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ORIGINAL ARTICLE

Late-onset primary dystonia in Zhejiang province of China: a service-based epidemiological study

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Abstract Dystonia is characterized by sustained muscle contractions, causing repetitive movements and abnormal postures. The epidemiological study of dystonia of Chinese population was limited reported. In this study, we investigated the epidemiology of primary dystonia, and its clinical characteristics in an adult population in China. We identified all dystonia patients from the movement disorders database and botulinum toxin clinic between 2009 and 2013. The medical records were reviewed to verify the diagnosis of dystonia, and demographic and clinical data were collected. A total of 1481 patients with primary dystonia were studied. The most common focal dystonia were blepharospasm (56.4 %), cervical dystonia (36.7 %), limb dystonia (3.4 %), oromandibular dystonia (2.9 %) and laryngeal dystonia (0.6 %). Males with primary dystonia were found to have an earlier age of onset. A female predominance was noted for most of the primary dystonia, with a men to women ratio (M:F) of 1:2.01. The minimum estimate of prevalence of primary dystonia was 27.0 (95 % confidence interval: 25.6–28.3) per million persons in this study. Despite the difference in genetic background and geographic area, the epidemiological features of dystonia in China from our study share most features around the world, such as women dystonia dominance, early-onset age of dystonia with women, etc. But East Asia countries (China and Japan) may share more common features of dystonia.

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Introduction

Dystonia is a syndrome involving abnormal involuntary movements, which is characterized by sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures [1]. It often has an adverse effect on the quality of life, and induces disability [2]. However, it has been difficult to present precise information on the prevalence of dystonia, which would be useful for health service planning [2, 3]. The number of existing cases of primary dystonia in the population is not precisely known. A literature review on the epidemiology of dystonia revealed that the prevalence estimates for primary dystonia range from 2 to 50 per million for early-onset dystonia and from 30 to 7320 per million for late-onset dystonia [4]. In addition, there have been very few studies on the prevalence and clinical features of dystonia in Asia. The prevalence of this disorder varies widely. It was reported that the prevalence was from 61 to 151 per million in Japan [5–8], 136 per million in Thailand [9] and 439 per million in India [10]. In China, to the best of our knowledge, there has been only one door to door survey conducted in 1985, which showed a prevalence of 30 per million. Only two cases were found in a population of 63,195 [11].

Previous studies demonstrated that the most common type of dystonia was focal dystonia. And amongst the focal dystonias, cervical dystonia was the most occured throughout the world [12–17]. A botulinum toxin clinic-based epidemiological survey in China [18], which was conducted with 523 dystonia patients from six movement

disorder clinics, revealed that the most common focal dystonia in China was blepharospasm (59 %), which is different from the reports in western countries; but was similar to that reported in Japan [5–7]. However, this survey study in China covered patients who visited the clinics within only 5 months. Yet it is well known that the effect of botulinum toxin lasts from 3 to 6 months. Thus, some patients who had longer or irregular injection patterns might have been missed. In order to get more precise estimate, in this study, we have tried to evaluate the epidemiology and clinical variants of primary dystonia in an adult population visiting the outpatient clinics for movement disorders at Sir Run Run Shaw Hospital (SRRSH) of Zhejiang University in Zhejiang, China, over a five-year period.

Methods

Patients who participated in this study were all from Zhejiang Province of East China. The population of this area was 54,938,000 (2013 census). Sir Run Run Shaw Hospital is located in Hangzhou, the capital city of Zhejiang province, which is one of the affiliated hospitals of Zhejiang University, and has the most famous and largest clinical center for dystonia in Zhejiang. Although not all the neurological centers were involved in this study, the majority of the dystonia patients, especially those who received botulinum toxin injection treatment in Zhejiang, visited this hospital.

All patients that we choose for this study were late-onset (>26 years), and were assessed and treated for dystonia between January 2009 and December 2013 at the movement disorder and botulinum toxin clinic of SRRSH. This movement disorder and botulinum toxin clinic was initiated in 1994, and in 2009 the dystonia database was established. The patients for this study were identified from this database. Additionally, the botulinum toxin clinic records were reviewed to obtain demographic and clinical characteristics of each patient.

