Dystonia. Reflexions on movement
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Chapter 1

Dystonia: an overview
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General aspects

Dystonia is a syndrome characterized by twisting movements or abnormal postures (Fahn et al. 1987). Dystonic movements, although sustained at the height of the involuntary contraction, do not produce persistent deformity. In contrast, the term dystonic posture refers to a sustained twisting deformity that is either permanent or lasts for several minutes. Dystonia may be classified clinically according to its distribution: focal dystonia, affecting a single body part in isolation; segmental dystonia, affecting adjacent body parts or a segment of the body; multifocal dystonia, involving two or more non-contiguous parts of the body; hemidystonia, involving one side and generalized dystonia, representing a combination of segmental crural dystonia plus involvement of any other area of the body (Berardelli et al. 1998; Fahn 2000). Dystonia may be a symptom of a known underlying disorder, but in most instances the cause is unknown in which case it is referred to as primary or idiopathic dystonia. Primary torsion dystonia can be either sporadic or inherited, and is not associated with cognitive, pyramidal, cerebellar, or sensory abnormalities. Etiological classification further includes: dystonia plus syndromes, in which dystonia is associated with parkinsonism or myoclonus without known degeneration or loss of neurons, such as dopa-responsive dystonia; secondary dystonia, such as dystonia due to lesions causing structural brain damage, a metabolic disorder, or dopamine D2 receptor blocking agents, and heredodegenerative diseases, which typically do not produce pure dystonia and in which neuronal degeneration is present (Fahn 2000). Childhood onset dystonias often become generalized and there seems to be a caudal-rostral progression depending on the age of onset; legs are involved at an earlier age than arms and cranial structures. Dystonic movements can occur at rest or during a certain voluntary motor action ("action dystonia") (Fahn et al. 1987). One form of action dystonia is the focal task-specific dystonia present only during specific activity, best exemplified by writer's cramp. Sometimes, voluntary motor activity in one part of the body leads to involuntary movements, "overflow", in another part of the body. Many patients experience a progression from task-specific focal action dystonia to an "overflow" dystonia, and finally to dystonic movements present at rest. The intensity of dystonic movements can be influenced by various conditions, for example, activities such as walking, running, writing, talking and changing position. Dystonic movements often are more severe during emotions, stress and fatigue. On the other hand, dystonic movements can
sometimes be relieved by rest, self-hypnosis, and various sensory tricks. Much less common is the reverse, i.e., for dystonia at rest to be relieved by talking or other active movements (Fahn 2000). Dystonic movements usually cease during sleep, but certain dystonic postures can persist during various sleep stages. Some patients experience large fluctuations of symptoms over the day, without noticeable dystonia on awakening but worsening during the day. An epidemiological study of primary torsion dystonia in the population living in Rochester, Minnesota, found the prevalence of generalized primary dystonia to be 3.4 per 100,000 population, and focal dystonia 30 per 100,000 (Nutt et al. 1988). The prevalence of primary dystonia in Europe is at least 15.2 per 100,000, with a prevalence of focal dystonia of 11.7 per 100,000 (the epidemiology study of dystonia in Europe collaborative group 2000)

Generalized, segmental and focal primary dystonias belong probably to the same disorder (Fahn et al. 1987) but are different only in the body distribution. As such one may consider focal and segmental dystonia to be a form fruste of generalized dystonias as originally suggested by Zeman et al. (1960). Arguments in favor are that both idiopathic and hereditary generalized dystonia almost always begin as a focal dystonia. In families with dystonia, various members may have generalized, segmental or focal dystonia (Waddy et al. 1991; Bressman et al. 2000)

Until recently the assumption was held by many physicians that movement disorder syndromes such as torticollis (dystonia of the neck), blepharospasm (dystonia of the eyelids), oromandibular dystonia (dystonia of the mouth and jaw) and writer's cramp (dystonia of the arm during writing) were the manifestation of a psychogenic rather than an organic disease. Since the publications of Marsden (1976) and Sheehy and Marsden (1982), these syndromes have been recognized to represent a focal form of dystonia by many physicians. The interest in dystonia of neurologists in dystonia increased largely due to the availability of a specific treatment, e.g., botulinum toxin. This capability of treatment stimulated investigations after the pathophysiology of dystonic movement disorders.
Anatomical and etiological considerations

Different factors may relate to the origin of dystonia. Although lesions of basal ganglia may induce dystonia, the origin of the lesion is uncertain in most patients and may well lie beyond the nervous system.

