

The Epidemiological Study
of Dystonia in Europe (ESDE)
Collaborative Group

A prevalence study of primary dystonia in eight European countries

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Abstract There have been few epidemiological studies of dystonia. Most previous studies have provided estimates based on few cases. A European prevalence study was undertaken to provide more precise rates of dystonia by pooling data from eight European countries. Diagnosed cases were ascertained by adult neurologists with specialist movement disorder (and botulinum toxin) clinics. The crude annual period prevalence rate (1996–1997) for primary dystonia was 152 per million (95 % confidence interval 142–162), with focal dystonia having the highest rate of 117 per million (108–126). Prevalence rates for cervical dystonia, blepharospasm and writer's cramp were as follows: 57 (95 % confidence interval 51–63), 36 (31–41), and 14

(11–17). The age-adjusted relative rates were significantly higher in women than in men for segmental and focal dystonias with the exception of writer's cramp. Comparing rates between centres demonstrated significant variations for cervical dystonia, blepharospasm and writer's cramp, probably due to methodological differences. Our results provide the first data on the prevalence of primary dystonia and its subtypes across several European countries. Due to under-ascertainment of cases, our rates should be seen as conservative and an under-estimate of the true prevalence of dystonia.

Key words Dystonia · Prevalence · Epidemiology

Introduction

There have been few published epidemiological studies of dystonia, unlike with other neurological diseases, although the condition has been recognised for almost 100 years [20]. There are several possible reasons for this. Firstly, the disease is thought to be relatively rare, especially for specific sub-types of dystonia, and this has important methodological implications. However, dystonias as a group are still more common than muscular dystrophy, Huntington's disease and motor neurone disease [17]. Secondly, the disease is perceived to have relatively low morbidity compared to other neurological conditions and is generally non-fatal. This prevents the use of routine mortality and hospital admission data as either proxy measures of preva-

lence or for case ascertainment. The condition nevertheless clearly has an important impact on the quality of life of sufferers and can be markedly disabling [12]. Thirdly, family studies have highlighted the problem of under-diagnosis. One study of focal dystonia identified an additional undiagnosed affected relative for 25 % of index cases [27]. For an index case of generalised dystonia this figure is higher [9]. Finally, the diagnosis is solely clinical and only some patients receive a specific treatment. This prevents case identification through computerised records of investigations or medications, as has been done for conditions such as multiple sclerosis or Parkinson's disease.

We have been able to identify only 13 prevalence studies in world literature, three of which exist in abstract form alone (see Table 1). In six studies there are no data for focal dystonias, and only four studies report data on the sub-

Table 1 Prevalence rates per million from previous studies of dystonia: number of cases, prevalence rate (95 % confidence intervals taken from the original report or calculated based on available data)

Focal Population	Type of dystonia											
	General		All focal types		Blepharospasm		Cervical		Writer's cramp		Laryngeal	
	<i>n</i>	Prevalence	<i>n</i>	Prevalence	<i>n</i>	Prevalence	<i>n</i>	Prevalence	<i>n</i>	Prevalence	<i>n</i>	Prevalence
USA, 1970 [6]	578	2.9 (2.7–3.1)										
Tel Aviv, Israel 1980 [14]	35	10 (7–13)										
Panay, Phillipines 1976 [15]	23	12 (7–17)										
Israel, 1984 [28]	11	24 (12–43)										
China, 1985 [16]	3	50 (10–150)					2	30 (4–110)				
Spain, 1988 [11]	1	5 (0.1–28)										
Rochester, USA 1988 [19]	2	34 (4.1–124)	17	295 (172–479)	1	17 (1–96)	5	89 (29–207)	4	69 (19–176)	3	52 (11–151)
Assiut, Egypt 1994 [13]			4	100 (26–243)								
Segovia, Spain 1994 [23]			41	279 (193–364)	24	163 ^a (104–243)	5	34 (11–79)	9	61 (28–116)	3	20 (4.2–60)
Yonago, Japan 1995 [18]			15	61	4	16 ^a (1–32)	7	29 (8–49)	4	16 (1–32)		
SW Finland, 1996 [7]							92	209 (168–256)				
Podolian region, Ukraine 1997 [2]				42								
Northern England, 1998 [5]	37	14 (10–19)	294	113 (100–127)	78	30 (24–37)	159	61 (52–71)	19	7 (4–11)	22	8 (5–13)
ESDE			677	117 (108–126)	208	36 (31–41)	330	57 (51–63.5)	81	14 (11–17)	39	7 (5–9)

