SHORT REPORT

Does sex influence age at onset in cranial-cervical and upper limb dystonia?

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The relation between age at dystonia onset and sex was investigated in 264 patients with cranial-cervical dystonia and 56 patients with upper limb dystonia. In cranial-cervical dystonia, women had a significantly greater age at the onset of dystonia than men. The association was independent of duration of disease and distance of referral, but it was no longer detectable after adjustment for educational level. In upper limb dystonia, men and women did not differ for age at dystonia onset, duration of disease, education level, or distance of referral. A significant inverse association between age at the onset of dystonia and education was observed in both cranial-cervical dystonia and upper limb dystonia series.

Prevalence surveys and large clinical studies have shown sex related differences in the clinical expression of primary adult onset dystonia.[1–5] There is a female predominance in dystonia affecting the cranial-cervical area and a male predominance in limb dystonia.[1 2 5] Recently the European study on dystonia in Europe (ESDE) collaborative group[5] reported a significantly earlier age at onset of cranial-cervical dystonia in men than in women, whereas in limb dystonia the trend was reversed. These observations suggested that sex hormones or sex linked genetic factors may be implicated in the clinical expression of adult onset dystonia.[5] Alternatively, the difference in age of onset between men and women might merely reflect recall or medical surveillance biases inherent to retrospective studies.[6–8] Because the ESDE study left this issue open, we investigated the influence of potential confounders—including disease duration, level of education and distance of referral—on the age of onset in men and women with cranial-cervical dystonia and upper limb dystonia.

METHODS

Patients were selected from January 2000 to July 2001 among consecutive outpatients attending four Italian University centres (Genoa, Rome, Bari, and Messina). Inclusion criteria were a diagnosis of blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia, or upper limb dystonia (either alone or combined) according to published criteria[9], age at dystonia onset more than 20 years, and duration of disease more than one year. Exclusion criteria were neurological abnormalities in addition to dystonia (except tremor associated with dystonia), a history of exposure to dopamine receptor blocking agents, and features suggesting dopa responsive dystonia, paroxysmal dystonia, alcohol responsive myoclonic dystonia, or other secondary dystonias.[9]

In all, 264 patients with cranial-cervical dystonia and 56 patients with upper limb dystonia met the eligibility criteria. Computed tomography or magnetic resonance imaging of the head, or both procedures, excluded secondary causes in 274 patients. In the remaining 27 cases, neither the history nor the neurological signs suggested secondary causes of dystonia.

Information collected included age at the onset of dystonia (defined as time of first symptom), sex, educational level (years of schooling), duration of disease, and residence. Simple and multiple linear regression models—with "age at onset" as the outcome (y) variable and sex (categorised as: 1, if the subject was a woman; 0, if a man), education, duration of disease, and distance of referral (categorised as: 1, if patients resided in the province where the referral centre was located; 0, if patients resided outside the province of the referral centre) as explanatory (x) variables—were used to assess the strength of the association between covariates and outcome. Age at onset, duration of disease, and education were analysed as continuous variables. Regression coefficients (R) estimated using the least squares method, two sided 95% confidence intervals (CI), and p values (t statistics) were calculated by a standard statistical package (STATA7). p Values less than 0.05 were considered statistically significant. The assumption of normality was verified by skewness/kurtosis tests for normality.

RESULTS

Of the 264 subjects with cranial-cervical dystonia, 210 (146 women and 64 men) had focal dystonia: 129 (91 women and 38 men) had blepharospasm, 67 had cervical dystonia (42 women and 25 men), eight had oromandibular dystonia (seven women and one man), and six had laryngeal dystonia (all women). The mean (SD) age at onset in cases of focal dystonia was 52 (14.5) years. Mean age at onset was greater in patients with blepharospasm (57.5 (10.2) years) and oromandibular dystonia (59.4 (10.9) years) than cervical dystonia (41.4 (15.8) years) and laryngeal dystonia (34.3 (11.3) years). The remaining 54 participants with cranial-cervical dystonia (39 women and 15 men) had segmental dystonia: 47 had blepharospasm, 44 had oromandibular dystonia, 13 had cervical dystonia, and two had laryngeal dystonia. Five patients had dystonia in more than two sites. The mean age at onset of segmental cranial-cervical dystonia was 53.1 (13.8) years.