Patient information that was collected included the type of dystonia, date of birth, location of residence, gender, age at onset, prior diagnoses, etiology, botulinum toxin treatment interval, as well as past medical and family history. The anatomical classification of dystonia was performed by the study coordinator (Xingyue Hu) (Table 1) [19]. For patients with dystonia that spread to multiple body parts during the 5 years, the final anatomical diagnosis was recorded.

In term of etiology, dystonia can be classified into primary and secondary dystonia. Primary dystonia is the cases in which the only sign or symptoms is dystonia. The medical team cannot identify any disease or neurological damage that may have caused the dystonia. And secondary dystonia is the cases when dystonia signs and symptoms occur as a consequence of an underlying condition—usually genetic, neurological or an injury which affects the nervous system. Secondary dystonia includes tardive dystonia and levodopa-induced dystonia. Patients of secondary dystonia were excluded from this study. Patients, who were not local residents, were also excluded. The protocol was approved by the Ethics Committee. All patients gave informed written consent.

Table 1 Definition of dystonia types

Focal dystonia	Only one part of the body is affected
Segmental dystonia	Two or more regions of the body are affected. The regions are somehow connected to each other, for example, the neck and shoulder
Multifocal dystonia	At least two regions of the body that are not connected to each other are affected. Such as an arm on one side as well as one leg on the other side of the body
Hemidystonia	Half of the entire body is affected
Generalized dystonia	Leg + trunk + one other body part are affected

Statistical methods

Continuous variables were defined as mean ± standard deviation, 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 to compare the age of onset and diagnosis time between patients with different subtypes. All *p* values are two-tailed, and significance level was set at 0.05. All statistical analyses were performed using the SPSS software (version 11.5; SPSS Inc., USA).

Results

Total 1481 patients were identified with primary late-onset dystonia. All patients were ethnic Chinese, and lived in the Zhejiang province. Among these patients, 486 of them were men and 995 of them were women, with a mean age of 53.82 years (range from 26 to 87 years) (Fig. 1a). Focal dystonia accounted for 1134 cases of all cases. The remaining cases included 301 patients of segmental dystonia, 24 patients of multifocal dystonia and 22 patients of generalized dystonia (Fig. 1b). Among the 1134 patients with focal dystonia, the most common diagnoses in descending order were 640 cases of blepharospasm, 416 cases of cervical dystonia, 38 cases of limb dystonia, 33