^a Rate includes both oromandibular and blepharospasm combined

types of focal dystonia. In almost every study except those of Eldridge and Gottlieb [6] and Duffey et al. [5] prevalence rates are based on relatively few cases, and hence estimates have wide confidence intervals. Only one study reports age- and sex-specific rates [18]. No sex difference for the prevalence of focal dystonias was found in Japan [18], in contrast to the results from the north of England which found that rates in women were twice as high those in men [5]. This female predominance has been noted in case series for all sub-types of focal dystonia except writer's cramp [3, 4, 10, 19, 22, 26]. A Finnish survey of cervical dystonia also found women had 60% greater relative rate [7]. The Japanese study noted that rates initially increased with age, peaking in the fifth decade with a subsequent decline [18].

Ideally one would wish to carry out door-to-door surveys, as has been successfully employed for Parkinson's disease [21], identifying all dystonia cases regardless of prior diagnosis and clinical severity. Only two previous studies [13, 16] have used such an approach, but despite screening between 63,000 and 84,000 individuals these only identified five and four cases, respectively. Whilst this provides the most accurate data, it is limited by cost, practical considerations and statistical precision. Furthermore, these data cannot examine age- and sex-specific effects.

Given the paucity of prevalence data on dystonia, we set up the Epidemiological Study of Dystonia in Europe (ESDE) to provide more precise age and sex specific rates of clinically diagnosed dystonia and its sub-types across European centres.

Methods

Study design

We undertook a cross-sectional study in several European countries to determine the period prevalence of dystonia. In some cases more than one centre was recruited in each country. Cases were ascertained in a defined population through dystonia specialists, who provided regular botulinum toxin treatment (see "Appendix A"). Patients not seeking medical advice or incorrectly diagnosed would clearly not be ascertained by this method. Cases of correctly diagnosed dystonia, particularly those requiring botulinum toxin treatment (e.g. cervical, blepharospasm, writer's cramp) are most likely to be ascertained as each centre was well known in its locality for having a special interest in this disorder.

The appropriate population at risk was defined at the outset of the study for each centre. This usually comprised the resident population for a district or supradistrict area. Investigators were then asked to highlight within this defined area any other units to which patients with dystonia may be referred. This approach resulted in three distinct patterns: type a centres, where all patients would be referred to them (Innsbruck, Turku, Bordeaux, Segovia, Oxford); type b centres, where patients might have been referred to another unit, but where collaboration between units meant that all these patients could be identified (Rome, Munich, Berlin); and type c centres, with more than one specialist unit but without collaboration between units (Barcelona, Lisbon). In the latter group we restricted our population denominator to only populations living in administrative areas very close to the specialist centre. It is known that marked "proximity effects" exist for accessing specialist services, and therefore that patients living close to a unit are more likely to obtain such a service [1, 24]. To examine whether differences in rates between centres could be artefactual due to differential ascertainment, we examined rates by the above classification.

Case ascertainment

All centres were asked to identify potential cases through the following methods where applicable: dystonia database, prospectively from neurology clinics, botulinum clinics and/or pharmacy records, retrospective review of hospital computerised data, contact with other neurologists and clinicians. The centres participating in ESDE were adult neurology units, and therefore only data on cases over the age of 20 years (irrespective of age at onset) were included. For each potential case of dystonia, the investigators had to verify that they were alive and residing in the respective catchment area between July 1996 and June 1997 so that the annual period prevalence could be calculated. An anonymous data collection sheet was completed and sent to the coordinating centre in London. Information was collected on the type of dystonia, age and sex of the patients. Data on age at onset and the presence of a family history were also collected. All data sheets were entered on the central database, and the anatomical classification of dystonia was performed by the study coordinator and independently verified according to previously defined criteria [8].

Case definition and classification

Standardised definitions of dystonia were used in the study and agreed by all participants [8]. Dystonia was divided into primary, dopa responsive, paroxysmal kinesigenic, paroxysmal choreoathetotic and myoclonic. We excluded cases of secondary and psychogenic dystonia after appropriate investigation [8].

