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Study to Evaluate the Spectrum of Adult Onset Focal Dystonias and Dyskineasis Presenting in Neurology OPD in a Tertiary Care Hospital

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ABSTRACT
Dystonia is a movement disorder characterised by sustained muscle contraction, frequently causing twisting and repetitive movement or abnormal posture. Tremors occur commonly with dystonia and either involve affected body parts (dystonic tremors) or other body parts not affected by dystonia (tremor associated with dystonias). Dystonia is often aggravated by voluntary movement. The underlying neurochemistry of dystonia is not known but dopaminergic, cholinergic and glutaminergic neurotransmitter systems may be involved. Efforts are ongoing to develop a practical, reliable and validated screening tool for dystonia that can be applied to large populations. The study was conducted at a tertiary care hospital. 18 patients over 12 years of age presenting to neurology OPD with diagnosis of focaldystonias and dyskinesias (cervical dystonia, blepharospasm, hemifacial spasm, writer's cramps, any others). Genetic testing for Huntington for selected patients who have a positive family history and a combination of movement disorders with psychiatric symptoms, will be done. Baseline severity of dystonia will be assessed at point of diagnosis using visual analogue scale. Data will be recorded and analyzed. Age of patients ranged from 12 years to 68years, with the mean age being 46 years. 18 patients, 38.9% had hemifacial spasm,16.7% had blepharospasm, 22.2% had cervical dystonias, 5.6% had facial dystonia, 16.7% had jaw opening dystonias and5.6% had hemidystonias. out of 18 patients 2 had sensory tricks. 5.6% had neurological (hemiplegia) additional finding and 12.2% had systemic (polio leg, KF ring) additional finding. Stressors were present in 50% of patients, seen in 5/7 patients with hemifacial spasm, 2/4 patients with cervical dystonia and 1/3 patients with blepharospasm. Sensory tricks were used for relieving of symptoms by 1 patient each of cervical dystonia and blepharospasm.

INTRODUCTION

Dystonia is a movement disorder characterized by sustained muscle contraction, frequently causing twisting and repetitive movement or abnormal posture. Oppenheim introduced the term dystonia muscularum deformans to describe abnormal posturing in four unrelated Jewish children. The Polish neurologists Flatau and Sterling published similar observations in the same year. 1 The abnormal postures are typically not fixed, are caused by co-contraction of agonist and antagonist muscles and tend to be repetitive and patterned, consistingly involving the same muscle groups. Tremors occur commonly with dystonia and either involve affected body parts (dystonic tremors) or other body parts not affected by dystonia (tremor associated with dystonias). Dystonia is often aggravated by voluntary movement. The classification system for dystonia is based on clinical characteristics and etiology. The etiological characteristics are the presence or absence of nervous system pathology and the pattern of inheritance. The underlying neurochemistry of dystonia is not known, but dopaminergic, cholinergic and glutaminergic neurotransmitter systems may be involved. Focal dystonia is more common than generalized dystonia. Cervical dystonia is the most frequent type of focal dystonia. The diagnosis of dystonia is based mainly upon clinical features, although the diagnostic laboratory can provide supportive evidence. Age and anatomic distribution of dystonia at onset are important clues for diagnosis. The treatment of dystonia is symptomatic. No curative therapies are available. Management options include oral medications, botulinum toxin injection and deep brain stimulation. Botulinum toxin is a potent neurotoxin produced by Clostridium botulinum that causes regional muscle weakness through its action as a zinc endopeptidase cleaving specific proteins involved in vesicular fusion which interferes with the release of acetylcholine at the neuromuscular junction, resulting in localized muscle weakness. It is beneficial for patients with cervical dystonia and blepharospasm. It is also viewed as the treatment of choice for spasmodic dysphonia, limb dystonia and oromandibular dystonia. Several observational studies of the long term effect of botulinum toxin demonstrate continued efficacy over at least 1 year and up to 10 years. Limited data suggest that botulinum toxin is more effective for cervical dystonia than anticholinergic treatment with trihexyphenidyl.

The above study was conducted to evaluate the spectrum of adult onset focal dystonias & dyskineasis presenting in neurology OPD in a tertiary care hospital.

MATERIALS AND METHODS

Study place: The study was conducted at a tertiary care hospital for a period of 18 months.

Study design: Prospective observational study.

Inclusion criteria: Patients over 12 years of age presenting to neurology OPD with diagnosis of focal dystonias and dyskinesias (cervical dystonia, blepharospasm, hemifacial spasm, writer's cramps, any others), ready to give written informed consent for participation.

Exclusion criteria: Patients below 12 years of age and unwilling to give written informed consent.

Sample size: 18 patients.

