Original research

Does sex influence the natural history of idiopathic adult-onset dystonia?

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ABSTRACT

Background Several earlier studies showed a female predominance in idiopathic adult-onset dystonia (IAOD) affecting the craniocervical area and a male preponderance in limb dystonia. However, sex-related differences may result from bias inherent to study design. Moreover, information is lacking on whether sex-related differences exist in expressing other dystonia-associated features and dystonia spread.

Objective To provide accurate information on the relationship between sex differences, motor phenomenology, dystonia-associated features and the natural history of IAOD.

Methods Data of 1701 patients with IAOD from the Italian Dystonia Registry were analysed.

Results Women predominated over men in blepharospasm, oromandibular, laryngeal and cervical dystonia; the sex ratio was reversed in task-specific upper limb dystonia; and no clear sex difference emerged in non-task-specific upper limb dystonia and lower limb dystonia. This pattern was present at disease onset and the last examination. Women and men did not significantly differ for several dystonia-associated features and tendency to spread. In women and men, the absolute number of individuals who developed dystonia tended to increase from 20 to 60 years and then declined. However, when we stratified by site of dystonia onset, different patterns of female-to-male ratio over time could be observed in the various forms of dystonia.

Conclusions Our findings provide novel evidence on sex as a key mediator of IAOD phenotype at disease onset. Age-related sexual dimorphism may result from the varying exposures to specific age-related and sex-

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous smaller scale studies on idiopathic adult-onset dystonia (IAOD) reported a female predominance in craniocervical dystonia and a male preponderance in limb dystonia. Information on sex differences in dystonia-associated features and spread is lacking.

WHAT THIS STUDY ADDS

⇒ The present study provided new information indicating that sexual dimorphism in IAOD persisted even after adjusting for the general population in the same age range and that sex appears to have little or no influence on several dystonia-associated features and spread.

⇒ We also showed for the first time that female-to-male ratio may vary according to both the site and the age at dystonia onset. This might reflect age-related and sex-related differences in the frequency of putative environmental risk factors triggering specific focal dystonias, as well as age-related and sex-related biological factors such as hormonal influences.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sex is a key mediator of IAOD phenotype at onset. Accurate profiling of dystonia-onset female-to-male ratio over time may help to identify environmental risk factors for different focal dystonias.

related environmental risk factors interacting in a complex manner with biological factors such as hormonal sex factors.

INTRODUCTION

Several earlier clinical series and prevalence surveys highlighted some sex-related differences in the clinical expression of idiopathic adult-onset dystonia (IAOD). These studies showed a female predominance in dystonia affecting the craniocervical area and a male preponderance in limb dystonia; at the same time, data on age at IAOD onset in men and women are inconsistent.[1–4] These observations led to the belief that sex may be an essential element of IAOD and that understanding sex-related mechanisms is important for a better understanding of the pathogenesis of this condition.[5]

Prior studies highlighting the sex-related differences, however, analysed at best no more than a few hundred patients and provided sex ratios that were not adjusted to the reference populations. Therefore, the variable frequency of men and women in IAOD may result, at least partly, by referral and medical surveillance biases inherent to study design and sample size. In addition, whether there are sex-related differences in the expression of other dystonia-associated motor and non-motor features has never been systematically explored, and information on the influence of sex on a relevant dystonia feature, like the spread of dystonia in different body segments, is also lacking.

In this study, we analysed data from 1701 patients with various forms of IAOD in order to provide more accurate information on the influence of sex on the motor phenomenology and on the natural history of IAOD.

METHODS

Data were obtained from the Italian Dystonia Registry, a database established since 2016 that collects demographic and clinical information of patients with dystonia.[6] A total of 42 Italian movement disorder centres from all Italian macro-areas (Northern, Central, Southern and Insular Italy) contributed to the database. Centres used a common clinical protocol that included careful clinical retrospective data collection on entry and at follow-up. In each movement disorder centre, data were recorded only by neurologists with expertise in dystonia in order to ensure accuracy in data collection.