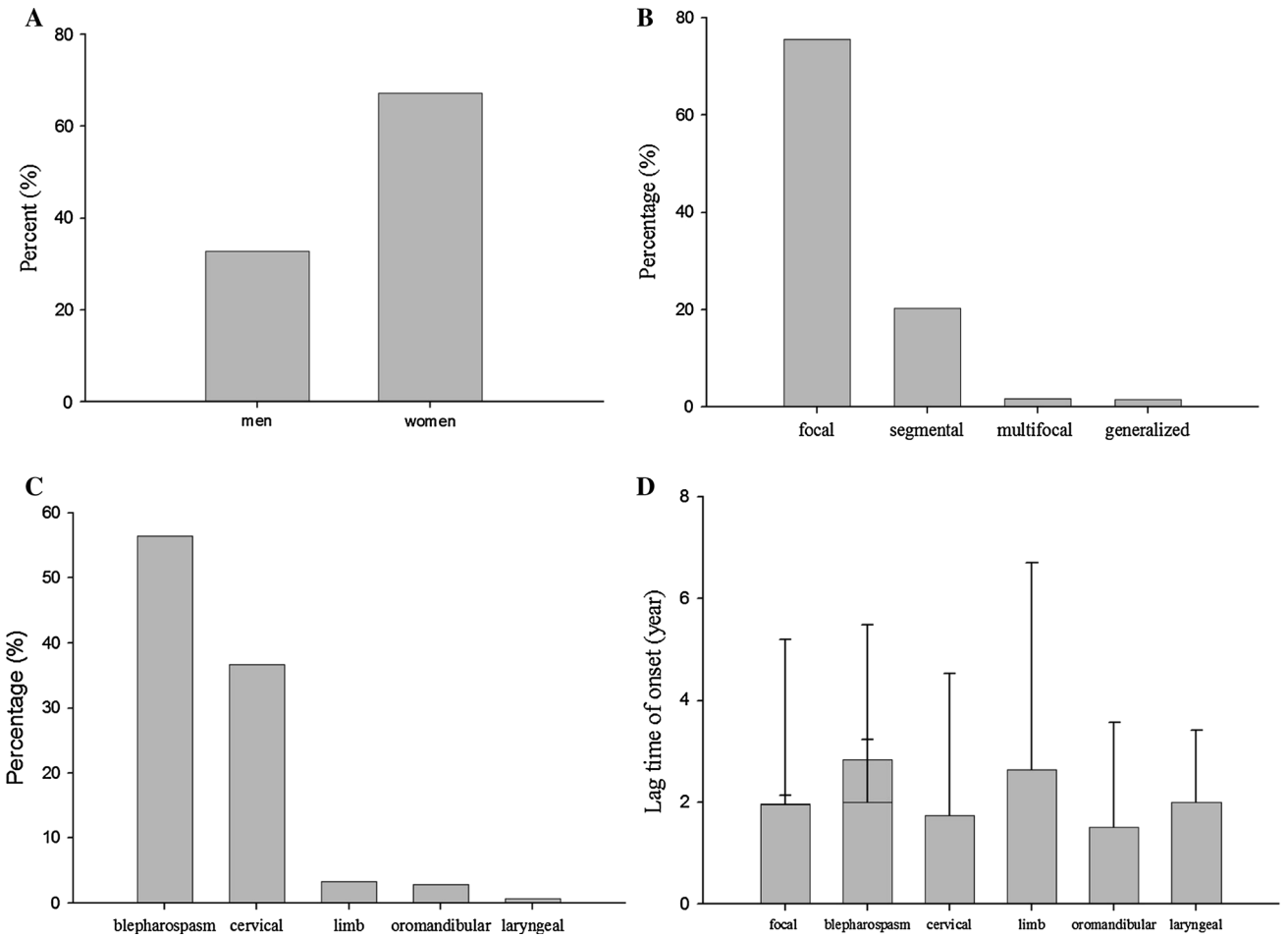

Fig. 1 The epidemiological features of primary dystonia patient in this study. **a** Dystonia in different gender; **b** The distribution of classified late-onset dystonia enrolled in this study; **c** The distribution of different focal dystonia in this study; **d** The time lag of diagnosis in different subtypes of focal dystonia

cases of oromandibular dystonia and seven cases of laryngeal dystonia (Fig. 1c). Among the 38 cases with limb dystonia, 31 cases were upper limb dystonia and 7 of them were lower limb dystonia. Twenty three cases out of 31 cases were task specific upper limb dystonia, which took up about 2.03 % of all focal dystonia.

The age and gender-specific rates for different subtypes of dystonia are shown in Table 2. Of the 1481 patients with primary dystonia, 486 were males and 995 were females, with a gender ratio of 1:2.04 (Table 2). A female predominance was noted for majority of the primary dystonia subtypes with a male to female ratio (M:F) ranging from 1:1.75 to 1:2.67. Only for limb dystonia, there was a male predominance with a male to female ratio of 1:0.73.

The mean onset age of dystonia was 48.54 years (SD = 13.08 years). Overall, males with primary dystonia were found to have an earlier age of onset in all types of dystonia, except for cervical dystonia. However, the onset age between males and females in all subgroups was not statistically different, except in the limb dystonia group ($p = 0.016$). Of the focal dystonia subtypes, the age of onset was earliest in patients with limb dystonia, whereas blepharospasm was usually present in older patients ($p < 0.001$).

The time lag from the onset of symptoms to being diagnosed in different dystonias is summarized in Fig. 1d. About half of patients (45.1 %) were initially misdiagnosed or misjudged to have no health problems. Most of the patients (95.4 %) in this study received the botulinum toxin injection treatment. Majority of the patients (85 %) received botulinum toxin injection at least two times.