Central nervous system

Torsion dystonia is generally considered to be a disease of the basal ganglia, but evidential support is still unconvincing. Disorders which lead to torsion dystonia, such as Wilson's and Leigh's disease or carbon monoxide intoxication often are not pathologically restricted to the basal ganglia (Fahn et al. 1987). Well documented reports of patients with dystonia secondary to focal brain lesions are rare. In a series of 28 patients with focal dystonia or hemidystonia secondary to a localized lesion, the site of the lesion was in the contralateral caudate nucleus, the lentiform nucleus, the thalamus, or a combination of these structures (Rothwell and Obeso 1987). The dystonic features occurred spontaneously, or in action only, or in a combination of both. In patients with torticollis the lesion often was situated in the caudate nucleus whereas in most patients with hand or arm dystonia the lesion involved the thalamus. In another study done in 22 symptomatic hemidystonia patients basal ganglia pathology with relative sparing of the corticospinal tracts was considered to be essential in the pathogenesis of secondary dystonia (Pettigrew and Jankovic 1985). In a review of 240 patients, who had lesions that affected the caudate nucleus, the putamen or the globus pallidus, dystonia was the most frequently recorded motor disorder (36%) (Bhatia and Marsden 1994). Lesions of the lentiform nucleus most commonly caused dystonia (49%), particularly when the putamen was included (63%). In patients with lesions of the caudate nucleus dystonia was present in only 9%. In patients who develop dystonia secondary to a cerebrovascular lesion, onset of dystonia may be delayed and may occur after an interval of one week to 14 years (Marsden et al. 1985).

In some patients the development of dystonia may originate from anatomical lesions outside the basal ganglia. Cervical dystonia may develop in association with cerebellopontine angle tumors (Krauss et al. 1997) and has also been reported to be due to a frontal menigioma (Soland et al. 1996). Central pontine myelinolysis has been associated with development of persistent upper extremity and orolingual dystonia (Salerno et al. 1993). Isolated blepharospasm may be associated with a brainstem lesion.
Peripheral nervous system

In some patients dystonia coincides with abnormalities in the peripheral nerves, nerve roots or the plexus. Foot dystonia has been reported to be the result of lumbar canal stenosis, and improved by lumbar laminectomy (Blunt et al. 1996). One patient has been documented who showed focal hand dystonia attributed to a thoracic outlet syndrome which improved after resection of a rudimentary cervical rib (Quartarone et al. 1998). In a study performed by Charness et al. (1996) on 73 musicians with occupational hand cramps 28 patients had an ulnar neuropathy. Twenty-four of these patients presented with flexion dystonia of the fourth and fifth digits. With surgical or nonsurgical treatment ulnar neuropathy recovered in 14 of these patients, of whom 13 patients showed improvement of dystonic features. Improvement of dystonia did not occur in the other patients. Murphy (1989) reported a retrospective study done in 60 patients with brachialgia due to a right sided ruptured C6 disk. Twenty of these patients had writer’s cramp, of whom 13 had complete relief of pain and writer’s cramp after surgery. It was suggested, that weakness of the extensor and flexor carpi radial muscles caused the hand to turn outwards and downwards during writing as a consequence of relative overactivity of the muscles innervated by the ulnar nerve.

Peripheral trauma

The concept of a movement disorder secondary to a peripheral trauma, without direct injury to the peripheral nervous system is controversial (Lang 1990; Ecker 1990; Wiener and Shulman 1995; Gálvez-Jiménez and Lang). To minimize the possibility that a peripheral injury and the subsequent dystonic movement disorder are linked only by coincidence, a close temporal and anatomic correlation between injury and the onset of the movement disorder is mandatory (Jankovic and Van der Linden 1988; Jankovic 1994).

Reflex sympathetic dystrophy, recently renamed complex regional pain (CRP) syndrome consists of a combination of vasomotor, sudomotor and trophic changes. It is usually accompanied by persistent burning pain, allodynia and hyperpathy and may occur after peripheral trauma. In addition, some patients develop fixed dystonic
postures (Schwartzman and Kerrigan 1990; Bhatia et al. 1993, van Hilten et al. 2000). Some, however, show dystonic postures without other signs of the CRP syndrome (Schott 1985, 1986; Jankovic and van der Linden 1988; Jankovic 1994). Cranial dystonia may follow dental procedures within hours in some patients associated with painful paresthesia at the site of dystonia (Sankhla et al. 1998; Schrag et al. 1999). Head, neck or shoulder trauma may precede cervical dystonia. Acute-onset posttraumatic cervical dystonia is characterized by a markedly limited neck motion, absence of phasic involuntary movements and a poor response to treatment and appears to be clinically a distinct syndrome. It is distinct from delayed post traumatic cervical dystonia which is indistinguishable from non-traumatic primary dystonia (Tarsy 1998). In a case control study a positive association is suggested to exist between local body injury and the development of dystonia in the same area of the body (Defazio et al. 1998). Predisposition, such as specific central susceptibility to an altered afferent input, may probably be required for the movement disorder to occur. In a study done in 20 patients with a history of peripherally induced movement disorders possible predisposing factors were identified in 65% of them (Jankovic and van der Linden 1988). It was suggested that these factors include perinatal problems, the use of neuroleptics or a familial history of essential tremor or dystonia.