Women with cranial-cervical dystonia had a significantly earlier age at onset and lower education level than men, but no sex related differences were found for duration of disease and distance of referral (table 1). This pattern was observed for all focal and segmental categories of cranial-cervical dystonia (not shown). On simple linear regression, a significant association with the outcome was found for female sex ($R = 4.9$; 95% CI, 1.1 to 8.6; $p = 0.011$), education ($R = -1.5$; 95% CI, −1.9 to −1.1; $p < 0.001$), and duration of disease ($R = -0.7$; 95% CI, −0.9 to −0.5; $p < 0.001$), but not for distance of referral ($R = 0.4$; 95% CI, −3.1 to 3.9; $p = 0.8$). The significant effect of sex did not change noticeably after controlling for duration of disease or distance of referral, but was no longer detectable after adjusting for education (table 2). Controlling

Table 1 Demographic characteristics of 264 patients with cranial-cervical dystonia

	Women (n=185)	Men (n=79)	p Value*
Age at onset of dystonia (years)	54.3 (13.4)	48.8 (15.8)	0.004
Duration of disease (years)	8.8 (7.1)	8.1 (5.8)	0.44
Education level (years of schooling)	6.2 (3.7)	8.0 (2.8)	<0.001
Number of patients residing in the province of the referral centre	44	17	0.81

Values are mean (SD) for age at onset, duration of disease, and education level.
*By Student's *t* test or χ^2 test.

Table 2 Changes in the estimate of the association between age at the onset of cranial-cervical dystonia and female sex after controlling for potential confounding factors

Adjustment	Regression coefficient	95% CI	p Value
None	4.9	1.1 to 8.6	0.011
Duration of disease	5.2	2 to 8.9	0.003
Education level	2.2	–1.5 to 6.01	0.24
Distance of referral	4.9	1.1 to 8.7	0.011
Duration of disease, education level, and distance of referral	3.2	–0.2 to 6.8	0.07

The models were fitted on 185 women and 79 men.
CI, confidence interval.

simultaneously for all the covariates confirmed the significant association of education (adjusted $R = -1.5$; 95% CI, −1.9 to −1.1; $p < 0.001$) and duration of disease (adjusted $R = -0.8$; 95% CI, −1.1 to −0.6; $p < 0.001$) with the outcome.

Limiting regression analysis to the patients with focal cervical dystonia/laryngeal dystonia (as their age at onset was lower than facial dystonias and relatively similar to upper limb dystonia) yielded results similar to those obtained in the whole cranial-cervical dystonia group. In particular, sex was significantly associated with the outcome (crude $R = 5.5$; 95% CI, 1.5 to 9.1; $p = 0.009$) and the effect was confounded by education (adjusted $R = 2.5$; 95% CI, −1.1 to 7.3; $p = 0.25$); education was inversely associated with the outcome and the association was independent of the other variables (adjusted $R = -1.0$; 95% CI, −1.9 to −0.14; $p = 0.023$).

