Botulinum Toxin Dystonia Writer`s Cramp and other movement disorders – Part I

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Abstract
This study involves the historical perspectives of the writer`s cramp and the dystonia for which the botulinum toxin therapy is used and is proving better results. In this part I, we explained generalized sytonia and focal dystonia occurring in India. Academically for the researchers benefit point of view especially for PhD scholars in neurology and neuroscience.

Keywords: Dystonia, General dystonia, Focal dystonia, Writer`s cramp.

Introduction
In this paper, botulinum toxin and the other movement disorders discussed very rigorously.

Dystonia
It was in 1911 when the term "dystonia" was first used by Oppenheim to describe a disorder causing variable muscle tone and recurrent muscle spasm.[1] Dystonia is currently defined as a neurological syndrome characterized by involuntary, sustained, patterned, and often repetitive muscle contractions of opposing muscles, causing twisting movements or abnormal postures.[2]

Historical perspective of dystonia and writer's Cramp
Generalized dystonia
One of the earliest descriptions of dystonia was provided by Gower's in 1888, who coined the term tetanoid chorea to describe the movement disorder in two siblings, later found to have Wilson's disease.[3]

Three years prior to Oppenheim, Marcus Walter Schwalbe described a family of three siblings with a similar disease, which he described as chronic cramp syndrome with hysterical symptoms and considered it to be a psychogenic disorder.[4]

In 1911, Hermann Oppenheim[5] and George Theodor Ziehen published almost simultaneous reports[6] describing primary torsion dystonia. Oppenheim was the first to coin the terms 'dysbasia lordotica progressiva dystonia: musculorum deformans', and for describing its 'dromedary gait.

But the terms were criticized as fluctuating muscle tone was not necessarily characteristic of the disorder, the term musculorum incorrectly implied that the involuntary movement was due to a muscle disorder, and not all patients became deformed. Herz et al with the help of electromyographic recordings defined the disorder as slow sustained postures. Finally in 1984, an ad hoc committee of Dystonia Medical research foundation gave the widely acceptable present definition[2].

Review of Literature
Writer's cramp
Writer's cramp is one of the commonest focal dystonias and was described 200 years before primary torsion dystonia. One of the earliest references dates back to 1713, when Ramazinni described it in his book *De Morbis Artificum* "An acquaintance of mine, a notary by profession, still living, used to spend his whole life continually engaged in writing, and he made a good deal of money from it; first he began to complain of intense fatigue in the whole arm, but no remedy could relieve this, and finally the whole right arm became completely paralyzed. In order to offset this infirmity he began to train himself to write with the left hand, but it was not very long before it too was attacked by the same malady." [7]

Later it was described by Bell and Bruck in 1831 as scrivener's palsy. With the onset of the Victorian era at that time, London's commercial centre created a large number of scriveners who were responsible for copying documents by hand using a quill firmly and some of them developed 'scrivener's palsy' which initially disabled writing and later affected other tasks.[8] However until 1930s it was considered to be a psychological disease, called as occupational neurosis by Gowers.[9] It was only in the later in the twentieth century that a neurological basis was considered after Collier and Adi first suggested abnormalities of basal ganglia as the underlying pathophysiology.[10] Even in the later half of the twentieth century many neurologists including Sir John Walton considered writer's cramp to be of psychogenic origin as described in the ninth edition of Brain's disease of the nervous system- "In my experience when even subtle physical signs are absent in the many 'simple' (Writer's cramp) cases that I have seen and neither other focal dystonias nor any other organic disorders could in my view impair movements only when they take part in one co-ordinated act while leaving totally unaffected all other precise and complex voluntary actions involving the affected member".[11] Writer's cramp were first recognized to share common features with and was included in the group of focal dystonias by Marsden and Sheehy. They also further classified writer's cramp into simple and dystonic writer's cramp.[12] With the, advent of various more sophisticated

imaging signal modalities the organic nature of writer's cramp is no more in doubt.

Classification of dystonia

Classifications of dystonia can be based on
A. Topographic distribution
B. Age at onset
C. Cause
D. Genetics.[13-17]

A. Topographical

Dystonia can be classified as focal (single region), segmental (2 or more regions), multifocal (2 or more non adjacent regions) or generalized (leg or legs, trunk and one other region) or hemidystonia (ipsilateral arm and leg), based on the region involved.[14]
Writer's cramp is a task specific focal dystonia.

B. Age at onset determines the distribution of dystonia, childhood onset dystonia usually are generalized whereas adult onset dystonia (> 26 years) usually remain localized or segmental.