Primary dystonia was sub-divided into various categories based on the anatomical distribution [8]. Focal dystonia was defined as involving only a single body part, for example, blepharospasm, torticollis, writer's cramp. Segmental dystonia had to involve two or more contiguous body parts and multifocal dystonia two or more non-contiguous parts. Generalised dystonia involved a combination of segmental crural (dystonia of one leg and trunk or both legs +/- trunk) and any other segment. Hemidystonia was defined as involvement of ipsilateral arm and leg. It is likely that some cases in older studies would have been classified as focal whilst in this study we would have classified them as segmental. We therefore also calculated a combined rate for these two sub-types for comparison.

Statistical methods

We calculated age- and sex-specific rates using data from our cases and population data from the nearest respective census for each country. As we did not include paediatric cases, we excluded all cases and respective denominator data under the age of 20 years. Confidence intervals were calculated using the Poisson distribution. To calculate relative rates and 95% confidence intervals (CI) by sex we adjusted for age using the Mantel-Haenszel method including a χ^2 test for heterogeneity to test whether relative rates differed by age strata. All *P* values are two-tailed, and significance was set at the 5% level. We also used directly standardised and relative rates, using the standard European population [25], for comparing our data with that from Yonago [18].

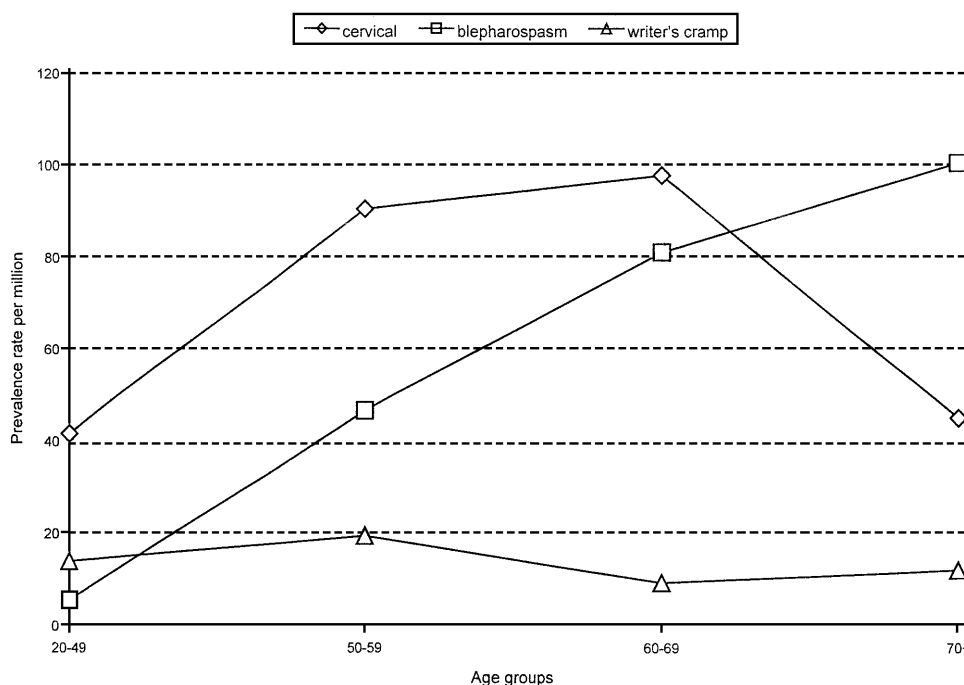
Results

The study identified a total of 879 patients with primary dystonia from 10 centres and 8 countries covering a total population of 5,792,937 individuals giving a crude rate of 152 per million (CI 142–162). Sixteen cases of dopa responsive, paroxysmal kinesigenic, paroxysmal choreoathetotic and myoclonic types were identified and were not analysed due to small numbers. The results for generalised dystonia are not presented as we only identified adult cases, and hence they are not comparable with previous studies. The rates for the main types of dystonia were as follows; focal (*n*=677) 117 (CI 108–126), segmental (*n*=183 cases) 32 per million (CI 27–36) and multi-focal (*n*=14 cases) 2.4

Table 2 Age- and sex-specific rates per million for segmental and all focal dystonias (no. of cases)

