

Botulinum Toxin Clinic-Based Epidemiologic Survey of Adults with Primary Dystonia in East China

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Background and Purpose: Primary focal or segmental dystonia is a rare clinical condition. The clinical features of dystonia have not been evaluated in China. We performed a study to investigate the epidemiology of primary dystonia and its clinical variants in an adult population. **Methods:** A Botulinum Toxin Clinic-based study was conducted in the period 18 May through 8 October 2010 in East China. We identified 523 dystonia patients from the Movement disorders and Botulinum Toxin clinic Cases. **Results:** The most common focal dystonia were blepharospasm (59%), cervical dystonia (35%), limb dystonia (3%), oromandibular dystonia (2%) and laryngeal dystonia (1%). Males with primary dystonia were noted to have earlier age of onset. A female predominance was noted for most of the primary dystonias with a male to female ratio (M : F) ranging from 1 : 1.48 to 1 : 3. **Conclusions:** The epidemiological features of dystonia in East China we collected were similar to the report in Japan which contrasts partly with that reported in Europe. **Journal of Movement Disorders 2012;5:9-13**

Key Words: Epidemiology, China, Primary dystonia.

Dystonia is a neurological syndrome characterized by involuntary, sustained, patterned and often with repetitive contractions in opposing muscles, causing twisting movements or abnormal postures that result in significant pain and functional disabilities. The effect of the traditional medical and physical treatment was limited before the introduction of botulinum toxin therapy. Now botulinum toxin therapy is widely used and is the preferred treatment for this disease. Moreover patient outcomes are better with botulinum toxin.

Because dystonia is considered rare and associated with a low morbidity and is generally non-fatal, there have been only a few studies investigating the epidemiology of dystonia. The prevalence of late-onset dystonia has been found to range from 30 to 7320 cases per million (Table 1).¹⁻¹⁵ To the best of our knowledge there have been no detailed clinical or epidemiological studies in China except one door to door survey conducted by Li et al.¹ in 1985. It is our clinical observation that blepharospasm accounts for the highest proportion of primary focal dystonia seen in China, which is similar to that reported in Japan^{7,11} but is quite different from the reports in western countries⁴ where cervical dystonia is more common. These observations prompted us to perform a service-based study to investigate the epidemiology of primary dystonia and its clinical variants in an adult population.

Methods

This study encompassed an area in East China that includes six provinces and one municipality (Jiangxi, Jiangsu, Zhejiang, Shandong, Fujian, Anhui and Shanghai). A total of 1599 outpatients were included in this study. All patients were either referred to the movement disorder specialists or were seen in botulinum toxin clinics at six centers. Each center provides regular botulinum toxin treatment and each is well known locally for having a special interest in this disorder. The study included patients from May 18 to October 8, 2010. Among the cases, 523 patients were diagnosed as primary or idiopathic dystonia while 1045 patients were diagnosed with hemifacial spasm and 31 were diagnosed with other conditions

Table 1. Published prevalence of dystonia in different populations

Study	Nation	Period	Study design	Sample (ages)	Number of cases	Prevalence rate per million (95% CI)
Li et al. ¹	China	1983	Door to door	63195 (all ages)	2	30 (4-110)
Nutt et al. ²	USA	1950-1982	Record-linkage	406976 (all ages)	19	329 (172-479)
Nakashima et al. ³	Japan	1988-1993	Service-based	244935 (all ages)	15	61 (34-101)
ESDE ⁴	Eight European countries	1996-1997	Service-based	5792937 (> 20 years)	879	152 (108-126)
Müller et al. ⁵	Italy	2000	Population sample	707 (> 50 years)	6	7320 (3120-15640)
Castelon Konkiewitz et al. ⁶	Germany	1996-1997	Service-based	1807000 (all ages)	186	104 (84-119)
Matsumoto et al. ⁷	Japan	2000	Service-based	1459130 (all ages)	147	101 (84.5-118)
Le et al. ⁸	Norway	1999-2002	Service-based	508726 (all ages)	129	254 (212-301)
Pekmezović et al. ⁹	Serbia	2001	Service-based	1602186 (all ages)	165	136 (116-159)
Butler et al. ¹⁰	England	1993-2002	Record-linkage	101766 (all ages)	43	430 (306-569)
Fukuda et al. ¹¹	Japan	2000-2003	Service-based	247973 (> 50 years)	34	137 (91-183)
Sugawara et al. ¹²	Japan	2003	Service-based	1166967 (all ages)	177	151 (68-144)
Asgeirsson et al. ¹³	Iceland	2003	Record-linkage	288201 (all ages)	107	371 (304-449)
Das et al. ¹⁴	India	2003-2004	Population sample	52377 (all ages)	29	439 (284-648)
Papantonio et al. ¹⁵	Italy	2001-2002	Service-based	541653 (> 17 years)	69	137 (102-166)

ESDE: Epidemiological Study of Dystonia in Europe, CI: confidence interval.

