of all patients with cervical dystonia (70). Although sonography is non-invasive, cheap, easy to handle, and without any side-effects, in clinical practice it is only used to rule out other differential diagnoses such as Parkinson’s disease (71). Additionally, it is a good method supporting EMG-guided botulinum toxin injections by localizing deep muscles, so that undesirable side-effects like dysphagia can be eliminated (72).
Although routine imaging procedures are useful to detect abnormalities in the osseous and muscular system, they are often not helpful in identifying the cause of cervical dystonia. Nevertheless, imaging techniques are preferable to electromyography because of their lower invasiveness (64).

1.2.6 Treatment

At the beginning, the most limiting factors of cervical dystonia should be detected such as pain, abnormal posture, tremor, functional limitation, social embarrassment and depression but also secondary diseases (46). Depending on the most restricting factor, the focus of therapy should be adapted.

Below, different treatment possibilities of cervical dystonia like chemodenervation with botulinum toxin, oral medication, surgery, and physiotherapy will be explained.

1.2.6.1 Botulinum toxin

The most commonly used treatment of cervical dystonia is the so-called chemodenervation therapy with botulinum toxin. Botulinum toxin injections are currently the first line treatment for cervical dystonia (Figure 9) (73,74).
The neurotoxin botulinum toxin is produced by the gram-positive bacteria "Clostridium botulinum". In total, there are seven serotypes A-G releasing different antigenically distinct toxins (75). The most important ones are serotype A, B and F (46). Usually, botulinum toxin A is used for the treatment of cervical dystonia. At the moment, three different forms are available in Austria: Onabotulinum toxin A (Botox®, Allergan Inc, Irvine, CA), Abobotulinum toxin A (Dysport®, Ipsen Ltd, Boulogne Billancourt, France) and Incobotulinum toxin A (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt/M, Germany) (76). The storage of the first two substances in the refrigerator is necessary, whereas Xeomin® can be stored at room temperature. Another difference concerns the preparation. One ampoule of Botox® contains 100 mouse units (MU) dry matter of botulinum toxin A dissolving in 1-2 ml (milliliters) sodium chloride (NaCl). For dilution of 500 MU Dysport® 2.5 ml NaCl is used (77). Three to four units of Dysport® are almost equal to one unit of Botox® or one unit of Xeomin® (78). Also, 100 MU of Xeomin® are usually diluted with 2 ml NaCl (77). Furthermore, this substance differs from the others with regard to its botulinum toxin complex which does not contain any accessory proteins (79).

In case of resistance against botulinum toxin A, therapy with botulinum toxin type B can be started. Rimabotulinum toxin B (Neurobloc®, Eisai GmbH, Frankfurt/M, Germany) is the only available serotype B substance in Austria. There are different available doses: 2500, 5000 and 10.000 MU which are already dissolved in 2 ml aqueous solution. The substance has also to be stored in a cool place (77).
In some cases serotype F could be used for therapy of cervical dystonia as well (80).

Table 6 gives a summary of all botulinum toxin substances which are used in Austria.

	Botox®	**Dysport®**	**Xeomin®**	**Neurobloc®**
Serotype	A	A	A	B
Botulinum toxin complex	Onabotuli-num toxin	Abobotuli-num toxin	Incobotuli-num toxin	Rimabotuli-num toxin
Conversion factor	1	3-4	1	-
Storage	refrigerator	refrigerator	room temperature	refrigerator
Preparation	dry matter 100 MU in 1-2 ml NaCl	dry matter 500 MU in 2.5 ml NaCl	dry matter 100 MU in 2 ml NaCl	aqueous solution 2500, 5000, 10000 MU dissolved in 2 ml NaCl

Table 6: Different substances of botulinum toxin used in Austria

Botulinum toxin is a polypeptide with a molecular weight of 150 kilo Dalton (kD) and consists of a long and a short protein chain. Cholinergic synapses can be blocked selectively by this substance and consequently release of acetylcholine is inhibited. After application of the medication, temporary muscular deficiency appears (77).

In order to avoid side effects, the injection is conducted intramuscularly. Therefore, knowledge of the affected muscles is essential. There are different possibilities to find the appropriate muscles. While moving the patients' head the physician can palpate the affected muscles to specify which muscles to treat and to determine the dose of botulinum toxin in every single patient (81). Rarely, imaging-guided injections are required. Therefore, electromyography, sonography or computed tomography are available to find deeply located muscles. According to the study by Comella et al.(82), EMG-guided injections deliver better results in some cases.

With appropriate injections abnormal head posture and pain level can be reduced and quality of life of treated patients increases (83-85) .
Knowing about the duration of effectiveness of botulinum toxin is also important. First effects after application are noticeable after about two days. Patients recognize the peak after two weeks lasting for about eight weeks. Afterwards, the effect of the substance decreases (86). In the majority, the effect lasts for about three months and injections should be repeated periodically.
However, therapy with botulinum toxin also has disadvantages. First, it is a very expensive treatment.
Sometimes, botulinum toxin therapy does not improve cervical dystonia. These non-responders may be primary or secondary. In the latter, therapy with botulinum toxin has induced the development of neutralizing antibodies, which decrease the effect of the drug. Over time, about 5 to 10% of the patients lose responsiveness to botulinum toxin (87). Alternatively, serotype B can be administered (56).
Also, every injection with botulinum toxin may cause side effects. The most common ones are dysphagia, neck weakness and local pain. But also symptoms like dizziness, dry mouth, or generalized weakness may occur due to wrong application sides. The higher the dose, the more frequent adverse effects occur (46,88).
Finally, there are some diseases constituting a contraindication for botulinum toxin therapy such as diseases of the neuromuscular transmission like myasthenia gravis, myopathy or motor neuron diseases. Also, pregnancy and lactation period belong to it. Anticoagulation is a relative contraindication (89).

Figure 9: Different types of botulinum toxin
(Botox® adopted from New Albany Surgical Hospital Foundation. Industry resources-Botulinum toxin Type A; Dysport® adopted from Ageless Pharmacy. Botulinum toxins-Dysport; Xeomin® adopted from Ageless Pharmacy. Botulinum toxins- Xeomin; Neurobloc® adopted from http://i.ytimg.com/vi/5BZSdAwY3-4/0.jpg)

1.2.6.2 Drugs

Pharmacological therapy for cervical dystonia includes a lot of different drugs such as anticholinergic agents, GABAmimetic agents (gamma-aminobutyric acid), and substances influencing the dopamine metabolism. Dopamine receptor agonists, dopamine receptor antagonists and dopamine-depleting agents belong to them.

Treating cervical dystonia, drug therapy is usually only used in combination with chemodenervation with botulinum toxin. Thus, reduction of pain and involuntary head movements can be achieved (90). Moreover, oral drug therapy may offer an alternative to botulinum toxin in non-responders.

For a long time, anticholinergic drugs have been the first-line oral treatment for cervical dystonia (90). One of these substances is trihexyphenidyl. Greene at al.

proved a better outcome in patients using anticholinergics than other drugs (91). Low doses in the beginning and slow dose titration are helpful to avoid side effects. Initially, dose of trihexyphenidyl should not pass 1 to 2.5 mg/day (milligram per day). The maximum dose may be as high as 50-100 mg daily. Basically, the dosage should be as low as possible with a satisfying effect. Nevertheless especially by using high dosages in severe stages, the appearance of side effects is possible. On one hand, there are treatable peripheral actions such as dry mouth or constipation. Cholinesterase inhibitor pyridostigmine has positive effects on them. On the other hand, central nervous system actions like confusion or memory loss can be recognized. The only way to improve these conditions is dose reduction (90-93).

Benzodiazepines and baclofen belong to the GABAmimetic agents. They are also used to treat cervical dystonia but with less effect than anticholinergics (91). When ending the therapy, both have to be discontinued slowly. Benzodiazepines are useful in patients with a mild stage of disease (94). They support and potentiate the neural inhibition which is achieved by GABA. One important side effect is sedation. Baclofen is a GABA receptor agonist and inhibits stimulus conduction (90). Side effects include lethargy, and dizziness (95). In individual cases, baclofen can be delivered intrathecally, which is currently only a research possibility (56).

Drugs influencing the dopamine metabolism include dopamine receptor agonists and antagonists as well as dopamine-depleting agents. Apparently, it is not important if dopaminergic neurotransmission is increased or decreased by the drug. These drugs seem to be less effective than anticholinergics and adverse effects occur as well (90). Dopamine-depleting drugs like tetrabenazine may cause depression or parkinsonism for example (96). Haloperidol, a dopamine receptor antagonist, sometimes generates tardive dyskinesia (90). The use of dopamine receptor agonists such as levodopa is restricted because cervical dystonia may get worse under this therapy (97).

A certain number of other drugs like lidocaine or mexiletine were considered to treat cervical dystonia but they have to be used with caution because of their potential side effects (98). Furthermore, botulinum toxin injections are the first-line treatment in patients with cervical dystonia (73,74).

An overview of all drugs for treatment of cervical dystonia is given in table 7 and 8.

Class of drugs	Active substance	Side effects
Anticholinergics	trihexyphenidyl	peripheral effects • dry mouth • blurred vision • constipation • urinary retention CNS effects • confusion • memory loss • hallucinations • behavioral changes
GABAmimetic agents	benzodiazepines (e.g. clonazepam) baclofen	benzodiazepines • sedation • confusion baclofen • lethargy • dizziness • gastrointestinal complaints • urinary frequency
Dopamine-depleting drugs	tetrabenazine	parkinsonism hypotension depression drowsiness fatigue
Dopamine receptor antagonists	haloperidol	tardive dyskinesia

Table 7: Different drugs for the treatment of cervical dystonia 1

Class of drugs	Active substance	Side effects
Dopamine receptor agonists	levodopa bromocriptine	worsening of dystonia
Others	lidocaine mexiletine	mexiletine • abdominal pain • nausea • cardiac conduction block in patients with heart disease

Table 8: Different drugs for the treatment of cervical dystonia 2

1.2.6.3 Surgery

For patients with cervical dystonia surgical approaches are often the last options to treat their disease. They are used if traditional pharmacotherapy and chemodenervation fail to provide sufficient relief of complaints. However, before conducting surgery symptoms should exist for at least more than one year (90). Currently, the most important methods are selective peripheral denervation and deep brain stimulation (DBS) (56).

Selective peripheral denervation has been developed by Bertrand (99) in the early 90's. For this purpose a posterior ramisectomy from C1 to C6 including denervation of the accessory nerve is conducted. Depending on the affected muscles, an additional myotomy or myectomy can be performed (100-102). It is an extradural and extraspinal method and only has few side effects like dysphagia or occipital neuralgia. Up to 60% of the patients with cervical dystonia benefit from this procedure. Nowadays however, selective peripheral denervation is not used very often compared with deep brain stimulation (103).

The globus pallidus internus (GPi) is the target of choice in deep brain stimulation for cervical dystonia. In this procedure microelectrodes are inserted bilaterally into the GPi (Figure 10). There are advantages as well as disadvantages of this technique. It has to be noted that this procedure is reversible, it is possible to adjust the stimulation parameters and continued access to the therapeutic target is guaranteed (56). However, infections, fractures, battery failures, and perioral tightness are possible side effects (104).

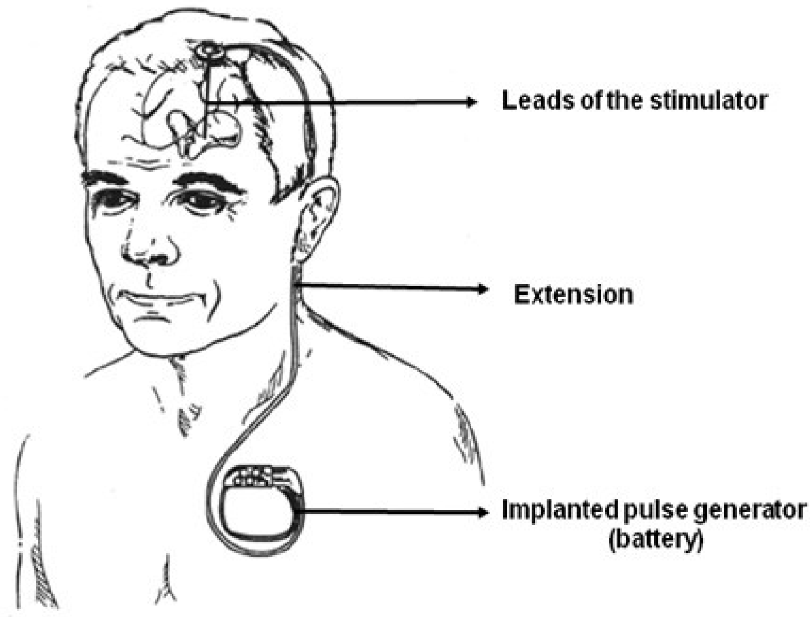


Figure 10: Scheme of deep brain stimulation (DBS) (adopted from the University of North Carolina at Chapel Hill School of Medicine, Department of Neurology. Deep Brain Stimulation- DBS)

1.2.6.4 Physiotherapy

Physiotherapy is often used in treatment of cervical dystonia. Sometimes, this method is practiced as a single therapy form but usually it supports treatment with botulinum toxin (105). Although scientific evidence is lacking, physiotherapy may be helpful in some patients (106). Physiotherapists have a wide range of different exercises but in general they create a rehabilitation program which targets selectively on the underperforming muscles and does not strain other muscles (105). At the beginning, a clinical examination of the patient should be conducted. On one hand, affected muscles are evaluated and on the other hand, standardized scales such as TSUI scale and TWSTRS have to be gathered. According to these facts, an individual therapy regime can be developed by the physiotherapist (107). Basically, there are four steps treating cervical dystonia. First, patients try to stop abnormal movements performing specific relaxation techniques. Then, movement to the opposite side of the torticollis should be practiced to strengthen the antagonistic muscles. Also, an overflow onto affected muscles has to be avoided.

Lastly, independent movements of the head replace spastic activity (108). Success of physiotherapy is dependent on the patient's motivation since exercises have to be performed consequently and every day (105). However, in combination with botulinum toxin injections symptoms can be reduced effectively (39).

1.2.7 Prognosis and outcome

First of all, the patient has to be informed by the physician that cervical dystonia is a non-fatal disease but additional symptoms such as head tremor or neck pain may occur (46). Cervical dystonia is often difficult to diagnose because of its discrete onset. Therefore, an accurate history and neurological examination is important (63). Nevertheless, sometimes it takes a while till the patients visit a movement disorder clinic and get the right diagnosis. In many cases, the disease progresses within the first five years before it stabilizes (51). It may spread segmentally but usually does not become generalized. In less than 20% of patients symptom remission occurs, but most of these patients suffer a relapse later (5).

Specific symptoms of cervical dystonia can be influenced by different factors. Activity, fatigue or stress can exacerbate these symptoms, whereas relaxation, alcohol and "geste antagoniste" may improve them (52,53).

Due to the lack of knowledge about etiology, therapy of cervical dystonia is not curative, but symptomatic. Before starting treatment, the most limiting factor such as abnormal posture, pain or tremor has to be evaluated and treatment should focus on the worst disability (46).

Today, chemodenervation with botulinum toxin is the most effective therapy of cervical dystonia compared with other methods like drugs or surgical intervention since it has a good effect on all symptoms (57,84,109-112).

1.3 Structural changes in the cervical spine in patients with cervical dystonia

In affected muscles, hypertrophy or muscle thickening can be found. Rarely, expanded neck size or asymmetry of the sternocleidomastoid muscle may occur if patients do not get a sufficient treatment over a long time (67). Regarding the bony structures, there is no evidence that degeneration of the cervical spine appears secondary due to cervical dystonia. According to the study of Risvoll and Kerty, degenerative osseous changes can be detected in almost 65% of patients with cervical dystonia (63). However, these changes rather seem to be age-related as imaging procedures also showed degenerative changes in asymptomatic subjects (113,114). Therefore, it is not proven that cervical dystonia is responsible for the occurrence of degenerative abnormalities.

Nevertheless, due to the good soft tissue visualization, an MRI of the brain and the cervical column in all patients with cervical dystonia is suggested by Dauer et al. (46).

1.3.1 Evidence for structural changes in patients with cervical dystonia

According to the guidelines of the German Society of Neurology, an MRI of the brain is recommended in every patient with idiopathic cervical dystonia (independent of the patient's age) as well as in patients with suspicion of secondary dystonia (115). This examination is proposed if additional symptoms such as pyramidal tract signs, ophtalmoplegia, and/or dementia occur. For documenting abnormalities such as spinal stenosis or radiculopathy, MRI of the cervical spine can be helpful (116).

1.3.1.1 Cranial magnetic resonance imaging

There are several studies analyzing changes of the brain in patients with cervical dystonia. However, abnormalities can only be evaluated in special imaging techniques because in conventional cranial magnetic resonance imaging usually no structural changes can be detected (117-121).

Risvoll and Kerty reported that conventional MRI showed no abnormalities of the brain compared to healthy controls. In 8.1% of patients with cervical dystonia atrophy could be detected, which was in concordance with findings in the normal population (63). Therefore, implementation of special MRI sequences is necessary (117).

In 1994, Schneider et al. measured extended MRI T2 times of the lentiform nucleus in idiopathic cervical dystonia. Proton density-weighted as well as T2-weighted imaging of the brain was assessed. T2 times of the bilateral putamen and pallidum summarized as lentiform nucleus were significantly increased. Since MRI images with focal lesions of the brain, which occur in the putamen for example, were excluded, the hypothesis that cervical dystonia may occur due to a dysfunction of the basal ganglia could not be supported in this study (117).

Furthermore, there are two studies using diffusion tensor imaging (DTI) of the brain in patients with cervical dystonia. Colosimo et al. evaluated 17 different regions of interest. They documented increased fractional anisotropy values in the left and the right putamen and decreased values in the corpus callosum. Additionally, lower mean diffusity values in the left pallidum and putamen as well as in the right and left caudate could be detected. This work suggests that a dysfunction of the basal ganglia may be responsible for cervical dystonia (122).

Another study about cervical dystonia and diffusion tensor imaging before and after treatment with botulinum toxin was published by Blood et al. (123). They observed a white matter hemispheric asymmetry in patients before botulinum toxin injection, which was not recognizable after botulinum toxin injections, and suggested that botulinum toxin has an indirect effect on motor afferent feedback to brain motor regions influencing the basal ganglia (124,125). Therefore, more studies are required to get further information about the influence of botulinum toxin on the central nervous system (123).

In addition to white matter abnormalities, grey matter changes have been observed. A study by Draganski et al. is based on a three-dimensional structural MRI with voxel-based morphometry (VBM) analysis. On one hand, they found a significant grey matter density increase in the right globus pallidus internus and also bilaterally in the motor cortex and the cerebellar flocculus. Based on grey matter increase, structural changes in the basal ganglia can be assumed. On the other hand, grey matter was decreased in the right caudal supplementary motor area and the right dorsal lateral prefrontal and occipital cortex. It is still unclear if these grey matter changes are the cause or the consequence of cervical dystonia (126).

Pantano et al. also performed a VBM study in patients with primary cervical dystonia. They found significant grey matter volume reduction in the left caudate head and putamen and bilaterally in the premotor and primary sensorimotor cortices. Contrary to the above mentioned study, no increase of grey matter volumes could be detected. However, grey matter abnormalities including the basal ganglia support the hypothesis that this region of the brain is involved in the pathophysiology of primary dystonia (127).

The above mentioned studies found different abnormalities in the brain of patients with cervical dystonia. Nevertheless, further studies are warranted to investigate the association of structural changes and pathophysiology of cervical dystonia which is still unclear.

1.3.1.2 Cervical spine magnetic resonance imaging

There are only a few studies investigating changes in the cervical spine in patients with cervical dystonia. Different opinions exist if an MRI of the cervical spine is necessary or useful. Dauer et al. proposed to do this examination in every patient with cervical dystonia in order to get more information about structural changes (46), whereas Kruer et al. suggested a cervical spine MRI only in patients with chronic dystonia. Thereby, abnormalities such as spinal stenosis or radiculopathy developing over many years can be documented (116).

There is only one study which evaluated magnetic resonance imaging of the cervical spine in patients with cervical dystonia compared to healthy participants. Reichel et al. used T1 and T2 weighted sequences observing structural changes in the cervical spine as well as in the soft tissues of the neck. Every neck muscle was analyzed according to its diameter and its shape. Additionally, head, neck and shoulder position was evaluated. Referring to the maximum diameter, they observed asymmetric neck muscles in more than 50% of the patients but also in the control group. Most affected muscles were the sternocleidomastoid muscle, the obliquus capitis inferior muscle, the splenius capitis muscle, the levator scapulae muscle and the scalenus anterior muscle. According to the shape of a muscle, asymmetry could only be detected in the levator scapulae muscle and the obliquus capitis inferior muscle, but in less than 30% of all cases. They concluded that an imaging investigation is necessary to get information about the origin or the attachment of the affected muscle. This knowledge is obligatory for the treatment with botulinum toxin. In their opinion, an MRI of the cervical spine is also required if treatment with botulinum toxin is not successful (128).

1.3.2 Differences in patients with and without cervical spine changes

There are a number of different symptoms in patients with cervical dystonia. Patients may suffer from neck pain, tremor, and several abnormal postures. Also, response to botulinum toxin as the first-line treatment of cervical dystonia can vary from good results to non-responders and the reason for non-responsiveness is not always clear.

So far, no study investigated the association of imaging abnormalities and clinical outcome parameters.

The aim of our study includes following target questions:

1. Are structural abnormalities in the MRI of the spine more common in patients with cervical dystonia compared to age-matched healthy controls?
2. Are there any differences in clinical symptoms in patients with cervical dystonia having an abnormal or inconspicuous MRI of the cervical spine?
3. Are there clinical predictors for significant abnormalities in the magnetic resonance imaging of the cervical spine?
4. Are there any clinical parameters which strengthen the indication for an MRI of the cervical spine in patients with cervical dystonia?

We hypothesized that patients with cervical dystonia show structural abnormalities in the MRI of the spine more frequently compared to age-matched healthy controls.

We further hypothesized that patients with cervical dystonia and abnormalities in the MRI of the cervical spine differ with regard to clinical parameters from those with normal MRI.

2 Methods

2.1 Data protection/Ethics committee

We conducted a consecutive case-control study to investigate patients with cervical dystonia. It was part of the so-called PROMOVE study (prospective data collection study in patients with movement disorders). Application for ethical approval was accepted by the ethical committee of the Medical University of Graz, Austria (21-345 ex 09/10).

Prior to the study, all participants had to sign an informed consent. Consecutive numbers were assigned to every recorded participant, which guaranteed pseudo-anonymization. These numbers including results of baseline and follow-up examination as well as MRI ratings were gathered in a Microsoft Office Excel Table. Only investigators involved in the study had access to original data.

2.2 Data collection

All patients with cervical dystonia seen between August 2011 and August 2013 at the movement disorders outpatient clinic of the Department of Neurology, Medical University of Graz, Austria were invited to participate in our study. Those who agreed to take part and fulfilled inclusion and exclusion criteria were enrolled. Data were collected during a baseline visit and a follow-up examination after three months. All subjects had an MRI of the cervical spine between three months before the baseline visit and three months after the follow-up visit. Healthy control subjects had a baseline clinical examination and an MRI of the cervical spine.

2.2.1 Clinical examination

Baseline and follow-up examination took place in a three-monthly interval, in which identical data were collected. These included inquiry of demographical data and medical history, and a standardized neurological examination and performance of various rating scales as listed below.

2.2.1.1 Demographics and medical history

First of all, a detailed medical history was inquired. This included age at onset and progression of cervical dystonia, treatment and response to botulinum toxin, potential secondary causes like trauma or head, neck, and spine surgery. Family history and long-term medication were evaluated as well. Additionally, age, sex, and disease duration were evaluated.

2.2.1.2 Neurological examination

In all subjects a detailed neurological examination was performed.

Cranial nerves, with the exception of olfactory and vestibulocochlear nerves, were evaluated one after the other. Changes in smelling and hearing were only subjectively inquired. The optic nerve was checked by visual acuity and visual field testing. To assess eye movements, smooth pursuit and saccades were tested. Also, pupil reaction was evaluated. Examination of trigeminus nerve included its three pressure points and sensitivity testing of both sides of the face. Frowning, wrinkling the nose, whistling and baring the teeth showed normal function of the facial nerve. Adequate movement of the soft palate and missing of hoarseness represented intact glossopharyngeal and vagus nerve functions. Accessory nerve was evaluated by testing the sternocleidomastoideus and the trapezius muscles. Finally, normal movement of the tongue to both sides showed an intact hypoglossal nerve.

Evaluating motor status, muscle trophism and muscle tone as well as muscle strength were investigated. Monosynaptic reflexes like biceps, triceps, brachioradial, patellar and achilles tendon reflexes were tested. Also, Babinski reflex as a pathological pyramidal sign was examined. Sensibility was divided into superficial sensory function and proprioception. There were several tests checking coordination and gait of the patient: finger-nose test, heel-knee test, diadochokinesis, walking, tandem gait, Romberg's test and Unterberger's test.

Aim of this detailed examination was the detection of movement disorders and symptoms and signs of root or myelon compression.

The detailed neurological examination is illustrated in Appendix 4.

2.2.1.3 Rating scales

In our study we used three different rating scales considering all aspects of cervical dystonia. We performed the TSUI Score, the Toronto Western Spasmodic Torticollis Rating Scale and the Burke-Fahn-Marsden Scale.

The **TSUI** Score focuses on the observation of head and neck movements.
The attending physician determined the severity of cervical dystonia by observing the abnormal head position in the patients sitting in an upright position without leaning against the chair. Additionally, the presence of tremor and shoulder elevation was evaluated. Head rotation, lateral head tilt, anterocollis, retrocollis, and shoulder elevation were each rated with 0 to 3 points. The duration of movement (intermittent or constant) was rated with 1 or 2 points. Severity of tremor was rated with 0 to 2 points and the duration of tremor was evaluated with occasional (1 point) or constant (2 points). The total score was calculated by using following formula: (subpoint A x subpoint B) + subpoint C+ subpoint D. The maximum total score is 25 points. Additionally, pain level was rated with 0 to 3 points. TSUI Score is presented in Appendix 1 (57).