Patients included in the present study fulfilled the following eligibility criteria: (1) age of dystonia onset ≥18 years; (2) a diagnosis of dystonia, either focal or as part of a segmental/multifocal or generalised dystonia, according to published criteria[7]; and (3) idiopathic aetiology.[7]

Assessments included standardised collection of demographic, historical and clinical data. Information on age at dystonia-onset and dystonia-associated features (sensory trick, eye symptoms, tremors and family history of dystonia or tremor) was supported by informed family members and prior medical records. Patients also underwent clinical examination of all body sites potentially affected by dystonia. The year and age of dystonia onset were recorded for each affected body region.

Brain MRI or CT scan was performed in all patients to identify any lesions possibly causing an acquired form of dystonia. Tests for Wilson's disease and common pathogenic variants causing monogenic, non-degenerative dystonia (like TOR1A, THAP1, ANO3, GNAL) were performed as appropriate.

A statistical analysis was carried out using SPSS V.23.0 statistical package. Data were expressed as mean±SD unless otherwise indicated. Differences between groups were examined using the χ^2 test, Mann-Whitney U test and Bonferroni correction as appropriate. The female-to-male ratio (F:M ratio) and 95% CI were computed as described.[8] Age-adjusted F:M ratios were calculated according to the 2023 Italian population.[9] The spread of dystonia was estimated by Kaplan-Meier curves and

Table 1 Anatomical distribution of dystonia on last examination in 1108 women and 593 men

	Total sample	Women	Men	F:M ratio (95% CI)	P value
Body distribution of dystonia					
Focal	1255	821	434	1.9 (1.8 to 2.0)	<0.00001
Segmental/multifocal	427	276	151	1.8 (1.6 to 2.1)	<0.00001
Generalised	19	11	8	1.4 (0.7 to 2.5)	0.5
Dystonia at different body sites					
Blepharospasm	735	505	230	2.2 (2.0 to 2.4)	<0.00001
Oromandibular dystonia	214	139	75	1.9 (1.6 to 2.2)	0.00001
Laryngeal dystonia	114	89	25	3.6 (2.9 to 4.4)	<0.00001
Cervical dystonia	848	558	290	1.9 (1.8 to 2.1)	<0.00001
Task-specific upper limb dystonia	125	51	74	0.7 (0.5 to 0.9)	0.04
Non-task-specific upper limb dystonia	135	76	59	1.3 (1.0 to 1.6)	0.1
Lower limb dystonia	40	20	20	1.0 (0.6 to 1.5)	1.0

After Bonferroni correction, significance was set at the 0.005 level (0.05/10).

Table 2 Dystonia-associated features on last examination in 1108 women and 593 men

	Total sample	Women	Men	P value
Sensory trick	483/1701 (28.4%)	300/1108 (27.1%)	183/593 (30.1%)	0.1
Tremor	516/1701 (30.3%)	355/1108 (32.0%)	161/593 (27.2%)	0.04
Eye symptoms in blepharospasm	370/735 (50.3%)	264/505 (52.3%)	106/230 (46.1%)	0.1
Neck pain in cervical dystonia	488/848 (57.5%)	324/558 (58.1%)	164/290 (56.6%)	0.7
Family history of dystonia or tremor	188/1701 (11.1%)	127/1108 (11.5%)	61/593 (10.3%)	0.5

After Bonferroni correction, significance was set at the 0.01 level (0.05/5).

Table 3 Anatomical distribution of dystonia at disease onset

	Total sample	Women	Men	F:M ratio (95% CI)	P value
Body distribution of dystonia at onset					
Focal	1574	1022	552	1.8 (1.7 to 2.0)	<0.00001
Segmental/multifocal	123	84	39	2.2 (1.7 to 2.7)	0.00006
Generalised	4	2	2	1.0 (0.1 to 3.6)	0.4
Dystonia onset at different body sites					
Blepharospasm	634/1574	441/1022	193/552	2.3 (2.1 to 2.5)	<0.00001
Oromandibular dystonia	35/1574	25/1022	10/552	2.5 (1.6 to 3.7)	0.01
Laryngeal dystonia	58/1574	48/1022	10/552	4.8 (3.5 to 6.3)	<0.00001
Cervical dystonia	681/1574	443/1022	238/552	1.9 (1.7 to 2.0)	<0.00001
Task-specific upper limb dystonia	100/1574	35/1022	65/552	0.5 (0.4 to 0.7)	0.003
Non-task-specific upper limb dystonia	48/1574	22/1022	26/552	0.8 (0.5 to 1.3)	0.6
Lower limb dystonia	16/1574	7/1022	9/552	0.8 (0.3 to 1.6)	0.6

After Bonferroni correction, significance was set at the 0.005 level (0.05/10).