Table 2. Definition of dystonia types¹⁶

Focal dystonia: single body region
Segmental dystonia: two or more contiguous regions
Multifocal dystonia: two or more non-contiguous regions
Hemidystonia: affecting ipsilateral arm and leg
Generalized dystonia: leg + trunk + one other body part

(e.g. tics, secondary dystonia, etc.). All the patients with dystonia are late-onset (> 26). Standardized definitions of dystonia were used in this study and were agreed by all investigators. Primary dystonias were sub-divided into subtypes based on the anatomical distribution (Table 2).¹⁶ Cases of secondary dystonia were excluded.

The demographic and clinical characteristics were recorded by using a standardized data collection form for each eligible case. This included name of the center enrolling the patient, the type of dystonia, date of birth, sex, date of diagnosis of dystonia was confirmed, all prior diagnoses and treatment, province of residence and botulinum toxin treatment interval.

The protocol was approved by the Ethics Committee. All patients gave informed written consent.

Statistical methods

Continuous variables were defined as means \pm standard deviation (SD) if they were normally distributed. When age and time of diagnosis were compared between males and females, the *t*-test was used if they were distributed normally and variance was equal, otherwise *t*-test was used. One-way factorial analysis of variance (ANOVA) was used when compared with age of onset and diagnosis time between patients

with different subtypes, and post hoc comparisons were made by using least significant difference (LSD). All *p* values are two-tailed, and significance was set at the 0.05 level. All statistical analyses were made by using SPSS software (version 11.5; SPSS Inc., Chicago, IL, USA)

Results

We identified a total of 523 patients with primary dystonia. All patients were ethnic Chinese. Focal dystonia accounted for 67.69% (354 cases) of primary dystonia. The remaining cases were segmental dystonia in 165 patients (31.55%), and multifocal dystonia in 4 patients (0.76%). See Table 3 for specifics of each case. In the 354 patients with focal dystonia, the most common specific diagnoses in decreasing order were blepharospasm in 206 cases (59%), cervical dystonia in 124 cases (35%), limb dystonia in 11 cases (3%), oromandibular dystonia in 8 cases (2%) and laryngeal dystonia in 5 cases (1%) (Figure 1). And in segmental dystonia, majority was segmental-cranial (26.39%).

The age and sex-specific rates for different subtypes of dystonia are shown in Table 3. Of the 523 patients with primary dystonia, 176 were male and 347 were female, with a gender ratio of 1 : 1.97 (Table 3). The mean age at onset of dystonia was 47.89 years (SD = 12.79 years). Overall males with primary dystonia were noted to have earlier age of onset. The difference between the onset age of males and females did not reach statistical significance except in the group with limb dystonia (*p* = 0.007). Of the focal dystonia subtypes, age of onset was earliest in patients with limb dystonia whereas

Table 3. The age and sex-specific rates for different subtypes of dystonia

Types of dystonia	Number of cases			M : F ratio	Mean age of onset (years \pm SD)			
	Total (%)	Male	Female		Total	Male	Female	<i>p</i>
All types	523 (100)	176	347	1 : 1.97	47.89 \pm 12.79	46.40 \pm 13.06	48.65 \pm 12.6	0.107
Focal dystonia	354 (67.69)	133	222	1 : 1.67	46.14 \pm 13.13	45.14 \pm 13.52	46.74 \pm 12.89	0.268
Blepharospasm	206	83	123	1 : 1.48	49.35 \pm 11.32	48.45 \pm 12.02	49.97 \pm 10.83	0.345
Cervical dystonia	124	40	84	1 : 2.1	40.38 \pm 12.96	40.23 \pm 13.49	40.45 \pm 12.78	0.928
Limb dystonia	11	6	5	1 : 0.83	44.00 \pm 20.28	30.67 \pm 11.99	60.00 \pm 16.17	0.007
Oromandibular dystonia	8	2	6	1 : 3	48.38 \pm 18.17	46.00 \pm 32.53	49.17 \pm 15.73	0.849
Laryngeal dystonia	5	2	3	1 : 1.5	57.80 \pm 11.54	49.00 \pm 15.56	63.67 \pm 4.04	0.192
Segmental dystonia	165 (31.55)	41	124	1 : 3	51.82 \pm 11.04	51.27 \pm 9.76	52.00 \pm 11.46	0.714
Multifocal dystonia	4 (0.76)	2	2	1 : 1	40.75 \pm 14.82	30.50 \pm 14.85	51.00 \pm 4.24	0.201

SD: standard deviation, M: male, F: female.