Of the 56 subjects with upper limb dystonia, 47 (17 women and 30 men) had focal dystonia; their mean age at onset was 37.7 (12.6) years. The remaining nine patients (two women and seven men) had neck (n = 7) and oromandibular (n = 2) involvement; their mean age at onset was 38.2 (15.6) years. Men and women did not differ significantly in age at the onset of upper limb dystonia (36.5 (15.3) *v* 39.1 (13.5) years, $p = 0.52$), duration of disease (7.4 (4.6) *v* 8.2 (4.9) years, $p = 0.56$), education level (12.1 (5.0) *v* 12.8 (3.5) years, $p = 0.54$), and number of patients residing in the province of the referral centre (8/37 *v* 5/19, $p = 0.95$). On simple linear regression, a significant inverse association with the outcome was found for education ($R = -1.3$; 95% CI −2.1 to −0.4; $p = 0.006$) and duration of disease ($R = -1.2$; 95% CI −1.9 to −0.4; $p = 0.002$). Sex ($R = -2.7$; 95% CI −10.7 to 5.3; $p = 0.51$) and distance of referral ($R = 4.1$; 95%CI −9.1 to 17.3; $p = 0.53$) failed to reach significance. Crude estimates did not changed after multiple testing involving all the variables examined (not shown).

DISCUSSION

Because this was not a population based study, we corrected for bias in case selection by designing a multicentre investigation and recruiting all the consecutive patients with focal/segmental cranial-cervical dystonia or upper limb dystonia who met the eligibility criteria during the study period. Except for the relatively large number of patients who had blepharospasm, our case population had similar demographic features (including sex ratio and age at onset) to those of previous series.[3–5] The predominance of blepharospasm has been noted in other large Italian series[10] and might suggest differences in the clinical expression of adult onset dystonia across countries.

Despite these differences, the data presented here confirm the previously reported female preponderance in the various cranial-cervical dystonia categories (including blepharospasm, oromandibular dystonia, cervical dystonia, and laryngeal dystonia) and the male preponderance in upper limb dystonia,[1–5] as well as the inverse relation between sex ratio and age at onset observed by the ESDE group in cranial-cervical dystonia.[5] Our analysis provides new information indicating that the greater age at onset in women with cranial-cervical dystonia resulted from confounding by the level of education. We also observed a significant inverse relation between duration of disease and outcome (probably related to the use of prevalent cases), but neither duration of disease nor distance of referral contributed to the sex related difference in age at onset in cranial-cervical dystonia.

The hypothesis that the sex related difference in age at dystonia onset results from differences in education is further supported by the observation that men and women with upper limb dystonia who had a similar education level also had similar age at dystonia onset. In addition, a significant inverse association between age at onset and education was observed in both cranial-cervical dystonia and upper limb dystonia series. This inverse relation may have more than one explanation. A low level of education may affect both the patient's awareness of the disease and the likelihood of seeking medical attention.[8] Alternatively, educational level may be related to socioeconomic status or to lifestyle characteristics that could be involved in the clinical expression of dystonia in a causal or non-causal fashion.[10]

Conclusions

Our findings raise doubts about the significance of the sex related difference in age at onset observed in patients with adult onset dystonia.[5] The difference may merely reflect confounding by exogenous factors (such as educational level) which should be controlled for before valid conclusions can be drawn from studies analysing the relation between sex and dystonia.

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ECHO

Equal use of heath services does not mean equal care for stroke victims of low socioeconomic status

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Authors of a Dutch study suggest that more community based healthcare programmes should be developed for stroke patients of lower socioeconomic status, who have more long term disability and handicap, even though they seemed to have received equal care.

Disability and handicap among all patients was high—601% and 59% respectively—but for patients grouped according to their socioeconomic status, both were significantly higher among the lower socioeconomic group, and significantly more in this group were in nursing homes. They were likely to have more disability up to three years after their stroke and handicap up to five years afterwards, after adjustment for demographic and clinical profiles. However, patients in the lower socioeconomic group were not significantly more likely to use any of the healthcare services more or less. Nevertheless the authors still claim some detrimental effect and argue for more coordination of community services for this group.

The prospective study included 465 patients admitted with stroke six months before to 23 hospitals in the Netherlands and entered into a study of quality of care. They were followed up for five years. Data on outcomes and use of healthcare services were derived from interviews with patients or carers at six months, three years, and five years after their stroke. Educational level determined socioeconomic status.

Low socioeconomic status carries an increased risk of stroke, of death after a stroke, and poor recovery of function, but its effects on long term outcome and use of healthcare services are less clear.

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