TWSTRS evaluates disabilities in everyday activities in patients with cervical dystonia. The scale also assesses the presence of pain and sensory tricks and their influence in daily tasks.
Zero to 5 points were given depending on the limitation in daily-life. TWSTRS is divided in three subscales. Subscale I was omitted from our study because of its similarity to the TSUI Score. Subscale II refers to disability and has a maximum of 30 points. Pain Scale (Subscale III) has a maximum score of 20 points. TWSTRS is displayed in Appendix 2 (53).

The **Burke-Fahn-Marsden Scale** assesses dystonia in nine different parts of the body. These included eyes, mouth, speech and swallowing, neck, trunk, left and right arm and leg. For every body part, a provoking factor (0-4 points) and severity (0-4 points) were determined by the examiner. Finally, values were multiplied with 0.5 or 1.0. The maximum total sum is 120 points. BFM Scale is described in Appendix 3 (59).

2.2.2 MRI of the cervical spine

Every participant in our study underwent a 3Tesla (3T) MRI of the cervical spine at the Department of Radiology, Division of Neuroradiology, Medical University of Graz, Austria according to a standardized protocol. Ten subjects had received a routine MRI of the cervical spine (1.5 Tesla) within three months prior to the baseline visit at an external radiologic clinic and did therefore not receive another scan at our institution.

MRI of the cervical spine was performed in supine position on a 3.0-T whole-body scanner (Trio; Siemens, Erlangen, Germany). Our protocol included sagittal T2-weighted TSE (Turbo spin echo) sequences (TR 4000, TE 112 ms, slice thickness 3 mm) and sagittal T1-weighted TSE sequences (TR 550, TE 11 ms, slice thickness 3 mm). No Intravenous contrast agent was given.

MRI images were imported into PACS VIEW (radiologic workstation to evaluate and compare images). Three experienced neuroradiologists, who were blinded to the diagnosis of the participants, independently analyzed all available scans according to a standardized protocol. The grading system was introduced by raters training and by a written description including pictorial or diagrammatic examples.

Raters evaluated each cervical spine segment (C2/C3 to C6/7) and the whole cervical spine (C2-C7) by eight scales, which focused on different radiologic abnormalities.

1. According to a scale published by *Kang et al. 2010*, T2-weighted, sagittal images were used to assess **cervical canal stenosis**. Grade 0 refers to the absence of central canal stenosis. Almost total obliteration of subarachnoid space including obliteration of the arbitrary subarachnoid space by more than 50% but without signs of cord deformity describes Grade 1. In Grade 2 central canal stenosis with spinal cord deformity but without spinal cord signal changes is found. Existence of signal changes of the spinal cord close to the compressed level represents Grade 3. In contrast to the study by Kang et al., each cervical segment was evaluated (Table 9) (129).

Cervical Canal Stenosis (Kang)	
Grade 0	absence of central canal stenosis
Grade 1	nearly complete obliteration of subarachnoid space, including obliteration of the arbitrary subarachnoid space exceeding 50%, without signs of cord deformity
Grade 2	central canal stenosis with cord deformity but without spinal cord signal change
Grade 3	presence of spinal cord signal change near the compressed level on T2-weighted images

Table 9: Cervical canal stenosis (adopted from Kang et al. New MRI grading system for the cervical canal stenosis, 2011)

Following figures (Figures 11-14) show the different grades of the scale "cervical canal stenosis" by Kang et al. (129).

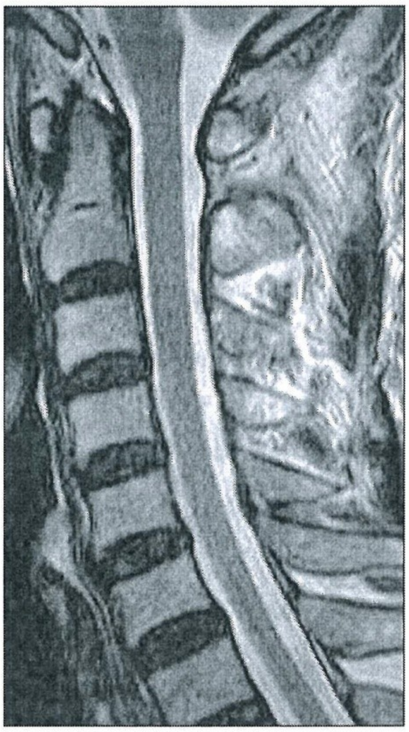


Figure 11: Grade 0
(adopted from Kang et al. New MRI grading system for the cervical canal stenosis, 2011)

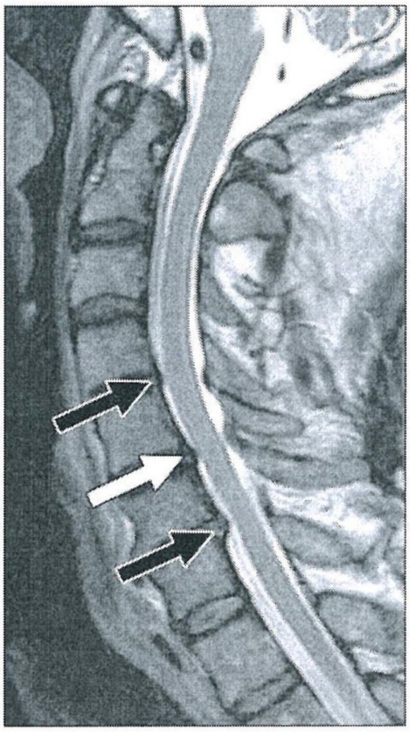
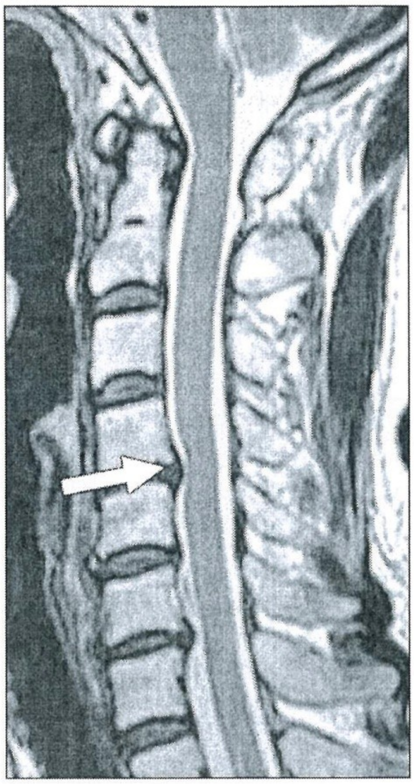


Figure 12: Grade 1
(adopted from Kang et al. New MRI grading system for the cervical canal stenosis, 2011)



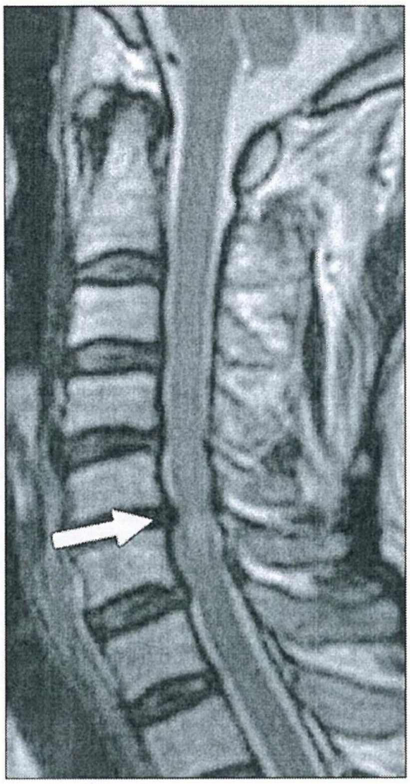


Figure 13: Grade 2
(adopted from Kang et al. New MRI grading system for the cervical canal stenosis, 2011)

Figure 14: Grade 3
(adopted from Kang et al. New MRI grading system for the cervical canal stenosis, 2011)

2. According to *Matsumoto et al.* we analyzed different degenerative changes in the cervical intervertebral discs by MRI and evaluated disc degeneration by loss of signal intensity, posterior and anterior disc protrusion, narrowing of the disc space and foraminal stenosis. In each subject, five disc levels from C2/C3 to C6/C7 and C2-C7 were evaluated (five different subscales) (130).

Subscale 1 refers to **disc degeneration** in the cervical spine. It is classified into Grades 0 to 2 according to changes on T2-weighted sagittal images. The raters evaluated brightness of the intervertebral discs. If they are bright as or slightly less bright than CSF, it is Grade 0. Grade 1 refers to presence of dark and/or speckled disc changes. Grade 2 describes almost black discs (Table 10) (130).

Disc Degeneration (Matsumoto)	
Grade 0	bright as or slightly less bright than CSF
Grade 1	dark and/or speckled
Grade 2	almost black

Table 10: Disc degeneration (adopted from Matsumoto et al. MRI of cervical intervertebral discs in asymptomatic subjects, 1998)

Subscale 2 (**posterior disc protrusion**) was omitted because of its similarity to Kang et al. (see above) (130).

Subscale 3 evaluates **anterior disc protrusion** and is divided in to Grade 0 and 1. If on T1-weighted sagittal images disc material is protruding beyond the anterior margin of the vertebral body, it is rated as Grade 1 while Grade 0 represents normal imaging (Table 11) (130).

Anterior Disc Protrusion (Matsumoto)	
Grade 0	disc material confined within the anterior margin of the vertebral body
Grade 1	disc material protruding beyond the anterior margin of the vertebral body

Table 11: Anterior disc protrusion (adopted from Matsumoto et al. MRI of cervical intervertebral discs in asymptomatic subjects, 1998)

Subscale 4 evaluates **narrowing of the disc space** on sagittal scans. Compared to the normal disc space, Grade 0 has no narrowing or less than 25% loss in height. Grade 1 has between 25 to 50% height reduction and Grade 2 has more than 50% reduction in height (Table 12) (130).

Narrowing of the disc space (Matsumoto)	
Grade 0	no narrowing or less than 25% loss in height compared with the most adjacent normal disc space
Grade 1	25% to 50% loss of height
Grade 2	more than 50% loss of height

Table 12: Narrowing of the disc space (adopted from Matsumoto et al. MRI of cervical intervertebral discs in asymptomatic subjects, 1998)

Subscale 5 describes **foraminal stenosis** on T1-weighted sagittal images. Grade 0 refers to no obliteration of intraforaminal fat. Grade 1 refers to uni- or bilateral obliteration of intraforaminal fat by disc material or osteophytes (Table 13) (130).

Foraminal Stenosis (Matsumoto)	
Grade 0	no obliteration of intraforaminal fat
Grade 1	disc material or bony spurs obliterating intraforaminal fat unilaterally or bilaterally

Table 13: Foraminal stenosis (adopted from Matsumoto et al. MRI of cervical intervertebral discs in asymptomatic subjects, 1998)

3. The **MODIC score** assesses MRI signal intensity changes in vertebral body marrow adjacent to the endplates of degenerative discs. According to the MODIC scale, the raters can distinguish between three types depending on hypo- or hyperintense signal in T1 and T2 weighted sagittal images. Normal images are scored as 0. Type 1 describes presence of hypointense signal in T1-weighted images and hyperintense signal in T2-weighted images. Hyperintense signal in T1-weighted and also in T2-weighted images correlates with Type 2. Type 3 refers to hypointense signal in T1- and T2-weighted images (Table 14) (131).

Modic classification (Modic)	
Type 1	hypointense signal in T1-weighted imaging and hyperintense signal in T2-weighted imaging corresponding to vertebral body edema and hypervascularity
Type 2	hyperintense signal in T1-weighted imaging and hyperintense signal in T2-weighted imaging reflecting fatty replacements of the red bone marrow
Type 3	hypointense signal in T1-weighted imaging and hypointense signal in T2-weighted imaging consisting of subchondral bone sclerosis

Table 14: Modic classification (adopted from Modic et al. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging, 198)

MRI images listed below (Figures 15-17) show the three different types of the Modic classification (131).

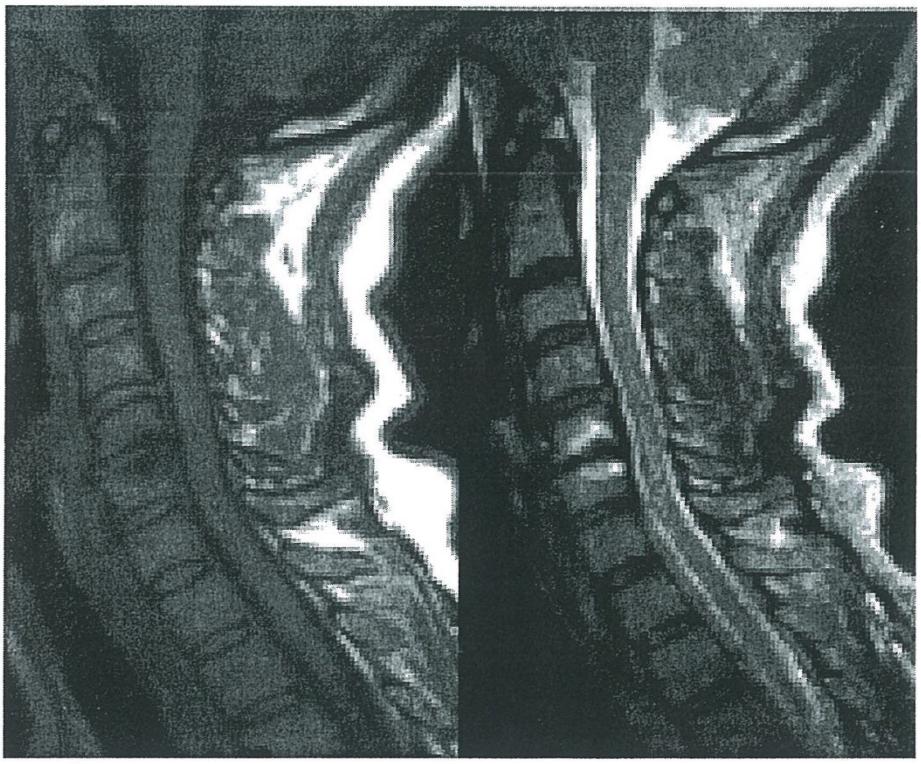


Figure 15: Type 1 (adopted from Modic et al. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging, 1988)

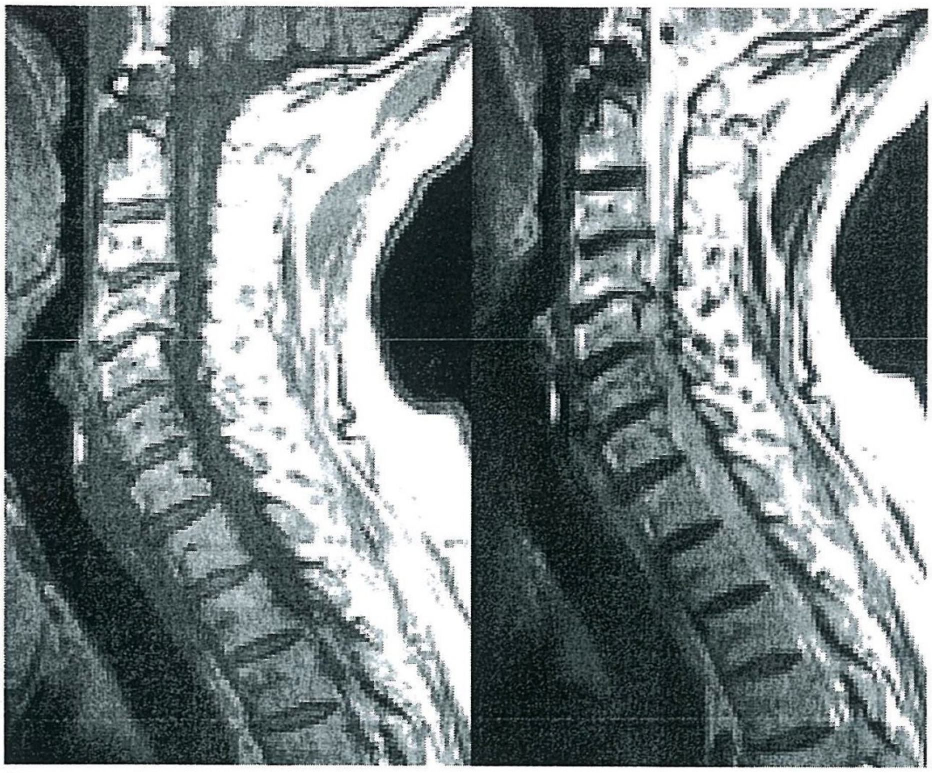


Figure 16: Type 2 (adopted from Modic et al. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging, 1988)

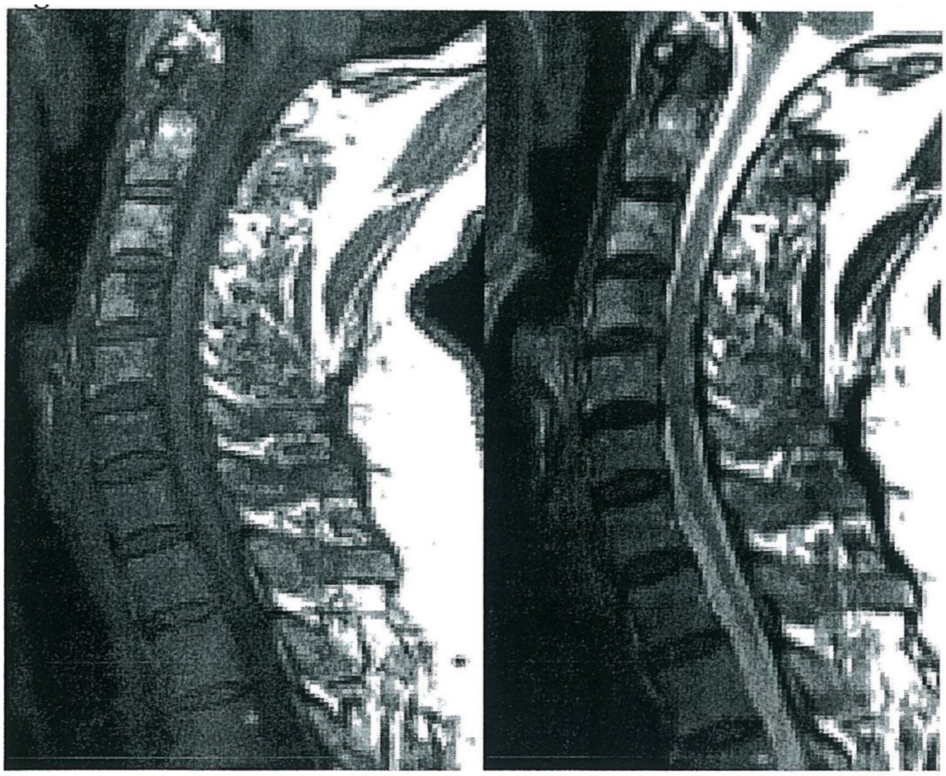


Figure 17: Type 3 (adopted from Modic et al. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging, 1988)

2.2.3 Inclusion criteria

All patients with cervical dystonia who agreed to participate in our study and were willing to sign an informed consent were included in our study.

2.2.4 Exclusion criteria

People with contraindication for magnetic resonance imaging were excluded from our study. This refers to patients with claustrophobia or pregnant women. Also, people with metal implants for example cardiac pacemaker, metal clips, cochlear implants or shell splinters were excluded.

2.2.5 Control group

The control group of our study consisted of healthy, neurological inconspicuous participants who agreed with our study procedures. Patients with contraindication for MRI were not included in our study. All of them had a baseline clinical examination (medical history, complete neurologic examination, and rating scales). Additionally,

an MRI of the cervical spine was performed according to the protocol described above.
We tried to match the control group in decades based on their age. The first three decades (21-30, 31-40, 41-50 years) were 1:1 matched. In higher age, matching was more difficult (see 3.1.2 Age).

2.2.6 Data evaluation

All participants of our study received a serial number for pseudo-anonymization. Patients with cervical dystonia and healthy control participants were separated into two groups. Collected data were summarized in Microsoft Office Excel Table. For evaluation, predictive analytics was used. Statistical analysis was performed using program SPSS and R.
First of all, we determined different demographic data like age and sex ratio. (see 3.1 General)
Following this, we specified the inter-rater reliability for MRI images of the cervical spine in our study population. On one hand, we calculated the intraclass correlation coefficient (ICC) for different scales: Kang's cervical canal stenosis, Matsumoto's disc degeneration, narrowing of the disc space and the Modic classification. Additionally, we calculated the sum score of all subscales of Matsumoto (Matsumoto total score) as well as the total score of all scales for each segment of the cervical spine (MRI total score). We also calculated the ICC for these two total scores. On the other hand, we used Fleiss' kappa (κ) value to evaluate inter-rater reliability of Matsumoto's anterior disc protrusion and foraminal stenosis because of their binary variables.
Next, we calculated the mean for every scale and every segment of the MRI images and correlated different clinical parameters with the structural changes in MRI images. The unstandardized regression coefficient B as well as the significance level p were calculated with the help of a linear regression. A p-level of <0.05 was considered significant. In total, 20 clinical parameters were correlated with cervical spine changes in MRI images. All calculations were adjusted for age and sex. Additionally with regard to the duration of botulinum toxin therapy of our patients, the results were adjusted for age, sex and disease duration.

2.2.7 Literature research

Literature research was conducted in PubMed and google.

3 Results

3.1 General

In total, 51 people took part in this study. 58.8% of them (n=30) suffered from cervical dystonia, whereas 41.2% (n=21) participated as healthy controls (Figure 18).

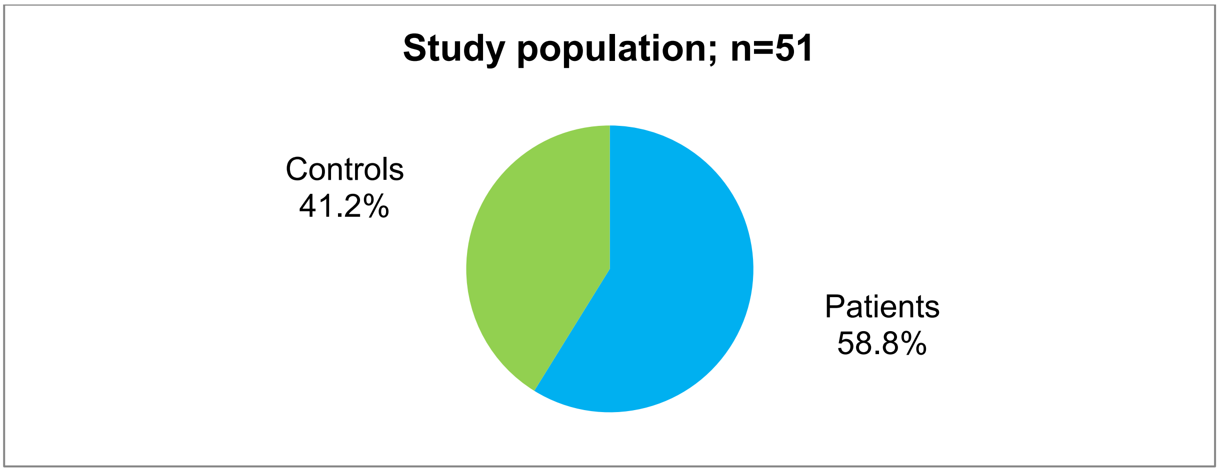


Figure 18: Study population

3.1.1 Gender

Out of 30 patients with cervical dystonia, 73.3% were female (n=22) and 26.7% were male (n=8) (Figure 19).

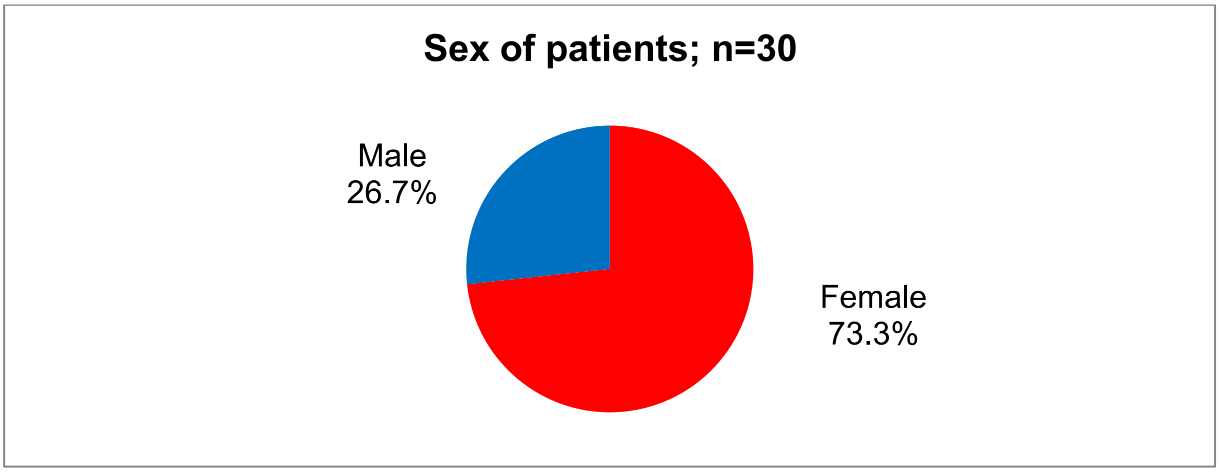


Figure 19: Sex ratio 1

In our control group, 71.4% were women (n=15) and 28.6% were men (n=6) (Figure 20).