C. The etiologic classification divides dystonia into primary dystonia, secondary dystonia (secondary to an underlying cause –for example Wilson's disease, Parkinson's disease, corticobasal degeneration etc) dystonia-plus syndromes (Dopa responsive dystonia, Rapid onset dystonia parkinsonism and dystonia-myoclonus syndrome) , and paroxysmal dystonia

D. Genetic classification of dystonia is based on the loci of genes involved. Dystonia loci DYT1 through DYT15 include autosomal dominant, autosomal recessive and X-linked causes of primary dystonia and dystonia-plus syndromes, among which DYT 7 gene is associated with adult onset focal dystonia including writer's cramp with AD inheritance and gene defect on chromosome 8p13.

Epidemiology of dystonia and writer's cramp

Prevalence rate of generalized dystonia and focal dystonia according to various studies[18-31] varies from 0.17 to 5 per 100,000 population and 3 to 732 per 100,000 populations respectively. (Table 1)

Table 1: Prevalence rate of generalized and focal dystonia in various countries

Country	Reference	Years	Study design	Prevalence rate –per 100000,	
				Generalized	Focal
USA	Nutt et al	1952-1980	Record linkage	3.4	29.5
Europe	ESDE	1990-1997 (>20 yr)	Service-based		11.7
Germany	Catselon-Konkiewitz et al.	1996-1997	Service-based	0.3	10.1
Italy	Muller et al	2000-2002 (>50 yr)	Random sample		732
Italy	Defazio et al.	1987-99	Service-based		13.3
Norway	Khank-Dung et al	1999-2002	Service-based		25.4
N. England	Duffey et al.	1995		1.42	12.86
Serbia	Pekmezovic et al	2001	Service-based		13.6
Israel	Korczyn et al.	1980		0.96 (Jews) 0.17(non-Jews)	
China	Li et al.	1983	Door-to-door	5.0	3.0
Japan	Nakashima et al.	1995	Service-based	0.4	6.12
Japan	Matsumoto et al.	2000	Service-based	0.07	10.1
Egypt	Kandil et al.	1988-90	Door-to-door		10

In a community based study from Kolkata, by Das et al. crude prevalence rate of primary dystonia was 53.91 per 100,000 population and that of focal dystonia varied according to the type of dystonia.

Table 2: Prevalence rates of various focal dystonia in India (Das et al)

Type of dystonia	N	Sex ratio	Age of onset men	Age of onset women	Crude prevalence rate per 100000	Standardized rate
Blepharospasm	3	0:1	0	57.6 (52-63)	5.72 (1.18-16.72)	7.22 (1.49-21.10)
Cervical dystonia*	2	1:1	58	40	3.81 (0.46-13.75)	3.96 (0.48-14.30)
Writer's cramp	11	4.5:1	41.1 (14-60)	31 (17-45)	21.00 (10.48-37.57)	21.14 (10.55-37.82)
Writing tremor	7	2.5:1	62.6 (48-75)	36.5 (11-62)	13.35 (5.35-27.50)	14.85 (5.95-30.59)

In contrast to studies from North America and Europe where blepharospasm and cervical dystonia were the most prevalent focal dystonia, among Indians writers cramp was the commonest type of focal dystonia. Many authors have expressed that as other focal dystonia are more disabling and disfiguring compared to writer's cramp, those patients were more likely to seek medical attention and the prevalence of writer's cramp may be much higher in the community

Among patients with writer's cramp the onset was seen between the third and fifth decade with slight male preponderance and male: female ratio of 1.3:1

Classification of writer's cramp

Sheehy and Marsden classified writer's cramp into three types

Simple: Dystonic posturing of hand and arm is seen only during writing.

Progressive: Initially dystonia occurs only during writing later progresses to involve other tasks.

Dystonic: Dystonia occurs during other specific tasks such as shaving, typing, brushing and with writing since the onset of disease.

Simple writer's cramp is the commonest type followed by progressive and dystonic types.

Etiology

Most cases are idiopathic

Approximately 5% of patients have a positive family history of a similar condition. Patients with DYT1 gene mutation may initially present with writer's cramp before developing generalized dystonia and may have a history of writer's cramp among their family members.

