Botulinum toxin dystonia writer`s cramp and other movement disorders – Part II

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Abstract
In this part II study, we discussed clinical features of Writer`s cramp, dystonic writer`s cramp and focal dystoniaa and what are the typical diagnosis and differential diagnosis for those other movement disorders followed by assessment and the treatments which includes therapeutic and clinically.

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

Introduction
In this study, clinical features and diagnosis like clinical and differential diagnosis are explained thoroughly.

Clinical features
Occasional patients may report a history of trauma or strain to the affected limb.[1] Most patients initially complain of feelings of tension in the fingers or forearms that interfere with the fluency of writing; a minority may also experience pain. Then the pen is held forcefully with abnormal excessive contraction (dystonia) of the hand and/or forearm muscles, causing different patterns of deviation from the normal or premorbid pen grip and hand posture, Writing may begin normally with dystonic posturing occurring after a few alphabets or words; In some patient develops dystonia of hand even before commencement of writing, as soon as they reach up to pick the pen. A common pattern of writer's cramp involves excessive flexion of the thumb and index finger, with pronation of the hand and ulnar deviation of the wrist. Other patients may have abnormal activation of wrist flexors, with supination of the hand and flexion of the wrist. Individual patients may experience involuntary lifting off of the index or thumb from the pen or isolated extension of other fingers as well. When dystonic cramps affect up to three fingers only, Cohen and Hallett have suggested the term of 'localized' (Vs non-localized) writer's cramp. The forearm muscles most often involved in writer's cramp are the flexor carpi ulnaris and radialis, flexor digitorum superficialis, flexor pollicis longus, and extensor digitorum communis muscles.[2,3] Up to 50% of patients with writer's cramp may also show upper limb tremor. Although sensations of strain and aching in dystonic forearm muscles are common in writer's cramp, pain – unlike in cervical dystonia is rarely a prominent feature, presumably due to the task-specific and intermittent nature of the disorder where the build-up of pain would normally stop individuals from performing the task.

In patients with simple writer's cramp, no other abnormal signs are evident except for postural tremor of the outstretched hand in 50% of cases. In progressive and dystonic writer's cramp, dystonic posturing of the outstretched arms is also present. Subtle loss of associated arm swing of the affected arm when walking occurs in 20-30% of patients. Many patients also demonstrate mirror dystonia, which is defined as abnormal posturing and involuntary movements of the resting dominant hand while writing with the non dominant hand. Various studies have demonstrated incidence ranging from 44%[4] to 70%[5] in patients with writer's cramp has been documented and may be useful on characterizing the muscles involved.

The intensity of dystonic movements is influenced by various conditions with voluntary motor activity-walking, talking etc, stress and fatigue exacerbating it. As is common with other focal dystonia sensory tricks (geste antagonistique) such as holding the arm against the table, rest and sleep decrease dystonia.

Diagnosis
The diagnosis of writer's cramp is based on clinical history and the appearance of dystonia on writing. There are no tests to confirm the diagnosis of writer's cramp. Further testing with nerve conduction studies and electromyography may be done to evaluate for underlying neuropathy and to identify which muscles are involved and to what extent.

Differential diagnosis
The hand may be involved in various other disorders and a clear history and detailed neurological examination will help in differentiating it from various other disorders.

1. Pain in the hand: Carpal tunnel syndrome secondary to median nerve compression and musculoskeletal problems like arthrtitis, tendon injuries and muscle cramps can all cause pain in the hand but does not cause dystonia,
2. Primary writing tremor is usually misdiagnosed as writer's cramp. It is a large amplitude tremor occurring during writing only. However it is not associated with dystonia or pain and in contrast to essential tremor, action and postural tremors are not seen.
3. Generalized dystonia especially idiopathic generalized dystonia may manifest initially as writer's cramp. Search for other co-existing dystonia apart from hand dystonia helps in diagnosis.
4. Writing abnormalities may be the initial features to be noted in patients with secondary dystonia like Wilson's

disease and Parkinson's disease. Presence of other features like micrographia, bradykinesia and postural instability in Parkinson's disease, KF ring in the cornea, dystonic smile, behavioral disturbances and rubral tremor consisting of tremor occurring during posture, action and intention in Wilson's disease helps in distinguishing these syndromes.