Cox regression analysis using two models. In the first model, study time was represented by the time elapsed between dystonia onset and spread; in the second model, study time was represented by age at spread. Patients in whom spread never occurred were included in the survival functions for the duration of the observation. Kaplan-Meier curves were compared by log-rank test. Significance was set at 0.05 level unless otherwise indicated.

RESULTS

Patient characteristics at the last visit

In May 2023, the Italian Dystonia Registry contained data from 1701 patients with IAOD. There were 1108 (65.1%) women and 593 (34.9%) men aged 64.6±13.6 years, with a F:M ratio of 1.9:1 (95% CI 1.8 to 2.0). Age-adjusted F:M ratio was 1.8:1 according to the 2023 Italian population. The proportion of female patients was comparable (p=0.6) across Northern (412/613, 67.2%), Central (212/328, 64.6%), Southern (355/557, 63.7%) and Insular Italy (129/203, 63.5%). The duration of dystonia was 11.9±9.7 years. The body distribution of dystonia and dystonia-associated features is shown in tables 1–3.

Stratifying by women and men yielded a significant 3-year difference in age at the last visit between women and men (65.6±13.1 vs 62.7±14.2 years, p=0.00002) but no significant difference in dystonia duration (11.9±9.4 vs 11.8±10.3 years, p=0.8).

When we examined sex distribution in the diagnostic subgroups of focal, segmental/multifocal and generalised dystonia, women outnumbered men in all groups, even though the difference was not significant in the generalised dystonia group (table 1). Sex distributions regarding dystonia in specific body regions (regardless of how many body regions were involved) yielded more women than men in dystonia from the craniocervical area, and no significant difference in task-specific upper limb dystonia (ULD), non-task-specific ULD and lower limb dystonia (LLD) after Bonferroni correction. F:M ratios did not consistently change when adjusted to the Italian population (data not shown).

Women and men were characterised by a similar proportion of sensory trick, eye symptoms in blepharospasm (BSP), neck pain in cervical dystonia (CD) and family history of dystonia or tremor; tremors in the neck and/or in the upper limb tended to be more frequent in women than in men, but the difference did not reach the level of statistical significance after Bonferroni correction (p=0.05/5=0.01) (table 2).

Overall, similar findings were obtained when we separately analysed subpopulations from the four Italian macroareas (data not shown).

Sex and site of dystonia onset

Dystonia started as focal dystonia in 1574 patients (92.5%), as a segmental/multifocal dystonia in 123 (7.2%), and as a generalised dystonia in 4 (0.2%).

In the 1574 patients with focal onset, dystonia started as BSP in 634 patients (age at BSP onset, 58.4±11.5 years), as oromandibular dystonia (OMD) in 35 (age at OMD onset, 50.5±15.7 years), as laryngeal dystonia (LD) in 58 (age at LD onset,

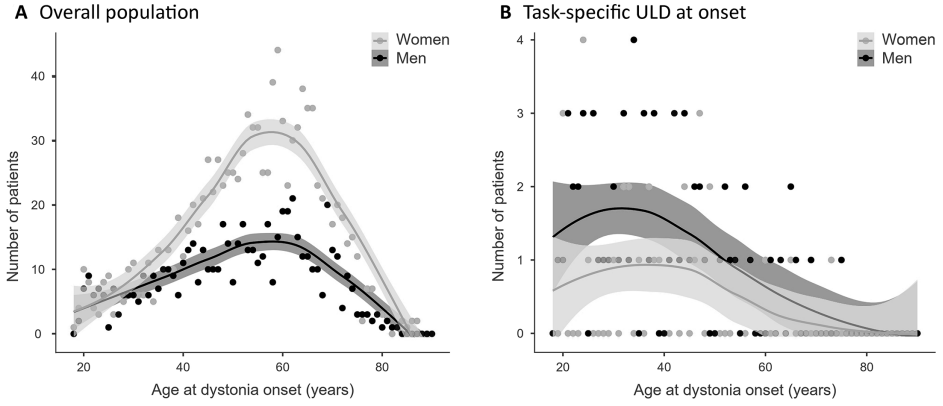

Figure 1 Curvilinear scatter plots displaying the number of onset cases for each age year in the overall population (A), and in patients with task-specific ULD at onset (B), stratified by sex.