Not very frequently, around five percent report an accident or injury to the hand or arm immediately preceding the onset of symptoms.[33] Writer's cramp frequently affects persons who write a great deal or perform other repetitive hand movements such as typing. However in a study by Jedyanak et al in 2001, less than fifty percent (<50%) of their patients with writer's cramp gave a history of intensive writing before dystonia onset and they did not find a correlation between the estimate of writing hours and the age of onset. They also noted that prolonged rest from writing did not result in remission. They noted that in some patients dystonia developed on writing at a fast pace in an uncomfortable position Hence, the most likely scenario is that, like most diseases, writer's cramp is a product of a genetic background and an environmental insult. That is, writer's cramp develops with excessive writing only in those persons who are genetically predisposed. Rare associations have been reported, including C6 ruptured disk, lithium use, basal ganglia or cortical tumors, arteriovenous malformations (AVMs), and stroke, but their role in causing dystonia is still unknown.

Pathophysiology

Abnormal electrophysiological activation

Cohen and Hallet observed abnormal EMG pattern in 19 patients with hand dystonia. They exhibited excessive co-contraction of agonists and antagonist muscles with prolongation of EMG bursts. In healthy individuals while the EMG bursts lasted for 100 milli-seconds, they lasted for 200-300 ms in patients with dystonia. There was occasional failure of willed activity to occur and there was lack of selectivity in attempts to perform independent finger movements.[35] The finding of abnormal co-contraction of agonists and antagonists is the underlying feature of all dystonia and suggests abnormal motor control and muscle selection by the basal ganglia

The exact pathophysiology of dystonia is still unclear. There are three proposed mechanisms –loss of inhibition, abnormal plasticity and abnormal sensory activation, which individually or together has been noted in dystonia.

Loss of inhibition

A principal finding in focal dystonia is that of loss of inhibition.The abnormally long bursts of EMG activity, co-contraction of antagonist muscles, and overflow of activity into muscles not intended for the task may be explained by the loss of inhibition various studies have demonstrated loss of inhibition at spinal, brainstem and cortical level.

Spinal and brainstem reflexes

A study by Nakashima et al recorded reciprocal inhibition between forearm muscles in 16 patients with writer's cramp, other occupational cramps, hemidystonia and hemi paresis due to stroke and 10 healthy controls. In this study, early disynaptic phase of reciprocal inhibition was normal but there was a reduction in later presynaptic inhibition in writer's cramp patients Panizza et al studied H reflex recovery curve and reciprocal inhibition in different dystonias and found a decrease in the amount of reciprocal inhibition among patients with writer's cramp

Similarly in other focal dystonia like blepharospasm, abnormalities of blink reflex recovery have been demonstrated Loss of reciprocal inhibition can be partly responsible for presence of co-contraction of antagonist muscles that characterizes voluntary movement in dystonia.

Motor cortical functioning

Loss of inhibition has also been be demonstrated for motor cortical function via studies on short intracortical inhibition, long intracortical inhibition, and the silent period.

Short intracortical inhibition

Using transcranial magnetic stimulation, short intracortical inhibition (SICI) is obtained with paired pulse methods and reflects interneuron influences in the cortex.[41]In such studies, an initial conditioning stimulus is given, enough to activate cortical neurons, but small enough that no descending influence on the spinal cord can be detected. A second test stimulus, at suprathreshold level, follows at short interval.

Intracortical influences initiated by the conditioning stimulus modulate the amplitude of the motor evoked potential (MEP) produced by the test stimulus. At short intervals, less than 5 ms, there is inhibition that is largely a GABAergic effect, mediated via GABA-A receptors called short intracortical inhibition or SICI At intervals between 8 and 30 ms, there is facilitation, called intracortical facilitation, (ICF).

In studies on patients with focal hand dystonia, there was a loss of SICI which was seen in both hemispheres.[43]

Long intracortical inhibition

Intracortical inhibition can also be assessed with paired suprathreshold TMS pulses at intervals from 50 to 200 mSec. This is called long intracortical inhibition, or LICI. LICI and SICI differ in that on increasing test pulse strength, LICI decreases but SICI tends to increase, and LICI is mediated via GABA-B receptors Chen, Wassermann, Caños, and Hallett (1997) investigated long intracortical inhibition in patients with writer's cramp and found a deficiency only in the symptomatic hand and only with background contraction.[46]This abnormality is particularly interesting as it is restricted to the symptomatic setting, and therefore might be a correlate of the development of the task specific dystonia.

Silent period

The silent period (SP) is a pause in ongoing voluntary EMG activity produced by TMS. While the first part of the SP is due in part to spinal cord refractoriness, the latter part is entirely due to cortical inhibition. This type of inhibition is likely mediated by GABA-B receptors and is shortened in focal dystonia.