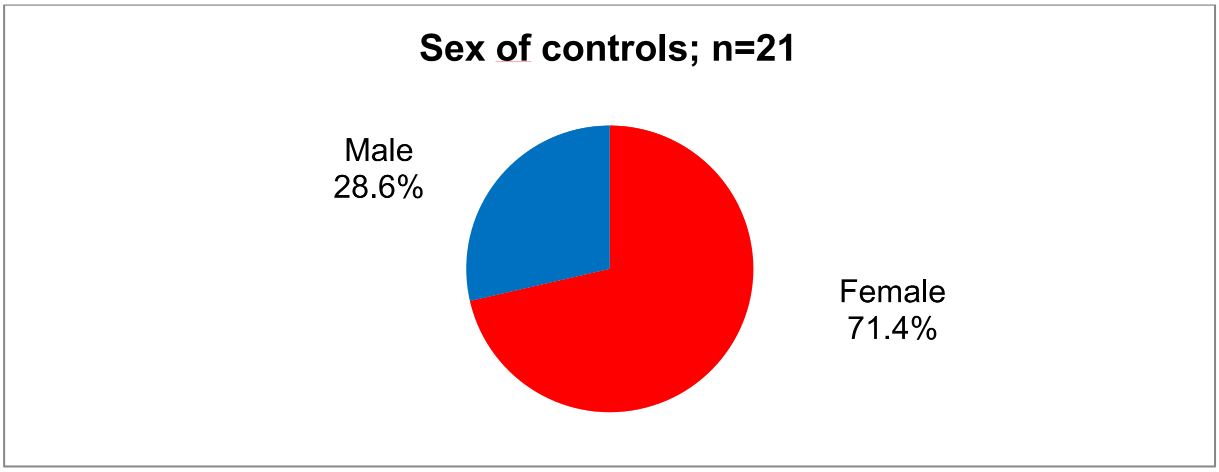


Figure 20: Sex ratio 2

Sex ratio between our patients and healthy controls did not reveal any significant difference between both groups (p=0.881). Women were matched at a ratio of 1.5:1 (patients:controls) and men were matched at a ratio of 1.3:1 (patients:controls). The following figure (Figure 21) shows the sex ratio between our patients and controls.

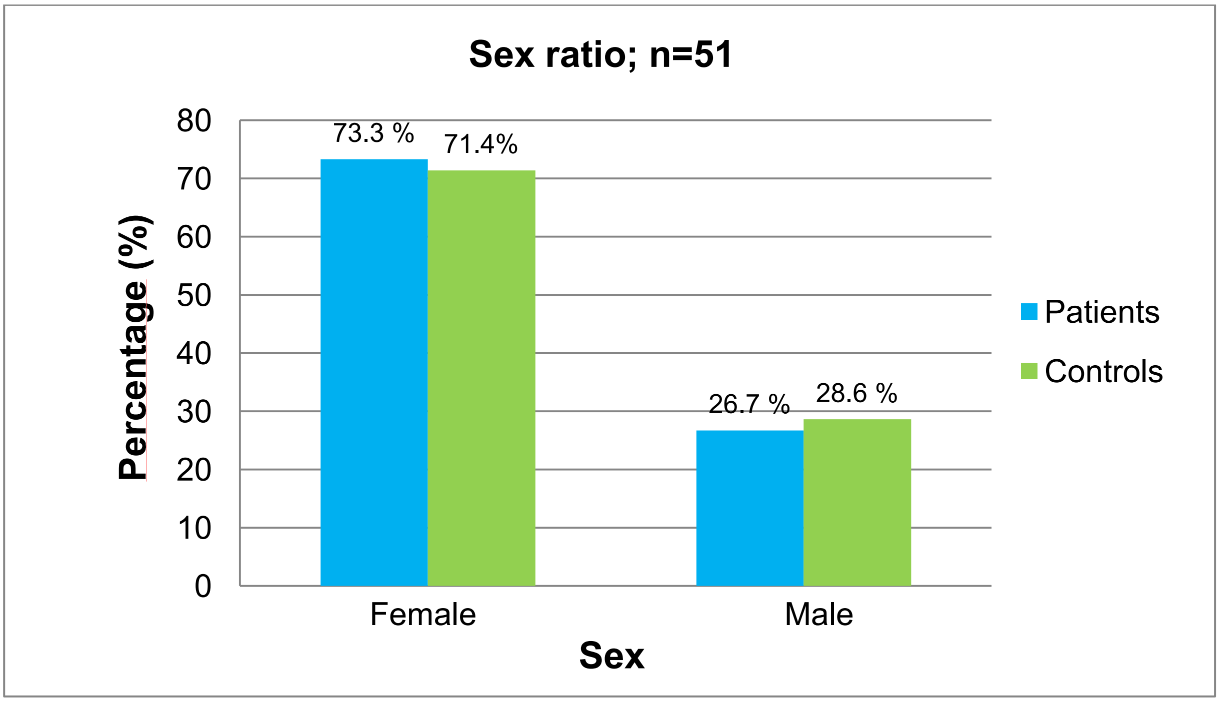


Figure 21: Sex ratio 3

3.1.2 Age

The mean age of our patients was 58.7 ± 14.1 years (median 61 years, range from 27 to 75 years). In the control group, the mean age was 55.5 ± 16.3 years with a median of 59 years and ranged from 26 to 79 years (Figure 22).

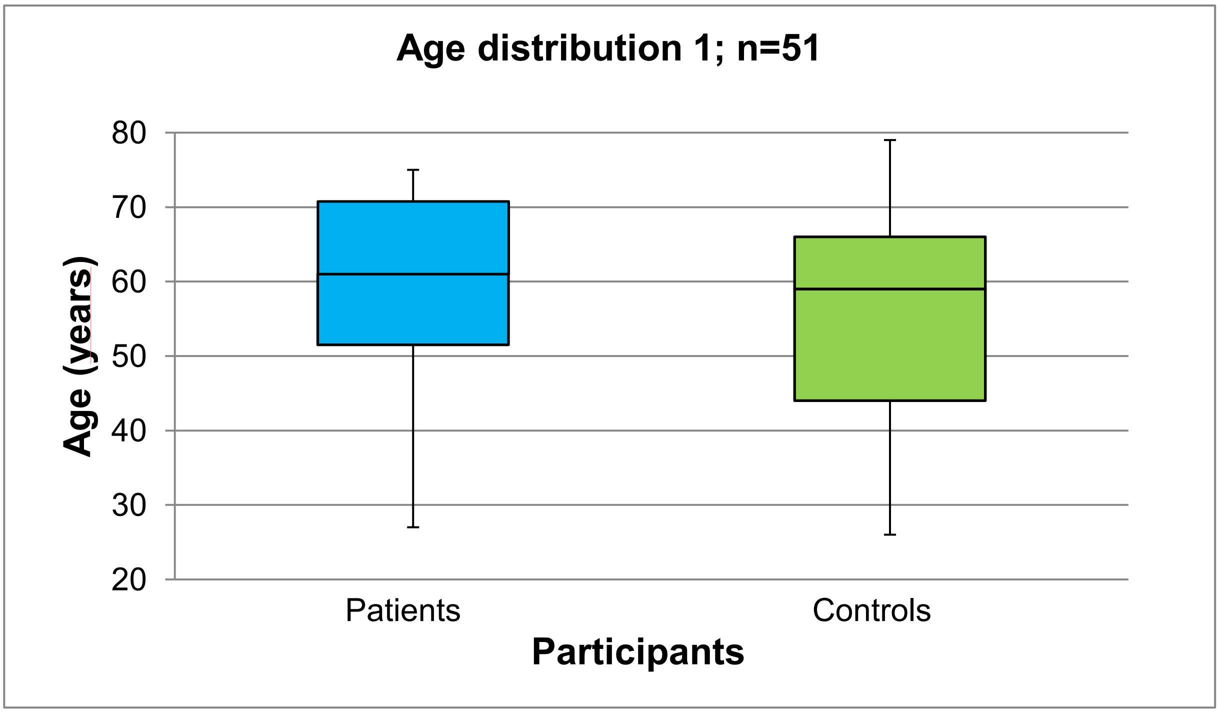


Figure 22: Age distribution 1

Furthermore, age distribution based on decades was compared between patients and controls (Figure 23). In the first three decades (21-30; 31-40; 41-50 years), patients and controls were 1:1 matched. Between age 51 to 60 patients were matched at a ratio of 1.6:1 (patients:controls). The following decade (61-70 years) showed a ratio of 1.4:1 (patients:controls) and in the last decade (71-80 years) the ratio was 2:1 (patients:controls). Comparison of both groups with regard to the decades did not show any statistical significant difference (p=0.449).

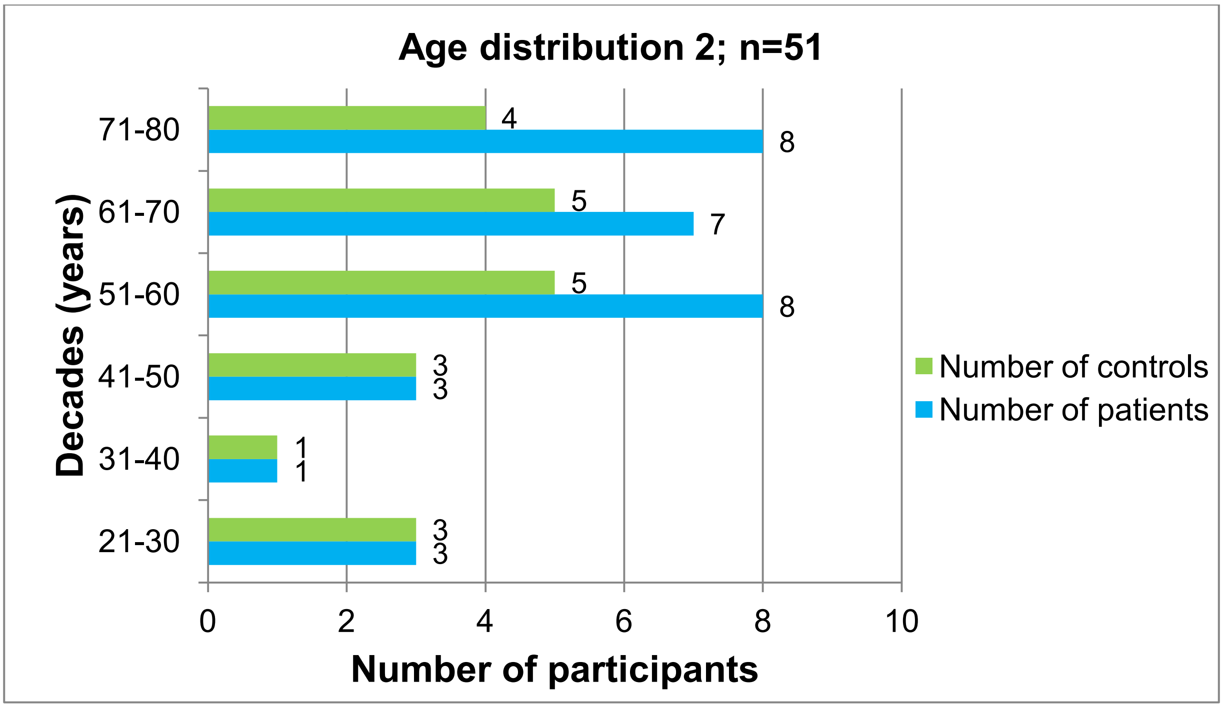


Figure 23: Age distribution 2

3.1.3 Medical history

A detailed medical history of all patients with cervical dystonia was taken. Age at onset varied from 5 to 70 years with a mean of 42.0 ± 17.3 years and a median of 45 years. The following figure (Figure 24) illustrates the distribution of age at onset based on decades.

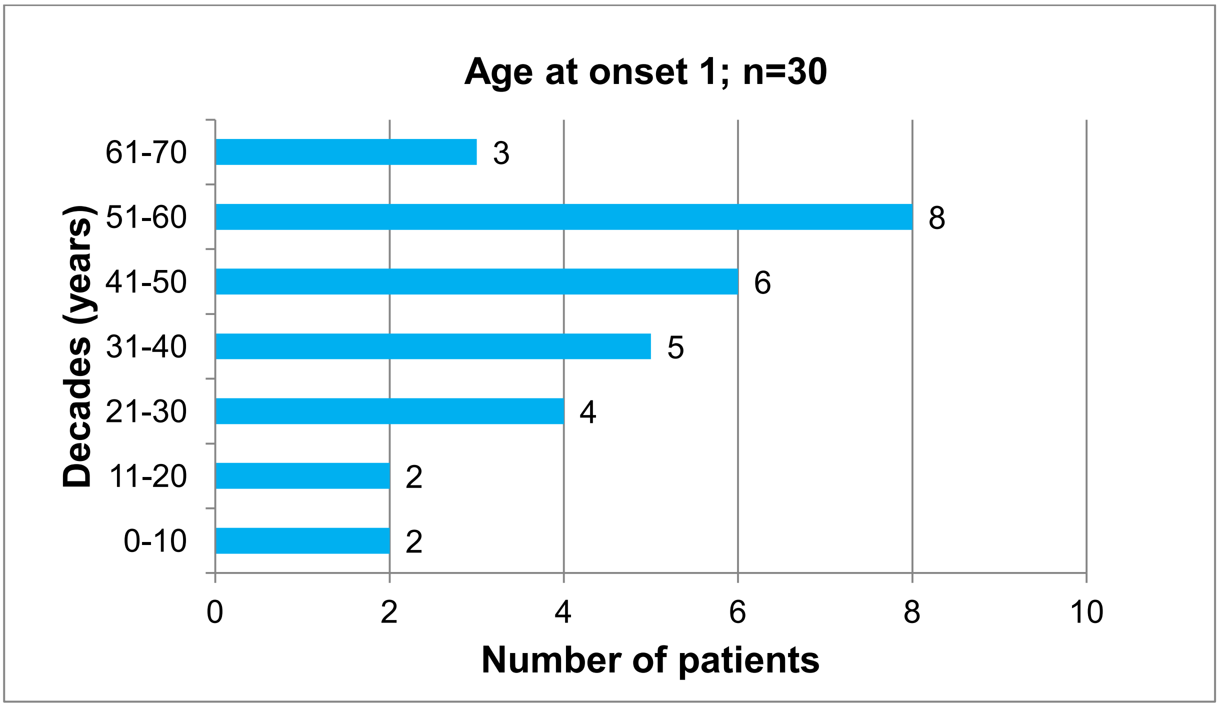


Figure 24: Age at onset in patients with cervical dystonia 1

Disease duration ranged from 0.5 to 35 years. Mean disease duration was 15.8 ± 11.4 years with a median of 15.5 years. The following figure (Figure 25) shows the distribution of disease duration based on 5-year intervals.

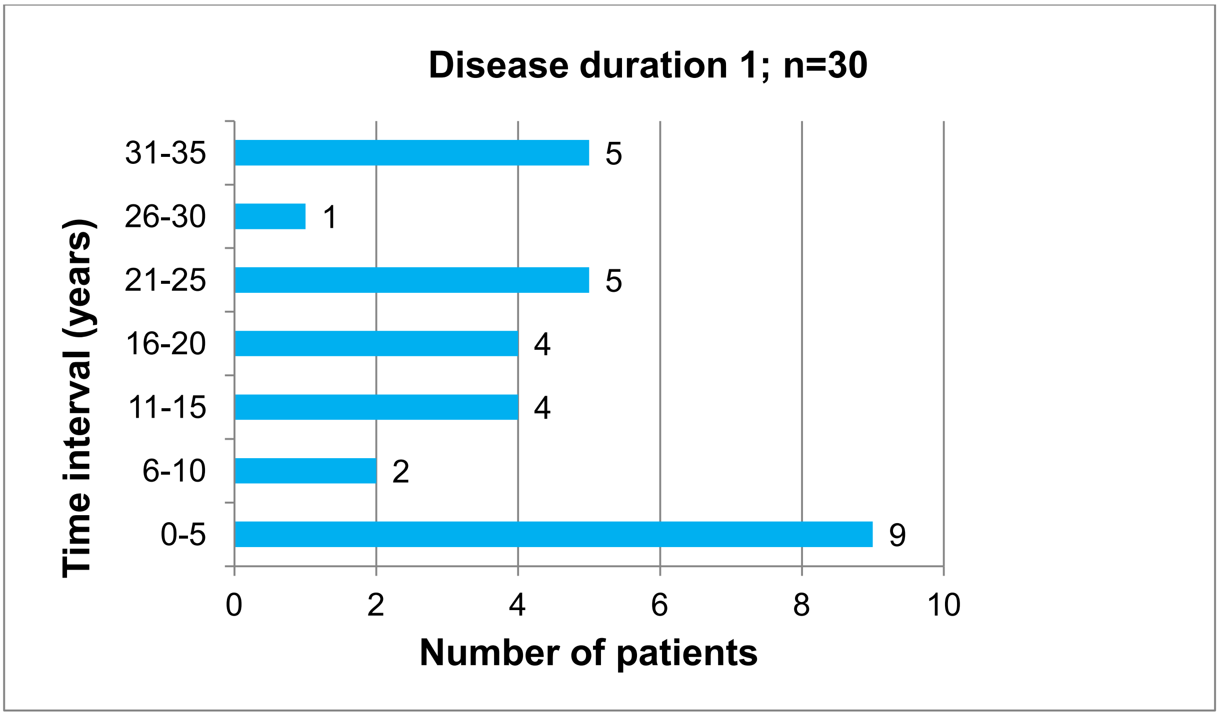


Figure 25: Disease duration 1

The following boxplots (Figures 26-27) show the distribution of age at onset and of the disease duration in our patients.

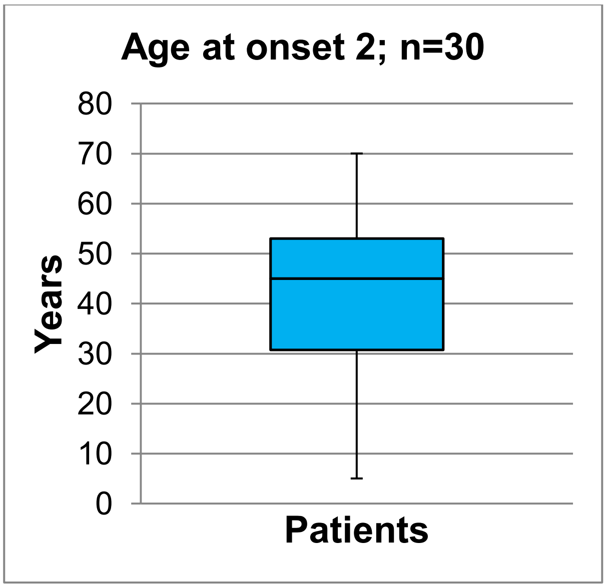


Figure 26: Age at onset in patients with cervical dystonia 2

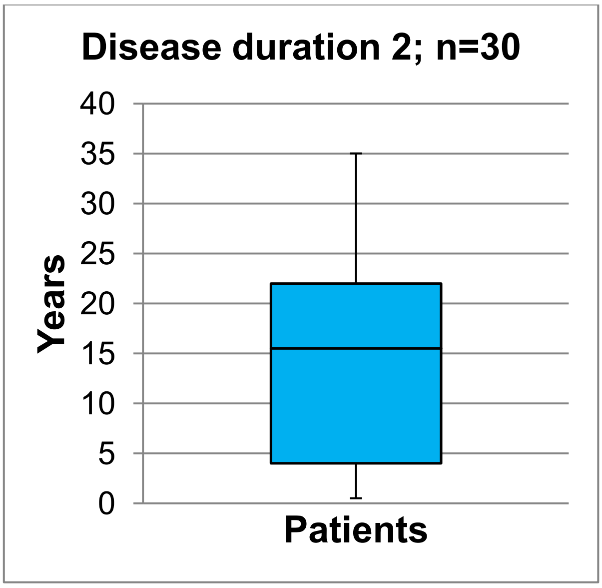


Figure 27: Disease duration 2

66.7% of the patients (n=20) had a negative family history for dystonia, in 33.3% of the patients (n=10) the family history was positive (Figure 28).

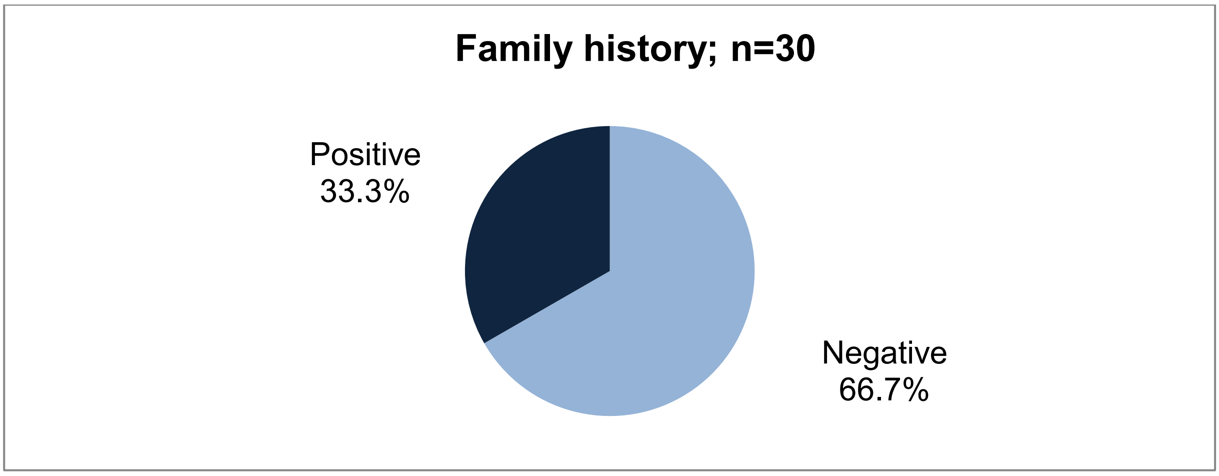


Figure 28: Family history

80% of the patients (n=24) did not have any history for a head or neck trauma. 20% (n=6) reported a trauma to the head or neck prior to the disease onset (Figure 29).

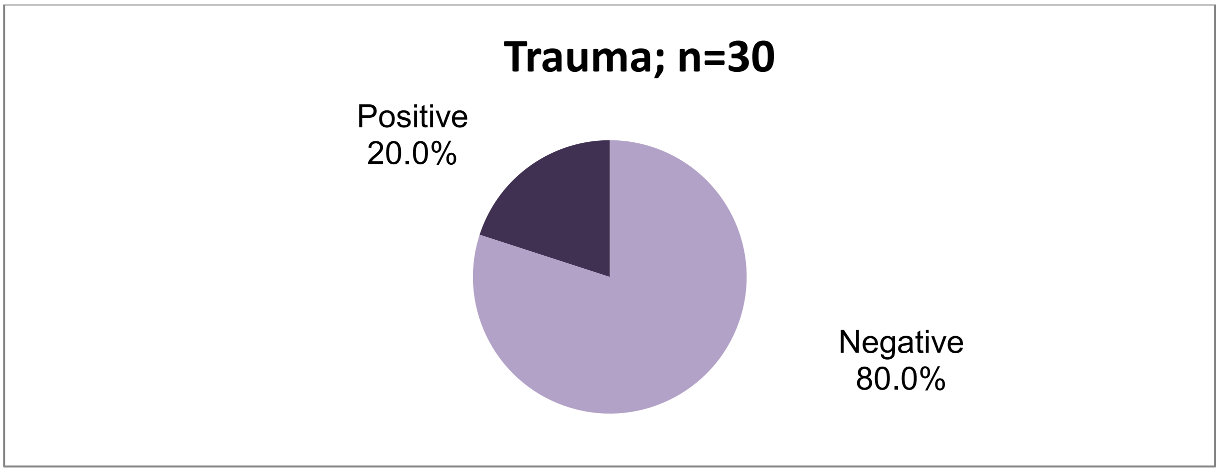


Figure 29: Precipitating trauma

With regard to the type of dystonia, 83.3% (n=25) suffered from isolated cervical dystonia. In contrast, 16.7% of our participants (n=5) showed a segmental distribution with adjacent body parts affected (Figure 30).

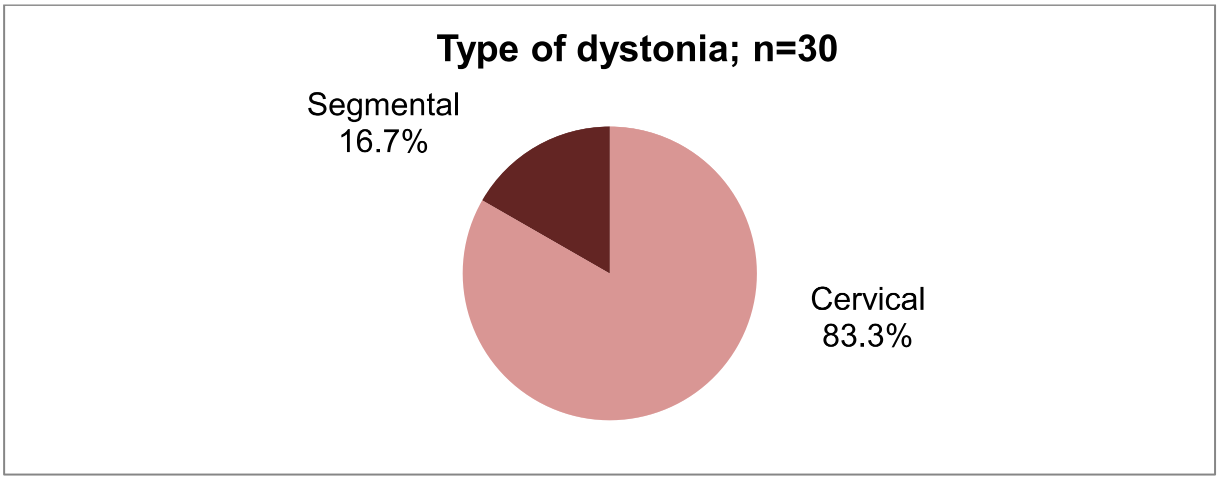


Figure 30: Type of dystonia

Out of 30 patients, 90% (n=27) were treated with botulinum toxin injections. The drug most commonly used was Dysport® (83.3% (n=25)), Botox® and Xeomin® was given to 3.3% each (n=1 each). Three patients (10%) did not receive any treatment with botulinum toxin. The following figure (Figure 31) shows the distribution of the different types of botulinum toxin in our study participants.