Data analysis: Data was collected and analyzed using SPSS 21 version. All the information was entered n Microsoft Excel sheet.

Ethical consideration: The Institutional Ethics Committee approval was taken before beginning the study.

Patients with focal dystonia who are coming on OPD basis were identified based on clinical features of focal dystonias. Clinical features of focal dystonia included reduced abnormal head positions, including horizontal turning (torticollis), tilting (laterocollis), flexion (anterocollis), or extension (retrocollis), Blepharospasm causing contraction of the orbicularis oculi muscles, Spasmodic dystonia (SD) resulting from dystonia of vocal cords, Oromandibular dystonia (OMD) with abnormal activity in lower facial, tongue, jaw and pharyngeal muscles, Primary lingual dystonia, Adult onset limb dystonia eg. writer's cramps. Investigations such as CBC, Renal function test, Liver function test, Random blood sugar, Thyroid function test, peripheral smear for acanthocytes were done. Genetic testing for Huntington for selected patients who have a positive family history and a combination of movement disorders with psychiatric symptoms, was done. MRI brain was also to be done to find out any cause of dystonia, in selected patients who have neurological signs beyond the primary focal dystonias. Video recording of the movement disorder will be done at point of diagnosis after appropriate written consent. Baseline severity of dystonia will be assessed at point of diagnosis using visual analog scale. All patients will be started on standard oral medications (Tetrabenzine, trihexiphenidyl, Baclofen, clonazepam). Local injection of on botulinum toxin at standard site will be given after appropriate counselling and written consent from patients. Clinical response of all patients will be assessed every monthly using visual analog scale up to 6 months and also side effects, if any, will be identified. Video recording of movement disorder will be repeated.

RESULTS

Age of patients ranged from 12 years to 68 years, with the mean age being 46 years. In Table, out of 18 patients ,38.9% had hemifacial spasm,16.7% had blepharospasm,22.2% had cervical dystonias,5.6%had facial dystonia,16.7% had jaw opening dystonias and5.6 %had hemidystonias. Out of 18 patients 44.4% had stressors. Out of 18 patients 2 had sensory tricks.

The patients were examined using the visual analog scale. A scale was given to the patient with the rating of severity of disorder from 0-10, with 10 being worst symptoms. Improvement by 2 points was taken as significant improvement for documentation. The table shows that out of 18 patients, at 4 months of follow up 11were improved and 7 were not improved; at 5 month follow up 7 were improved, 10 were not improved and 1 was deteriorated; at 6 month follow up 4 were improved and 14 were not improved.

Out of 18 patients 9 patients received injection onobotulinum toxin at 4 months of follow up 7 patients were improved, 2 were not improved, at 5 months of follow up 3 were improved,5 were not improved, one was deteriorated, at 6 months of follow up 3 were improved,6 were not improved. Patients who received only standard medication among 9 patients at 4 months 4 were improved, 5 did not, at 5 months 4 were improved, 5 did not, at 6 months only 1 improved, 8 were not improved. Comparing treatment response between the subgroups of patients only on oral medications and those on onobotulinum toxin plus oral medications at 4 month follow up using fisher exact test, two tailed p value 0.334 was not significant.

Table 1: Distribution of study subjects according to the age group (N = 18)

Age (Years)	No.	Percentage
= 30	3	16.7
31-40	3	16.7
41-50	5	27.8
51-60	3	16.7
>60	4	22.2
Mean (SD)	46.11 (15.38)	
Range	12-68	

Table 2: Distribution of study subjects according to the type of movement disorder (N =18)

Type of movement disorder	No.	Percentage
Hemifacial spasm	7	38.9
Blepharospasm	3	16.7
Cervical dystonia	4	22.2
Facial dystonia	1	5.6
Jaw opening dystoni	2	11.1
Hemidystonia	1	5.6

Table 3: Distribution of study subjects according to the stressor(N = 18)

Stressor	No.	Percentage
Yes	8	44.4
No	10	55.6

Table 4: Distribution of study subjects according to the sensory tricks (N = 18)

Sensory Tricks	No.	Percentage
Yes	2	11.1
No	16	88.9

Table 5: Distribution of study subjects according to the visual analogue scale symptoms improved or deteriorated (N = 18)

Visual scale symptoms	4 months	5 months	6 months
Improved	11 (61.1)	7 (38.9)	4 (22.2)
Not improved	7 (38.9)	10 (55.6)	14 (77.8)
Deteriorated		1 (5.6)	

Table 6: Association between injection onobotulinum toxin and Improvement at 4,5 and 6 months (N = 18)

Injection onobotulinum toxin	No.	Improved	Not improved	Deteriorated
At 4months	9	7 (77.8)	2 (22.2)	
At 5 months	9	3 (33.3)	5 (55.6)	1 (11.1)
At 6 months	9	3 (33.3)	6 (66.7)	
p-value = 0.167				

