

Sex-related influences on the frequency and age of onset of primary dystonia

Article abstract—We studied 957 cases of primary (idiopathic) dystonia and found a significant excess of female patients for segmental and focal dystonia. A novel observation was a significantly earlier age at onset in males as opposed to females for primary segmental (mean age, 44.6 versus 53.3) and focal dystonia (43.8 versus 47.8). This trend was also apparent in cervical dystonia, blepharospasm, and laryngeal dystonia. For writer's cramp and focal limb dystonia, this trend was reversed with an earlier age at onset in females. These results suggest that focal dystonia should not be treated as an homogenous group, and sex-linked factors may play a role. **Key words:** Dystonia—Sex ratio—Age at onset.

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Epidemiologic Study of Dystonia in Europe (ESDE) Collaborative Group*

Dystonia is defined as a syndrome of sustained involuntary muscle contractions, frequently causing twisting or repetitive movements or abnormal postures.¹ Primary or idiopathic dystonia is most frequently encountered and has the phenotype of dystonia alone, although tremor can also be seen. The spectrum of primary dystonia is wide, but the most common subtype is focal dystonia. Previous case studies of focal dystonia have shown a female predominance for cervical dystonia, blepharospasm, and laryngeal dystonia,^{2–5} but this appears to be reversed in writer's cramp.⁶ This article describes the sex ratios and association between sex and age at onset for the various dystonia subtypes in the largest reported series of primary dystonia.

Methods. The Epidemiologic Study of Dystonia in Europe (ESDE) was established to provide point prevalence for dystonia around 13 European neurologic centers in 11 cities (see Appendix). Each center had a specialist movement disorders clinic and also offered botulinum toxin injections. Data were collected on all patients with dystonia resident in a predefined catchment area who were alive during the prevalence period of July 1996 to July 1997. Information was collected on age and sex of patients, type of dystonia, and age at onset. Dystonia was subdivided into various categories based on standardized anatomic classification.¹ Comparisons of normally distributed continuous variables were performed using Student's *t*-test. For some variables, which were extremely skewed, the nonparametric Mann–Whitney *U* test was used for hypothesis testing. Tests of sex ratios were performed using the one-sample binomial test. Significance testing for differences between proportions was calculated using the chi-square test. All *p* values are two-sided and at the 5% level.

Results. We identified 957 prevalent cases, which makes this the largest series of clinically diagnosed patients with primary dystonia (table 1). A female predominance was noted for all anatomic categories of primary dystonia. Most cases were either segmental or focal, and in these groups, the excess of female patients was most significant. This sex difference has only been reported previously for focal dystonia as a group.^{2–9} Our results are consistent with previous studies for cervical dystonia, blepharospasm, and laryngeal dystonia. However, for focal dystonia arising in a limb (including writer's cramp), there was no excess of female cases and, if anything, the ratio was reversed, although this failed to reach conventional levels of statistical significance. A male predominance in writer's cramp has also been noted once before.⁶

Discussion. The patients in this study were all identified by adult neurology clinics with a specialist interest in movement disorders and, as such, will underascertain the total number of cases of dystonia by excluding pediatric cases and those not referred to the center. However, the results on the sex ratios are compatible with previous studies that have used similar methodology and suggest that this is a real phenomenon.^{2,4,6–9} In addition, bias leading to selective ascertainment of one sex would not explain why the sex ratios are reversed for writer's cramp compared to craniocervical focal dystonia.

The large number of cases in this series has also allowed further analysis of the relationship between sex and age at onset, which has not been reported previously. The overall mean age at onset for various types of primary dystonia, age at onset by sex, difference in means, and 95% confidence intervals (CI) are presented in table 2. For generalized, segmental, and focal dystonia, males have a statistically significantly earlier age at onset. This trend was also observed for the focal subtypes of cervical dystonia and blepharospasm but was reversed for writer's cramp. We believe that this is the first time that gender has been shown to influence the age at onset of dystonia. Focal limb dystonia also showed an earlier onset in females, but this did not reach statistical significance. No significant difference was seen for the multifocal group, but this group only had a small number of cases. Reclassifying the focal dystonias

*See the Appendix on page 1873 for a list of the Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group members.

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Address correspondence and reprint requests to Dr. T.T. Warner, PhD, Department of Clinical Neurosciences, Royal Free Hospital School of Medicine, Rowland Hill St, London NW3 2PF, UK; e-mail: thom63@rftsm.ac.uk

Table 1 Proportion of dystonia cases according to their anatomic distribution

Type of primary dystonia	Number of cases (%)	Female-to-male ratio (<i>p</i> Value*)
Generalized	12 (1.3)	1.4:1 (NS)
Multifocal	17 (1.8)	3.2:1 (0.05)
Segmental	200 (20.9)	1.8:1 (<0.001)
Focal	728 (76.1)	1.5:1 (<0.001)
Blepharospasm†	210 (28.9)	2.3:1 (<0.001)
Cervical dystonia	358 (49.2)	1.4:1 (0.002)
Writer's cramp	94 (12.9)	1:1.3 (NS)
Laryngeal dystonia	40 (5.5)	2.6:1 (0.06)
Limb dystonia	15 (2.1)	1:1.8 (NS)
Oromandibular dystonia	7 (0.9)	2.5:1 (NS)
Total	957 (100)	

* *p* Value from a single sample binomial test.