Discussion

It has been reported that the prevalence of late-onset dystonia varies widely [20]. This wide range in prevalence estimates can be explained by the ways of selecting patients, such as age or genetic background of different populations, the specific clinical phenotypes and the methods of case

Table 2 Age and gender-specific rates for different subtypes of dystonia

Types of dystonia	Number of cases			M:F ratio	Mean age of onset (years ± SD)			*p* value
	Total (%)	Male	Female	M:F	Total	Male	Female	
All types	1481	486	995	1:2.04	48.54 ± 13.08	47.28 ± 14.04	49.16 ± 12.55	0.012
Focal dystonia	1134 (76.57 %)	382	752	1:1.97	49.98 ± 13.85	46.82 ± 13.92	48.28 ± 12.65	0.077
Blepharospasm	640 (56.44 %)	203	437	1:2.15	52.25 ± 10.91	51.71 ± 11.36	52.50 ± 10.71	0.394
Cervical dystonia	416 (36.68 %)	146	270	1:1.85	41.64 ± 12.62	42.23 ± 13.87	41.33 ± 11.90	0.051
Limb dystonia	38 (3.35 %)	22	16	1:0.73	38.42 ± 17.22	32.78 ± 15.34	46.19 ± 17.05	0.016
Oromandibular dystonia	33 (2.91 %)	9	24	1:2.67	48.69 ± 15.99	44.89 ± 17.24	50.12 ± 15.64	0.441
Laryngeal dystonia	7 (0.62 %)	2	5	1:2.50	51.14 ± 15.10	49.00 ± 15.56	52.00 ± 16.69	0.842
Segmental dystonia	301 (20.32)	85	216	1:2.54	52.46 ± 11.51	51.39 ± 12.43	52.89 ± 11.12	0.308
Multifocal dystonia	24 (1.62)	11	13	1:1.89	46.75 ± 13.43	45.36 ± 17.64	47.92 ± 9.14	0.652
Generalized dystonia	22 (1.49)	8	14	1:1.75	35.95 ± 10.78	31.50 ± 8.44	38.5 ± 11.14	0.157

ascertainment. So far, most reported data are derived from Caucasian populations [12, 14–17, 20]. In Oriental populations very limited reports were found [5, 11, 13, 18]. In 2012, a survey study was conducted in East China, which covered 523 primary dystonia patients, who visited clinics from six provinces within 6 months. In this study, we limited our study area to only one province in East China; however we increased the number of primary dystonia patients by covering clinic visit over a 5 year period.

In comparison to this survey study, our study demonstrated the similar findings that the most common form of dystonia was focal dystonia, and amongst the focal dystonias, blepharospasm was the mostly observed subtype. This finding is in contrast with the studies reported from Europe, where the most common type of dystonia was cervical dystonia [12, 14, 20]. Among other Asian countries, Japan [6] shared a similar distribution to what we found in China, where blepharospasm was the most common (41 %) followed by cervical (29 %) and hand dystonia (19 %). Singapore (with 77 % Chinese population), however, shared similarities with the European countries where the most common focal dystonias were cervical dystonia (47 %), writer's cramp (32 %), and blepharospasm (11 %) [13]. In Thailand, cervical dystonia was the most common (47.8 %) [9]. All these studies are based on service-based collection method. Many reasons may contribute to these variations in patterns, such as genetic background, environmental factors, etc. Yet, clear answer may need further studies.

In the current study, we did not find obvious difference between blepharospasm and cervical dystonia in terms of time lag from onset of symptoms to being diagnosed (Fig. 1d). A long-term assessment of spread risk in primary late-onset focal dystonia indicated that patients whose dystonia started with blepharospasm had a higher spread risk than those patients whose disease occurred originally from cervical dystonia or focal hand dystonia. And this spread usually happened within the first 5 years from onset [21]. Another study [22] in USA also showed that patients with adult-onset focal dystonia (31 %) were at greater risk of spread than those with dystonia starting in the neck (9 %), larynx (12 %), or upper extremities (16 %). Similar results were not observed from our current study. Whether most patients of blepharospasm in China tend to remain focal is still an open question.