5. Repetitive strain injury refers to the various symptoms occurring during prolonged use of keyboard resulting in pain in the hand, write and shoulder and is becoming more common nowadays. However they are more musculoskeletal disorders and does not manifest as dystonia.[2,8]

Assessment of Dystonia

Dystonia in writer's cramp is assessed while the patient performs the following tasks and is rated as per the writer's cramp rating scale (WRCS)

1. Writing of a test paragraph dictated to them.
2. Writing of 2 lines of eeeeeeeeeeeee
3. Drawing of 2 spirals
4. Drawing of 2 straight lines[6]

Table 1: Writer's cramp rating scale (WCRS)

Writing movement score		
1. Dystonic score		
Dystonic posture elbow score (ES) (0-2)		
Pathological flexion		Pathological extension
0	No	0
1	Moderate	1
2	Marked	2
Wrist score (WRS) (0-4)		
Pathological flexion		Pathological extension
0	No	0
1	Moderate	1
2	Marked	2
Pathological ulnar abduction		Pathological radial abduction
0	No	0
1	Moderate	1
2	Marked	2
Finger score (FS) (0-6)		
Finger I		
Pathological flexion		Pathological extension
0	No	0
1	Moderate	1
2	Marked	2
Finger II		
Pathological flexion		Pathological extension
0	No	0
1	Moderate	1
2	Marked	2
Finger III		
Pathological flexion		Pathological extension
0	No	0
1	Moderate	1
2	Marked	2
2. Latency of dystonia (L)		
At least 3 letters possible		1
At the onset of writing		2
3. WRITING TREMOR (WT)		
No writing tremor		0
Moderate writing tremor		1
Marked writing tremor		2
WRCS sub-score= (ES+WRS+FS) x L + WT x 2		

Treatment

1. Approximately 5% of patients have spontaneous remission, most probably in the first 5 years. However, the majority of these patients have relapses.
2. Treatment with oral medication is generally disappointing. Since cortical inhibition is deficient, medication which facilitate gabergic transmission like clonazepam and baclofen have shown some benefit.
3. Slow rates of repetitive TMS (1Hz) to the primary motor cortex, that increased cortical inhibition, may be helpful.[7]
4. Transcutaneous electrical nerve stimulation (TENS) delivered to the forearm flexor muscles for a 2-week period has been found to improve symptoms for up to 3 weeks after treatment.
5. Behavioral changes may help.
6. Motor training has been tried to use the mechanism of plasticity to counteract dystonia[8] Sensorimotor retuning has been tried initially in piano players and similarly in patients with writer's cramp. Patients were asked to practice writing with individual fingers with specialized finger pens while the other fingers were splinted[9] Some improvement in the dystonia was found but was comparatively less than that found in piano players.
7. Another technique that might utilize mechanisms of plasticity is immobilization.[10] The arm and hand were immobilized in a cast for about 4weeks; following which the arm and fingers were slowly "re-trained" to move again. This may result in dedifferentiation of the sensorimotor cortex during the immobilization and an eradication of the abnormal dystonic patterns.
8. As dystonia may be secondary to abnormal sensory function, sensory training has been tried and has improved sensory discrimination and improved motor function[11] in some patients. Sensory training was accomplished by training each individual finger to read Braille.
9. Another therapeutic approach arising from the idea of sensory dysfunction is muscle afferent block[12] Injection of dilute lidocaine into muscle also was found to improve focal hand dystonia transiently. For all of the rehabilitative type therapies, most studies have been short term and there are no reports of lasting benefit. In the sensory training studies, participants were followed after they stopped training both the improvement in sensory discrimination and motor performance reverted to the baseline abnormal state[13] If there is abnormal

homeostatic plasticity, there would be a drive to the abnormal state again.