† Four additional cases of task-specific focal dystonia are not included in the subclassification.

NS = not statistically significant.

into either craniocervical or limb dystonia highlights these sex differences. For the craniocervical group, men showed a younger mean age at onset of 5.9 years (95% CI, 3.3–8.4; *p* = 0.001), whereas for the limb group, women showed a younger mean age at

onset of 7.6 years (95% CI, 2.4–12.8; *p* = 0.004). For women as a whole, those with craniocervical dystonia were on average 15.7 years older (95% CI, 11.4–19.9; *p* = 0.001) than those with limb dystonia, whereas for men, the reverse trends in age at onset meant that there was no significant age difference between the two groups (2.2 years; 95% CI, –1.9–6.3).

The data presented in this article confirm previously reported differences in sex ratios for primary dystonia but also suggest a paradoxical inverse association between sex ratios and age at onset. For blepharospasm and cervical dystonia, in which there are more female cases, males have a significantly earlier age at onset. This pattern is reversed for writer's cramp. This observation has not been reported previously by any other study and requires further confirmation. Because men in the general population have lower life expectancy, one explanation that must be considered is the possibility that differential mortality selectively removes older male cases of dystonia, producing an excess of female cases and younger mean age at onset for male cases. This explanation would not, however, explain the opposite trends seen for writer's cramp and limb dystonia. Another possibility is that this pattern reflects an underlying genetic basis that may be sex linked. For the majority of primary focal dystonia, the role of genetic susceptibility factors is uncertain, but certainly in dopa-

Table 2 Age at onset of dystonia by subtype and sex

Type of primary dystonia	Mean age at onset, y	Female, age, y	SD	Male, age, y	SD	Mean difference (95% confidence interval), <i>p</i> value
Generalized	16.8	24.7	20.2	5.6	4.7	19.1 (0.4 to 37.8) <i>p</i> = 0.01
Multifocal	44.9	45.2	21.2	44.0	19.3	1.2 (–27.8 to 30.3) NS
Segmental	49.7	53.3	14.9	44.6	19.3	8.7 (3.8 to 13.5) <i>p</i> = 0.001
Focal (total)	46.3	48.7	16.4	43.8	14.9	4.9 (2.6 to 7.3) <i>p</i> = 0.0001
Blepharospasm	58.8	60.2	11.5	55.5	12.6	4.7 (1.0 to 8.3) <i>p</i> = 0.03
Cervical dystonia	41.4	42.9	14.3	39.2	14.0	3.7 (0.7 to 6.7) <i>p</i> = 0.01
Writer's cramp	37.9	34.4	13.5	41.7	12.8	–7.3 (–1.8 to –12.7) <i>p</i> = 0.007
Laryngeal dystonia	50.7	52.3	14.9	46.3	11.5	6.0 (–3.5 to 15.6) NS
Limb dystonia	42.1	35.8	13.1	45.6	18.6	–9.8 (–28.5 to 8.9) NS
Oromandibular dystonia	61.7	61.8	11.5	61.3	13.9	0.5 (–29.0 to 30.0) NS

NS = not statistically significant.

responsive dystonia, caused by a dominant mutation in the gene for guanosine triphosphate (GTP) cyclohydrolase I, female predominance has been observed.¹⁰ Alternatively nongenetic factors that show sex differences may also be important. These may either be endogenous, such as estrogens, or exogenous, such as occupational toxins.

Our results need to be confirmed in other series but suggest that focal dystonia should not be considered as an homogeneous entity and that sex-related factors may be important in determining the development of different forms.

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Appendix

The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group: London, UK—Dr. T. Warner, Ms. L. Camfield, Prof. C.D. Marsden; Innsbruck, Austria—Dr. J. Wissel, Prof. W. Poewe; Turku, Finland—Dr. R.J. Marttila, Dr. H. Erjanti; Bordeaux, France—Dr. P. Burbaud, Prof. A. Lagueny; Munich 1, Germany—Dr. C. Kamm, Dr. T. Gasser, Dr. P. Franz; Munich 2, Germany—Dr. E. Castelon-Konkiewitz, Dr. I. Trender, Dr. A. Ceballos-Baumann; Berlin, Germany—Dr. A. Nebe, Dr. B. Freudenberg; Rome 1, Italy—Dr. A. Bentivoglio, Dr. E. Cassetta, Prof. A. Albanese; Rome 2, Italy—Dr. A. Curra, Dr. L. Vacca, Prof. A. Berardelli; Lisbon, Portugal—Dr. J. Ferreira, Dr. C. Sampaio, Dr. V. Passao; Barcelona, Spain—Dr. F. Marti, Prof. E. Tolosa; Segovia, Spain—Dr. L. Claveria, Dr. J. Duarte; Oxford, UK—Dr. A.H. Nemeth, Dr. N. Hyman, Dr. D. Harley; Writing Committee: Drs.

T. Warner and Y. Ben-Shlomo; Study Co-ordinator: Dr. T. Warner; Study Epidemiologist: Dr. Y. Ben-Shlomo; ESDE Management Committee: Dr. T. Warner, Dr. Y. Ben-Shlomo, Mr. A. Newton, Ms. L. Camfield.

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