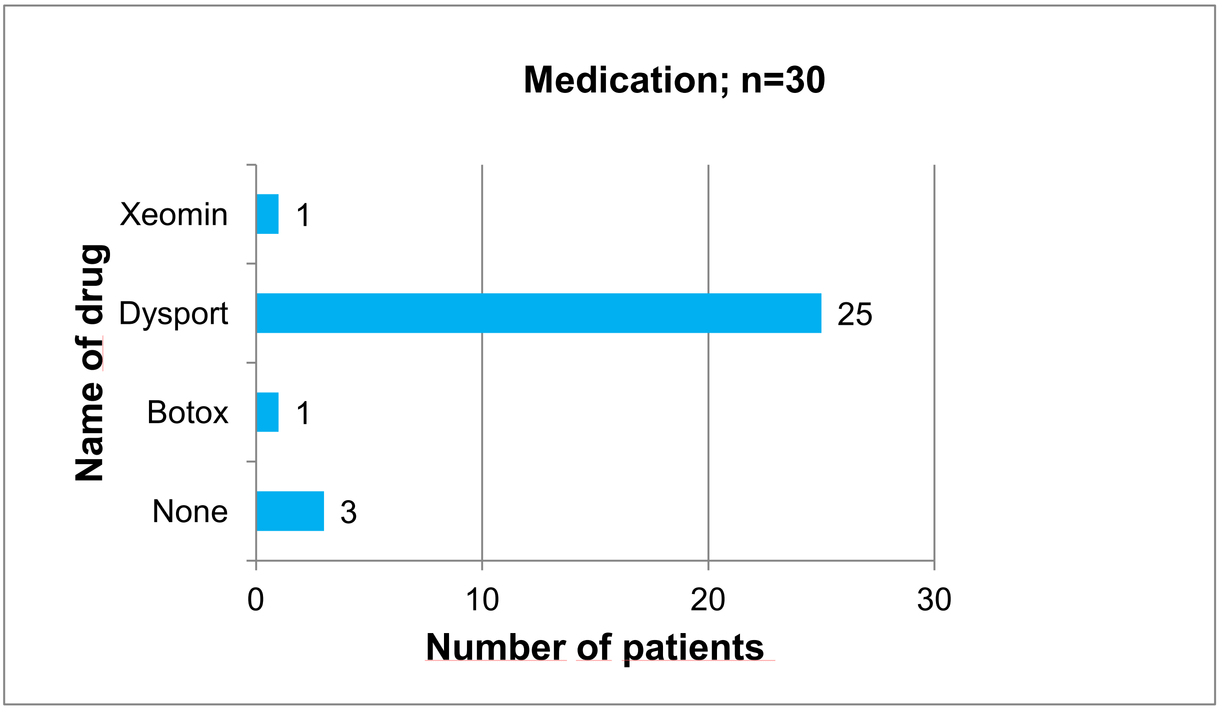


Figure 31: Botulinum toxin therapy

Potential side effects were evaluated in 70% of the patients (n=21). Out of 21 patients, no side effects were reported by 76.2% (n=16) whereas 23.8% (n=5) suffered from side effects like dysphagia, local pain or weakness of the neck (Figure 32).

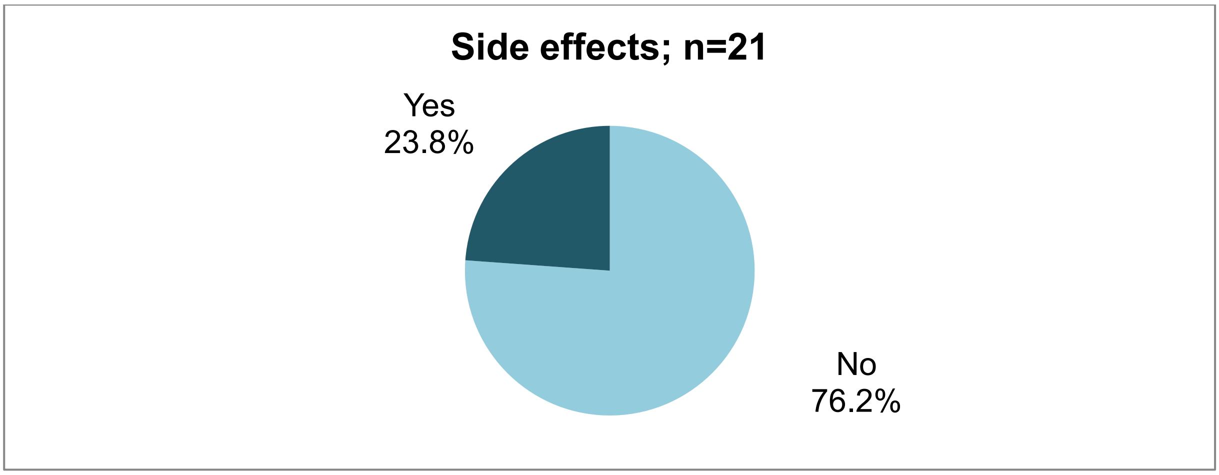


Figure 32: Side effects of botulinum toxin therapy

3.1.4 Patients with botulinum toxin therapy

Twenty-seven patients on botulinum toxin injections were included in this subanalysis.

Duration of botulinum toxin therapy ranged from 1 to 23 years with a mean of 7.3 ± 5.9 years and a median of 7 years. Figure 33 illustrates the duration of botulinum toxin therapy based on 5-year intervals.

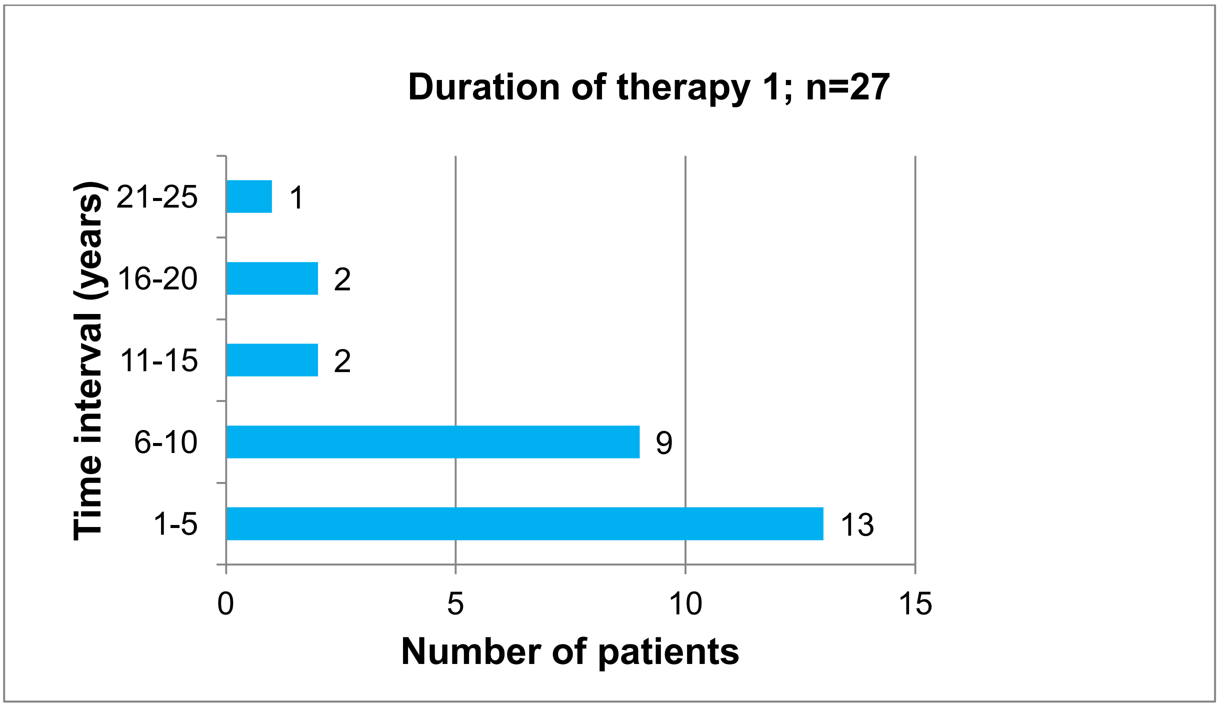


Figure 33: Duration of botulinum toxin therapy 1

Dosage of botulinum toxin at baseline examination varied from 150 to 900 MU Dysport® with a mean value of 467.4 ± 187.7 MU and a median of 400 MU. The dosage of the two patients on Botox® and Xeomin® were converted to Dysport® equivalent (conversion factor: Botox®:Xeomin®:Dysport® 1:1:3) (Figure 34).

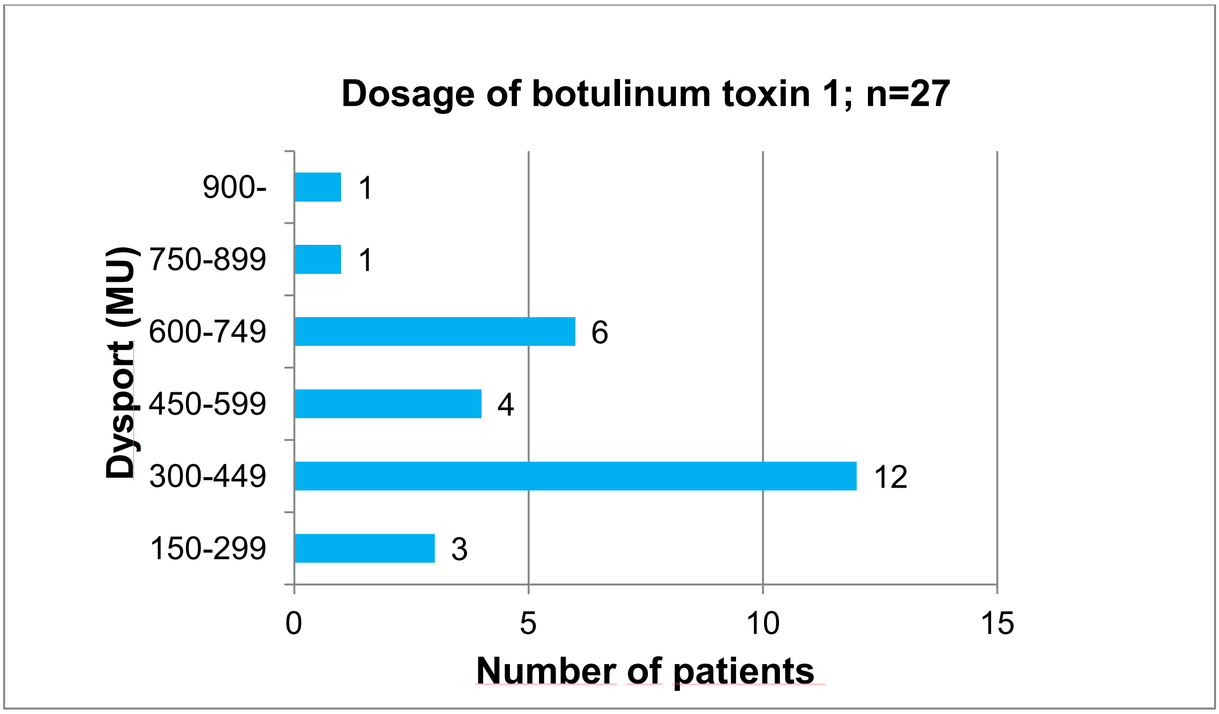


Figure 34: Dosage of botulinum toxin 1

Figures 35-36 show the duration of botulinum toxin therapy and the dosage at the baseline examination.

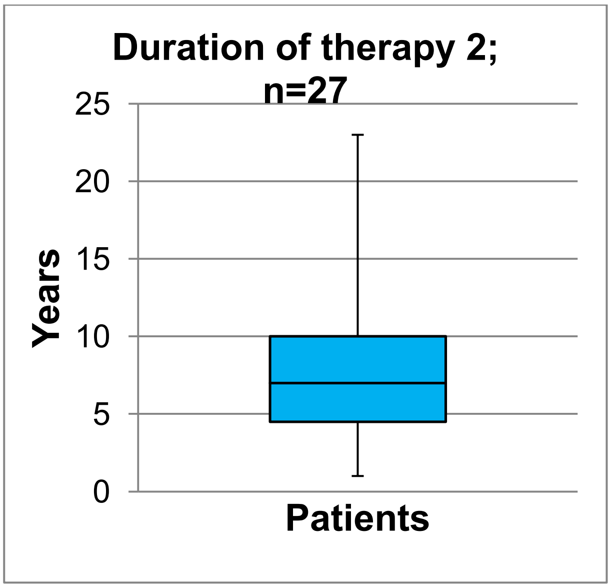


Figure 35: Duration of botulinum toxin therapy 2

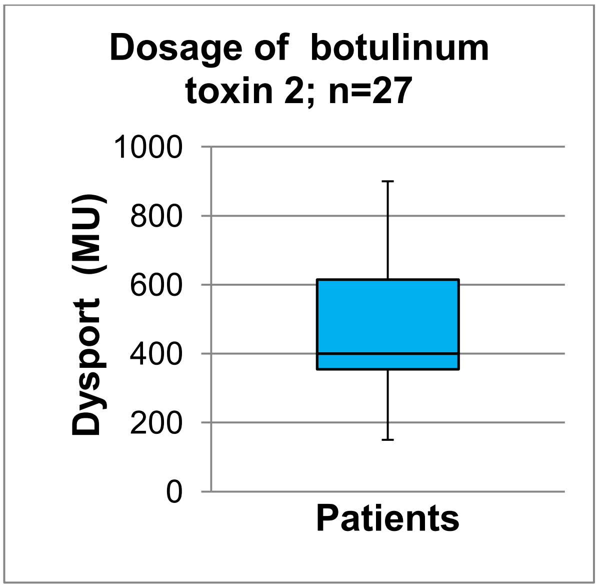


Figure 36: Dosage of botulinum toxin 2

The latency until a positive effect was recognizable ranged from 1 to 14 days with a mean value of 7.5 ± 4.1 days and a median of 7 days.
The effect of botulinum toxin lasted between 0 and 105 days with a mean of 56.2 ± 25.6 days and a median of 60 days. The latency and effect duration are illustrated in figure 37 and 38.

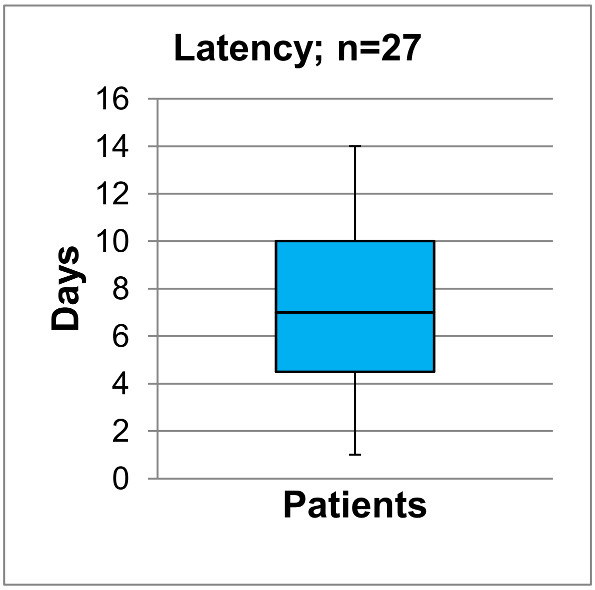


Figure 37: Latency of botulinum toxin

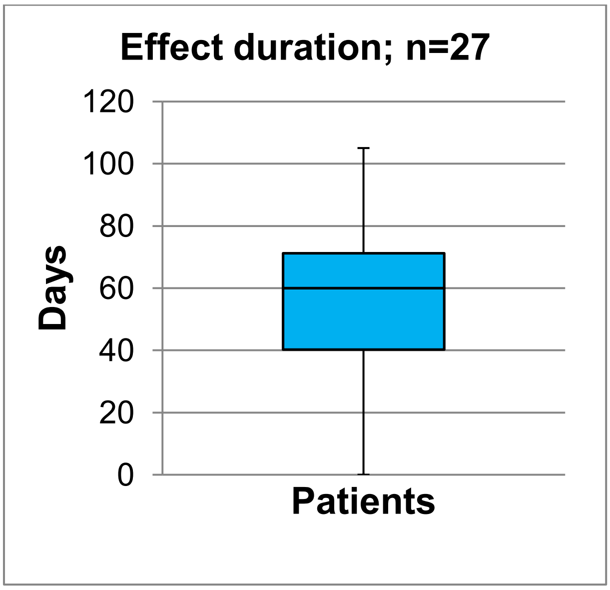


Figure 38: Effect duration

The efficacy of botulinum toxin was subdivided into efficacy in total, efficacy on abnormal posture, pain and tremor. Patients evaluated the effect in total (maximum decrease of the symptoms) from 0 to 100%. Mean value was 61.2 ± 26.5%. Effect on abnormal posture, pain and tremor also varied from 0 to 100%. The mean effect on abnormal posture was 56.9 ± 28.9%. The mean of effect on pain was 44.3 ± 37.4% and the mean effect on tremor was 50.0 ± 36.7%. In some patients, botulinum toxin only influenced the abnormal posture but had no effect on pain or tremor and vice versa. The following figure (Figure 39) demonstrates the different mean values with regard to the effect on abnormal posture, pain and tremor.

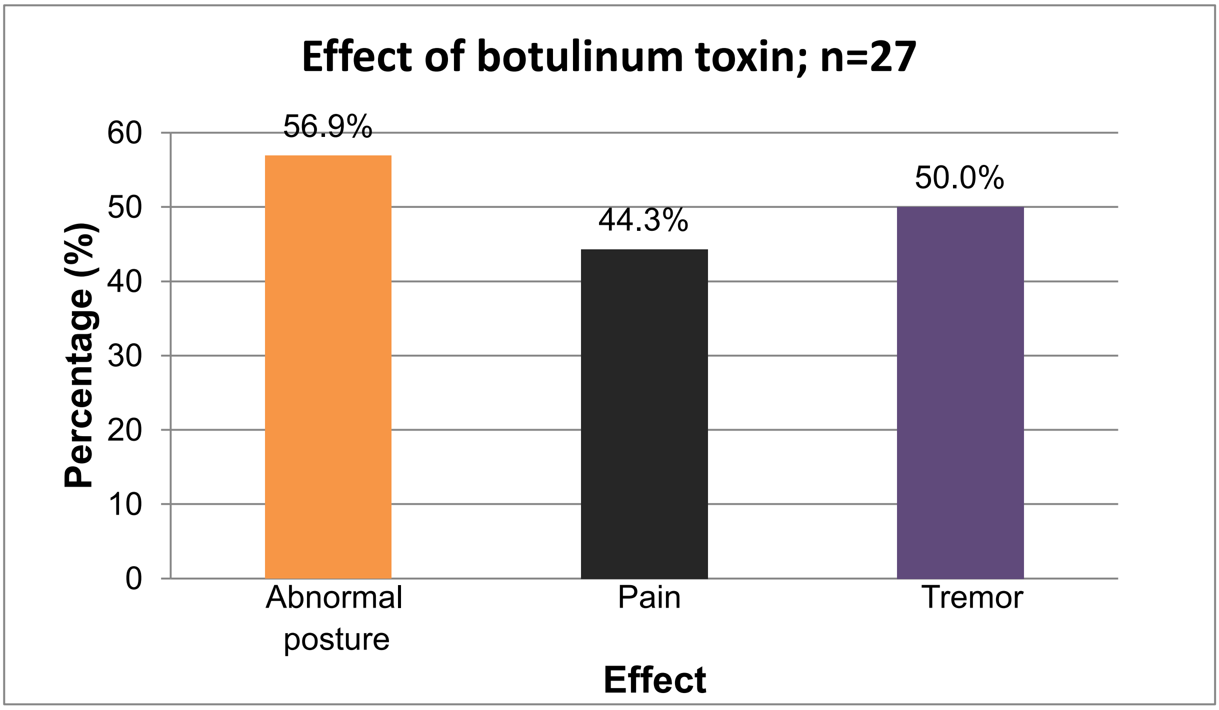


Figure 39: Effect of botulinum toxin on abnormal posture, pain and tremor

Finally, rating scales for cervical dystonia were evaluated. TSUI Score varied from 2 to 15 points with a mean value of 6.7 ± 3.2 points. A subscale, TSUI Pain, ranged from 0 to 3 points with a mean value of 1.2 ± 1.2 points.

TWSTRS Subscale II ranged from 0 to 19 points with a mean of 6.6 ± 5.2 points. TWSTRS Subscale III A ranged from 0 to 6.8 points with an average of 2.2 ± 2.2 points. TWSTRS Subscale III was in between 0 and 15.8 points with a mean of 5.7 ± 5.6 points.

Burke-Fahn-Marsden Scale ranged from 2 to 25 points with a mean of 7.2 ± 5.0 points.

Table 15 gives an overview of the different rating scales.

	Minimum	Maximum	Mean value (*M*) and Standard deviation (*SD*)	Maximal total score
TSUI	2	15	*6.7 ± 3.2*	25
TSUI Pain	0	3	*1.2 ± 1.2*	3
TWSTRS II	0	19	*6.6 ± 5.2*	30
TWSTRS IIIA	0	6.8	*2.2 ± 2.2*	10
TWSTRS III	0	15.75	*5.7 ± 5.6*	20
BFM	2	25	*7.2 ± 5.0*	120

Table 15: Overview of the rating scales

3.2 MRI of the cervical spine

3.2.1 Intraclass correlation coefficient (ICC)

Table 16 shows the ICC classes we used to evaluate the inter-rater reliability of the MRI rating scales. The ICC classes were introduced by Fisher (132).

Intraclass correlation coefficient (ICC)	
0-0.4	poor to fair agreement
0.41-0.6	moderate agreement
0.61-0.8	excellent agreement
0.81-1	almost perfect agreement

Table 16: Interpretation of the intraclass correlation coefficient

Inter-rater reliability of the rating scale “cervical canal stenosis” by Kang (129) showed excellent agreement in following segments: C3/C4 (ICC=0.637), C4/C5 (ICC=0.702) and C6/C7 (ICC=0.624). Overall, MRI of the whole cervical spine (C2-C7) also had an excellent ICC with a value of 0.729. All other segments only showed poor to fair or moderate agreement (for all comparisons ICC≤0.533).

Rating of “disc degeneration” by Matsumoto (130) revealed moderate or excellent agreement in all segments investigated. Excellent inter-rater reliability was found in segment C3/C4 (ICC=0.618) and in C6/C7 (ICC=0.727). Overall, ICC of C2-C7 was excellent with 0.630. In all other segments moderate agreement was found (for all comparisons ICC≤0.511).

Matsumoto's "narrowing of the disc space" (130) showed at least excellent agreement in following segments: C3/4 (ICC=0.689), C5/C6 (ICC=0.770), C6/C7 (ICC=0.847) and in the total cervical spine (C2-C7) (ICC=0.756). Moderate agreement was found in the two other segments (for all comparisons ICC≤0.605).

We also calculated a total score of Matsumoto's subscales and evaluated its inter-rater reliability. With segment C2/C3 (ICC=0.374) being the only exception, the "Matsumoto total score" showed excellent or almost perfect agreement. ICC was 0.690 (C3/C4), 0.667 (C4/C5), 0.795 (C5/C6) and 0.803 (C2-C7) representing excellent agreement. The lowest part of the cervical spine (C6/C7) revealed an almost perfect agreement with an ICC of 0.858.

Rating of the Modic classification (131) showed maximal moderate agreement (for all comparisons ICC≤0.594).

The "MRI total score" of all rating scales for each segment showed excellent or almost perfect agreement except for segment C2/C3 (ICC=0.294). Segment C3/C4 (ICC=0.706) and C4/C5 (ICC=0.718) showed excellent agreement. ICC of the two lower parts of the cervical spine had almost perfect agreement with values of 0.826 (C5/C6) and 0.867 (C6/C7).

3.2.2 Fleiss' kappa

For binary variables such as "anterior disc protrusion" and "foraminal stenosis" by Matsumoto (130) we used Fleiss' kappa to evaluate inter-rater reliability. According to the guidelines suggested by Landis and Koch, κ-values could be classified as follows (Table 17) (133,134).

Fleiss' kappa	
<0	poor agreement
0.01-0.2	slight agreement
0.21-0.4	fair agreement
0.41-0.6	moderate agreement
0.61-0.8	substantial agreement
0.81-1	almost perfect agreement

Table 17: Interpretation of the Fleiss' kappa values

With regard to Matsumoto's "anterior disc protrusion" scale (130), only segment C6/C7 (κ=0.636) showed substantial agreement. In all other segments maximal fair agreement was found (for all comparisons Fleiss' $\kappa \leq 0.395$).

Also, Fleiss' kappa in "foraminal stenosis" by Matsumoto (130) showed moderate agreement only in segment C5/C6 (κ=0.506). All other segments did not show better inter-rater reliability than fair agreement (for all comparisons Fleiss' $\kappa \leq 0.287$).

Table 18 gives an overview of ICC and Fleiss' kappa of the inter-rater reliability in our patients with cervical dystonia.