Repetitive strain

Many patients with writer’s cramp attribute the onset of dystonia to a period of intensive writing (Sheehy and Marsden 1982). Musician’s cramp has also been linked to the long-term use of repetitive movements. Anatomical anomalies such as abnormal tendon connections may predispose to the development of musician’s cramp (Leijnse 1997; Wilson et al. 1993). In these patients tendon release may improve the dystonia. Byl et al. (1996) trained two monkeys to perform a precise grip. While performing the grip the hand was passively opened and closed. The motor performance after five months deteriorated, and a movement disorder resembling dystonia occurred (Byl et al. 1996). In a later study in one monkey dysfunction of movement occurred already after five weeks. In this monkey an anatomical restriction of the flexor profundus tendon was present which may have modified the time course for the development of the movement dysfunction. Tendon or nerve inflammation are, however, not a prerequisite for the occurrence of the movement disorder (Topp and Byl 1999).
Environmental factors

In many patients environmental factors may elicit dystonic movements. For example, in patients with blepharospasm bright light or wind may provoke the dystonic eyelid activity (Aramideh 1995). Patients with oromandibulair dystonia may be symptom free in the presence of other people, but when left alone oromandibulair dystonia emerges or vice versa (personal observation). In a patient with laryngeal dystonia the absence of background noise provoked the dystonia (Stojanovic et al. 1997). Writer’s cramp may occur after loss of a relative or during a written examination (Sheehy and Marsden 1982; personal observation). One patient developed writer’s cramp during hospital admission. It disappeared gradually within three weeks after discharge from hospital, and it reoccurred during readmission two years later (personal observation).

Genetic studies

Association studies indicate that a number of genes are linked with dystonia. Mutations in DYT 1, a gene mapped to chromosome 9q34 and transmitted as an autosomal-dominant trait with reduced penetrance of 30% to 40%, account for most patients with early limb-onset primary dystonia, i.e., occurring at an age younger than 28 years (Ozelius et al. 1997, 1998; Bressman et al. 1998). The mutation concerns the gene that encodes torsin A, a protein that by sequence homology is a human member of the HSP/Clp family of proteases. These proteins act as stress response proteins important in refolding or degradation of denatured proteins. High rates of expression of the torsin A gene are found in dopamine containing neurons of the midbrain, hippocampus and cerebellum. Gene expression is found in the brains of all patients hospitalized more than 24 hours, but in only some of the brains of patients who died after cardiac arrest outside the hospital. This finding suggests that this gene is involved in stress responses (Penney 1998; Augood et al. 1998). Unlike early onset dystonia, the genetic contribution to late onset primary dystonia, i.e., later than 28 years of age, is not established (Bressman et al. 1998). The rates of dystonia in first-degree relatives of late-onset probands compromise about 5%, which is significantly lower than the rates in first-degree relatives of early onset probands being 15%. However, in an area of Northwest Germany most of the patients with an apparently sporadic idiopathic focal dystonia inherited the same mutation on chromosome 18p (DYT 7) as was found in a large three-generation family with focal dystonia, suggesting an important role also for genetic factors in late onset focal dystonia (Leube et al. 1997). However the
allelic association with 18p markers seen in this German focal dystonia population could not be reproduced by another group (Klein et al. 1998).

Dopa-responsive dystonia (DRD) is linked to mutation of the gene coding for GTP cyclohydrolase involved in the synthesis of tyrosine hydroxylase necessary for the production of dopamine. In most patients with DRD the onset of dystonia is in the legs from where it leads to generalized dystonia. However, atypical presentations of DRD have been described also (Bandmann et al. 1998).