Age groups (years)	Population		Segmental		Focal		Cervical		Blepharospasm		Writer's cramp	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
20–49	1,579,722	1,707,298	(13) 8.2	(16) 9.4	(97) 61.4	(112) 65.6	(63) 39.9	(73) 42.8	(7) 4.4	(10) 5.9	(20) 12.7	(25) 14.6
50–59	412,816	471,469	(21) 50.9	(16) 33.9	(62) 150.2	(96) 203.6	(32) 77.5	(48) 101.8	(13) 31.5	(28) 59.4	(12) 29.1	(5) 10.6
60–69	362,972	413,967	(17) 46.8	(42) 101.5	(64) 176.3	(96) 231.9	(33) 90.9	(43) 103.9	(21) 57.9	(42) 101.5	(5) 13.8	(2) 4.8
70–95	353,108	491,585	(13) 36.8	(45) 91.5	(43) 121.8	(107) 217.7	(9) 25.5	(29) 59.0	(22) 62.3	(63) 128.2	(8) 22.7	(2) 4.1

Fig. 1 Age-specific rates for cervical dystonia, blepharospasm and writer's cramp



per million (CI 1.3–4.1). Recalculating the focal prevalence rate including data on segmental dystonia, to enable more direct comparison with other studies, yields a rate of 148 per million (CI 139–159).

The overall prevalence rates per million for the more common types of dystonia were: cervical dystonia 57 (CI 51–63), blepharospasm 36 (CI 31–41), and writer's cramp 14 (CI 11–17). The prevalence rates for the rarer sub-types of focal dystonia were as follows: oromandibular 0.9 per million (CI 0.3–2.0), laryngeal 6.7 per million (CI 4.8–9.2), limb dystonia 2.1 per million (CI 1.1–3.6). The number of identified cases limited further analysis to all focal dystonias and the three most common sub-types.

The age and sex-specific rates for segmental and focal dystonias are shown in Table 2. The age-adjusted relative rates were significantly higher in women than in men: segmental 1.6 (CI 1.2–2.1), focal 1.3 (CI 1.1–1.6). The figure for segmental dystonias must be interpreted with caution as the elevated relative rates for women were only seen for the older age groups (test for heterogeneity on 3 degrees of freedom $\chi^2=10.7$, $P=0.01$). The rates for both segmental and focal dystonia increased with age but declined in the oldest age group. From Table 2 it is clear that women also had significantly higher relative rates than men for both cervical dystonia and blepharospasm: cervical 1.3 (CI 1.0–1.6), blepharospasm 1.9 (CI 1.4–2.5). For writer's cramp the pattern was reversed, with women having lower relative rates: 0.7 (CI 0.4–1.0). Again, there was significant heterogeneity with age as the relative difference between women and men increased with age (test for heterogeneity on 3 degrees of freedom $\chi^2=7.9$, $P=0.05$). A comparison of

the age-specific rates for cervical dystonia, blepharospasm and writer's cramp (Fig. 1) reveals different patterns. The rate for cervical dystonia shows an increase with age but tails off for the oldest age group. Blepharospasm shows a fairly consistent increase with age, whilst the rates for writer's cramp show, if anything, a mild decline with age. Only one study (Yonago, Japan) has previously reported age-specific rates for all focal dystonias [18]. The age-adjusted relative rates for ESDE compared to those of Yonago was 1.4 (CI 0.8–2.7).

We examined whether there were differences in the rates of cervical dystonia by centre. This is the most com-

Table 3 Prevalence rates per million for cervical dystonia by type of centre

Centres	n	Rate (95 % CI)
Type a centres		
Bordeaux, France	38	33 (22–43)
Innsbruck, Austria	25	41 (25–58)
Oxford, England	34	59 (39–78)
Segovia, Spain	6	41 (8–74)
Turku, Finland	100	233 (187–278)
Type b centres		
Berlin, Germany	53	47 (35–60)
Munich, Germany	59	46 (35–58)
Type c centres		
Barcelona, Spain	4	15 (4–30)
Lisbon, Portugal	7	9 (2–15)
Rome, Italy	8	8 (2–13)

mon type of dystonia and is usually managed solely by neurologists and therefore is less likely to be under-ascertained by our methods. Table 3 presents the rates by centres stratified by type of centre. Our results show fairly similar prevalence rates across different countries, with the lowest rates for type c centres, as one might have expected. The rates for Turku were an outlier and much higher than all other centres. This is artefactual and almost certainly the result of a previous prevalence study of cervical dystonia [7] which included ascertaining cases through the media and other sources.