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	ICC: 0.310	ICC: 0.637	ICC: 0.702	ICC: 0.533	ICC: 0.624	ICC: 0.729
Disc degeneration	ICC: 0.511	ICC: 0.618	ICC: 0.504	ICC: 0.483	ICC: 0.727	ICC: 0.630
Anterior disc protrusion	κ: -0.0233	κ: 0.395	κ: 0.271	κ: 0.318	κ: 0.636	κ: 0.217
Narrowing of the disc space	ICC: 0.152	ICC: 0.689	ICC: 0.605	ICC: 0.770	ICC: 0.847	ICC: 0.756
Foraminal stenosis	κ: -0.0227	κ: -0.0215	κ: 0.287	κ: 0.506	κ: 0.171	κ: 0.229
Matsumoto total score	ICC: 0.374	ICC: 0.690	ICC: 0.667	ICC: 0.795	ICC: 0.858	ICC: 0.803
Modic classification	ICC: 0.210	ICC: 0.160	ICC: 0.395	ICC: 0.594	ICC: 0.561	ICC: 0.465
MRI total score	ICC: 0.294	ICC: 0.706	ICC: 0.718	ICC: 0.826	ICC: 0.867	

Table 18: ICC and Fleiss' kappa values of our study

3.3 MRI and clinical parameters

The following section describes the relation between structural changes of the cervical spine on MRI imaging based on the rating scales mentioned above and the clinical parameters collected.
A detailed overview on the calculated values (p-values and unstandardized regression coefficients B) is given in Appendix 5.

3.3.1 Group

Comparison of MRI images of the cervical spine between patients with cervical dystonia and healthy controls showed no major differences.
Only in segment C3/C4 a significant difference in Kang's "cervical canal stenosis" was found (p=0.006). Cervical canal stenosis was more prominent in patients with cervical dystonia compared to the control group.
Subscale "anterior disc protrusion" by Matsumoto showed a significant difference between patients and controls in segment C4/C5 (p=0.042) Anterior disc protrusion was found more frequently in patients than in healthy controls.
For the "MRI total score", a significant difference could be revealed for segment C3/C4 (p=0.038). Patients with cervical dystonia had more prominent changes in this part of the cervical spine than the control group.
No statistical significant differences were demonstrated for all other segments and rating scales (for all comparisons p≥0.066).

3.3.2 Disease duration

With regard to the disease duration, MRI images showed significant correlations in segment C3/C4 in the following rating scales: "narrowing of the disc space" (p=0.028), the "Modic classification" (p=0.016), and the "MRI total score" (p=0.017). The longer patients suffered from cervical dystonia the more pronounced changes of the cervical spine were found.
The "Matsumoto total score" showed a trend in segment C2/C3 (p=0.054) and in C3/C4 (p=0.055). Abnormalities in MRI images were more frequent in patients with longer disease duration.

No significant correlations were found for all other rating scales and segments (for all comparisons p≥0.080).

3.3.3 Type of dystonia

Correlating MRI changes with the type of dystonia, we only found one significant result in Matsumoto's subscale "anterior disc protrusion" and segment C3/C4 (p=0.017). Cervical dystonia was associated with a higher degree of disc protrusion in the frontal part of the cervical spine compared to patients with segmental dystonia.

All other results did not reveal any significant correlations (for all comparisons p≥0.063).

3.3.4 Trauma

The correlation between the presence of a trauma prior to the disease onset and MRI changes did not show major results.

Only Matsumoto's "anterior disc protrusion" revealed a significant association in segment C2/C3 (p=0.004) with no other significant correlation in all other scales or segments (for all comparisons p≥0.084). Disc protrusion in the frontal part of the cervical spine occurred more often in case of a history for a head or neck trauma.

3.3.5 Botulinum toxin therapy

A significant correlation was found between botulinum toxin therapy and "cervical canal stenosis" (p=0.050) in segment C4/C5. The narrowing of the spinal canal in this segment was more prominent in patients with botulinum toxin treatment than in patients without this therapy. All other correlation did not reveal any significant results (for all comparisons p≥0.072).

3.3.6 Duration of botulinum toxin therapy

With regard to the duration of botulinum toxin therapy, we found a significant correlation with “cervical canal stenosis” ($p=0.009$) in segment C4/C5 and the “MRI total score” ($p=0.033$). Changes in the spine were more common the longer patients were on botulinum toxin. All other scales and segments did not show any association with the duration of botulinum toxin therapy (for all comparisons $p \geq 0.075$).

3.3.7 Dosage of botulinum toxin

MRI changes of the cervical spine and the dosage of botulinum toxin in our patients with cervical dystonia were not associated.

Only Kang’s “cervical canal stenosis” showed a trend in segment C3/C4 ($p=0.057$). The higher the administered dosage of botulinum toxin was, the lesser the degree of spinal canal stenosis.

All other correlations did not show any significant result (for all comparisons $p \geq 0.092$).

3.3.8 Side effects of botulinum toxin

With regard to the side effects of botulinum toxin therapy, we calculated a significant correlation with Kang’s “cervical canal stenosis” ($p=0.049$) in C5/C6 and the “MRI total score” ($p=0.019$) in C2/C3. Subscale “anterior disc protrusion” showed a trend in segment C5/C6 ($p=0.057$). The lesser side effects after botulinum toxin injections in patients with cervical dystonia occurred, the more frequent cervical spine changes were found.

For all other segments and scales no significant results were found (for all comparisons $p \geq 0.066$).

3.3.9 Latency of botulinum toxin effect

A relation between MRI changes of the cervical spine and the latency until a botulinum toxin effect was recognizable was found for “cervical canal stenosis” ($p=0.044$) and the “Modic classification” ($p=0.004$) in segment C4/C5. The shorter

the latency of a botulinum toxin effect was, the more frequent changes in MRI images were found.
All remaining segments and scales did not reveal any significant association (for all comparisons p≥0.096).

3.3.10 Effect in total

With regard to the total effect of botulinum toxin (maximum decrease of the symptoms) in our patients, significant results were revealed for the "Modic classification" in segment C2/C3 (p=0.041), in C4/C5 (p=0.032), and the "MRI total score" in C4/C5 (p=0.022).
A trend was shown for segment C4/C5 in Matsumoto's "narrowing of the disc space" (p=0.057). The higher the effect of botulinum toxin was, the more often patients suffered from cervical spine abnormalities. In segment C2/C3, the Modic types were more frequent the lower the effect of botulinum toxin was.
All remaining segments and scales did not reveal significant results (for all comparisons p≥0.071).

3.3.11 Effect on tremor

Correlation of MRI changes and the effect on tremor demonstrated the following significant results: "Cervical canal stenosis" in segment C4/C5 (p=0.048), "disc degeneration" (p=0.031) and "anterior disc protrusion" (p=0.030) in C3/C4 and the "Modic classification" in C2/C3 (p=0.014) and in C4/C5 (p=0.049). The "MRI total score" and the effect on tremor were correlated in segment C4/C5 (p=0.029), whereas for all remaining segments and scales the results were unremarkable (for all comparisons p≥0.077).
The more prominent cervical canal stenosis, anterior disc protrusion, and Modic changes were, the better the botulinum toxin effect on tremor was. In contrary, disc degeneration and Modic changes in segment C2/C3 were more prominent, the lesser the effect on tremor was.

3.3.12 TSUI total

MRI changes and the TSUI rating scale (57) were associated with Matsumoto's subscale "foraminal stenosis" ($p=0.028$), "Modic classification ($p=0.013$), and "MRI total score" ($p=0.014$) in C6/C7. A trend was evaluated for the "Matsumoto total score" ($p=0.053$) in this segment. The higher the TSUI Score the more common abnormalities of the cervical spine in the MRI images were present.
All other scales and segments did not show any significant results (for all comparisons $p \geq 0.069$).

3.3.13 TWSTRS IIIA total (Severity of Pain)

Concerning the part "Severity of Pain" of the TWSTRS (53), our results showed only one significant correlation with Matsumoto's subscale "disc degeneration" ($p=0.024$) in segment C5/C6 with no significant result in all remaining segments and scales (for all comparisons $p \geq 0.114$).
The lower the score in the "Severity of Pain" scale was, the more often degeneration of the intervertebral discs occurred.

3.3.14 TWSTRS III (Pain scale)

A relation between MRI changes and the "Pain Scale" (III) of the TWSTRS (53) was found for Matsumoto's "disc degeneration in C5/C6 ($p=0.027$). The higher the sum score of the "Pain scale" the less frequent degeneration of the spinal discs was present.
In all other segments and scales no significant results were found (for all comparisons $p \geq 0.079$).

3.3.15 Burke-Fahn-Marsden Scale

With regard to the BFM rating scale (59), we calculated statistical significant correlations for the following MRI rating scales: Matsumoto's subscale "disc degeneration" in C2/C3 ($p=0.039$), subscale "anterior disc protrusion" by Matsumoto in C3/C4 ($p=0.050$), in C5/C6 ($p=0.040$), and in C2-C7 ($p=0.006$), and "Matsumoto total score" in C2/C3 ($p=0.019$) and in C3/C4 ($p=0.039$).

The lower the BFM sum score was, the more frequent changes of the cervical spine were present.
All other segments and scales did not reveal any significant results (for all comparisons $p \geq 0.051$).

3.3.16 Clinical parameters and MRI changes without correlation

In our calculations, several clinical parameters did not correlate with MRI changes in patients with cervical dystonia.
The correlation between the effect duration of botulinum toxin therapy in our patients and imaging changes were not statistical significant (for all comparisons $p \geq 0.075$).
Neither the effect of botulinum toxin on abnormal posture (for all comparisons $p \geq 0.066$) nor the botulinum toxin effect on pain (for all comparisons $p \geq 0.088$) was correlated with MRI changes.
A correlation between imaging changes and TSUI Pain (57) did not demonstrate statistical significant results (for all comparisons $p \geq 0.075$).
Our calculations regarding the “Disability Scale” (II) of the Toronto Western Spasmodic Torticollis Rating Scale (53) were without any significant result (for all comparisons $p \geq 0.065$).

4 Discussion

The aim of our study was to investigate if patients with cervical dystonia have structural abnormalities of the cervical spine on MRI more frequently than age-matched healthy controls. Additionally, we analyzed the inter-rater reliability of the MRI rating scales and whether there were any clinical predictors for significant abnormalities in the magnetic resonance imaging of the cervical spine. Finally, we investigated if there are any clinical parameters which strengthen the indication for an MRI of the cervical spine in patients with cervical dystonia.

Overall, the frequency of structural abnormalities in the MRI of the cervical spine did not differ significantly between patients with cervical dystonia and healthy controls.

The majority of our study population showed some structural changes in the cervical spine. Especially in older age, the cause of these abnormalities seems to be degenerative. However, degenerative changes of the cervical spine were also found in participants in the mid-twenties.

We could not determine clear clinical predictors for significant abnormalities in MRI of the cervical spine. We observed that the clinical symptom pain in patients with cervical dystonia does not correlate with MRI changes. This assumption is supported by non-significant correlations with the TSUI Pain, the “Severity of Pain” Scale and the total “Pain” Scale of TWSTRS. Additionally, no association between botulinum toxin effect on pain and cervical spine changes on MRI images were found.

The correlations between abnormal posture of the head and neck, which was evaluated with the BFM Scale, did not reveal any meaningful results either. Also, the botulinum toxin effect on abnormal posture did not correlate with MRI changes. Based on this finding, we cannot define abnormal posture as a clinical predictor for cervical spine changes. In contrary, a positive correlation between dystonia severity by means to the TSUI total score and MRI changes was found. In addition to a more detailed assessment of the abnormal head posture, the shoulder position and tremor also influence this rating scale.

We did not find any clinical parameters that strengthen the indication for an MRI of the cervical spine in patients with cervical dystonia. Structural abnormalities were frequent in our patients and in our healthy controls. These abnormalities most likely seem to be degenerative in nature. In our opinion, the clinical symptom pain does not justify an MRI of the cervical spine. A reasonable indication, for example the suspicion of a vertebral disc protrusion, is required to legitimate this examination.

Overall, inter-rater reliability in our study showed acceptable results. The three independent raters reached good agreements in most of the scales.
Calculation of the intraclass correlation coefficient provided satisfying results. In the majority, excellent to almost perfect agreement could be achieved. Only in segment C2/C3 inter-rater reliability expressed by the ICC did not show acceptable results in any of the rating scales, probably due to the overlap with anatomic structures in this area. Also, the upper part of the cervical spine in the "Modic classification" was difficult to evaluate and the inter-rater reliability revealed only poor to fair agreement. In this regard, it needs to be mentioned that the "Modic classification" was introduced for the investigation of the lumbar spine and not for the cervical spine (131).
We decided to use Fleiss' kappa for the calculation of binary variables, which did not reveal a good inter-rater reliability. In almost every segment (except for C6/C7 in Matsumoto's subscale "anterior disc protrusion" and C5/C6 in Matsumoto's subscale "foraminal stenosis") κ-values only showed poor to maximum fair agreement. One explanation for the poor agreement might be that it was more difficult for the three raters to decide between two possibilities instead of three or more. Another difficulty was to evaluate foraminal stenosis in sagittal images. In their original study, Matsumoto et al. used T1-weigthed axial images for the assessment of foraminal stenosis of the cervical spine (130).

In general, the majority of the MRI rating scales we used in our study seem to be useful for the evaluation of MRI images of the cervical spine.
With the help of several rating scales, different structural changes like cervical canal stenosis or the narrowing of the disc space could be assessed by three independent radiologists.
The scale "cervical canal stenosis" by Kang et al. is a grading system for MRI images of the spine published in 2011 (129). It was introduced to expand and improve the classification of Muhle et al. (135) and is based on the examination of

100 partly symptomatic patients older than 60 years. The presence of a good to excellent inter- as well as intraobserver reliability in this study permits to use this rating scale as a reliable evaluation of cervical canal stenosis. In our study, we also reached excellent agreement in most segments. Previous studies about cervical canal stenosis were often based on radiographs. Edwards and Larocca (136) evaluated the sagittal diameter of the cervical spinal canal, whereas a calculation of the ratio between the sagittal diameter and the diameter of the vertebral body was proposed by Pavlov et al. and Torg et al. (137,138).

In their MRI study Matsumoto et al. (130) assessed 497 asymptomatic subjects with degenerative changes in the cervical spine. They focused on changes in the spinal cord such as disc degeneration, posterior and anterior disc protrusion, narrowing of the disc space and foraminal stenosis. In this study, the frequency of all degenerative changes increased linearly with age and all subscales showed good inter-rater reliability. In our study, we also reached excellent agreement in most of the segments in the subscales “disc degeneration” and “narrowing of the disc space” based on the intraclass correlation coefficient. The subscales “anterior disc protrusion” and “foraminal stenosis” were evaluated with binary nominal variables and did not show good inter-rater reliability according to Fleiss’ kappa. In contrast to the study of Matsumoto et al. (130), we only used sagittal images for the evaluation of MRI changes. Our results imply that foraminal stenosis is more difficult to evaluate in sagittal images than in axial images as used in the other study.

In addition, we expressed the sum of all Matsumoto subscales by the “Matsumoto total score”. Inter-rater reliability revealed a remarkable result with excellent to almost perfect agreement.

Due to its similarity to Kang’s “cervical canal stenosis”, we decided to exclude the subscale “posterior disc protrusion”.

The grading system of Modic et al. (131) classifies degenerative changes of the vertebral bodies next to spinal discs in MRI images. Originally, this classification was introduced for the lumbar spine, but a few studies also assessed Modic changes in the cervical spine. Mann et al. (139) observed the presence of Modic types especially in segments C5/C6 and C6/C7. Inter-rater reliability showed acceptable results; hence they recommended this rating scale also as reliable for the evaluation of the cervical spine. In 2012, Matsumoto et al. (140) evaluated MRI images of asymptomatic subjects in a 10-year follow-up study with good inter-rater reliability. Higher frequency of different Modic types in the follow-up examination was thought to be related to the higher age of the patients at follow-up and presumably due to degenerative changes. In our study, inter-rater reliability showed acceptable results in the lower segments of the cervical spine but not in the upper parts. Potentially, this evaluation was complicated by an overlap of anatomic structures and one has to bear in mind, that the "Modic classification" was not invented for the evaluation of the cervical spine but rather for the lumbar spine. Another difficulty lies in the classification itself. The three different types correspond to three different structural changes and not to the severity of a specific change. Therefore, it is not an ordinal scale but a nominal scale meaning type 1 is equivalent to the presence of edema and hypervascularity, type 2 correlates with fatty replacements of the red bone marrow and type 3 represents subchondral bone sclerosis (131).

Finally, a "MRI total score" for each segment of the cervical spine was calculated. It was composed of the sum of all subscales and revealed excellent to almost perfect agreement according to the inter-rater reliability.

In conclusion, the rating scales used were considered to be reliable based on the literature and the overall good inter-rater reliability in our study.

We could not detect clear differences on MRI imaging between our patients with cervical dystonia and our healthy controls. Only in segment C3/C4 Kang's "cervical canal stenosis" and the "MRI total score" were significantly higher in patients. In segment C4/C5 Matsumoto's "anterior disc protrusion" scale revealed more prominent changes in patients than in controls. Structural changes in MRI imaging of the cervical spine seem to be frequent in general and even more with increasing age, probably due to degenerative changes.

Most frequently MRI changes of the cervical spine in our patients with cervical dystonia were found in segment C4/C5 followed by segment C3/C4. This is in contrast to the literature in healthy controls, where changes were predominantly found in segment C5/C6 and C6/C7. It is thought, that these changes are due to the high strain on this part of the cervical spine (129,139,140). This might be different in patients with cervical dystonia, where, due to the abnormal head position, changes in the cervical spine seem to be more frequent in segments higher up.

Our calculations did not reveal evidence for a clear relation between structural changes on MRI imaging of the cervical spine and clinical parameters in patients with cervical dystonia.

Although we found several significant correlations, they do not necessarily represent meaningful results and would probably not withstand corrections for multiple comparisons.

A positive correlation between disease duration and MRI changes was found in segment C3/C4. This might imply that segment C3/C4 is in particular vulnerable and, the longer patients suffer from cervical dystonia, the more frequent changes of the cervical spine occur especially in this part.

Referring to the type of dystonia (cervical or segmental) and a history of trauma previous to the onset of dystonia, no relevant correlations were found. Even though anterior disc protrusion in segment C2/C3 was more prominent in case of a previous trauma, this was not true for all other segments.

With regard to botulinum toxin therapy, we found a positive correlation with Kang's "cervical canal stenosis" in segment C4/C5. Patients on botulinum toxin treatment had more prominent narrowing of the cervical canal in this segment than patients without injections. The duration of botulinum toxin treatment and changes in the cervical spine at this level assessed with "cervical canal stenosis" and the "MRI total score" were also correlated implying that the longer patients were treated with botulinum toxin the more often abnormalities of the cervical spine at this segment were found. The significance of these results is debatable since the structural changes were restricted to one segment only.

Interestingly, the total effect, side effects, latency, and duration of botulinum toxin effect did not reveal any meaningful correlations with imaging abnormalities in any segment.

Significant correlations were calculated for the effect of botulinum toxin on tremor and MRI changes of the cervical spine based on the "Modic classification" in C2/C3 and "disc degeneration" and "anterior disc protrusion" of Matsumoto in C3/C4. In segment C4/C5 Kang's "cervical canal stenosis, the "Modic classification", and the "MRI total score" revealed positive correlations with the botulinum toxin effect on tremor. The more prominent cervical canal stenosis,

anterior disc protrusion, and Modic changes were in these segments, the better the botulinum toxin effect on tremor was.
The correlation of severity of cervical dystonia based on the TSUI total score and imaging changes of the cervical spine revealed significant results in Matsumoto's subscale "foraminal stenosis", in the "Modic classification", and in the "MRI total score" for segment C6/C7. The higher the sum score, representing a more severe stage of the disease, the more common structural abnormalities in MRI imaging were present in the lowest segment of the cervical spine. Kang et al. (129), Mann et al. (139), and Matsumoto et al. (140) determined in their studies that cervical spine changes mostly occur in the lower part of the spine. The significance of this result is however questionable since the correlations were restricted to structural changes in segment C6/C7. This is in contrast to clinical parameters, whose correlations with imaging changes were confined to segment C3/C4 and C4/C5. These include disease duration, botulinum toxin therapy, its dosage and duration, and the botulinum toxin effect on tremor.
Interestingly, "Severity of Pain" by means of the TWSTRS IIIA score, "Pain" by means of the TWSTRS III score and dystonia severity based on the BFM scale did not reveal any meaningful correlations in any of the segments investigated.
For all other clinical parameters no correlation with structural changes on MRI imaging could be determined. Interestingly, neither the dose nor the effect duration of botulinum toxin seems to have influence on visible changes in the cervical spine in MRI images. Also, we did not find an association between abnormalities in the cervical spine and the effect of botulinum toxin on abnormal posture in patients with cervical dystonia. No significant correlation between structural changes and pain by means of the TSUI Pain scale and the botulinum toxin effect on pain was found. Finally, TWSTRS II "disability scale" did not reveal any statistical significant results. Limitations in daily-living skills due to cervical dystonia do not seem to be associated with changes in MRI images.
Since there is no literature about clinical parameters in patients with cervical dystonia and MRI images of the cervical spine, it is difficult to compare our study with other investigations. There are some studies about MRI of the cervical spine in context with asymptomatic subjects or other disease patterns and we tried to discuss our results in terms of these studies as mentioned above.

Rather unexpectedly, the results of our study on MRI changes of the cervical spine showed that patients with cervical dystonia do not suffer from structural abnormalities in the spine more frequently than healthy controls. We could not find significant and relevant differences between our patients and our healthy control group. In both groups abnormalities in the MRI images were found. MRI changes in healthy subjects are probably related to their age. According to the literature, the majority of older people suffer from degenerative changes (129,140), even though no symptoms are present.

Recommendations regarding imaging of the cervical spine in patients with cervical dystonia are inhomogeneous. While Dauer et al. (46) propose to perform MRI examination of the cervical spine in every patient with cervical dystonia, Kruer et al. (116) suggest performing this examination only in patients with secondary dystonia. According to a study by Reichel et al. (128), this investigation is only recommended if the therapy with botulinum toxin is insufficient and CT of the cervical spine does not deliver enough results for the evaluation of cervical dystonia. Based on our results we concluded that it is not obligatory to conduct MRI of the cervical spine in every patient with cervical dystonia. It seems reasonable to restrict imaging of the cervical spine to those patients in whom, based on clinical findings (e.g. radicular pain, radicular sensory or motor signs and weak corresponding deep tendon reflexes/ or signs of a myelopathy) a morphological correlate is suspected. However, neck pain with or without lack of response to botulinum toxin injections as the sole complaints should not prompt a MRI examination of the spinal cord.

There are several limitations of our study. In total, we included 51 participants in our study. 30 participants suffered from cervical dystonia which is a rather small sample size to get meaningful results.

The age of our study population, in particular of our patients, was relatively high (mean age of patients 58.7 years). Since imaging changes were also quite frequent in healthy controls, this points to the fact, that structural changes are not necessarily due to the presence of cervical dystonia but rather represent degenerative changes in the cervical spine.

Accurate age-matching of the control group was not possible especially in higher age because we did not accept participants with any neurological or spine

diseases. For this reason, the ratio between patients and controls of the highest age decade was only 2:1, which makes it difficult to compare these both groups.
Due to an overlap of anatomic structures on the MRI images, segment C1/C2 had to be excluded from our investigation. For the same reason, assessment of the upper part of the cervical spine (especially segment C2/C3) was more difficult than the lower part of the cervical spine.
Another limitation might be that different examiners were included in our study. Rating scales like the TSUI Score are based on the subjective evaluation of the examiner. Even though experienced neurologists in Movement disorders work at the Department of Neurology, differences regarding the clinical rating may occur. A number of data collected such as pain or the effect of botulinum toxin depend on the patients' subjective perception and may therefore also contribute to the limitations of this study. With regard to the evaluation of the MRI images by three independent radiologists, inter-rater reliability was good in general.

5 Conclusion

This is the first study prospectively investigating structural MRI of the cervical spine in patients with cervical dystonia compared to healthy controls. Based on our results we propose the following conclusions.

First, the chosen rating scales for the evaluation of MRI images of the cervical spine were reliable and resulted in good inter-rater reliability by means of the intraclass correlation coefficient and Fleiss' kappa.

Second, we could not detect relevant differences on MRI imaging between our patients with cervical dystonia and our healthy controls. In previous studies, in healthy subjects changes of the cervical spine were mainly found in segments C5/C6 and C6/C7, thought to be due to the high strain in the lower part of the cervical spine (139,140). In contrast, we found abnormalities more frequently in segment C4/C5 followed by segment C3/C4. Patients with cervical dystonia suffer from an abnormal posture with or without tremor of the head and often adopt a relieving posture due to the neck pain. An altered mechanical burden in patients with cervical dystonia might explain why structural changes can appear in segments different from healthy subjects.

Third, we did not find evidence for a clear association between structural changes on MRI imaging of the cervical spine and clinical parameters in patients with cervical dystonia.

Fourth, structural changes in the cervical spine are very common. In the majority of our healthy controls asymptomatic imaging abnormalities could be found, most likely due to degenerative changes. Based on our results, we conclude that the frequency and severity of structural changes in the cervical spine do not differ significantly between patients with cervical dystonia and healthy controls and most probably represent degenerative changes. Therefore, magnetic resonance imaging in patients with cervical dystonia should only be considered if a morphological correlate is suspected based on clinical signs indicative of a radiculopathy or a myelopathy.

To our knowledge, this is the first study on MRI of the cervical spine in patients with cervical dystonia and clearly more data are warranted to broaden our knowledge about this topic.

Literature

(1) Oppenheim H. Über eine eigenartige Krampfkrankheit des kindlichen und jugendlichen Alters (Dysbasia lordotica progressiva, Dystonia musculorum deformans). Neurol Centrabl 1911;30:1090-107.

(2) Defazio G, Abbruzzese G, Livrea P, Berardelli A. Epidemiology of primary dystonia. Lancet Neurol 2004 Nov;3(11):673-8.

(3) Fahn S. Classification of movement disorders. Mov Disord 2011 May;26(6):947-57.