Pathophysiological aspects

Although dystonia is considered to be a movement disorder, pathophysiological mechanisms may not be confined to the motor or the integrative sensory-motor parts of the nervous system. The primary pathophysiology may relate to the central sensory or even the peripherally sensory nervous system as well.

Motor unit

The motor unit is the final common motor pathway and therefore, different pathophysiological studies in dystonia concern the activity in motor units and their reflex activation properties.

The characteristic electromyographic (EMG) abnormalities in dystonia present themselves as an inappropriate activity of motor units (Yanagisawa and Goto 1971; Rothwell et al. 1983; Cohen and Hallett 1988, van der Kamp et al. 1989). Both agonistic and antagonistic muscles may be activated simultaneously, or more or less, in a random order giving rise to movements with or without increased muscle tone. In task-specific dystonia agonistic and antagonistic muscles are contracting simultaneously, concurrent with more distant muscles being normally not involved in the specific action. An inability to activate the appropriate muscle may also be considered to be part of dystonia (Berardelli et al. 1998) and further broadens the definition of dystonia.

Cross-correlation studies of simultaneous recorded EMG activity of extensor and flexor carpi radialis muscles during motor tasks in dystonic patients, revealed broad-peak motor unit synchronization, which did not occur in voluntarily cocontraction. However, in patients with task specific focal hand dystonia, such as writer's cramp, this motor unit synchronization was absent. This observation suggests that co-
contraction in some forms of dystonia is neurophysiologically distinct from voluntary cocontraction (Farmer et al. 1998). Similar results were seen with frequency analysis of EMG activity in patients with idiopathic torticollis (Tijssen et al. 2000). In torticollis patients EMG activity in the splenius capitis and sternocleidomastoid muscles showed a 4-7 Hz drive, while in control subjects mimicking the dystonic posture the dominant peak was at 10-12 Hz. The activity of the splenius capitis muscle and of the sternocleidomastoid muscle was in phase in the patients, but not in the controls. The results are consistent with an abnormal corticoreticular and corticospinal drive in dystonic torticollis.

Stretch reflexes have been investigated in the flexor muscles of the thumb, wrist and elbow (Rothwell and Obeso 1987). These reflexes can be elicited during exerting a constant background contraction of the appropriate flexor muscle against a small force offered by a low inertia electrical motor. At irregular intervals, the force supplied by the electrical motor is suddenly increased so as to extend the joint and stretch the flexor muscle. The response consists of two main components: a first component (M1) is a short latency response with a latency of about 20 ms which, probably, reflects action mediated through the same neuronal pathways as are responsible for the tendon jerk. The second component is a so called long latency response (M2) with a latency of about 50 ms and a duration of 30-49 ms. In dystonia some authors have found the amplitude levels of M1 and M2 components of the stretch reflex to be in the normal range. However, when using lower rates of stretch the M2 is prolonged. Furthermore, in dystonia the stretch reflex response, normally being rather localized to the agonist and synergist muscles, shows a conspicuous overflow of response activity to muscles distant from the site of the extended joint and stretched flexor muscles.

Spinal cord

The excitability of the motor neuronal pool and the actions of interneuronal networks in the spinal cord can be tested by H-reflex studies. Studies of reciprocal inhibition have been performed in forearm muscles. In these experiments the effect of a conditioning stimulus to the radial nerve has been investigated upon the size of the H-reflex response in the flexor muscles, evoked by median nerve stimulation. Three periods of inhibition are seen. The first inhibitory period occurs with a conditioning test stimulus interval of 1 to 4 ms. It can also be elicited by cortical stimulation. Therefore, the first period of inhibition probably represents postsynaptic
inhibition onto spinal motoneurons and hence affects all inputs to these neurons. The second period of inhibition is not present after cortical stimulation and may, therefore, be due to presynaptic inhibition of flexor 1a afferent terminals. Reciprocal inhibition in the arm is disturbed in patients with generalized dystonia, torticollis, blepharospasm and writer’s cramp. Attenuation of inhibition is found in all three inhibitory periods in all patient groups by Panizza et al. (1990) while the third inhibitory period instead of inhibition showed potentiation in spasmodic torticollis and generalized dystonia. However, attenuated inhibition in the first inhibitory period in writer’s cramp, spasmodic torticollis and in symptomatic hemidystonia could not be confirmed (Nakashima et al.1989; Deuschl et al.1992). There was a tendency for the second inhibitory period to be more abnormal in dystonic writer’s cramp than in simple writer’s cramp, but this difference did not reach significance. Attenuation of reciprocal inhibition may also be found in the asymptomatic hand in writer’s cramp patients (Chen et al. 1995).