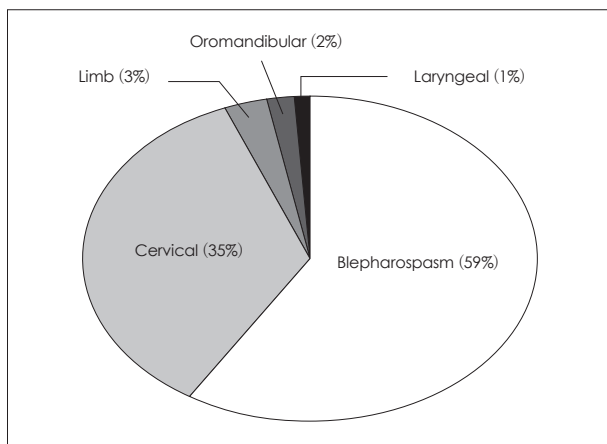


Figure 1. Three hundred fifty four patients with focal dystonia classified by distribution.

laryngeal dystonia tended to present in older patients ($p < 0.001$). A female predominance was noted for most of the primary dystonias with a male to female ratio (M : F) ranging from 1 : 1.48 to 1 : 3. For limb dystonia and multifocal dystonia there was a male predominance with the ratios of male to female of 1 : 0.83 and 1 : 1 respectively.

All prior diagnoses for every patient were recorded in this survey to assess the proportion of misdiagnoses. In patients seen early in the disease or in mild cases of dystonia the patients were seen by many subspecialists including the departments of neurology, ophthalmology, neurosurgery, psychiatry, orthopaedics, and physical medicine and rehabilitation. Of the patients with primary dystonia, 221 patients (42.26%) had diagnoses other than dystonia initially or were judged as no problem. Sixty two cases of blepharospasm (30%) were initially diagnosed as dry eyes, myasthenia gravis, hemifacial spasm, or psychogenic disease. Seventy two cases of cervical dystonia (58%) were diagnosed as cervical spondylosis, muscle disease or psychogenic disease at initial presentation.

Almost all the patients in this study received the botulinum toxin treatment. 80% of patients had the regular injection interview. About 50% of patients had the interview from third

month to sixth month, while 30% over six months. Before initiation of botulinum toxin treatment, 382 patients (65.52%) took oral medications, 67 patients (11.49%) received acupuncture therapy and 30 patients (5.14%) received physical therapy. Only 91 patients (15.61%) received botulinum toxin treatment as the primary treatment modality.

Discussion

In China only one epidemiological study of dystonia has been conducted. In 1985, Li et al.¹ reported two patients with cervical dystonia in a door to door survey of over 60000 patients. In the present study 523 cases of primary dystonia were found in a review of six centers and clinical characteristics were recorded. The most common dystonia was focal dystonia and among these blepharospasm was the most common type. This finding contrasts with studies reported from Europe where the most common type of dystonia was cervical dystonia.^{4,6,9} In two Asian countries, Japan^{7,12} shared a similar distribution to that found in China. Singapore (77% Chinese), however, shared the similarities with European countries where the most common focal dystonias were cervical dystonia (47%), writer's cramp (32%), and blepharospasm (11%).¹⁷ All of these studies are based on similarity of collecting method of service-based. In a Canadian survey,¹⁸ which was also a botulinum toxin clinic-based study in 14 movement disorders centers, the most common diagnose were cervical dystonia (51.6%) and blepharospasm (9.8%). The reason for these variations of patterns in different populations is difficult to explain, but may be due to either genetic or environmental factors.

In some recent studies in South-West China,¹⁹⁻²¹ which were not epidemiologic studies but genetic studies, the authors found the most common form of focal dystonia was cervical dystonia (range from 53.0% to 58.47%) followed by blepharospasm. These studies were in the same center, which is the biggest medical center in West China and also provide the botulinum toxin treatment. While cervical dystonia is more difficult to treatment with botulinum toxin than blepharo-

spasm, such patients tended to the well-known center. And these genetic studies required detailed clinical assessment including cranial computerized tomography, magnetic resonance imaging, electroencephalogram, electromyogram and many laboratory measurements. This can cause the difficulty to get the informed written consent in patients who only need rapidly symptomatic treatment. These may be the reason why the result is different with our study.