Table 7: Association between oral medication and Improvement at 4,5 and 6 months

Received oral medication	No.	Improved	Not improved	Deteriorated
At 4months	9	4 (44.4)	5 (55.6)	
At 5 months	9	4 (44.4)	5 (55.6)	
At 6 months	9	1 (11.1)	8 (88.9)	
p-value = 0.223				

Table 8: Comparison of treatment response between 2 groups at 4 months follow up

At 4 months	improved	not improved
Injection onobotulinum toxin plus oral medications	7	2
oral medications	4	5

DISCUSSIONS

In the above study, the mean age of participants in our study was 46 years, with a range of 12 years-68 years. Maximum participants were in the age group of 41-50yrs, followed by the group with age over 60 years. Adult onset isolated focal dystonias usually involve upper body and begin after the age of 30 years. The median age for development of DYT6 dystonia is 28 years. Patients with dopa-responsive dystonia and Wilson's disease usually develop symptoms before 20 years of age, but most investigators encourage testing for these diagnoses at least through the age of 40, because they are treatable.

Out of 18 patients, 38.9% had hemifacial spasm,16.7% had blepharospasm, 22.2% had cervical dystonias,5.6%had facial dystonia, 16.7% had jaw opening dystonias and5.6% had hemidystonias. The most common type of focal dystonis is cervical dystonia. Cervical dystonia also known as spasmodic torticollis, it affects muscles of the neck and shoulder.it may appear as horizontal turning of head (torticollis), lateral tilt of neck(laterocollis), flexion of head (anterocollis), extension of head (retrocollis). Studies from various geographic areas indicate that BSP and CD are more frequent than laryngeal and focal hand dystonia (FHD) Defazio *et al*.[2] International prevalence trends nevertheless seem discordant. In prevalence studies from the USA and Northern Europe CD was more frequent than BSP whereas in studies from Italy and Japan the trend was reversed, BSP being more frequent than CD Defazio *et al*.[2]. Owing to methodological problems from differences in

ascertainment across studies Defazio *et al*.[2], however, we can draw few inferences about geographical variability in the prevalence of different forms of primary late-onset dystonia.

Also, out of 18 patients 44.4% patients had stressors. These included the following-50% had anxiety, 12.5 %had lack of sleep, 25% had fatigue 12.5 % reported walking as the stresso. Several lines of evidence suggest that mood and anxiety disorders are intrinsic to the neurobiology of dystonia, as opposed to coincidental conditions or emotional reactions to motor symptoms. Evidence that different forms of dystonia have different prevalence rates for stressors. For example, anxiety and depression are more common in CD.3-4 depression is most common in blepharospasm.

Two patients had sensory tricks for terminating the dyskinesia. One patient had right hemifacial spasm had motor type of tricks and another one had cervical dystonia had imaginary type of sensory tricks. Sensory tricks that can ameliorate dystonic movements or posture in various parts of the body are a clinical feature of different focal dystonias but the usefulness of sensory tricks differs among the various types. Sensory tricks are common in CD and less common in cranial and hand dystonia[5]. In addition to the association of meaningful and distressing life events with the onset of symptoms, several other reasons were regarded as supportive of a "functional" basis for focal dystonias[2] the bizarre nature of the movements, female preponderance[3], relief of dystonic postures by use of a sensory trick, i.e., "geste antagoniste. The relationship of disease severity and effectiveness of the sensory trick found in this study has also been found in other studies, 6-7 whereas this relationship was not significant in another recent study on sensory tricks by Martino *et al*.[8].

The patients were examined using the visual analog scale. A scale was given to the patient with the rating of severity of disorder from 0-10, with 0 being worst symptoms. Improvement by 2 points was taken as significant improvement for documentation. The patients were evaluated using this visual analog scale at 4 different points through their history 1) At presentations 2) At 4 months 3) At 5 months 4) 6 months after starting treatment. At presentation, half the patients had grading of 2 while the other half had grading of 4. Four months after starting the therapy, 61% patients improved while the rest 39% patients showed no improvement, but their condition didn't deteriorate either. However, of these 7 patients, 1 patient temporarily worsened when examined at the 3rd point in their examination timeline. Nonetheless, when examined again at 6 months, 78% showed no change in condition while only 21% patients had an improved condition. The change in patient assessed improvement was concordant with the clinician assessment at 4,5 and 6 months. Clinician assessed rating scales are important in quantitative assessment of treatment response and further planning of therapy. The interpretation of treatment outcome is mainly based on the clinical experience and on the scientific value of the rating scales applied. The Fahn Marsden dystonia scale has been developed for the assessment of generalized dystonia, originally for use in a therapeutic trial of trihexyphenidyl (Burke et al. 1985). The scale rates the severity of movements affecting different body parts, each on a 5 -point scale, but it includes only one item of CD (i.e. neck). The Fahn Marsden scale also takes into account provoking factors 1 (dystonia appearing only with action) and 4 (persistent dystonia at rest). Truncal and limb movements are assigned a weight of 0.5 and cranial movements are assigned a weight of 1.0 for a maximal total score of 120. In addition, there is a separate disability scale for activities of daily life (speech, handwriting, feeding, eating/swallowing, hygiene, dressing, walking) rated from 1 (normal) to 4 (complete disability). Assessment of treatment outcome in clinical studies and in daily practice is only as reliable and valid as the instrument applied.