**Brainstem**

The first pathophysiological evidence that blepharospasm and oromandibular dystonia are organic diseases caused by an increased excitatory drive upon facial nerve motoneurons and bulbar interneurons was given by studies of the blink reflex by Berardelli et al. (1985). The blink reflex, elicited by electrical stimulation of the supraorbital nerve, consists of two responses in the orbicularis oculi muscle. The first (R1) response occurs at a latency of about 10 ms homolateral to the side of the stimulation. The second (R2) response has a latency of about 30 ms and occurs bilaterally. In patients with blepharospasm and oromandibular dystonia, the blink reflex responses show normal latencies but increased amplitudes and durations. The excitability cycle of the recovery of R2 responses elicited after a first conditioning shock is enhanced. In addition in these patients, voluntary blinks are preceded by a movement related cortical potential, the Bereitschaftspotential, whereas this is not the case with involuntary blinks. Abnormalities of the recovery curve of blink-reflex responses in patients with blepharospasm relate to a specific type of eye closure abnormality (Aramideh et al.1995). Recovery of the second period of the blink reflex was enhanced mainly in patients with involuntary discharges only in the orbicularis muscle. In contrast, recovery was normal when involuntary eyelid closure was due to involuntary levator palpebrae inhibition only.

In generalized dystonia and torticollis patients the recovery of blink reflex responses
was also enhanced. However, in patients with task specific focal dystonia of the arm it was normal (Nakashima et al. 1990). As such a disturbance in the blink reflex recovery curve may be related to the extent of the site of involvement. Abnormalities of the blink reflex recovery are thought to be secondary to a disturbed input from descending supra segmental pathways.

Cortical motor areas

Transcranial magnetic stimulation allows the evaluation of excitability of corticospinal pathways that impinge upon motoneurons by motor evoked potential (MEP) characteristics or inhibitory motor action. In focal task specific hand dystonia there is no significant difference in motor threshold levels for cortical magnetic stimulation between patients and controls, and between both hemispheres as well (Ridding et al. 1995; Currà et al. 1996; Ikoma et al. 1996). However, results obtained by low-intensity magnetic stimulations in patients with focal hand or arm dystonia suggest that the relationship between MEP amplitude measured at rest and during voluntary contractions is different from those seen in healthy controls. The amplitude increase induced by voluntary contraction is greater in the dystonic group (Mavroudakis et al. 1995; Ikoma et al. 1996). These findings contrast with those in Parkinson’s disease in which the increase of MEP’s during facilitation is smaller. The silent period, in which sustained muscle contraction is inhibited, can be recorded after the MEP when the stimulated subject tries to maintain a tonic contraction during and after the stimulus. The silent period increases with increase of magnetic stimulus intensity. It is, probably, mediated by spinal mechanisms during its first part, and by supraspinal, probably, cortical mechanisms during its second part. In patients with focal hand dystonia the silent period reaches its maximal duration at lower stimulus intensity than is needed in healthy control subjects. This observation suggests that some patients with focal dystonia saturate more rapidly cortical inhibitory mechanisms during voluntary motor activity.

In controls, in a double cortical stimulus paradigm with a submotor threshold stimulus preceding a supramaximal stimulus in rest, there is a suppression of the MEP after the supramaximal stimuli with short time intervals from 1 to 15 ms between the two stimuli. In patients with focal task specific hand dystonia this MEP suppression is decreased at these stimulus intervals. There is no difference in suppression obtained after stimulation of either the right or left hemisphere. These results suggest deficient cortical inhibitory mechanisms in focal dystonia (Ridding 1995). However, during
voluntary contraction this short-latency inhibition was similar in patients with dystonia and control subjects (Currà et al. 1998). On the other hand, Currà et al. (1998) and Rona et al. (1998) found in dystonic patients test responses elicited by stimuli with interstimulus intervals of 100 to 150 ms being markedly inhibited in comparison with those in controls. From this finding they suggested that the enhanced inhibition seen at long interstimulus intervals is related to slowness of movement present in patients with dystonia. Chen et al. (1997) found a diminished inhibition elicited by interstimulus intervals between 60 and 80 ms in patients with writer’s cramp during isometric wrist extension. They suggested that less inhibition may relate to the overflow phenomenon of muscle activity that characterizes writer’s cramp.