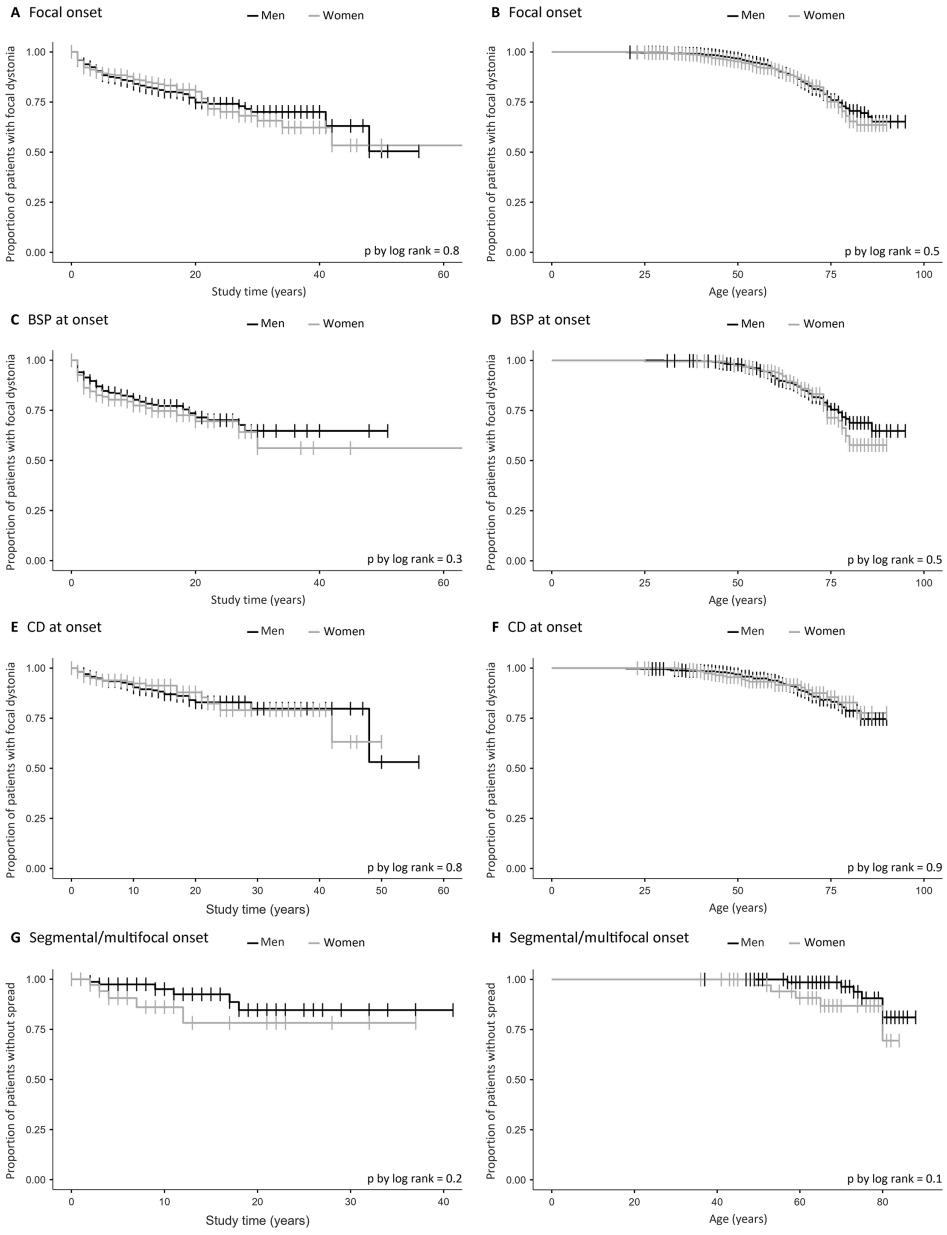

Figure 2 Kaplan-Meier survival analysis of dystonia spread in patients who initially presented with focal dystonia, isolated blepharospasm (BSP), isolated cervical dystonia (CD) and segmental/multifocal dystonia. (A–C–E–G) Study time was represented by the time elapsed between dystonia onset and spread, and patients in whom spread never occurred were included in the survival functions for the duration of the observation. (B–D–F–H) Study time was represented by age at spread, and patients in whom spread never occurred were censored at the age of data collection.

59.6±14.8 years), as CD in 681 (age at CD onset, 49.2±13.9 years), as task-specific ULD in 100 (age at task-specific ULD onset, 39.6±13.8 years), as non-task-specific ULD in 48 (age at non-task-specific ULD onset, 49.2±14.1 years) and as LLD in 16 (age at LLD onset, 55.3±15.9 years).

Stratifying by sex, women significantly outnumbered men in the groups with focal dystonia and segmental/multifocal dystonia at onset; the difference was not significant in the group with generalised dystonia at onset (table 3). In the patients with focal dystonia at onset, more women than men presented with BSP, LD and CD; more men than women presented with task-specific ULD (this subgroup included 75 patients with writer's cramp and 25 with musician's dystonia); no significant sex difference could be observed after Bonferroni correction in patients who presented with OMD, non-task-specific ULD and LLD (table 3).

Sex and age at dystonia onset

In the overall population, the average age at dystonia onset was 53.0±14.2 years; age at dystonia onset was significantly higher in women than in men (54.0±13.7 vs 51.2±15.0 years, p=0.0002).

Data regarding age at onset were examined by computing the scatter plots displaying the number of patients affected by dystonia in relation to the age of dystonia onset. In the overall population, the absolute number of individuals who developed dystonia tended to increase from 20 to 60 years and then declined, a trend that was evident in both women and men (figure 1A) and in all subgroups with different sites of dystonia onset except patients who presented with task-specific ULD at onset (figure 2B).