It was also seen that among the 9/18 who received injection onobotulinum toxin, the details of response were as follows-at 4 months of follow up 7 patients were improved, 2 were not improved, at 5 months of follow up 3 were improved, 5 were not improved, one was deteriorated, at 6 months of follow up 3 were improved,6 were not improved. Although there was improvement up to 77.8% of patient at 4 months this drops to 33% at 5 and 6 months with patients failing to sustain improvement at 5 months more of follow up. Botulinum neurotoxin (BoNT) is a toxic protein produced by the bacterium Clostridium botulinum. It selectively blocks the cholinergic innervation of striate and smooth muscles and exocrine glands De *et al*.[9] BoNT injections in dystonia are given intramuscularly, often under electromyography (EMG) guidance and need to be repeated every 3-6 months. Contraindications for the use of BoNT include history of neuromuscular disease, e.g. myasthenia gravis, Lambert– Eaton syndrome or motor neuron disease, and a history of hypersensitivity to BoNT, albumin or saline. BoNT injections are also contraindicated in combination with aminoglycoside, penicillamine, quinine and calcium-channel blockers as the effect of these drugs may be potentiated. As teratogenicity of BoNT is still unknown, it is advised not to use BoNT during pregnancy and lactation. BoNT injections

are the first-line therapy for cervical dystonia (CD). Meta-analysis of several double-blind, placebo-controlled trials have demonstrated a beneficial effect of the BoNT type A (BoNT-A) versus placebo on multiple domains, such as dystonia severity, pain and the patient's and physician's subjective judgement. Adverse events are usually transient and mild. The most relevant side effects, of increasing frequency with higher doses and therefore dose-limiting, are neck weakness, dysphagia, dry mouth/sore throat and voice changes/hoarseness. Others are dose-independent and include pain at the site of injection, malaise, upper respiratory infection and headache Costa *et al*.[10].

The patient each category who had not improved at 4 month continue to remain same, among the patient who had improved at 4 months the majority did not improved further. Conventional drug treatment has been the cornerstone in dystonia treatment for many years but BoNT has taken over its position over the last 15-20 years, particularly for the focal subtypes. Still, oral medication is widely used, particularly in generalized dystonia or in focal dystonias when there is an unsatisfactory response to BoNT. Anticholinergic drugs block the action of acetylcholine on central muscarinic receptors. In a retrospective analysis of open-label trials of initial treatment with anticholinergic agents, data from 358 primary focal and generalized dystonia patients were reviewed Greene et al.11 A "good" response, defined as a slight, moderate or marked improvement, was experienced by 40-50% of patients. There was no correlation between a good response and distribution of dystonia, sex or disease severity. Burke and colleagues reported an improvement up to 72% in a double-blind, randomized crossover study using trihexy-phenidyl versus placebo in 31 primary segmental or generalized dystonia patients, all younger than 32 years.

In above study while comparing the group on only oral medications and the group on medications plus botulinum toxin. There was no significant difference between the 2 groups. This could have been due to delayed assessment at 4 months after the injection (due to pandemic situation, earlier assessments were not possible), or due to the very small sample size.

CONCLUSION

Among 18 adult patients of focal dystonias and dyskinesias, 7 patients presented with hemifacial spasm, 4 patients presented with cervical dystonia, 3 patients presented with blepharospasm, 3 patients presented with jaw opening dystonia, 1 presented with facial dystonia and one had hemidystonia. Stressors were present in 50% of patients, seen in 5/7 patients with hemifacial spasm, 2/4 patients with cervical dystonia and 1/3 patients with blepharospasm. Sensory tricks were used for relieving of symptoms by 1 patient each of cervical dystonia and blepharospasm. Among the patients who received oral medication and injection onobotulinum toxin, 77.8% had improvement at 4 months follow up. Among them, only 42.8% had sustained the initial improvement, at 5 months of follow up.

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