Studies investigating the cortical representation of upper limb muscles of patients with writer’s cramp with use of transcranial magnetic stimulation show a displacement of the maps of corticomotor projections when compared with maps of healthy controls (Byrnes et al. 1998). In some patients the maps were distorted in shape with extensions of the lateral borders and emergence of almost discrete secondary motor areas. After injection of botulinum toxin into affected muscles map topography normalized during the period when the optimal effects of the injection were greatest, with the maps returning to their original abnormal positions as the favorable effect of the injection wore off. These results suggest that there are slowly evolving reorganizational changes in the primary motor cortex in writer’s cramp patients.

Movement related cortical potentials (Bereitschaftspotential) in patients with writer’s cramp in response to a simple, self-paced, brisk index finger abduction movement, showed a decrease for the average amplitude of the early part of the negative-slope peak, 200-300 ms before the electromyographic onset, restricted to the electrodes overlying the contra-lateral and midline central regions (Deuschl et al. 1995). The activity recorded during the period of the negative slope peak can be sufficiently explained by the bilateral activation of generators in the sensory-motor cortex. This result suggests insufficient contralateral motor cortex activation just before the initiation of voluntary movements in patients with focal dystonia. The Bereitschaftspotential preceding muscle relaxation after voluntary contraction of the wrist extensor is diminished significantly in focal hand dystonia compared to the one seen in healthy controls. This feature suggests a deficiency in motor cortical activation prior to relaxation as well (Yazawa et al. 1999).

Positron emission tomography (PET) scans also show alterations in cortical
metabolism in patients with dystonia during activity. On the one hand, performance of freely selected finger movements in patients with primary dystonia leads to greater increase of regional cerebral blood flow over the contralateral rostral supplementary motor area and contralateral premotor and prefrontal areas. On the other hand, regional cerebral bloodflow is decreased over the primary motor cortex and posterior supplementary motor area (Ceballos-Baumann et al. 1995). These findings signify that disordered functions in dystonia are widespread and include a deficit of motor executive function. Abnormal corticocortical influences from prefrontal motor areas upon the motor cortex may disrupt normal activation of the motor cortex. However, in patients with acquired hemidystonia due to structural lesions, a significant overactivity of the sensorimotor cortex was found during movement (Ceballos-Baumann et al. 1995). These differences may reflect fundamental variation in the way a discrete brain injury produces dystonia, in contrast to mechanisms responsible for primary dystonia (Berardelli et al. 1998).

Basal ganglia

Microelectrode recordings from basal ganglia performed in dystonic patients during pallidotomy demonstrated highly irregular and reduced patterns of spontaneous neuronal activity in the internal and external segments of the globus pallidus. These patterns consisted of intermittent grouped discharges separated by periods of pauses (Vitek et al. 1999). Furthermore, the activity of neurons in the internal segment of the globus pallidus elicited by passive and active movements were widened and receptive fields less specific than those reported in normal monkeys. Thalamic neuronal recordings during thalamotomy in dystonic patients revealed an increase in the number of cells located in the ventral intermediate thalamic nucleus, activated by passive joint movement compared to observations in control patients undergoing surgery for treatment of pain or tremor (Lenz et al. 1999; Lenz and Byl 1999). Recordings from cells located in the ventral oral posterior thalamic nucleus, a pallidal relay nucleus, showed activity that was phase advanced on EMG activity during dystonic arm movements. Microstimulation of the ventral intermediate thalamic nucleus produced simultaneous contraction of multiple forearm muscles, similar to the simultaneous muscle contractions observed in dystonia (Lenz et al. 1999).

In DYT 1 carriers, the global and regional metabolic rates, studied with $^{18}$F fluorodeoxyglucose PET scan investigations, show two independent regional metabolic
Covariance patterns. The first pattern was characterized by a relative metabolic overactivity of the cerebellum, the lentiform nucleus and the supplementary motor cortex (Eidelberg et al. 1995, 1998). This relative metabolic overactivity was not movement related as it was also found in non-manifesting DYT 1 carriers as well as in manifest carriers during sleep when movements are suppressed (Eidelberg et al. 1998). The second, “movement-related”, PET scan pattern is present in manifest carriers with sustained contractions at rest. It is characterized by overactivity of metabolism in the cerebellum, thalamus, and midbrain. From these observations it was concluded that in DYT 1 patients functional neuronal networks in the brain relate separately to gene status and the abnormal movements.

PET and SPECT studies suggest a reduced dopamine D2 receptor binding in the putamen in patients with idiopathic dystonia affecting either the face or hand compared to healthy controls. This finding may, therefore, indicate that a preferential decrease in D2 mediated inhibition of the indirect striatopallidal pathways may induce an increased thalamic drive to the premotor neuronal network (Horstink et al. 1996; Naumann et al. 1998; Perlmutter et al. 1998).