Our study demonstrated that there was a marked female predominance in all types of primary dystonias (M:F, 1:1.75–1:2.67), except for limb dystonia (M:F, 1:0.73). This is consistent with the most studies in western countries and Japan (M:F, 1:1–1:3.8) [6, 12, 16, 20, 23]. But it is in contrast to the reports from Singapore (M:F, 1.6:1) [13] and Egypt (M:F, 3:1) [24]. Limb dystonia has a male predominance in majority of the studies [12, 23, 25, 26]. It was suggested that the gender difference may result from the effects of hormone [6, 13, 26, 27]. For example, estrogen was reported to act as either a neurotrophic factor to prevent or modulate insults to the dopaminergic system [6, 26] or an antagonist to suppress and block central dopaminergic activity [6, 28]. However, the differences in focal dystonia dominance with different gender in different geographic area could not be explained by effects of hormone.

In terms of mean onset age of dystonia, we found that men start dystonia earlier in comparison to women. This onset age difference between men and women is statistically significant (Table 2). However, the previous report from the study in East China did not show statistically significant difference with onset age of dystonia between men and women. The reason may result from the fact that our study covers more patients in a long duration. Our result is actually similar to most studies from Europe and Japan [6]. By far only one study conducted in an Indian

city reported a complete different result: the onset age of dystonia in males is much earlier than females. But this is not service-based study; it is a house-to-house survey [10]. Among the focal dystonia subtypes, the age of onset was found to be youngest for limb dystonia and oldest for blepharospasm in most studies [6, 12, 13, 16].

The key for a successful clinical diagnosis of dystonia depends on the abnormal postures (with or without tremor) and the presence of specific features. The absence of specific diagnostic tests in dystonia patients implies that it is highly recommended to have a special expert to perform the clinical examination for dystonia diagnosis [4]. At present, the proportion of misdiagnosed patients with primary dystonia remains high. In our study, the proportion of misdiagnosis is about 45.1 %. The time lag between the onsets of symptoms to being diagnosed is 1.95 ± 3.24 years. In the early phase of the disease or in mild cases of dystonia, symptoms could be overlooked or misdiagnosed due to the failure of dystonia identification by healthcare providers.

A previous survey [18] in East China showed that 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. In our study, we did not collect any prior treatment data. However, due to the study was performed in the similar situation; we assume the patients enrolled in our study had similar treatment history. On the other hand, not all physicians are familiar with the botulinum toxin as an effective treatment for dystonia. Oral medicine is still the most common initial treatment. Therefore, epidemiological survey in botulinum toxin clinics does not include most patients in the early phase of the disease.

Similarly, most previous studies were based on treatment settings or record linkage systems. These service-based studies also did not take into account the subjects who did not seek medical advice or who were misdiagnosed. The number of patients seeking treatment is almost certainly lower than the prevalence of primary dystonia in the general population. Additionally, patients who had previously been diagnosed with dystonia, but have stopped treatment or were last examined before the study period, may be missing in service-based estimates.

Taken together, these findings suggest that the accurate prevalence of dystonia is very hard to be determined by a service-based study. Based on the minimum estimates, the prevalence of primary dystonia in this study was 27.0 (95 % confidence interval: 25.6–28.3) per million persons. This estimate is certainly lower than the actual prevalence.

The most significant limitation of this study is that its clinic-based design reflects the selection bias of the patients. Therefore, a community-based study is needed in the future in order to determine the precise prevalence of primary dystonia in China. Despite this limitation, our current study covered the dystonia cases in a movement disorders clinic over a period of 5 years, and described the spectrum of dystonia in China. As expected, blepharospasm was found to be the most common subtype of focal dystonia in China. The proportion of misdiagnosis remains high, and the delay in diagnosis needs to be urgently reduced. The data in this study may help us to initiate a process of increasing the awareness of dystonia among both patients and healthcare providers.

Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

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