The mean age of onset of dystonia was earlier in men compared to women but this was not statistically significant. This finding is similar to studies from European and Japan,^{5,7,9} but opposite to the pattern observed in an Indian study.¹⁴ Of the focal subtypes the age of onset was youngest for limb dystonia which is an observation made in most studies.^{7,13,17} We also found that age of onset for laryngeal dystonia was in the oldest group. In prior studies blepharospasm has been reported as the most common dystonia in the oldest population.^{4,13,17} The difference in our study may be partly due to the limited number of cases of laryngeal dystonia found in our study.

There was a marked female predominance in all types of primary dystonia except limb dystonia which was consistent with most other studies made in western countries and Japan (M : F, 1 : 1-1 : 3.8).^{4,7,9,13,15,22} This is opposite to what had been reported in Singapore (M : F, 1.6 : 1)¹⁷ and Egypt (M : F, 3 : 1).²³ Limb dystonia has a male predominance in the majority of studies that have been reported.^{4,9,22,24,25} Some authors have raised the possibility of the sex difference due to the effects hormones.^{7,17,25,26} The role of estrogens in dopaminergic systems has been reported to be either a neuroprotective agent which acts as a neurotrophic factor to prevent or modulate insults to the dopaminergic system,^{7,26} or as an antagonist to suppress and block central dopaminergic activity.^{7,27} The geographic differences that have been noted in the dominant focal dystonia based on the sex of individuals are difficult to explain on the basis of hormones.

The present study covers a region of East China which is an important transportation and economic center. There are many medical facilities in this region receiving a large daily inflow of patients for outpatient medical visits from surrounding communities. Although most of the centers with movement disorder clinics that provide botulinum toxin treatment in East China participated in this study, the patients with dystonia we collected were only one part of latent patients. Among all centers the number of patients enrolled in this study varied depending on how established the movement disorders clinic was in the community. This did lead, perhaps, to a biased sample and therefore our service-based study could not calculate the prevalence of primary dystonia in East China. On the other hand the prevalence estimates have shown a very low rate from other Asian countries such as Japan compared with western countries. This may be explained by service-based studies, as opposed to population based studies,

failing to detect those patients not seeking medical care.

At present, the proportion of misdiagnoses of patients with primary dystonia remains high. Early in the disease or in mild cases of dystonia signs and symptoms may have been overlooked or not reported by patients to health care providers or misdiagnosis was the result of failure to recognize dystonia by providers. In our study, the proportion of misdiagnosis is 42.26%. Authors in a Northern England survey concluded that 20-30% of the dystonic population were undiagnosed¹⁰ and 65% of cases were misdiagnosed at some stage. Family and population studies in Italy^{5,28} indicated that a half to two-thirds of the affected individuals had no prior diagnosis of dystonia. These results are similar to our study. The high rate of misdiagnosis or nondiagnosis increases the difficulty of prevalence estimate.

In recent years, botulinum toxin therapy has not been used widely despite being the preferred treatment for primary dystonia. Not all physicians are familiar with botulinum toxin as an effective treatment for primary dystonia. Oral medicine is still the most common treatment early in patients but is met with limited effect. In our survey most patients had received the traditional treatment in community hospitals before botulinum toxin therapy was initiated. Therefore the epidemiological survey in botulinum toxin clinics does not include most patients early in the course of their disease.

When we collected the dystonia patients, we also collected 1045 patients diagnosed with hemifacial spasm. Although hemifacial spasm does not belong to dystonia, we found it is the most common disease in botulinum toxin clinics. It seems that the prevalence of hemifacial spasm is higher in Asian countries or lies on more choice of operation of microvascular decompression in Euro-American countries.^{29,30}

The major limitation of our study is the method of case enrollment because we relied on the clinical recognition and treatment of dystonia. Patients early in the disease or mild cases were likely not included in this study and in particular patients not referred to a movement disorder clinic for botulinum toxin injection would not have been enrolled. Another limitation is the length of the observation period (6 months). To our knowledge the effect of botulinum toxin lasts 3 to 6 months. In our study, only 50% patients had the injection interview from three to six months. We also missed some patients who had a longer or irregular injection interview. These clearly warrant further study with a community-based study in order to determine the prevalence of primary dystonia in China.

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