Discussion

The prevalence estimates presented here are the most precise currently available and enable us to examine age- and sex-specific rates for several focal sub-types. However, they are clearly not the most accurate as the methods of case ascertainment will have missed undiagnosed cases and also those cases that were either misdiagnosed or not referred to the relevant specialist. For example, the survey carried out in the north of England [5] identified 3 previously undiagnosed cases out of a total of 19 patients (16%).

Despite these limitations our results are similar to and consistent with those of other studies, which have used more exhaustive methods of case ascertainment (see Table 1). For example, our rates for both multifocal and segmental dystonia are, if anything, greater than those that can be calculated from the northern England study (multifocal 0.8 per million, segmental 15.0 per million) [5].

Our results for all types of focal dystonia are similar to those reported from Egypt [13], Japan [18] and northern England [5] but less than those for Rochester [19] and Segovia [23], even after combining segmental cases with focal cases. It is unclear whether these differences merely reflect more thorough case ascertainment for the latter two studies or true differences in prevalence. When comparing specific sub-types of focal dystonia, our figures are, again, remarkably similar to those from the North of England, and close to those from Rochester and Segovia. For example, whilst the rate for cervical dystonia for Rochester is higher than the ESDE rate, the overlap of confidence intervals indicates this may merely reflect chance.

The ESDE results confirm other reports showing greater rates of most dystonias in women, except writer's cramp, which showed the opposite pattern. However, there was an interaction with age for both segmental dystonia and writer's cramp, and it is therefore more appropriate to present age-specific relative rates. The aetiological significance of these differences remains unclear but may reflect a true biological phenomenon, possibly implicating the role of sex hormones or sex-related genetic factors. Interestingly, the age-specific rates showed different patterns for specific sub-types. Cervical dystonia showed an in-

verted U shape, with lower rates amongst the young and old. It is possible that older patients were less likely to be detected by our methods, yet rates for blepharospasm showed a consistent increase across all age groups. It is hard to imagine why some but not all types of dystonia were selectively under-ascertained. One possible explanation is that the decline in rates of cervical dystonia in older age groups may reflect a higher remission rate for this particular subtype in the elderly. Writer's cramp showed fairly stable rates, with a slight decline. This difference compared to the other two types suggests that genetic and/or environmental factors differ in the way in which they determine phenotypic expression of this condition.

We found relatively similar rates for cervical dystonia across Europe except for Turku, Finland, which had much higher rates. This centre had previously undertaken a study solely focussed on cervical dystonia [7] and had attempted to identify all cases, including those not under the care of a specialist, by using media advertising and other methods. We believe this marked increase does not reflect higher risk of dystonia in Finland, as the rates for other types of focal dystonia were not elevated. Our data support a north-south gradient for cervical dystonia, with lower rates in southern Europe. However, we again believe that this is artefactual, as most centres with lower latitude were of type c and therefore were more likely to have under ascertained cases.

These results highlight the need for further studies that can identify all cases, regardless of prior diagnosis. Further exploration of a north-south gradient is warranted to determine whether our observations are truly artefactual. However, to have sufficient power to test for differences in prevalence rates, it will be necessary to survey an extremely large population (around 100,000). Improvements in computerisation of primary care consultations may enable future research to undertake relatively cheap case ascertainment over large populations, with clinical validation. This relies on correct diagnosis and classification, which still remain a problem. The dystonias, as with other rare neurological diseases, present a serious challenge when attempting to determine precise and accurate prevalence rates for both aetiological and health service planning needs.

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The participants in the Epidemiological Study of Dystonia in Europe are as follows (asterisks indicate members of the ESDE Steering Committee):

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- Turku, Finland: Dr. R. J. Marttila*, Dr. H. Erjanti
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- Study Coordinator: Dr. T. Warner
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- ESDE Management Committee: Dr. T. Warner, Dr. Y. Ben-Shlomo, Mr. A. Newton, Ms. L. Camfield

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