Table 4 Female-to-male ratio according to age and site of dystonia at onset

	18–34 years F:M ratio (95% CI)	35–49 years F:M ratio (95% CI)	50–64 years F:M ratio (95% CI)	65–89 years F:M ratio (95% CI)
Overall population (n=1701)	107/95 1.1 (0.9 to 1.4)	274/162 1.7 (1.5 to 1.9)	464/214 2.2 (2.0 to 2.4)	263/122 2.2 (1.9 to 2.4)
Blepharospasm (n=634)	15/11 1.4 (0.8 to 2.2)	72/26 2.8 (2.2 to 3.5)	222/93 2.4 (2.1 to 2.7)	132/63 2.1 (1.8 to 2.5)
Laryngeal dystonia (n=58)	4/1 4.0 (1.1 to 10.2)	5/2 2.5 (0.8 to 5.8)	16/4 4 (2.3 to 6.5)	23/3 7.7 (4.9 to 11.5)
Cervical dystonia (n=681)	64/39 1.6 (1.3 to 2.1)	145/91 1.6 (1.3 to 1.9)	166/78 2.1 (1.8 to 2.5)	68/30 2.3 (1.8 to 2.9)
Task-specific upper limb dystonia (n=100)	13/29 0.4 (0.2 to 0.8)	16/21 0.8 (0.4 to 1.2)	4/10 0.4 (0.1 to 1.1)	2/5 0.4 (0.1 to 1.4)

Figure 1 also suggested that the F:M ratio may change over time. Table 4 showed changes in F:M ratios over time in the overall population and in subgroups with different sites of dystonia at onset. F:M ratios from OMD, non-task-specific ULD and LLD subgroups could not be analysed owing to the small size of the samples (<50 patients). In the overall population, women and men were similarly frequent in the age range 18–34, whereas women significantly outnumbered men thereafter; it is worth noting that the F:M ratio peaked at 50 years and then plateaued. Findings varied when we separately analysed patients with different focal dystonia at onset (table 4): in the BSP group, the F:M ratio significantly increased at 35 years and then plateaued; in the OMD and LD groups, the ratio increased at 50 years and then tended to plateau; in the CD group, women significantly outnumbered men in all age classes, with estimates being substantially stable over time; and, finally, in patients who manifested task-specific ULD at disease onset men significantly outnumbered women in the age range 18–34, while the discrepancy tended to progressively narrow thereafter.