Botulinum Toxin

Injection with botulinum toxin in the duystonic muscles of writer's cramp is the most effective treatment available today[14]

Botulinum toxin is a protein produced by the bacterium Clostridium botulinum. It is the most toxic protein known[15] with an LD50 of roughly 0.005-0.05 µg/kg. It was noted in 1950s that injecting overactive muscles with minute quantities of botulinum toxin type-A would cause a decreased muscle activity by blocking the release of acetylcholine at the neuromuscular junction, thereby rendering the muscle unable to contract for a period of 3 to 4 months.

Alan Scott, a San Francisco ophthalmologist, first applied tiny doses of the toxin as a medicine to treat squint and a focal dystonia of the eye.[16] blepharospasm. Since then botulinum toxin injections have been used in various disorders including dystonia and writer's cramp. There are seven serologically distinct toxin types, designated A through G; 3 subtypes of A have been described. The toxin is a two-chain polypeptide with a 100-kDa heavy chain joined by a disulfide bond to a 50-kDa light chain.[17]

Type A, B and F, have been used for medical purposes and are currently marketed.

Mechanism of action: Following the attachment of the toxin heavy chain to proteins on the surface of axon terminals, the light chain is taken into the cell by endocytosis and is able to cleave endocytotic vesicles and reach the cytoplasm. This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction. These fusion proteins are required for anchoring the acetylcholine vesicles at the neuromuscular junction. By inhibiting acetylcholine release, the toxin interferes with transmission of nerve impulses to the muscles and causes paralysis of muscles.

Botulinum toxin (BoNT) in writer's cramp

The use of BoNT to treat limb dystonia requires thoughtful technique including customization of doses and muscle selection.

American Academy of Neurology (AAN) recently reviewed the various trials proving the efficacy of BoNT for focal limb dystonia.[18]

A large trial conducted by Kruisdijk JJ et al[19] randomized 40 patients (class I) with writer's cramp in a double-blind design to BoNT or an equivalent volume of saline placebo. Injected muscles were chosen based on clinical examination. Participants with inadequate or no response were offered a second injection 1 month later. The primary outcome measure was the subject's stated desire to continue injection. Seventy percent of those randomized to BoNT wished to continue treatment compared to 32% of those receiving placebo (p=0.03). Significant improvement was also found in BoNT-injected subjects compared to those receiving placebo in secondary outcome measures including a visual analog scale, symptoms severity scale, writer's cramp rating scale, and assessment of writing speed, but not in the functional status scale. Temporary weakness and pain at the injection site were the only adverse events reported

Similar results of various smaller placebo controlled trials evaluating the efficacy of BoNT in writer's cramp (Class II trial) are given below in the table

Table 2: Trials demonstrating efficacy of botulinum toxin

Class	Design	Cohort Size	Treatment -Serotype/ brand/dose	Follow-up	Outcome measures /Results (1-pri- mary, 2-secondary)	Drop outs	Adverse Events	Results/ Effect Size
II [82]	Double-blinded, randomized, prospective, placebo-controlled cross-over	17 limb dystonia: (10 occupational cramp, 3 idiopathic, 2 post-stroke, & 2 PD)	Serotype/ brand not specified 3 active doses: individualized, half, normal or double	1 mo	1.Blinded scoring of videos and handwriting analysis 2.Subjective patient rating	1	Focal weakness with 53% injections, more common with higher dose, lasted 6 wks; muscle stiffness, pain, malaise, muscle twitching, paresthesia, nausea	No significant change in blinded rating: 59% improved with BoNT vs. 38% with placebo Subjective patient rating improved in 82% with BoNT, vs. 6% with placebo
II[83]	Blinded, randomized, prospective, placebo-controlled cross-over	20/ writer's cramp	A/Botox® individualized	0.5 & 1.4 mo	1.Writing speed, accuracy, and writing samples and 2.patients'	none	100% had weakness in injected muscles; pen control worse in 1 pt injected with BoNT	Speed and accuracy improved in 35% with BoNT; Gibson maze improved; pain improved in 67% with pain