(4) Fahn S, Jankovic J, Hallett M. Principles and Practice of Movement Disorders. 2nd ed. Philadelphia: Elsevier; 2011.

(5) Phukan J, Albanese A, Gasser T, Warner T. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. Lancet Neurol 2011 Dec;10(12):1074-85.

(6) Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997 Sept;17(1):40-8.

(7) Edwards MJ. Dystonia: a clinical approach. Acta Neurol Taiwan 2008 Dec;17(4):219-27.

(8) Fahn S. Concept and classification of dystonia. Adv Neurol 1988;50:1-8.

(9) Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 1994 Aug;117(Pt 4):859-76.

(10) Edwards MJ, Quinn NP, Bhatia KP. Parkinson's Disease and Other Movement Disorders. Oxford: Oxford University Press; 2008.

(11) Defazio G. The epidemiology of primary dystonia: current evidence and perspectives. Eur J Neurol 2010 Jul;17(Suppl 1):9-14.

(12) Li SC, Schoenberg BS, Wang CC, Cheng XM, Rui DY, Bolis CL, et al. A prevalence survey of Parkinson's disease and other movement disorders in the People's Republic of China. Arch Neurol 1985 Jul;42(7):655-7.

(13) Kandil MR, Tohamy SA, Fattah MA, Ahmed HN, Farwiez HM. Prevalence of chorea, dystonia and athetosis in Assiut, Egypt: a clinical and epidemiological study. Neuroepidemiology 1994;13(5):202-10.

(14) Marras C, Van den Eeden SK, Fross RD, Benedict-Albers KS, Klingman J, Leimpeter AD, et al. Minimum incidence of primary cervical dystonia in a multiethnic health care population. Neurology 2007 Aug;69(7):676-80.

(15) Colosimo C, Suppa A, Fabbrini G, Bologna M, Berardelli A. Craniocervical dystonia: clinical and pathophysiological features. Eur J Neurol 2010 Jul;17(Suppl 1):15-21.

(16) Abbruzzese G, Berardelli A, Girlanda P, Marchese R, Martino D, Morgante F, et al. Long-term assessment of the risk of spread in primary late-onset focal dystonia. J Neurol Neurosurg Psychiatry 2008 Apr;79(4):392-6.

(17) Soland VL, Bhatia KP, Marsden CD. Sex prevalence of focal dystonias. J Neurol Neurosurg Psychiatry 1996 Feb;60(2):204-5.

(18) Le KD, Nilsen B, Dietrichs E. Prevalence of primary focal and segmental dystonia in Oslo. Neurology 2003 Nov;61(9):1294-6.

(19) Defazio G, Berardelli A, Abbruzzese G, Lepore V, Coviello V, Acquistapace D, et al. Possible risk factors for primary adult onset dystonia: a case-control investigation by the Italian Movement Disorders Study Group. J Neurol Neurosurg Psychiatry 1998 Jan;64(1):25-32.

(20) Waddy HM, Fletcher NA, Harding AE, Marsden CD. A genetic study of idiopathic focal dystonias. Ann Neurol 1991 Mar;29(3):320-4.

(21) Defazio G, Berardelli A, Hallett M. Do primary adult-onset focal dystonias share aetiological factors? Brain 2007 May;130(Pt 5):1183-93.

(22) Leube B, Rudnicki D, Ratzlaff T, Kessler KR, Benecke R, Auburger G. Idiopathic torsion dystonia: assignment of a gene to chromosome 18p in a German family with adult onset, autosomal dominant inheritance and purely focal distribution. Hum Mol Genet 1996 Oct;5(10):1673-7.

(23) Brancati F, Valente EM, Castori M, Vanacore N, Sessa M, Galardi G, et al. Role of the dopamine D5 receptor (DRD5) as a susceptibility gene for cervical dystonia. J Neurol Neurosurg Psychiatry 2003 May;74(5):665-6.

(24) Placzek MR, Misbahuddin A, Chaudhuri KR, Wood NW, Bhatia KP, Warner TT. Cervical dystonia is associated with a polymorphism in the dopamine (D5) receptor gene. J Neurol Neurosurg Psychiatry 2001 Aug;71(2):262-4.

(25) Xiao J, Zhao Y, Bastian RW, Perlmutter JS, Racette BA, Tabbal SD, et al. Novel THAP1 sequence variants in primary dystonia. Neurology 2010 Jan;74(3):229-38.

(26) Houlden H, Schneider SA, Paudel R, Melchers A, Schwingenschuh P, Edwards M, et al. THAP1 mutations (DYT6) are an additional cause of early-onset dystonia. Neurology 2010 Mar;74(10):846-50.

(27) Djamarti A, Schneider SA, Lohmann K, Winkler S, Pawlack H, Hagenah J, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. Lancet Neurol 2009 May;8(5):447-52.

(28) Velickovic M, Benabou R, Brin MF. Cervical dystonia pathophysiology and treatment options. Drugs 2001;61(13):1921-43.

(29) Dystonia Medical Research Foundation (DMRF). Drug-Induced. 2010; Available at: http://www.dystonia-foundation.org/pages/more_info/76.php. Accessed 12/10/2013.

(30) Burke RE, Fahn S, Jankovic J, Marsden CD, Lang AE, Gollomp S, et al. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology 1982 Dec;32(12):1335-46.

(31) Kiriakakis V, Bhatia KP, Quinn NP, Marsden CD. The natural history of tardive dystonia. A long-term follow-up study of 107 cases. Brain 1998 Nov;121(Pt 11):2053-66.

(32) Kühn U, Deutsche Dystonie Gesellschaft e.V. Tardive Dystonie- Symptome, Ursache, Diagnose, Behandlung. Available at: http://www.dystonie.de/krankheitsbilder/andere-formen/tardive-dystonie.html. Accessed 12/10/2013.

(33) Hagenah JM, Zühlke C, Hellenbroich Y, Heide W, Klein C. Focal dystonia as a presenting sign of spinocerebellar ataxia 17. Mov Disord 2004 Feb;19(2):217-20.

(34) Lang AE, Rogaeva EA, Tsuda T, Hutterer J, St George-Hyslop P. Homozygous inheritance of the Machado-Joseph disease gene. Ann Neurol 1994 Sep;36(3):443-7.

(35) Modi G, Modi M, Martinus I, Rodda J, Saffer D. The clinical and genetic characteristics of spinocerebellar ataxia type 7 (SCA 7) in three Black South African families. Acta Neurol Scand 2000 Mar;101(3):177-82.

(36) Singer C, Velickovic M. Cervical Dystonia: Etiology and Pathophysiology. Neurol Clin 2008 May;26(Suppl 1):9-22.

(37) Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. Mov Disord 1991;6(2):119-26.

(38) Lowenstein DH, Aminoff MJ. The clinical course of spasmodic torticollis. Neurology 1988 Apr;38(4):530-2.

(39) Rondot P, Marchand MP, Dellatolas G. Spasmodic torticollis- review of 220 patients. Can J Neurol Sci 1991 May;18(2):143-51.

(40) Samii A, Pal PK, Schulzer M, Mak E, Tsui JK. Post-traumatic cervical dystonia: a distinct entity? Can J Neurol Sci 2000 Feb;27(1):55-9.

(41) Tarsy D. Comparison of acute- and delayed-onset posttraumatic cervical dystonia. Mov Disord 1998 May;13(3):481-5.

(42) Kühn U, Deutsche Dystonie Gesellschaft e.V. Zervikale Dystonie- Symptome, Formen der zervikalen Dystonie, Ursache, Diagnose, Behandlung. Available at: http://www.dystonie.de/krankheitsbilder/fokale-formen/zervikale-dystonie.html. Accessed 12/10/2013.

(43) Dippon C. Zervikale Dystonien- Beschreibung der Symptomatik, Diagnostik, Therapie und Nebenwirkungen. 2005; Available at: http://www.botulinumtoxin-ambulanz.de/zervikale.htm. Accessed 12/10/2013.

(44) Putz R, Pabst R. Sobotta- Atlas der Anatomie des Menschen; Tabellen zu Muskeln, Gelenken, Nerven. München: Elsevier; 2006.

(45) Fahn S. The varied clinical expression of dystonia. Neurol Clin 1984 Aug;2(3):541-54.

(46) Dauer WT, Burke RE, Greene P, Fahn S. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. Brain 1998 Apr;121(Pt 4):547-60.

(47) Papapetropoulos S, Baez S, Zitser J, Sengun C, Singer C. Retrocollis: classification, clinical phenotype, treatment outcomes and risk factors. Eur Neurol 2008;59(1-2):71-5.

(48) Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. Neurology 1991 Jul;41(7):1088-91.

(49) Camargo CH, Teive HA, Becker N, Baran MH, Scola RH, Werneck LC. Cervical dystonia: clinical and therapeutic features in 85 patients. Arq Neuropsiquiatr 2008 Mar;66(1):15-21.

(50) Godeiro-Junior C, Felicio AC, Aguiar PC, Borges V, Silva SM, Ferraz HB. Head tremor in patients with cervical dystonia: different outcome? Arq Neuropsiquiatr 2008 Dec;66(4):805-8.

(51) Jahanshahi M, Marion MH, Marsden CD. Natural history of adult-onset idiopathic torticollis. Arch Neurol 1990 May;47(5):548-52.

(52) Jahanshahi M. Factors that ameliorate or aggravate spasmodic torticollis. J Neurol Neurosurg Psychiatry 2000 Feb;68(2):227-9.

(53) Consky ES, Lang AE. Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallet M, editors. Therapy with botulinum toxin New York: Marcel Dekker; 1994. 211-37.

(54) Friedman A, Fahn S. Spontaneous remissions in spasmodic torticollis. Neurology 1986 Mar;36(3):398-400.

(55) Tolosa ES, Marti MJ. Adult-onset idiopathic torsion dystonia. In: Watts RL, Koller WC, editors. Movement Disorders: Neurologic Principles and Practice New York: McGraw-Hill; 1997. 429-41.

(56) Crowner BE. Cervical Dystonia: Disease Profile and Clinical Management. Phys Ther 2007 Nov;87(11):1511-26.

(57) Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. Lancet 1986 Aug;2(8501):245-7.

(58) Cano SJ, Hobart JC, Fitzpatrick R, Bhatia KP, Thompson AJ, Warner TT. Patient-based outcomes of cervical dystonia: A review of rating scales. Mov Disord 2004 Sep;19(9):1054-9.

(59) Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985 Jan;35(1):73-7.

(60) Cano SJ, Warner TT, Linacre JM, Bhatia KP, Thompson AJ, Fitzpatrick R, et al. Capturing the true burden of dystonia on patients: the Cervical Dystonia Impact Profile (CDIP-58). Neurology 2004 Nov;63(9):1629-33.

(61) Jahanshahi M, Marsden C. Body concept, disability, and depression in patients with spasmodic torticollis. Behav Neurol 1990;3(2):117-31.

(62) Dystonia Medical Research Foundation (DMRF). How is dystonia diagnosed? 2010; Available at: http://www.dystonia-foundation.org/pages/how_is_dystonia_diagnosed_/40.php. Accessed 12/10/2013.

(63) Risvoll H, Kerty E. To test or not? The value of diagnostic tests in cervical dystonia. Mov Disord 2001 Mar;16(2):286-9.

(64) Sung DH, Choi JY, Kim DH, Kim ES, Son YI, Cho YS, et al. Localization of dystonic muscles with 18F-FDG PET/CT in idiopathic cervical dystonia. J Nucl Med 2007 Nov;48(11):1790-5.

(65) Van Gerpen JA, Matsumoto JY, Ahlskog JE, Maraganore DM, McManis PG. Utility of an EMG mapping study in treating cervical dystonia. Muscle Nerve 2000 Nov;23(11):1752-6.

(66) Dressler D. Electromyographic evaluation of cervical dystonia for planning of botulinum toxin therapy. Eur J Neurol 2000 Nov;7(6):713-8.

(67) Walker F. Botulinum toxin therapy for cervical dystonia. Phys Med Rehabil Clin N Am 2003 Nov;14(4):749-66.

(68) Hawley RJ. Preventing complications of electromyography. Electromyogr Clin Neurophysiol 2000 Sep;40(6):323-5.

(69) Oh SJ. Clinical Electromyography: Nerve Conduction Studies. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.

(70) Naumann M, Becker G, Toyka KV, Supprian T, Reiners K. Lenticular nucleus lesion in idiopathic dystonia detected by transcranial sonography. Neurology 1996 Nov;47(5):1284-90.

(71) Gaenslen A. Transcranial sonography in dystonia. Int Rev Neurobiol 2010;90:179-87.

(72) Hong JS, Sathe GG, Niyonkuru C, Munin MC. Elimination of dysphagia using ultrasound guidance for botulinum toxin injections in cervical dystonia. Muscle Nerve 2012 Oct;46(4):535-9.

(73) Jankovic J. Dystonia: medical therapy and botulinum toxin. Adv Neurol 2004;94:275-86.

(74) Comella CL, Thompson PD. Treatment of cervical dystonia with botulinum toxins. Eur J Neurol 2006 Feb;13(Suppl 1):16-20.

(75) Simpson LL. The origin, structure, and pharmacological activity of botulinum toxin. Pharmacol Rev 1981 Sep;33(3):155-88.

(76) Brashear A. Botulinum toxin type A in the treatment of patients with cervical dystonia. Biologics 2009;3:1-7.

(77) Poewe W, Wenning GK, Katzenschlager R. P-aktuell- Informationen zu Morbus Parkinson und extrapyramidalen Bewegungsstörungen, Newsletter der Österreichischen Parkinson Gesellschaft. 2006; Available at: http://www.parkinson.at/fileadmin/p-aktuell/2006/P-aktuell_1_06.pdf. Accessed 12/10/2013.

(78) Odergren T, Hjaltason H, Kaakkola S, Solders G, Hanko J, Fehling C, et al. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. J Neurol Neurosurg Psychiatry 1998 Jan;64(1):6-12.

(79) Merz Pharmaceuticals L. XEOMIN® (incobotulinumtoxin A) for injection- US Prescribing information. 2013; Available at: http://www.xeomin.com/files/Xeomin_PI.pdf. Accessed 12/10/2013.

(80) Greene PE, Fahn S. Use of botulinum toxin type F injections to treat torticollis in patients with immunity to botulinum toxin type A. Mov Disord 1993 Oct;8(4):479-83.

(81) Brashear A. The botulinum toxins in the treatment of cervical dystonia. Semin Neurol 2001;21(1):85-90.

(82) Comella CL, Buchman AS, Tanner CM, Brown-Toms NC, Goetz CG. Botulinum toxin injection for spasmodic torticollis: increased magnitude of benefit with electromyographic assistance. Neurology 1992 Apr;42(4):878-82.

(83) Hefter H, Benecke R, Erbguth F, Jost W, Reichel G, Wissel J. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). BMJ Open 2013 Apr;3(4).

(84) Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. Neurology 1990 Aug;40(8):1213-8.

(85) Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. J Neurol Neurosurg Psychiatry 1990 Aug;53(8):633-9.

(86) Dressler D. Botulinum toxin for treatment of dystonia. Eur J Neurol 2010 Jul;17(Suppl 1):88-96.

(87) Greene P, Fahn S, Diamond B. Development of resistance to botulinum toxin type A in patients with torticollis. Mov Disord 1994 Mar;9(2):213-7.

(88) Moore AP, Blumhardt LD. A double blind trial of botulinum toxin "A" in torticollis, with one year follow up. J Neurol Neurosurg Psychiatry 1991 Sep;54(9):813-6.

(89) Dippon C. Botulinumtoxin, das stärkste uns bekannte "Gift". 2005; Available at: http://www.botulinumtoxin-ambulanz.de/botulinumtoxin.htm. Accessed 12/10/2013.

(90) Adler CH, Kumar R. Pharmacological and surgical options for the treatment of cervical dystonia. Neurology 2000;55(12 Suppl 5):S9-14.

(91) Greene P, Shale H, Fahn S. Analysis of open-label trials in torsion dystonia using high dosages of anticholinergics and other drugs. Mov Disord 1988;3(1):46-60.

(92) Fahn S. Systemic therapy of dystonia. Can J Neurol Sci 1987 Aug;14(Suppl 3):528-32.

(93) Burke RE, Fahn S, Marsden CD. Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl. Neurology 1986 Feb;36(2):160-4.

(94) Ziegler DK. Prolonged relief of dystonic movements with diazepam. Neurology 1981 Nov;31(11):1457-8.

(95) Greene P. Baclofen in the treatment of dystonia. Clin Neuropharmacol 1992 Aug;15(4):276-88.

(96) Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. Neurology 1988 Mar;38(3):391-4.

(97) Lang AE. Dopamine agonists and antagonists in the treatment of idiopathic dystonia. Adv Neurol 1988;50:561-70.

(98) Ohara S, Hayashi R, Momoi H, Miki J, Yanagisawa N. Mexiletine in the treatment of spasmodic torticollis. Mov Disord 1998 Nov;13(6):934-40.

(99) Bertrand CM. Selective peripheral denervation for spasmodic torticollis: surgical technique, results, and observations in 260 cases. Surg Neurol 1993 Aug;40(2):96-103.

(100) Krauss JK. Selective peripheral denervation for cervical dystonia. In: Winn HR, editor. Youmans Textbook of Neurological Surgery Philadelphia: Elsevier; 2010.

(101) Taira T, Hori T. A novel denervation procedure for idiopathic cervical dystonia. Stereotact Funct Neurosurg 2003;80(1-4):92-5.

(102) Krauss JK, Toups EG, Jankovic J, Grossman RG. Symptomatic and functional outcome of surgical treatment of cervical dystonia. J Neurol Neurosurg Psychiatry 1997 Nov;63(5):642-8.

(103) Krauss JK. Surgical treatment of dystonia. Eur J Neurol 2010 Jul;17(Suppl 1):97-101.

(104) Krauss JK, Loher TJ, Pohle T, Weber S, Taub E, Bärlocher CB, et al. Pallidal deep brain stimulation in patients with cervical dystonia and severe cervical dyskinesias with cervical myelopathy. J Neurol Neurosurg Psychiatry 2002 Feb;72(2):249-56.

(105) Bleton JP. Physiotherapy of focal dystonia: a physiotherapist's personal experience. Eur J Neurol 2010 Jul;17(Suppl 1):107-12.

(106) Oberwittler C. Alternativbehandlung bei Dystonie- eine Umfrage. 1998; Available at: http://www.dystonie.de/aktuelles/archiv/dystonie-aktuell/alternativbehandlung-bei-dystonie-eine-umfrage.html. Accessed 12/10/2013.

(107) Bleton JP. Role of the physiotherapist. In: Warner TT, Bressman SB, editors. Clinical Diagnosis and Management of Dystonia London: Informa Healthcare; 2007. 223-32.

(108) Meige H, Feindel E. Traitement des tics. Traitement par l'immobilisation des mouvements et les mouvements d'immobilisation. Méthode de Brissaud. Presse méd 1901;22:125.

(109) Adler CH. Botulinum toxin treatment of movement disorders. In: Gilman S, Goldstein GW, Waxman SG, editors. Neurobase. 3rd ed. San Diego: Arbor Publishing; 1999.

(110) Greene P. Controlled trials of botulinum toxin for cervical dystonia: a critical review. In: Jankovic J, Hallet M, editors. Therapy with Botulinum Toxin New York: Marcel Dekker; 1994. 279-87.

(111) Lorentz IT, Subramaniam SS, Yiannikas C. Treatment of idiopathic spasmodic torticollis with botulinum toxin A: a double-blind study on twenty-three patients. Mov Disord 1991;6(2):145-50.

(112) Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. J Neurol Neurosurg Psychiatry 1990 Aug;53(8):640-3.

(113) Heller CA, Stanley P, Lewis-Jones B, Heller RF. Value of x ray examinations of the cervical spine. Br Med J (Clin Res Ed) 1983 Oct;287(6401):1276-8.

(114) Gore DR, Sepic SB, Gardner GM. Roentgenographic findings of the cervical spine in asymptomatic people. Spine (Phila Pa 1976) 1986 Jul-Aug;11(6):521-4.

(115) Volkmann J. Leitlinien für Diagnostik und Therapie in der Neurologie-Extrapyramidalmotorische Störungen. 2012; Available at: http://www.awmf.org/uploads/tx_szleitlinien/030-039l_S1_Dystonie_2012.pdf. Accessed 12/10/2013.

(116) Kruer M. Torticollis Workup- Approach Considerations. 2012; Available at: http://emedicine.medscape.com/article/1152543-workup. Accessed 12/10/2013.

(117) Schneider S, Feifel E, Ott D, Schumacher M, Lucking CH, Deuschl G. Prolonged MRI T2 times of the lentiform nucleus in idiopathic spasmodic torticollis. Neurology 1994 May;44(5):846-50.

(118) Bhatia K, Daniel SE, Marsden CD. Orofacial dystonia and rest tremor in a patient with normal brain pathology. Mov Disord 1993 Jul;8(3):361-2.

(119) Gibb WRG, Lees AJ, Marsden CD. Pathological report of four patients presenting with cranial dystonias. Mov Disord 1988;3(3):211-21.

(120) Tarlov E. On the problem of the pathology of spasmodic torticollis in man. J Neurol Neurosurg Psychiatry 1970 Aug;33(4):457-63.

(121) Garcia-Albea E, Franch O, Munoz D, Ricoy JR. Brueghel's syndrome, report of a case with postmortem studies. J Neurol Neurosurg Psychiatry 1981 May;44(5):437-40.

(122) Colosimo C, Pantano P, Calistri V, Totaro P, Fabbrini G, Berardelli A. Diffusion tensor imaging in primary cervical dystonia. J Neurol Neurosurg Psychiatry 2005 Nov;76(11):1591-3.

(123) Blood AJ, Tuch DS, Makris N, Makhlouf ML, Sudarsky LR, Sharma N. White matter abnormalities in dystonia normalize after botulinum toxin treatment. Neuroreport 2006 Aug;17(12):1251-5.

(124) Giladi N. The mechanism of action of botulinum toxin type A in focal dystonia is most probably through its dual effect on efferent (motor) and afferent pathways at the injected site. J Neurol Sci 1997 Nov;152(2):132-5.

(125) Curra A, Trompetto C, Abbruzzese G, Berardelli A. Central effects of botulinum toxin type A: evidence and supposition. Mov Disord 2004 Mar;19(Suppl 8):S60-4.

(126) Draganski B, Thun-Hohenstein C, Bogdahn U, Winkler J, May A. "Motor circuit" gray matter changes in idiopathic cervical dystonia. Neurology 2003 Nov;61(9):1228-31.

(127) Pantano P, Totaro P, Fabbrini G, Raz E, Contessa GM, Tona F, et al. A transverse and longitudinal MR imaging voxel-based morphometry study in patients with primary cervical dystonia. AJNR Am J Neuroradiol 2011 Jan;32(1):81-4.

(128) Reichel G, Stenner A, Jahn A. The phenomenology of cervical dystonia. Fortschr Neurol Psychiatr 2009 May;77(5):272-7.

(129) Kang Y, Lee JW, Koh YH, Hur S, Kim SJ, Chai JW, et al. New MRI grading system for the cervical canal stenosis. AJR Am J Roentgenol 2011 Jul;197(1):W134-40.

(130) Matsumoto M, Fujimura Y, Suzuki N, Nishi Y, Nakamura M, Yabe Y, et al. MRI of cervical intervertebral discs in asymptomatic subjects. J Bone Joint Surg Br 1998 Jan;80(1):19-24.

(131) Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 1988 Jan;166(1 Pt 1):193-9.

(132) Fisher RA. Statistical methods for research workers. 13th ed. New York: Hafner; 1958.

(133) Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33(1):159-74.

(134) Fleiss JL. Measuring nominal scale agreement among many raters. Psychol Bull 1971 Nov;76(5):378-82.

(135) Muhle C, Metzner J, Weinert D, Falliner A, Brinkmann G, Mehdorn MH, et al. Classification system based on kinematic MR imaging in cervical spondylitic myelopathy. AJNR Am J Neuroradiol 1998 Oct;19(9):1763-71.

(136) Edwards W, LaRocca H. The developmental segmental sagittal diameter of the cervical spinal canal in patients with cervical spondylosis. Spine (Phila Pa 1976) 1983 Jan-Feb;8(1):20-7.

(137) Pavlov H, Torg JS, Robie B, Jahre C. Cervical spinal stenosis: determination with vertebral body ratio method. Radiology 1987 Sep;164(3):771-5.

(138) Torg J, Pavlov H, Genuario SE, Sennett B, Wisneski RJ, Robie B, et al. Neurapraxia of the cervical spinal cord with transient quadriplegia. J Bone Joint Surg Am 1986 Dec;68(9):1354-70.

(139) Mann E, Peterson C, Hodler J. Degenerative marrow (modic) changes on cervical spine magnetic resonance imaging scans: prevalence, inter- and intra-examiner reliability and link to disc herniation. Spine (Phila Pa 1976) 2011 Jun;36(14):1081-5.

(140) Matsumoto M, Okada E, Ichihara D, Chiba K, Toyama Y, Fujiwara H, et al. Modic changes in the cervical spine: prospective 10-year follow-up study in asymptomatic subjects. J Bone Joint Surg Br 2012 May;94(5):678-83.