Sex and dystonia spread

In the 1574 patients with focal onset, 168/1022 women (16.4%) and 84/552 men (15.2%) spread to a second body part over 6.6±7.4 and 7.6±9.0 years, respectively (p=0.4). Disease duration in patients who did not spread was significantly longer than the time to spread of both women (11.4±9.0 vs 6.6±7.4 years, p<0.00001) and men (10.7±9.6 vs 7.6±9.0 years, p=0.008).

Figure 2A shows that Kaplan-Meier survival curves were similar in women and men based on the time elapsed between onset and spread. Likewise, the survival curves based on age at spread (figure 2B) were comparable in women and men. Visual inspection of the curves suggested that the spread started at around 50 years in both women and men. Stratifying by the site of dystonia onset also yielded no significant differences between women and men whatever the survival approach: as illustrative examples, Kaplan-Meier survival curves for BSP and CD are reported in figure 2C–F, respectively.

In the 123 patients who presented with segmental/multifocal dystonia at onset, 11 (8.9%) experienced spread to another body site over 8.0±5.9 years. In these patients, time to spread did not differ significantly from the disease duration of the patients who did not experience spread (8.0±5.9 years vs 11.4±9.9 years, p=0.3). Kaplan-Meier survival curves indicated that women and men had a similar spread tendency (figure 2G,H).

DISCUSSION

In this large cohort from the Italian Dystonia Registry, we observed that women predominated over men in BSP, OMD, LD and CD groups; the sex ratio was reversed in patients with task-specific ULD; and no clear sex difference emerged in patients with non-task-specific ULD and LLD. This pattern was present at disease onset and remained stable during disease course. Women and men did not significantly differ for several dystonia-associated features and tendency to spread. In both women and men, the absolute number of individuals who developed dystonia tended to increase from 20 to 60 years and then declined. However, when we stratified by site of dystonia onset, different patterns of F:M ratio over time could be observed in the various forms of dystonia.

The sex-related body distribution of dystonia herein is consistent with several prior studies showing a predominance of women in craniocervical dystonia and men in ULD.[1–4] The sex reversal observed in task-specific ULD does not appear to be related to task specificity, because LD, a task-specific dystonia, is more common in women. The sex reversal is also not related to the upper limb, since women were slightly more common for non-task-specific dystonia of the upper limb. It is therefore possible that the sex reversal reflects the type of task.

The novel finding of the present study is that we provided new information indicating that sexual dimorphism in IAOD persisted even after adjusting for the Italian population in the same age range and that sex appears to have little or no influence on several features often associated with dystonia (including coexisting tremor, sensory trick and others), as well as on the rate and age at the spread. Overall, the variable anatomical distribution of dystonia at onset in women and men, the low impact of sex on dystonia-associated features and spread, and the variability of the F:M ratio according to the site of onset suggest that sex may influence the development rather than the natural history of IAOD.

The various forms of IAOD are thought to result from the interaction between a common genetic predisposition and epigenetic factors that probably determine disease penetrance and contribute to variable clinical expression.[10] An influence of sex on the genetic substrate on which IAOD develops is unlikely because IAOD is not linked with sex chromosomes, and dystonia is thought to be characterised by an autosomal dominant transmission and reduced penetrance.[11] Consistently, we could not observe any difference in the frequency of family history of dystonia between women and men. An influence of sex on environmental risk factors possibly triggering focal dystonia in predisposed subjects seems to be more likely, particularly considering that risk factors for different focal dystonia may also variably occur in women and men.[12] Under this scenario, sex differences in the anatomical distribution of dystonia at disease onset and the variability of F:M ratio over time might reflect, at least in part, sex-related differences in the frequency of environmental risk factors. Although environmental risk factors triggering dystonia in predisposed subjects are poorly known, dry eye, a putative risk factor for BSP, is more frequent in aged women[13 14]; scoliosis, a possible risk factor for CD, seems to occur more frequently in young women[15]; and certain activities at work that possibly trigger ULD may be more frequently encountered in men, at least in certain societies and historical periods. It is therefore possible that the men preponderance in hand dystonia may reflect occupational biases.