It has been recently proposed that the basal ganglia support a basic attentional mechanism operating through synchronizing cortical activities in the executive forebrain in the 30 to 50 Hz band (Brown and Marsden 1998). In Parkinson disease impairment of EEG desynchronization has been demonstrated before and during movement. Improvement of EEG desynchronization concurrent with reduction in bradykinesia occurred during treatment with levodopa (Wang et al. 1999). Impairment of EEG desynchronization may also play a role in dystonia. In patients with writer's cramp event-related desynchronization of the EEG during self-paced simple index finger abduction movements was depressed over the contralateral central and midline regions compared to control subjects. This abnormality may point to a deficient motor command at the cortical level (Toro et al. 2000).

Cortical sensory areas

Patients with idiopathic dystonia may have a normal regional cerebral blood flow in the resting state. In two dystonic patients with upper extremity involvement, who were instructed to open and close their hands with a repetition rate of 2Hz, the blood flow response was diminished contra-laterally in the sensory-motor cortex in comparison with the response seen in controls (Perlmutter and Raichle 1988). However,
interpretation of these findings was ambiguous as it was doubted whether patients could perform the task as vigorously as normal subjects do. To avoid this ambiguity, the cerebral blood flow response in a totally passive activation paradigm, that is vibrotactile stimulation of a hand, was studied in 11 patients with upper extremity dystonia of whom seven had a task specific hand dystonia. Vibration induced cramps in six patients, of whom three had task-specific hand dystonia. Vibration did not provoke cramp in control subjects. In the dystonic patients resting state blood flow for the sensory-motor region was not significantly different from the one in control subjects. Vibrotactile stimulation of the hand produced a diminished increase in regional blood flow response in sensory-motor cortical regions in patients with unilateral dystonia, no matter whether vibration was given on the affected or unaffected hand. In controls, vibration during voluntary cocontraction of arm muscles that mimicked the postures seen in the dystonic patients during vibration, did not diminish the increase in vibration induced blood flow response. The bilaterally reduced cortical blood flow response in the patients may reflect a bilateral disturbed cortical function in idiopathic unilateral dystonia. Furthermore, it may signify an abnormal central sensory-motor processing. The study was the first one that revealed a possible disarrangement of receptive functions in dystonic patients.

Reilly et al. (1992) elaborated on alterations in receptive functions and studied somatosensory evoked potentials (SEPs) in dystonic patients. In a group consisting of six patients with focal dystonia, three with generalized dystonia, and one with segmental dystonia normal latencies and amplitudes of the cortical P15, N20 and P45 SEP potentials were seen after stimulation of the median nerve. However, the mean amplitude of the cortical N30 was increased after stimulations on either side. The N30 is thought to arise from the supplementary motor area to which the basal ganglia has a major output. In patients with Parkinson’s disease the N30 amplitude may be depressed, whereas in patients with cortical or reflex myoclonus it is enhanced. However, Grissom et al. (1995) could not confirm the occurrence of enlarged N30 potentials in a group of nine patients with dystonia. In their study the median nerve was stimulated with a low frequency of 0.2 Hz. In disagreement with the findings of Reilly et al. they found decreased amplitudes of N30, long latency N140 and P190 SEP potentials. In torticollis patients potentiation of N30 did not occur after median nerve stimulation. In 10 patients with idiopathic leg dystonia stimulation of the posterior tibial nerve elicited increased P37-N50 complexes, which may have their origin in the
Byl et al. (1996) studied cortical somatosensory projections in two adult monkeys which were trained to perform a precise grip 300 times a day, while during the grip passive rapid openings and closings of the hand were induced, as a model for the development of focal dystonia by repetitive stress. Both monkeys developed a movement control disorder after three months of training. Electrophysiological mapping of the primary somatosensory cortex with microelectrodes showed that cortical representations of the hand were markedly degraded. Dedifferentiation of cortical representations of the skin of the digits of the hand resulted in large overlapping digital receptive fields. This cortical dedifferentiation of sensory feedback information from the hand may contribute to the genesis of occupationally derived focal dystonia.