Appendix

1. TSUI Score

Zervikale Dystonien

Patienten ID:

Initialen: Geburtsdatum: Aufkleber

Zentrum: Patientennummer im Zentrum:

Untersuchungsdatum: Video:

TSUI Skala:

A

Drehung:	rechts □	links □	Seitwärtsneigung:	rechts □	links □
	0 Grad	0		0 Grad	0
	1-15 Grad	1		1-15 Grad	1
	15-30 Grad	2		15-30 Grad	2
	>30 Grad	3		>30 Grad	3

Vorwärts- □	Rückwärtsneigung □	
	Fehlend	0
	Leicht	1
	Mässig	2
	Schwer	3

B

Dauer der ablaufenden Bewegungen:

Intermittierend	1
Konstant	2

C

Schulterelevation: rechts □ links □

Fehlend	0
Leicht und intermittierend	1
Leicht und dauernd oder Stark und intermittierend	2
Stark und Konstant	3

D

Tremor:

Schweregrad:

Fehlend	0
Leicht	1
Schwer	2

Dauer:

Gelegentlich	1
Dauernd	2

horizontal □ vertikal □ gemischt □

Zusatz

Schmerzen:

Keine	0
Leichte	1
Moderate	2
Starke	3

Injektionen

Botox □ Dysport □ Xeomin □ Verdünnung: ______u/ml

Muskel	EMG-Kontrolle	Dosis re (units)	Dosis li (units)
Sternocleidomastoideus			
Splenius capitis			
Levator scapulae			
Trapezius			
Semispinalis cervicis			
Andere			

Wirkung:

_____ -1: Verschlechterung _____% maximale Abnahme
0: keine
1: mässige (<50%)
2: gut (>50%)
3: sehr gut (100%)

Latenz (in Tagen):_______ Wirkdauer:________

Wirksamkeit in % Abnahme:

Fehlstellung:______ Schmerz:______ Tremor:______

Nebenwirkungen: ja □ nein □

	Schwere(1:leicht, 2:mässig,3:schwer)	Latenz (in Tagen)	Dauer (in Tagen)
Dysphagie			
Nackenschwäche			
Lokaler Schmerz			
Andere			

2. Toronto Western Spasmodic Torticollis Rating Scale

I. Torticollis Severity Scale

Missing because of its similarity to the TSUI Score

II. Disability Scale (Maximum=30 points)

A. Work (occupation or housework/home management)

0 = No difficulty

1 = Normal work expectations with satisfactory performance at usual level of occupation but some interference by torticollis

2 = Most activities unlimited, selected activities very difficult and hampered but still possible with satisfactory performance

3 = Working at lower than usual occupation level; most activities hampered, all possible but with less than satisfactory performance in some activities

4 = Unable to engage in voluntary or gainful employment; still able to perform some domestic responsibilities satisfactorily

5 = Marginal or no ability to perform domestic responsibilities

B. Activities of Daily Living (e.g. feeding, dressing or hygiene, including washing, shaving, makeup, etc.)

0 = No difficulty with any activity

1 = Activities unlimited but some interference by torticollis

2 = Most activities unlimited, selected activities very difficult and hampered but still possible using simple tricks

3 = Most activities hampered or laborious but still possible; may use extreme tricks

4 = All activities impaired; some impossible or require assistance

5 = Dependent on others in most self-care tasks

C. Driving

0 = No difficulty (or has never driven a car)

1 = Unlimited ability to drive but bothered by torticollis

2 = Unlimited ability to drive but requires tricks (including touching or holding face, holding head against head rest) to control torticollis

3 = Can drive only short distances

4 = Usually cannot drive because of torticollis

5 = Unable to drive and cannot ride in a car for long stretches as a passenger because of torticollis

D. Reading

1 = Unlimited ability to read in normal seated position but bothered by torticollis

2 = Unlimited ability to read in normal seated position but requires use of tricks to control torticollis

3 = Unlimited ability to read but requires extensive measures to control torticollis **or** is able to read only in nonseated position (e.g. lying down)

4 = Limited ability to read because of torticollis despite tricks

5 = Unable to read more than a few sentences because of torticollis

E. Television

0 = No difficulty

1 = Unlimited ability to watch television in normal seated position but bothered by torticollis

2 = Unlimited ability to watch television in normal seated position but requires use of tricks to control torticollis

3 = Unlimited ability to watch television but requires extensive measures to control torticollis **or** is able to view only in nonseated position (e.g. lying down)

4 = Limited ability to watch television because of torticollis

5 = Unable to watch television more than a few minutes because of torticollis

F. Activities Outside the Home (e.g. shopping, walking about, movies, dining, and other recreational activities)

0 = No difficulty

1 = Unlimited activities but bothered by torticollis

2 = Unlimited activities but requires simple tricks to accomplish

3 = Accomplishes activities only when accompanied by others because of torticollis

4 = Limited activities outside the home; certain activities impossible or given up because of torticollis

5 = Rarely if ever engages in activities outside the home

III. Pain Scale (Maximum=20 points)

A. Severity of Pain

Rate the severity of neck pain due to spasmodic torticollis during the last week on a scale of 0-10 where a score of 0 represents no pain and 10 represents the most excruciating pain imaginable. Score calculated as: (worst + best + (2 x usual)) /4

Best ______

Worst ______

Usual ______

B. Duration of Pain

0 = None

1 = Present <10% of the time

2 = Present 10% - 25% of the time

3 = Present 26% - 50% of the time

4 = Present 51% - 75% of the time

5 = Present >76% of the time

C. Disability Due to Pain

0 = No limitation or interference from pain

1 = Pain is quite bothersome but not a source of disability

2 = Pain definitely interferes with some tasks but is not a major contributor to disability

3 = Pain accounts for some (less than half) but not all of disability

4 = Pain is a major source of difficulty with activities; separate from this, head pulling is also a source of some (less than half) disability

5 = Pain is the major source of disability; without it most impaired activities could be performed quite satisfactorily despite the head pulling

3. Burke-Fahn-Marsden Scale

3.1 The Burke-Fahn-Marsden (BFM) Scale: Movement Scale

Region	Provoking factor	Severity factor	Weight factor	Product
Eyes	0 – 4	x 0 – 4	x 0.5	0 – 8
Mouth	0 – 4	x 0 – 4	x 0.5	0 – 8
Speech/ Swallow	0 – 4	x 0 – 4	x 1.0	0 – 16
Neck	0 – 4	x 0 – 4	x 0.5	0 – 8
R arm	0 – 4	x 0 – 4	x 1.0	0 – 16
L arm	0 – 4	x 0 – 4	x 1.0	0 – 16
Trunk	0 – 4	x 0 – 4	x 1.0	0 – 16
R leg	0 – 4	x 0 – 4	x 1.0	0 – 16
L leg	0 – 4	x 0 – 4	x 1.0	0 – 16
				Sum:_______ Maximum:120

I. Provoking Factor

A. General

0 = No dystonia at rest or with action

1 = Dystonia only with particular action

2 = Dystonia with many actions

3 = Dystonia on action of distant part of body or intermittently at rest

4 = Dystonia present at rest

B. Speech and swallowing

0 = Occasional, either or both

1 = Frequent either

2 = Frequent one and occasional either

3 = Frequent both

II. Severity factors

Eyes

0 = No dystonia

1 = Slight. Occasional blinking

2 = Mild. Frequent blinking without prolonged spasms of eye closure

3 = Moderate. Prolonged spasms of eyelid closure, but eyes open most of the time

4 = Severe. Prolonged spasms of eyelid closure, with eyes closed at least 30% of the time

Mouth

0 = No dystonia present

1 = Slight. Occasional grimacing or other mouth movements (e.g. jaw opened or clenched; tongue movement)

2 = Mild. Movement present less than 50% of the time

3 = Moderate dystonic movements or contractions present most of the time

4 = Severe dystonic movements or contractions present most of the time

Speech and swallowing

0 = Normal

1 = Slightly involved; speech easily understood or occasional choking

2 = Some difficulty in understanding speech or frequent choking

3 = Marked difficulty in understanding speech or inability to swallow firm foods

4 = Complete or almost complete anarthria, or marked difficulty swallowing soft foods and liquids

Neck

0 = No dystonia present

1 = Slight. Occasional pulling

2 = Obvious torticollis, but mild

3 = Moderate pulling

4 = Extreme pulling

Arm

0 = No dystonia present

1 = Slight dystonia. Clinically insignificant

2 = Mild. Obvious dystonia, but not disabling

3 = Moderate. Able to grasp, with some manual function

4 = Severe. No useful grasp

Trunk

0 = No dystonia present

1 = Slight bending; clinically insignificant

2 = Definite bending, but not interfering with standing or walking

3 = Moderate bending; interfering with standing or walking

4 = Extreme bending of trunk preventing standing or walking

Leg

0 = No dystonia present

1 = Slight dystonia, but not causing impairment; clinically insignificant

2 = Mild dystonia. Walks briskly and unaided

3 = Moderate dystonia. Severely impairs walking or requires assistance

4 = Severe. Unable to stand or walk on involved leg

3.2 The Burke-Fahn-Marsden Score

Scored by: Name _______

Date ________

Videotape number ____

Region	**Provoking factor** **A. General**	**Severity factor**	**Weight**	**Score**
Eyes	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia 1= Slight. Occasional blinking 2= Mild. Frequent blinking without prolonged spasms of eye closure 3= Moderate. Prolonged spasms of eyelid closure, but eyes open most of the time 4= Severe. Prolonged spasms of eyelid closure, with eyes closed at least 30% of the time	**0.5**	
Mouth	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight. Occasional grimacing or other mouth movements (e.g. jaw opened or clenched; tongue movement) 2= Mild. Movement present less than 50% of the time 3= Moderate dystonic movements or contractions present most of the time 4= Severe dystonic movements or contractions present most of the time	**0.5**	
Speech/ Swallow-ing	**B. Speech and swallowing** 0= Occasional, either or both 1= Frequent either 2= Frequent one and occasional either 3= Frequent both	0= Normal 1= Slightly involved; speech easily understood or occasional choking 2= Some difficulty in understanding speech or frequent choking 3= Marked difficulty in understanding speech or inability to swallow firm foods 4= Complete or almost complete anarthria, or marked difficulty swallowing soft foods and liquids	1.0	

Region	Provoking factor A. General	Severity factor	Weight	Score
Neck	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight. Occasional pulling 2= Obvious torticollis, but mild 3= Moderate pulling 4= Extreme pulling	0.5	
Right Arm	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight dystonia. Clinically insignificant 2= Mild. Obvious dystonia, but not disabling 3= Moderate. Able to grasp, with some manual function 4= Severe. No useful grasp	1.0	
Left Arm	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight dystonia. Clinically insignificant 2= Mild. Obvious dystonia, but not disabling 3= Moderate. Able to grasp, with some manual function 4 = Severe. No useful grasp	1.0	

Region	Provoking factor A. General	Severity factor	Weight	Score
Right Leg	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight dystonia, but not causing impairment; clinically insignificant 2= Mild dystonia. Walks briskly and unaided 3= Moderate dystonia. Severely impairs walking or requires assistance 4= Severe. Unable to stand or walk on involved leg	1.0	
Left Leg	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight dystonia, but not causing impairment; clinically insignificant 2= Mild dystonia. Walks briskly and unaided 3= Moderate dystonia. Severely impairs walking or requires assistance 4= Severe. Unable to stand or walk on involved leg	1.0	
Trunk	0= No dystonia at rest or with action 1= Dystonia only with particular action 2= Dystonia with many actions 3= Dystonia on action of distant part of body or intermittently at rest 4= Dystonia present at rest	0= No dystonia present 1= Slight bending; clinically insignificant 2= Definite bending, but not interfering with standing or walking 3= Moderate bending; interfering with standing or walking 4= Extreme bending of trunk preventing standing or walking	1.0	

4. Neurological examination

<u>Neurologischer Status</u>

<u>1. Bewusstseinslage und Orientierung</u>

unauffällig: ja
nein

<u>2. Meningeale Zeichen</u>

unauffällig: ja
nein

<u>3. Kopf</u>

unauffällig: ja
nein

<u>4. Hirnnerven</u>

I	unauffällig:	ja nein	**II**	unauffällig:	ja nein
III, IV, VI	unauffällig:	ja nein	**V**	unauffällig:	ja nein
VII	unauffällig:	ja nein	**VIII**	unauffällig:	ja nein
IX – XII	unauffällig:	ja nein	**Sprache/Sprechen**	unauffällig:	ja nein

5. Motorik

Tonus	unauffällig:	ja nein	**Trophik**	unauffällig:	ja nein
Spontanmotorik	unauffällig:	ja nein	**Kraft**	unauffällig:	ja nein

6. Reflexstatus, Pyramidenbahnzeichen (PBZ)

MER	unauffällig:	ja nein	**PBZ**	unauffällig:	ja nein

7. Koordination

Finger-Nase Versuch (FNV)	unauffällig:	ja nein
Knie-Hacke Versuch (KHV)	unauffällig:	ja nein
Diadochokinese	unauffällig:	ja nein

8. Sensibilität

Berührung	unauffällig:	ja nein	**Lage**	unauffällig:	ja nein
Schmerz/Temperatur	unauffällig:	ja nein	**Vibration**	unauffällig:	ja nein

9. Vegetativum

	unauffällig:	ja
		nein

10. Gang

Gang	unauffällig:	ja
		nein
Strichgang	unauffällig:	ja
		nein
Romberg	unauffällig:	ja
		nein

5. Results

5.1 Group

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.103 p: 0.189	**B: 0.396 p: 0.006**	B: 0.031 p: 0.876	B: -0.020 p: 0.910	B: 0.007 p:0.969	B: 0.531 p: 0.278
Disc degeneration	B: 0.080 p: 0.563	B: 0.273 p: 0.090	B: 0.049 p: 0.689	B: -0.057 p: 0.623	B: 0.120 p: 0.339	B: 0.525 p: 0.181
Anterior disc protrusion	B: 0.008 p: 0.761	B: 0.132 p: 0.162	**B: 0.188 p: 0.042**	B: -0.055 p: 0.566	B: 0.089 p: 0.426	B: 0.362 p: 0.132
Narrowing of the disc space	B: 0.118 p: 0.168	B: 0.068 p: 0.681	B: 0.319 p: 0.100	B: 0.001 p: 0.998	B: -0.003 p: 0.990	B: 0.473 p: 0.381
Foraminal stenosis	B: 0.044 p: 0.160	B: 0.121 p: 0.115	B: 0.043 p: 0.655	B: -0.160 p: 0.166	B: -0.052 p: 0.482	B: -0.009 p: 0.974
Matsumoto total score	B: 0.207 p: 0.236	B: 0.568 p: 0.066	B: 0.588 p: 0.086	B: -0.216 p: 0.546	B: 0.192 p: 0.617	B: 1.424 p: 0.168
Modic classification	B: -0.162 p: 0.254	B: -0.015 p: 0.904	B: 0.100 p: 0.579	B: -0.406 p: 0.088	B: -0.110 p: 0.602	B: -0.562 p: 0.284
MRI total score	B: 0.137 p: 0.552	**B: 0.949 p: 0.038**	B: 0.719 p: 0.219	B: -0.633 p: 0.311	B: 0.078 p: 0.903	

Table 19: Correlation between MRI changes and the study groups

5.2 Disease duration

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.006 p: 0.370	B: 0.011 p: 0.201	B: 0.002 p: 0.890	B: 0.013 p: 0.271	B: 0.003 p: 0.829	B: 0.022 p: 0.503
Disc degeneration	B: 0.004 p: 0.665	B: 0.006 p: 0.472	B: 0.007 p: 0.341	B: 0.012 p: 0.080	B: -0.009 p: 0.261	B: 0.014 p: 0.585
Anterior disc protrusion	B: 0.003 p: 0.129	B: 0.010 p: 0.112	B: -0.004 p: 0.539	B: -0.003 p: 0.573	B: 0.001 p: 0.853	B: 0.007 p: 0.665
Narrowing of the disc space	B: 0.011 p: 0.082	**B: 0.022** **p: 0.028**	B: 0.014 p: 0.282	B: 0.003 p: 0.824	B: 0.013 p: 0.377	B: 0.064 p: 0.093
Foraminal stenosis	B: 0.002 p: 0.553	B: -0.003 p: 0.618	B: -0.002 p: 0.759	B: 0.004 p: 0.630	B: 0.001 p: 0.796	B: 0.003 p: 0.881
Matsumoto total score	**B: 0.020** **p: 0.054**	**B: 0.037** **p: 0.055**	B: 0.018 p: 0.436	B: 0.017 p: 0.419	B: 0.006 p: 0.820	B: 0.092 p: 0.194
Modic classification	B: 0.005 p: 0.564	**B: 0.015** **p: 0.016**	B: 0.016 p: 0.169	B: 0.003 p: 0.833	B: 0.007 p: 0.591	B: 0.041 p: 0.184
MRI total score	B: 0.021 p: 0.086	**B: 0.063** **p: 0.017**	B: 0.035 p: 0.380	B: 0.035 p: 0.357	B: 0.014 p: 0.744	

Table 20: Correlation between MRI changes and the disease duration

5.3 Type of dystonia

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.126 p: 0.450	B: 0.023 p: 0.926	B: 0.012 p: 0.974	B: 0.093 p: 0.773	B: -0.147 p: 0.639	B: -0.169 p: 0.849
Disc degeneration	B: 0.066 p: 0.777	B: 0.151 p: 0.502	B: 0.034 p: 0.863	B: 0.024 p: 0.899	B: 0.222 p: 0.313	B: 0.559 p: 0.417
Anterior disc protrusion	B: -0.042 p: 0.399	**B: 0.382** **p: 0.017**	B: 0.110 p: 0.507	B: 0.109 p: 0.511	B: -0.153 p: 0.350	B: 0.406 p: 0.310
Narrowing of the disc space	B: -0.160 p: 0.370	B: 0.468 p: 0.097	B: 0.169 p: 0.644	B: 0.385 p: 0.231	B: 0.378 p: 0.336	B: 1.268 p: 0.221
Foraminal stenosis	B: -0.070 p: 0.317	B: -0.010 p: 0.948	B: 0.040 p: 0.830	B: 0.270 p: 0.197	B: 0.137 p: 0.197	B: 0.402 p: 0.455
Matsumoto total score	B: -0.110 p: 0.702	B: 0.963 p: 0.063	B: 0.282 p: 0.651	B: 0.689 p: 0.217	B: 0.544 p: 0.410	B: 2.373 p: 0.212
Modic classification	B: -0.133 p: 0.558	B: 0.320 p: 0.069	B: 0.110 p: 0.722	B: 0.124 p: 0.750	B: 0.074 p: 0.832	B: 0.440 p: 0.598
MRI total score	B: -0.351 p: 0.292	B: 1.305 p: 0.076	B: 0.404 p: 0.711	B: 0.924 p: 0.363	B: 0.415 p: 0.721	

Table 21: Correlation between MRI changes and the type of dystonia (cervical versus segmental)

5.4 Trauma

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.125 p: 0.459	B: -0.243 p: 0.314	B: -0.602 p: 0.084	B: -0.081 p: 0.803	B: 0.092 p: 0.770	B: -0.983 p: 0.265
Disc degeneration	B: 0.295 p: 0.200	B: 0.031 p: 0.893	B: 0.160 p: 0.416	B: -0.019 p: 0.921	B: -0.177 p: 0.425	B: 0.513 p: 0.460
Anterior disc protrusion	**B: 0.130 p:0.004**	B: 0.116 p: 0.501	B: -0.174 p: 0.292	B: 0.264 p: 0.103	B: 0.155 p: 0.346	B: 0.491 p: 0.220
Narrowing of the disc space	B: -0.087 p: 0.631	B: 0.285 p: 0.325	B: -0.109 p: 0.767	B: -0.086 p: 0.794	B: -0.001 p: 0.997	B: 0.032 p: 0.976
Foraminal stenosis	B: 0.013 p: 0.855	B: -0.022 p: 0.892	B: -0.099 p: 0.596	B: 0.006 p: 0.979	B: 0.048 p: 0.658	B: -0.018 p: 0.973
Matsumoto total score	B: 0.453 p: 0.108	B: 0.382 p: 0.481	B: -0.251 p: 0.689	B: 0.151 p: 0.792	B: -0.013 p: 0.985	B: 0.885 p: 0.649
Modic classification	B: -0.221 p: 0.331	B: 0.127 p: 0.486	B: 0.003 p: 0.993	B: 0.086 p: 0.826	B: -0.030 p: 0.932	B: 0.164 p: 0.845
MRI total score	B: 0.041 p: 0.904	B: 0.266 p: 0.729	B: -0.851 p: 0.435	B: 0.089 p: 0.931	B: 0.080 p: 0.946	

Table 22: Correlation between MRI changes and the trauma of the head or neck

5.5 Botulinum toxin therapy

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.276 p: 0.191	B: 0.204 p: 0.510	**B: 0.861 p: 0.050**	B: -0.487 p: 0.234	B: 0.455 p: 0.250	B: 1.349 p: 0.229
Disc degeneration	B: -0.309 p: 0.295	B: -0.267 p: 0.353	B: 0.028 p: 0.911	B: -0.276 p: 0.250	B: 0.209 p: 0.460	B: -0.832 p: 0.344
Anterior disc protrusion	B: 0.050 p: 0.429	B: -0.273 p: 0.206	B: 0.276 p: 0.186	B: -0.356 p: 0.083	B: 0.027 p: 0.898	B: -0.276 p: 0.593
Narrowing of the disc space	B: 0.178 p: 0.437	B: -0.406 p: 0.269	B: 0.752 p: 0.098	B: -0.239 p: 0.566	B: -0.156 p: 0.759	B: 0.085 p: 0.950
Foraminal stenosis	B: 0.079 p: 0.378	B: -0.011 p: 0.957	B: 0.316 p: 0.176	B: 0.082 p: 0.764	B: -0.020 p: 0.884	B: 0.387 p: 0.577
Matsumoto total score	B: -0.149 p: 0.687	B: -0.903 p: 0.184	B: 1.384 p: 0.072	B: -0.728 p: 0.312	B: 0.134 p: 0.875	B: -0.394 p: 0.874
Modic classification	B: -0.061 p: 0.834	B: -0.363 p: 0.110	B: 0.154 p: 0.698	B: -0.338 p: 0.496	B: -0.109 p: 0.808	B: -0.687 p: 0.520
MRI total score	B: 0.056 p: 0.898	B: -1.062 p: 0.272	B: 2.399 p: 0.075	B: -1.563 p: 0.227	B: 0.578 p: 0.698	

Table 23: Correlation between MRI changes and the botulinum toxin therapy

5.6 Duration of botulinum toxin therapy

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.015 p: 0.183	B: -0.005 p: 0.764	**B: 0.072 p: 0.009**	B: -0.003 p: 0.884	B: 0.016 p: 0.468	B: 0.043 p: 0.485
Disc degeneration	B: 0.015 p: 0.336	B: 0.011 p: 0.495	B: 0.028 p: 0.075	B: 0.014 p: 0.276	B: -0.002 p: 0.900	B: 0.054 p: 0.256
Anterior disc protrusion	B: 0.005 p: 0.176	B: -0.001 p: 0.960	B: 0.002 p: 0.828	B: 0.003 p: 0.806	B: 0.012 p: 0.303	B: 0.021 p: 0.452
Narrowing of the disc space	B: -0.001 p: 0.913	B: -0.002 p: 0.932	B: 0.042 p: 0.087	B: 0.001 p: 0.949	B: 0.017 p: 0.532	B: 0.057 p: 0.432
Foraminal stenosis	B: -0.004 p: 0.420	B: -0.014 p: 0.186	B: 0.001 p: 0.929	B: -0.004 p: 0.805	B: 0.004 p: 0.560	B: -0.013 p: 0.733
Matsumoto total score	B: 0.015 p: 0.453	B: -0.003 p: 0.947	B: 0.072 p: 0.083	B: 0.016 p: 0.686	B: 0.031 p: 0.496	B: 0.121 p: 0.362
Modic classification	B: -0.012 p: 0.435	B: 0.013 p: 0.310	B: 0.033 p: 0.172	B: -0.005 p: 0.865	B: 0.024 p: 0.320	B: 0.055 p: 0.338
MRI total score	B: -0.011 p: 0.630	B: 0.005 p: 0.923	**B: 0.182 p: 0.033**	B: 0.009 p: 0.896	B: 0.073 p: 0.359	

Table 24: Correlation between MRI changes and the duration of botulinum toxin therapy

5.7 Dosage of botulinum toxin

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.000 p: 0.356	**B: -0.001** **p: 0.057**	B: 0.000 p: 0.651	B: -0.001 p: 0.489	B: 0.001 p: 0.244	B: -0.001 p: 0.499
Disc degeneration	B: 0.000 p: 0.857	B: 0.000 p: 0.681	B: 0.000 p: 0.638	B: 0.001 p: 0.092	B: 0.000 p: 0.494	B: 0.000 p: 0.814
Anterior disc protrusion	B: -6.050E-005 p: 0.619	B: 0.000 p: 0.185	B: 0.000 p: 0.436	B: -3.217E-005 p: 0.933	B: 1.314E-005 p: 0.974	B: -0.001 p: 0.388
Narrowing of the disc space	B: 0.000 p: 0.282	B: 0.000 p: 0.564	B: 0.000 p: 0.621	B: 0.000 p: 0.820	B: 0.001 p: 0.190	B: 0.000 p: 0.955
Foraminal stenosis	B: -4.104E-005 p: 0.813	B: 0.000 p: 0.599	B: -0.001 p: 0.213	B: -4.615E-005 p: 0.930	B: 0.000 p: 0.168	B: 0.000 p: 0.774
Matsumoto total score	B: 0.000 p: 0.510	B: -0.001 p: 0.314	B: -0.001 p: 0.364	B: 0.001 p: 0.641	B: 0.001 p: 0.430	B: -0.001 p: 0.773
Modic classification	B: 2.311E-005 p: 0.961	B: 0.000 p: 0.674	B: -1.836E-005 p: 0.980	B: 0.000 p: 0.662	B: 0.001 p: 0.185	B: 0.001 p: 0.677
MRI total score	B: 0.001 p: 0.311	B: -0.002 p: 0.229	B: -0.002 p: 0.497	B: 0.000 p: 0.916	B: 0.003 p: 0.246	