Theoretically, biological mechanisms involving sex hormones might also contribute to sex-related differences. If so, then the

F:M ratio variability over time should correlate with physiological oestrogen changes. In the overall IAOD population, our analysis showed that women started to outnumber men since at age 35 (well before the typical age at menopause) and peaked at around 50 years. This corresponds to the age of menopause in women without dystonia and, as far as we know, in women with IAOD.[16] However, when F:M ratio data were stratified by site of dystonia onset, different age patterns could be observed in different forms of IAOD, thus raising the possibility that oestrogen variably contributes to the development of different focal dystonias. For instance, in the CD group, women outnumbered men in all age classes, with estimates being substantially stable over time; this would suggest a lack of influence of estrogens on CD development. The men's preponderance in those forms of dystonia like ULD that mainly develop before menopause, and the women's preponderance in those forms of dystonia, like cranial dystonia, that mostly develop at around or after menopause, would suggest a protective role of oestrogens on dystonia development. Supporting this view, oestrogens have been proposed as a protective factor for GABAergic systems and the nigrostriatal dopaminergic system,[17–19] both implicated in developing animal models of dystonia.[20 21] If oestrogens contribute to developing at least some forms of IAOD, there may be a complex interaction between hormonal influences and putative environmental risk factors. As an example, task-specific ULD would preferentially emerge in men before the age of 40 due to both the high frequency of specific risk factors in this age range and the elevated oestrogen levels that slow down the development of dystonia in women; on the other hand, BSP would preferentially emerge in women at the fourth decade or thereafter due to both the increased occurrence with increasing age of putative environmental risk factors like dry eye and the decline in oestrogen levels that starts in the premenopause.

This study has limitations. Because our series was not population-based and dystonia was diagnosed by several examiners from the participating centres, a selection bias could not be ruled out. However, the consecutive recruitment of patients from many centres without any preference for sex and the diagnosis of dystonia by experts in movement disorders yielded a clinical series resembling the general Italian population of adult-onset dystonia. Likewise, we did not observe any differences in the gender distribution of the patient sample we studied across the main Italian geographical areas, and the proportion of patients from the different areas was consistent with the distribution of the Italian population.[9] The current study was much larger than most prior studies and incorporated a multicentre design that minimises bias that sometimes comes from single-centre studies. Bias caused by the examiners being unblinded to the case status was unlikely because they were unaware of the study hypotheses. Some important aspects of dystonia phenomenology (non-motor symptoms like psychiatric problems and sleep disturbances) could not be examined because the correspondent data were not included in the Italian Dystonia Registry. However, we assessed non-motor features like pain in CD and eye symptoms in BSP that are considered to be strictly associated with the motor phenomenology. The retrospective data collection might have been biased in terms of the accuracy of some information, for example, age of onset. However, our protocol required informed family members to confirm the patient's information. In addition, we have previously demonstrated a high test–retest reliability of patients with idiopathic adult-onset focal dystonia in self-reporting age at dystonia onset.[22] Nonetheless, the potential for recall bias could not be fully excluded. Finally, the size of the groups with generalised dystonia, OMD, non-task-specific ULD and LLD was small, and the results could not be accurate due to lack of study power.

Despite the foregoing limitations, the results from this large multicentre registry study provide compelling evidence of sex as a key mediator of phenotype at onset in IAOD. The subsequent natural history of IAOD does not seem to be affected by sex. Age-related sexual dimorphism in IAOD may result from the varying exposures to specific age-related and sex-related environmental risk factors interacting in a complex manner with biological factors such as hormonal sex influence factors. Accurate profiling of dystonia-onset F:M ratio over time may help to identify the largely unknown environmental risk factors for different focal dystonias and provide insights into the related pathophysiological mechanisms.

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