Elbert et al. (1998) observed in a magnetic source imaging study, that in musicians with hand dystonia the representations of the digits in the somatosensory cortex showed a smaller distance (fusion) between the digits than in non-musician control subjects. Mapping of SEP’s over the human cortical hand somatosensory area in six patients with focal hand dystonia showed a disordered organization of the homuncular finger representations in the primary somatosensory cortex (Bara-Jimenez et al. 1998). In that study the most prominent finding was that digital representations were closer to each other than observed in controls. All of these results may be related to disturbed sensory functions present in focal hand dystonia patients (Bara-Jimenez et al. 2000a,b).

An abnormal central integration of somatosensory input in dystonic patients is also suggested by the observation of an abnormal cortical potential obtained by a series of electrical stimulations simultaneously given to the median and ulnar nerve (Tinazzi et al. 2000). SEP recordings in patients yielded significant higher spinal N13, brainstem P14 and cortical N20, P27 and N30 components after dual stimulations than in control subjects. In contrast, no significant differences were found between SEP amplitudes and latencies after single stimulations of the median and ulnar nerve in dystonic patients and normal subjects. In dystonia recovery functions of median nerve SEPs assessed by means of paired stimulations interrupted by time intervals of 5, 20 and 40 ms showed a hyperexcitable state at multiple levels of the somatosensory trajectories, at the 20 and 40 ms time intervals. The enhanced excitability may indicate that in dystonic subjects diminished inhibitory actions at multiple levels of the central nervous system may contribute to excessive and inappropriate muscle activities (Frasson et al. 1998).
Peripheral afferent nerve fibers

Dystonic muscles may readily respond to vibration of muscles and tendons. In patients with writer’s cramp muscle tendon vibration may provoke dystonic movements similar to dystonic movements manifested in writer’s cramp itself. Dystonic movements and vibratory induced movements are blocked by lidocaine infiltration of the muscle. Lidocaine infiltration does not necessarily alter muscular function itself, as demonstrated by tests of strength and compound muscle action potentials evoked by electrical nerve stimulation (Kaji et al. 1995). Its effect is likely mediated by blocking impulse volleys running through muscle afferent fibers. Blocking these impulses by combined intramuscular applications of lidocaine and alcohol proved to be beneficially also in patients suffering from oromandibular dystonia (Yoshida et al. 1998). Another demonstration of a peripheral genesis in which deranged muscle afferent information may be involved originates from an observation in patients with upper limb dystonia showing an altered reciprocal inhibition after treatments by intramuscularly injected botulinum toxin (Priori et al. 1995). Twelve patients were studied before and three weeks after treatment with botulinum toxin. Before treatment a decreased second period of reciprocal inhibition was found in H-reflex responses elicited by stimulation of the median nerve, that normalized after treatment. In contrast, the first phase of reciprocal inhibition was unaltered. Although the muscle potential and H-reflex were both reduced the ratio between the amplitudes of the H-reflex response and the muscle potential (H/M ratio) was also unaltered. From this finding it is suggested that botulinum toxin affects the intrafusal motor endplates also. Paralysis of intrafusal fibers in the muscle decreases activation of group Ia and possibly group II muscle afferents as well. As such, it is suggested that normalization of reciprocal inhibition and the beneficial effect of botulinum toxin may, possibly, arise from changes in the afferent input from the specific muscles.

A study on sensory trick maneuvers done in patients with cervical dystonia demonstrated that skin contact between finger and the face was not necessarily needed to reduce the EMG activity of the various neck muscles. EMG recordings showed in half of 25 patients a marked reduction of neck muscle activity during arm movement, clearly before contact was carried out between the finger and the facial target area (Wissel et al. 1999).

Sensory symptoms may well precede the appearance of dystonia by weeks to months as was noted by Ghika et al. (1993) in 11 successive patients with cranial dystonia. For
these sensory symptoms an objective substrate could not be found. Patients put forward that the orofacial movements were at first willingly performed to diminish discomfort. These movements later on escaped voluntary control and became socially disturbing.

Conclusion

Pathophysiological mechanisms as well as anatomical locations involved in dystonia are diverse. No single causation can be held responsible for the development of dystonia. Too much weight has probably been adjusted to the basal ganglia as playing an essential role in its pathogenesis. An alternative causation as explanation may be dedifferentiation of cortical areas due to plastic changes induced by sensory stimuli. Hereditary, environmental, structural and biochemical factors may relate to cortical dedifferentiation and as such may be involved in the development of dystonia.

References


Murphey F. A cause and cure of some cases of "writer's cramp". Surg Neurol 1989; 31: 133-137.


Chapter 1


Schrag A, Bhatia KP, Quinn NP, Marsden CD. Atypical and typical cranial dystonia following dental procedures. Mov Disord 1999; 14: 492-496.


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