Table 25: Correlation between MRI changes and the dosage of botulinum toxin

5.8 Side effects of botulinum toxin

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.044 p: 0.765	B: -0.391 p: 0.152	B: 0.114 p: 0.731	**B: -0.725 p: 0.049**	B: -0.576 p: 0.094	B: -1.535 p: 0.116
Disc degeneration	B: -0.250 p: 0.267	B: -0.195 p: 0.411	B: -0.151 p: 0.499	B: -0.179 p: 0.386	B: 0.049 p: 0.819	B: -1.018 p: 0.123
Anterior disc protrusion	B: -0.048 p: 0.459	B: -0.126 p: 0.477	B: 0.082 p: 0.580	**B: -0.311 p: 0.057**	B: -0.121 p: 0.486	B: -0.524 p: 0.205
Narrowing of the disc space	B: -0.028 p: 0.908	B: -0.437 p: 0.176	B: -0.064 p: 0.870	B: -0.116 p: 0.704	B: -0.559 p: 0.211	B: -1.286 p: 0.289
Foraminal stenosis	B: -0.044 p: 0.501	B: 0.081 p: 0.569	B: 0.211 p: 0.274	B: -0.149 p: 0.536	B: -0.193 p: 0.078	B: -0.093 p: 0.880
Matsumoto total score	B: -0.617 p: 0.082	B: -0.666 p: 0.253	B: 0.114 p: 0.845	B: -0.720 p: 0.245	B: -0.799 p: 0.295	B: -2.816 p: 0.174
Modic classification	B: -0.344 p: 0.118	B: -0.136 p: 0.452	B: -0.167 p: 0.656	B: -0.191 p: 0.655	B: -0.726 p: 0.076	B: -1.627 p: 0.066
MRI total score	**B: -0.896 p: 0.019**	B: -1.193 p: 0.152	B: 0.060 p: 0.954	B: -1.615 p: 0.149	B: -2.101 p: 0.107	

Table 26: Correlation between MRI changes and the side effects of botulinum toxin

5.9 Latency of botulinum toxin

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.011 p: 0.317	B: -0.009 p: 0.779	**B: -0.077 p: 0.044**	B: -0.021 p: 0.685	B: 0.006 p: 0.905	B: -0.089 p: 0.435
Disc degeneration	B: -0.011 p: 0.713	B: 0.032 p: 0.323	B: 0.032 p: 0.309	B: 0.009 p: 0.768	B: 0.046 p: 0.116	B: 0.109 p: 0.264
Anterior disc protrusion	B: -0.006 p: 0.499	B: -0.024 p: 0.293	B: 0.001 p: 0.963	B: -0.024 p: 0.326	B: -0.005 p: 0.840	B: -0.059 p: 0.292
Narrowing of the disc space	B: 0.042 p: 0.198	B: 0.009 p: 0.847	B: -0.052 p: 0.343	B: -0.011 p: 0.800	B: 0.027 p: 0.674	B: 0.008 p: 0.963
Foraminal stenosis	B: 0.004 p: 0.658	B: -0.012 p: 0.519	B: -0.026 p: 0.328	B: -0.037 p: 0.232	B: -0.015 p: 0.318	B: -0.086 p: 0.278
Matsumoto total score	B: 0.006 p: 0.913	B: 0.008 p: 0.927	B: -0.034 p: 0.685	B: -0.054 p: 0.548	B: 0.061 p: 0.581	B: 0.003 p: 0.994
Modic classification	B: 0.003 p: 0.934	B: -0.027 p: 0.264	**B: -0.123 p: 0.004**	B: -0.028 p: 0.619	B: -0.038 p: 0.533	B: -0.202 p: 0.097
MRI total score	B: 0.015 p: 0.799	B: -0.028 p:0.825	B: -0.234 p: 0.096	B: -0.107 p: 0.517	B: 0.028 p: 0.883	

Table 27: Correlation between MRI changes and the latency of botulinum toxin

5.10 Effect in total

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.000 p: 0.967	B: 0.003 p: 0.530	B: 0.010 p: 0.091	B: -8.162E-005 p: 0.991	B: -0.001 p: 0.931	B: 0.012 p: 0.511
Disc degeneration	B: -0.003 p: 0.428	B: -0.004 p: 0.341	B: 0.001 p: 0.875	B: 0.001 p: 0.708	B: -0.003 p: 0.373	B: -0.016 p: 0.198
Anterior disc protrusion	B: 0.002 p: 0.133	B: 0.006 p: 0.071	B: 0.002 p: 0.540	B: -0.002 p: 0.629	B: -0.003 p: 0.296	B: 0.004 p: 0.593
Narrowing of the disc space	B: 0.003 p: 0.519	B: 0.007 p: 0.257	**B: 0.013 p: 0.057**	B: 0.003 p: 0.553	B: 0.002 p: 0.844	B: 0.027 p: 0.220
Foraminal stenosis	B: 0.000 p: 0.900	B: -0.001 p: 0.619	B: 0.002 p: 0.505	B: 0.001 p: 0.892	B: 5.961E-005 p: 0.977	B: 0.002 p: 0.888
Matsumoto total score	B: 0.001 p: 0.928	B: 0.007 p: 0.532	B: 0.016 p: 0.105	B: 0.003 p: 0.797	B: -0.006 p: 0.687	B: 0.014 p: 0.710
Modic classification	**B: -0.008 p: 0.041**	B: 0.005 p: 0.149	**B: 0.013 p: 0.032**	B: 0.004 p: 0.600	B: -0.004 p: 0.618	B: 0.005 p: 0.772
MRI total score	B: -0.006 p: 0.459	B: 0.014 p: 0.347	**B: 0.039 p: 0.022**	B: 0.009 p: 0.677	B: -0.010 p: 0.682	

Table 28: Correlation between MRI changes and the effect in total

5.11 Effect on tremor

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.002 p: 0.370	B: 0.005 p: 0.190	**B: 0.009 p: 0.048**	B: 0.002 p: 0.777	B: 0.001 p: 0.863	B: 0.018 p: 0.195
Disc degeneration	B: -0.004 p: 0.154	**B: -0.007 p: 0.031**	B: 0.001 p: 0.710	B: 0.001 p: 0.714	B: -0.002 p: 0.576	B: -0.013 p: 0.170
Anterior disc protrusion	B: 0.002 p: 0.077	**B: 0.005 p: 0.030**	B: 0.001 p: 0.548	B: 0.001 p: 0.639	B: -0.002 p: 0.393	B: 0.007 p: 0.244
Narrowing of the disc space	B: 0.001 p: 0.832	B: 0.004 p: 0.442	B: 0.008 p: 0.134	B: 0.002 p: 0.673	B: 0.002 p: 0.750	B: 0.017 p: 0.333
Foraminal stenosis	B: -0.001 p: 0.385	B: -0.001 p: 0.481	B: 0.002 p: 0.556	B: 0.001 p: 0.748	B: 0.002 p: 0.349	B: 0.002 p: 0.816
Matsumoto total score	B: -0.002 p: 0.699	B: 0.000 p: 0.989	B: 0.011 p: 0.167	B: 0.004 p: 0.657	B: -0.001 p: 0.933	B: 0.009 p: 0.754
Modic classification	**B: -0.007 p: 0.014**	B: 0.003 p: 0.176	**B: 0.010 p: 0.049**	B: 0.005 p: 0.422	B: -0.001 p: 0.817	B: 0.007 p: 0.596
MRI total score	B: -0.006 p: 0.302	B: 0.009 p: 0.473	**B: 0.030 p: 0.029**	B: 0.011 p: 0.479	B: -0.001 p: 0.940	

Table 29: Correlation between MRI changes and the effect on tremor

5.12 TSUI total

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.009 p: 0.580	B: -0.021 p: 0.562	B: -0.015 p: 0.733	B: 0.037 p: 0.425	B: 0.075 p: 0.069	B: 0.067 p: 0.575
Disc degeneration	B: -0.025 p: 0.337	B: -0.015 p: 0.600	B: -0.018 p: 0.499	B: -0.003 p: 0.912	B: 0.037 p: 0.126	B: -0.045 p: 0.580
Anterior disc protrusion	B: -0.002 p: 0.757	B: -0.031 p: 0.183	B: -0.029 p: 0.182	B: 0.007 p: 0.732	B: 0.012 p: 0.554	B: -0.044 p: 0.368
Narrowing of the disc space	B: -0.030 p: 0.276	B: -0.036 p: 0.415	B: -0.022 p: 0.657	B: 0.049 p: 0.157	B: 0.093 p: 0.071	B: 0.059 p: 0.678
Foraminal stenosis	B: 0.002 p: 0.828	B: 0.012 p: 0.574	B: 0.026 p: 0.291	B: 0.039 p: 0.151	**B: 0.027 p: 0.028**	B: 0.106 p: 0.142
Matsumoto total score	B: -0.042 p: 0.324	B: -0.074 p: 0.339	B: -0.057 p: 0.459	B: 0.080 p: 0.268	**B: 0.164 p: 0.053**	B: 0.041 p: 0.870
Modic classification	B: 0.045 p: 0.149	B: 0.002 p: 0.937	B: 0.014 p: 0.767	B: 0.028 p: 0.580	**B: 0.112 p: 0.013**	B: 0.191 p: 0.081
MRI total score	B: -0.003 p: 0.959	B: -0.093 p: 0.404	B: -0.058 p: 0.674	B: 0.148 p: 0.260	**B: 0.355 p: 0.014**	

Table 30: Correlation between MRI changes and the TSUI total score

5.13 TWSTRS IIIA total (Severity of Pain)

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.050 p: 0.135	B: -0.111 p: 0.114	B: -0.043 p: 0.618	B: -0.024 p: 0.794	B: 0.020 p: 0.821	B: -0.208 p: 0.382
Disc degeneration	B: 0.033 p: 0.543	B: 0.007 p: 0.908	B: -0.067 p: 0.195	**B: -0.106 p: 0.024**	B: -0.010 p: 0.843	B: -0.189 p: 0.234
Anterior disc protrusion	B: -0.006 p: 0.703	B: -0.071 p: 0.134	B: -0.031 p: 0.495	B: 0.006 p: 0.879	B: 0.016 p: 0.701	B: -0.085 p: 0.387
Narrowing of the disc space	B: -0.082 p: 0.129	B: -0.093 p: 0.286	B: -0.036 p: 0.709	B: 0.098 p: 0.155	B: 0.094 p: 0.383	B: -0.022 p: 0.938
Foraminal stenosis	B: 0.011 p: 0.466	B: 0.041 p: 0.341	B: 0.048 p: 0.321	B: 0.041 p: 0.462	B: 0.003 p: 0.914	B:0.145 p: 0.325
Matsumoto total score	B: -0.056 p: 0.517	B: -0.124 p: 0.426	B: -0.104 p: 0.499	B: 0.028 p: 0.848	B: 0.099 p: 0.582	B: -0.195 p: 0.693
Modic classification	B: -0.002 p: 0.971	B: -0.057 p: 0.271	B: -0.064 p: 0.483	B: 0.034 p: 0.746	B: 0.139 p: 0.153	B: 0.059 p: 0.798
MRI total score	B: -0.111 p: 0.275	B: -0.293 p: 0.184	B: -0.212 p: 0.441	B: 0.034 p: 0.900	B: 0.272 p: 0.387	

Table 31: Correlation between MRI changes and the "Severity of Pain" scale of TWSTRS (IIIA total)

5.14 TWSTRS III (Pain Scale)

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.022 p: 0.162	B: -0.052 p: 0.112	B: -0.037 p: 0.343	B: -0.018 p: 0.683	B: -0.007 p: 0.855	B: -0.136 p: 0.213
Disc degeneration	B: 0.007 p: 0.790	B: 0.000 p: 0.994	B: -0.028 p: 0.254	**B: -0.048 p: 0.027**	B: 0.000 p: 0.989	B: -0.078 p: 0.293
Anterior disc protrusion	B: -0.004 p: 0.621	B: -0.030 p: 0.168	B: -0.018 p: 0.387	B: 0.002 p: 0.914	B: 0.004 p: 0.853	B: -0.046 p: 0.309
Narrowing of the disc space	B: -0.043 p: 0.079	B: -0.043 p: 0.283	B: -0.037 p: 0.409	B: 0.043 p: 0.179	B: 0.041 p: 0.410	B: -0.040 p: 0.763
Foraminal stenosis	B: 0.004 p: 0.541	B: 0.021 p: 0.293	B: 0.019 p: 0.395	B: 0.021 p: 0.409	B: 0.002 p: 0.878	B: 0.068 p: 0.319
Matsumoto total score	B: -0.039 p: 0.318	B: -0.059 p: 0.419	B: -0.073 p: 0.305	B: 0.012 p: 0.865	B: 0.043 p: 0.605	B: -0.122 p: 0.595
Modic classification	B: 0.001 p: 0.965	B: -0.023 p: 0.346	B: -0.041 p: 0.327	B: 0.010 p: 0.828	B: 0.059 p: 0.191	B: 0.020 p: 0.853
MRI total score	B: -0.064 p: 0.170	B: -0.133 p: 0.193	B: -0.151 p: 0.228	B: -1.108E-005 p: 1.000	B: 0.100 p: 0.492	

Table 32: Correlation between MRI changes and the “Pain scale” of TWSTRS (III)

5.15 Burke-Fahn-Marsden Scale

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.011 p: 0.653	B: -0.031 p: 0.572	B: -0.054 p: 0.397	B: -0.071 p: 0.300	B: -0.013 p: 0.848	B: -0.157 p: 0.378
Disc degeneration	**B: -0.077 p: 0.039**	B: -0.037 p: 0.380	B: -0.020 p: 0.615	B: -0.055 p: 0.137	B: 0.058 p: 0.104	B: -0.171 p: 0.145
Anterior disc protrusion	B: -0.021 p: 0.058	**B: -0.067 p: 0.050**	B: -0.013 p: 0.705	**B: -0.058 p: 0.040**	B: -0.024 p: 0.436	**B: -0.183 p: 0.006**
Narrowing of the disc space	B: 0.005 p: 0.914	B: -0.104 p: 0.101	B: -0.126 p: 0.069	B: -0.023 p: 0.659	B: 0.027 p: 0.735	B: -0.235 p: 0.266
Foraminal stenosis	B: -0.006 p: 0.588	B: -0.021 p: 0.512	B: 0.005 p: 0.884	B: -0.021 p: 0.613	B: -0.007 p: 0.709	B: -0.051 p: 0.648
Matsumoto total score	**B: -0.139 p: 0.019**	**B: -0.228 p: 0.039**	B: -0.155 p: 0.169	B: -0.160 p: 0.129	B: 0.058 p: 0.668	B: -0.639 p: 0.069
Modic classification	B: 0.026 p: 0.587	B: -0.039 p: 0.319	B: -0.126 p: 0.051	B: -0.058 p: 0.450	B: -0.029 p: 0.699	B: -0.237 p: 0.156
MRI total score	B: -0.098 p: 0.196	B: -0.297 p: 0.064	B: -0.335 p: 0.090	B: -0.286 p: 0.142	B: 0.013 p: 0.957	

Table 33: Correlation between MRI changes and the BFM scale

5.16 Clinical parameters and MRI changes without correlations

5.16.1 Effect duration of botulinum toxin

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.003 p: 0.084	B: -0.002 p: 0.575	B: 0.004 p: 0.421	B: -0.004 p: 0.540	B: 0.003 p: 0.640	B: -0.003 p: 0.862
Disc degeneration	B: 0.005 p: 0.162	B: 0.000 p: 0.961	B: -0.002 p: 0.648	B: -0.004 p: 0.228	B: -0.007 p: 0.075	B: -0.011 p: 0.396
Anterior disc protrusion	B: 0.001 p: 0.382	B: 0.002 p: 0.408	B: 0.000 p: 0.920	B: 0.002 p: 0.616	B: 0.002 p: 0.519	B: 0.007 p: 0.335
Narrowing of the disc space	B: 0.003 p: 0.474	B: 0.004 p: 0.467	B: 0.002 p: 0.723	B: -0.003 p: 0.626	B: -0.005 p: 0.555	B: 0.002 p: 0.929
Foraminal stenosis	B: 0.000 p: 0.756	B: -0.002 p: 0.361	B: 0.001 p: 0.695	B: -0.001 p: 0.785	B: 0.000 p: 0.936	B: -0.002 p: 0.830
Matsumoto total score	B: 0.008 p: 0.226	B: 0.004 p: 0.702	B: 0.001 p: 0.927	B: -0.007 p:0.527	B: -0.010 p: 0.489	B: -0.006 p: 0.877
Modic classification	B: -0.003 p: 0.525	B: 0.004 p: 0.135	B: 0.009 p: 0.142	B: 0.002 p: 0.742	B: -0.007 p:0.329	B: 0.005 p: 0.779
MRI total score	B: 0.003 p: 0.724	B: 0.006 p: 0.693	B: 0.015 p: 0.437	B: -0.009 p: 0.683	B: -0.014 p: 0.565	

Table 34: Correlation between MRI changes and the effect duration of botulinum toxin

5.16.2 Effect on abnormal posture

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.001 p: 0.815	B: 0.004 p: 0.297	B: 0.005 p: 0.348	B: 0.003 p: 0.588	B: 0.002 p: 0.780	B: 0.014 p: 0.347
Disc degeneration	B: -0.002 p: 0.470	B: -0.003 p: 0.443	B: 0.004 p: 0.259	B: 0.001 p: 0.781	B: 0.000 p: 0.975	B: -0.005 p: 0.603
Anterior disc protrusion	B: 0.001 p: 0.138	B: 0.005 p: 0.066	B: -0.001 p: 0.730	B: -0.002 p: 0.397	B: -0.003 p: 0.247	B: 0.000 p: 0.986
Narrowing of the disc space	B: 0.003 p: 0.330	B: 0.006 p: 0.210	B: 0.006 p: 0.328	B: 0.001 p: 0.762	B: 0.006 p: 0.382	B: 0.022 p: 0.217
Foraminal stenosis	B: 0.000 p: 0.769	B: -0.003 p: 0.152	B: 0.001 p: 0.829	B: 0.000 p: 0.909	B: 0.000 p: 0.839	B: -0.001 p: 0.890
Matsumoto total score	B: 0.002 p: 0.714	B: 0.005 p: 0.586	B: 0.008 p: 0.330	B: 0.000 p: 0.978	B: 0.003 p: 0.820	B: 0.014 p: 0.674
Modic classification	B: -0.004 p: 0.215	B: 0.004 p: 0.189	B: 0.006 p: 0.314	B: 0.003 p: 0.693	B: 0.000 p: 0.961	B: 0.004 p: 0.780
MRI total score	B: 0.000 p: 0.961	B: 0.013 p: 0.319	B: 0.019 p: 0.224	B: 0.007 p: 0.699	B: 0.005 p: 0.827	

Table 35: Correlation between MRI changes and the effect on abnormal posture

5.16.3 Effect on pain

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.002 p: 0.228	B: -0.001 p: 0.896	B: 0.006 p: 0.088	B: -7.905E-007 p: 1.000	B: 0.002 p: 0.723	B: 0.006 p: 0.725
Disc degeneration	B: 0.001 p: 0.875	B: -0.001 p: 0.859	B: -0.001 p: 0.896	B: 0.000 p: 0.977	B: -0.006 p: 0.193	B: -0.016 p: 0.277
Anterior disc protrusion	B: 0.000 p: 0.838	B: 0.001 p: 0.718	B: 0.000 p: 0.890	B: 0.000 p: 0.900	B: -0.003 p: 0.430	B: -0.001 p: 0.821
Narrowing of the disc space	B: 0.002 p: 0.509	B: 0.004 p: 0.355	B: 0.009 p: 0.164	B: 0.000 p: 0.945	B: 0.002 p: 0.806	B: 0.018 p: 0.355
Foraminal stenosis	B: -0.001 p: 0.516	B: -0.001 p: 0.796	B: -0.001 p: 0.898	B: -0.004 p: 0.460	B: 0.000 p: 0.915	B: -0.006 p: 0.633
Matsumoto total score	B: 0.002 p: 0.737	B: 0.004 p: 0.727	B: 0.008 p: 0.410	B: -0.005 p: 0.677	B: -0.007 p: 0.648	B: -0.007 p: 0.826
Modic classification	B: -0.007 p: 0.134	B: 0.002 p: 0.472	B: 0.007 p: 0.364	B: 0.003 p: 0.698	B: 0.000 p: 0.968	B: -0.002 p: 0.944
MRI total score	B: -0.005 p: 0.538	B: 0.005 p: 0.712	B: 0.021 p: 0.225	B: 0.000 p: 0.986	B: -0.005 p: 0.856	

Table 36: Correlation between MRI changes and the effect on pain

5.16.4 TSUI Pain

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: -0.004 p: 0.950	B: -0.097 p: 0.433	B: -0.050 p: 0.736	B: 0.000 p: 0.999	B: -0.012 p: 0.938	B: -0.162 p: 0.694
Disc degeneration	B: 0.066 p: 0.465	B: 0.108 p: 0.255	B: -0.024 p: 0.789	B: -0.104 p: 0.221	B: 0.003 p: 0.971	B: -0.024 p: 0.930
Anterior disc protrusion	B: -0.023 p: 0.387	B: -0.116 p: 0.151	B: 0.060 p: 0.435	B: -0.084 p: 0.218	B: -0.038 p: 0.581	B: -0.201 p: 0.226
Narrowing of the disc space	B: -0.073 p: 0.437	B: -0.148 p: 0.320	B: 0.044 p: 0.792	B: 0.116 p: 0.333	B: 0.032 p: 0.863	B: -0.041 p: 0.934
Foraminal stenosis	B: 0.031 p: 0.220	B: 0.047 p: 0.534	B: 0.021 p: 0.801	B: 0.008 p: 0.937	B: -0.047 p: 0.292	B: 0.059 p: 0.817
Matsumoto total score	B: -0.035 p: 0.814	B: -0.093 p: 0.730	B: 0.124 p: 0.640	B: -0.028 p: 0.912	B: -0.022 p: 0.944	B: -0.103 p: 0.903
Modic classification	B: 0.038 p: 0.734	B: -0.153 p: 0.075	B: -0.187 p: 0.223	B: -0.052 p: 0.766	B: 0.074 p: 0.664	B: -0.261 p: 0.505
MRI total score	B: -0.007 p: 0.967	B: -0.343 p: 0.369	B: -0.113 p: 0.811	B: -0.086 p: 0.851	B: 0.067 p: 0.902	

Table 37: Correlation between MRI changes and the addition "Pain" of the TSUI score

5.16.5 TWSTRS II (Disability Scale)

Segment Scale	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	C2-C7
Cervical canal stenosis	B: 0.000 p: 0.978	B: -0.010 p: 0.674	B: -0.018 p: 0.528	B: 0.013 p: 0.680	B: -0.023 p: 0.416	B: -0.038 p: 0.629
Disc degeneration	B: -0.010 p: 0.570	B: -0.008 p: 0.681	B: 0.008 p: 0.651	B: 0.005 p: 0.742	B: 0.029 p: 0.065	B: 0.016 p: 0.757
Anterior disc protrusion	B: -0.003 p: 0.510	B: -0.010 p: 0.536	B: -0.013 p: 0.381	B: -0.014 p: 0.276	B: -0.012 p: 0.355	B: -0.052 p: 0.092
Narrowing of the disc space	B: -0.014 p: 0.442	B: -0.015 p: 0.598	B: -0.002 p: 0.958	B: 0.003 p: 0.896	B: 0.024 p: 0.487	B: -0.004 p: 0.965
Foraminal stenosis	B: 3.286E-005 p: 0.995	B: -0.001 p: 0.967	B: 0.001 p: 0.973	B: -0.001 p: 0.977	B: -0.003 p: 0.761	B: -0.003 p: 0.948
Matsumoto total score	B: -0.030 p: 0.278	B: -0.031 p: 0.546	B: -0.005 p: 0.919	B: -0.007 p: 0.886	B: 0.038 p: 0.519	B: -0.041 p: 0.798
Modic classification	B: 0.012 p: 0.560	B: -0.021 p: 0.213	B: -0.032 p: 0.273	B: 0.032 p: 0.341	B: 0.041 p: 0.196	B: 0.029 p: 0.703
MRI total score	B: -0.016 p: 0.627	B: -0.062 p: 0.397	B: -0.055 p: 0.539	B: 0.038 p: 0.661	B: 0.053 p: 0.609	

Table 38: Correlation between MRI changes and the “disability scale” of TWSTRS (II)

List of figures

List of tables

Abbreviations

B	unstandardized regression coefficient
BFM	Burke-Fahn-Marsden Scale
CBGD	cortical-basal ganglionic degeneration
CD	cervical dystonia
CDIP-58	Cervical Dystonia Impact Profile
CSF	cerebral spinal fluid
CNS	central nervous system
CT	computed tomography
C1-C7	each segment of the cervical spine
DBS	deep brain stimulation
DRD	dopa-responsive dystonia
DRD5	dopamine D5 receptor
DTI	diffusion tensor imaging
DYT1	gene locus for early-onset generalized dystonia on chromosome 9q
DYT7	gene locus for adult-onset focal dystonia on chromosome 18p
EMG	electromyography
GABA	gamma-aminobutyric acid
GPi	globus pallidus internus
ICC	intraclass correlation coefficient
ICD	idiopathic cervical dystonia
kD	kilo Dalton
LN	lenticular nucleus
MRI	magnetic resonance imaging
MU	mouse units
NaCl	sodium chloride
p	significance level (p-value)
PD	Parkinson’s disease
PSP	progressive supranuclear palsy

R	statistic software developed by The R Foundation for Statistical Computing
SCA	spinocerebellar ataxia
SNP	single nucleotide polymorphism
SPSS	IBM SPSS Statistics – Software for predictive analytics
T	Tesla
T1	spin-lattice relaxation time in MRI
T2	spin-spin relaxation time in MRI
TCS	transcranial sonography
TE	echo time
THAP1	THAP domain containing, apoptosis associated protein 1
TOR1A	torsin family 1, member A (torsin A)
TR	time of repetition
TSE	Turbo spin echo sequence
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
VBM	voxel-based morphometry
18-F-FDG	fludeoxyglucose
18-F-FDG PET/CT	fludeoxyglucose positron emission tomography in combination with computed tomography
κ	Fleiss' kappa