Surround inhibition

The concept of "surround inhibition is a well known phenomenon in sensory physiology and probably applies to the motor system also.

During a specific movement it is likely that the specific movement is generated, and, simultaneously, other possible movements are suppressed thus is 'surround inhibition'. In dystonia, a failure of surround inhibition may be responsible for the overflow movements.

Evidence from studies supports the principle of surround inhibition in motor activity. Sohn, Jung, Kaelin-Lang, and Hallett (2003) have shown that with movement of one finger there is widespread inhibition of muscles in the contra-lateral limb.Significant suppression of MEP amplitudes was observed when TMS was applied between 35 and 70 ms after EMG onset. Sohn et al. have also noted that there is some inhibition of muscles in the ipsilateral limb when those muscles are not involved in any way in the movement In a study when TMS was delivered to the left motor cortex 3 to 1000 ms after EMG onset in the flexor digitorum superficialis muscle, MEPs from abductor digiti minimi were slightly suppressed during the movement of the index finger in normal individuals with increased F-wave amplitude and persistence, indicating that cortical excitability is reduced. But in patients with focal hand dystonia MEPs were enhanced in both flexor digitorum superficialis and abductor digiti minimi muscles, indicating a failure of surround inhibition.

Using another experimental paradigm, Stinear and Byblow have also demonstrated a loss of surround inhibition in the hand[53] in patients with focal dystonia.

Abnormal plasticity

The possibility of increased plasticity in dystonia had been suspected for some time given that repetitive activity over long periods seems to be a trigger for its development. An animal model supported this idea Monkeys were trained to hold a vibrating manipulandum for long periods. After some time, they became unable to do so, and this motor control abnormality was interpreted as a possible dystonia. The sensory cortex of these animals was studied, and sensory receptive fields were found to be large and it was concluded that the synchronous sensory input caused the receptive field enlargement, which then led to abnormal motor function.

Similar mechanism has been proposed in humans with dystonia and studies have demonstrated an abnormal plasticity of the motor cortex in patients with focal hand dystonia.

Paired associative stimulation

In paired associative stimulation (PAS), a median nerve shock is paired with a TMS pulse to the sensorimotor cortex. The TMS pulse is timed to be immediately after the arrival of the sensory volley. This intervention increases the amplitude of the MEP produced by TMS to the motor cortex. It has been demonstrated that the process of PAS produces motor learning similar to long-term potentiation (LTP). In patients with dystonia, PAS produces a larger increase in the MEP than what is seen in normal participants

Another aspect of the abnormal plasticity has recently been identified. Not only is the plasticity increased, but there is a failure of its homeostatic property.[57]The homeostatic property is that plasticity ordinarily increases and decreases within bounds. If, for example, the excitability of the motor cortex is high, then it cannot be driven higher, only lower. The recent finding, using several types of brain stimulation, is that plasticity in dystonia may not be properly bounded and may increase abnormally.

Increased plasticity may be an important link in demonstrating how environmental influences can trigger dystonia.

Abnormal sensory function

Stimulated by the findings of sensory dysfunction in the primate model, investigators began examining sensory function in patients with focal hand dystonia and found it to be abnormal. Although there is no apparent sensory loss on a clinical level, detailed testing of spatial and temporal discrimination revealed subtle impairments.[58]The abnormality was present on both hands of patients with unilateral hand dystonia and also on hands of patients with cervical dystonia and blepharospasm. The identification of abnormality of sensation beyond the symptomatic body parts

indicated that the sensory abnormality was more likely to be a pre-existing physiological state rather than a learned act.

Sensory dysfunction has also been demonstrated with somatosensory evoked potential (SEP) testing which evaluates the integrity of the sensory pathway from the sensory ganglion to the cortex.The dipoles of the N20 from stimulation of individual fingers showed disordered representation in the primary sensory cortex and these abnormalities were present on both hands of patients with focal hand dystonia.

PET studies have shown that the sensory cortex is more activated than normal with writing and the activity correlated with the severity of dystonia.[61]Voxel-based morphometry studies in patients with focal hand dystonia have shown an increase in gray matter in the primary sensory cortex.[62]Recent studies have further shown patients with sensory abnormalities and decrease in gray matter in the sensorimotor cortex further indicating that the primary sensory deficit may be the causative factor for dystonia. Thus there are abnormalities documented in the sensory and motor control in patients with writer's cramp.

Conflicts of Interest

All contributing authors declare no conflicts of interest.

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