					subjective report			No improvement with placebo. NNT for significant improvement in writing = 5
II [84]	Blinded, randomized ,prospectiv e,placebo controlled cross-over	10/ focal hand dystonia	A/Botox®: Individualiz ed	0.5 mo	1.Patient subjective rating 2.Objective writing accuracy and speed 3.Physician rating	none	Focal weakness in 80% of BoNT-treated muscles	Subjective: 90% had at least mod improvement. Objective: 6 better with BoNT. 1 pt improved with placebo.

As per the guidelines issued by American Association of Neurology (AAN), botulinum toxin remains the currently available best treatment for Writer's cramp (Level B recommendation) (Based on the above trials AAN has issued a Level B recommendation for the use of botulinum toxin in patients with writer's cramp.)

Selection of muscles for botulinum toxin injection

Selection of appropriate muscles for injecting botulinum toxin is one of the main factors determining the effectiveness of therapy as the ideal therapy would be to inject in only the dystonic muscles sparing the non affected muscles.

Methods of Selection

Clinical and videographic examination: The patient is examined at rest and during writing a long paragraph, drawing a straight line or spirals. The test is done with the patient seated comfortably and writing on a table and the appearance of dystonia is noted. However, the complexity of such movements often makes it difficult to determine which movements are dystonic and which are part of the normal pattern for that activity. The analysis of dystonic patterns may be further complicated by the presence of compensatory movements that may not be voluntary or even conscious. To improve the selection of muscles, it has been suggested that patients should be examined for abnormal postures at rest and while carrying out the affected task in question as well as other tasks (such as using a cup or a comb) Simple techniques such as the localization of subjective pain and fatigue accompanied by palpation of the area of discomfort have also been used This can probably explain the difference in treatment efficacy with botulinum injection in wrist flexor and extensor dystonia. Previous studies have shown that treatment is more effective in wrist extensor compared to wrist flexor dystonia.

Mirror dystonia

Mirror dystonia in writer's cramp has been described since a long time. There is emergence of dystonic movement in the affected limb even when it is relaxed and the opposite limb is activated. The pathogenesis of this mirror dystonia is still not very clear but may be secondary to abnormal cortical inhibition and decreased selectivity of muscle patterns for highly skilled manual tasks. The importance of recognition of mirror dystonia in patients with writing dysfunction was initially highlighted by Jedynak et al.[34] He reported that 29 (44%) of 65patients with writer's cramp had evidence of mirror dystonia and suggested that mirror dystonia may be useful in muscle selection. Subsequently studies have shown a higher incidence of mirror dystonia (70% by Borgohain et al, 2002) among patients with writer's cramp. The concordance of mirror dystonia with the dystonic movements in writer's cramp has been studied and it has been shown that the best response occurs if there is concordance between the two parameters. In case of discordance as has been noted in wrist flexor dystonia, injection of muscles noted in mirror dystonia has been shown to lead to a better outcome. Mirror dystonia probably helps in differentiating the primary from the compensatory movements.

Conclusion

Electromyography (EMG) is routinely used for guiding botulinum injections into muscles once muscle selection is over. Use of routine EMG in selecting muscles for injecting botulinum toxin may be of assistance, but is limited by the fact that restricted random EMG sampling may give limited unrepresentative information. Further EMG findings may be confounded by compensatory movements and local discomfort caused by EMG wires. To overcome these issues, microelectrodes inserted into multiple muscles can record the EMG during the activation of the dystonia and can provide substantial information on the involvement of deep or not obvious muscles.

Conflicts of Interest

All contributing authors declare no conflicts of interest.

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None.

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