PAPER

Head trauma in primary cranial dystonias: a multicentre case-control study

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Background: The relationship between prior trauma and primary adult-onset dystonia is not well understood. Previous uncontrolled observations and exploratory case-control studies have yielded contradictory results.

Objective: To analyse the association between cranial dystonia and prior head trauma.

Methods: An ad hoc multicentre case-control study was performed using a semistructured interview to collect detailed information on the history of head trauma before disease onset in five Italian tertiary referral centres for movement disorders. The presence of a history of head trauma and of post-traumatic sequelae (loss of consciousness, bone fractures, scalp/facial wounds) before disease onset was recorded from 177 patients with primary adult-onset cranial dystonia and from 217 controls with primary hemifacial spasm matched by age strata and sex. Differences between groups were assessed by Mann-Whitney U test and Fisher's exact test, and the relationship between prior head trauma and case/control status was analysed by multivariate logistic regression models.

Results: No association was found between vault/maxillofacial trauma and cranial dystonia. Most reported traumas occurred several years before disease onset. None of the main post-traumatic sequelae altered the chance of developing cranial dystonia compared with patients with primary hemifacial spasm, nor did head trauma modify the age at onset of cranial dystonia.

Conclusions: These results do not support prior head trauma as a possible environmental factor modifying the risk of developing late-onset cranial dystonia. The lack of association may have pathogenetic and medical-forensic implications.

Cranial dystonia is an adult-onset dystonia most commonly affecting the orbicularis oculi and oromandibular muscles.^{1–3} Like other forms of primary adult-onset dystonia, cranial dystonias are thought to be multifactorial in origin, with a possible contribution of both genetic and environmental factors.⁴

Head trauma leading to structural lesions in the caudate, lentiform nuclei, thalami or midbrain is one of the possible causes of secondary dystonia.^{5–8} A few uncontrolled studies have also suggested an association between cranial dystonia and head trauma in the absence of overt brain lesions.^{9–10} Two possible pathogenic mechanisms have been proposed to explain the link between traumatic head injury and cranial dystonia.^{9–11} The first is discrete brain damage in "sensitive" areas such as the basal ganglia. The second mechanism is that of a peripheral maxillofacial trauma inducing topographically related dystonia^{12–13} through maladaptive plastic reorganisation of cortical and subcortical circuits.^{9–10–12–14} Two exploratory case-control studies nevertheless found no significant association with cranial dystonia.^{15–16} Because these studies assessed a large number of variables owing to multiple testing, they were more liable to a higher risk of false positive results than ad hoc hypothesis-testing studies. In addition, prior studies^{15–16} only partly explored the relationship between dystonia and clinical features of the trauma (loss of consciousness, scalp or facial wounds, cranial or maxillofacial bone fractures), the topographical distribution of the trauma (vault or maxillofacial localisation) and the time elapsed from the trauma to the development of dystonia.

To discuss these shortcomings and establish the relationship between previous head trauma and primary late-onset cranial

dystonia, we conducted an ad hoc multicentre case-control study, collecting detailed information on the history of head trauma antecedent to the onset of dystonia.

METHODS

Participants

Patients with a diagnosis of primary adult-onset focal or segmental cranial dystonia were consecutively recruited from the outpatient clinics of five Italian tertiary referral centres for movement disorders during an 8-month study period. The diagnosis of dystonia in the cranial area was made according to published standard criteria.¹ Patients with a duration of disease <1 year were excluded, to minimise possible misclassification errors in the aetiological diagnosis. Patients with neurological abnormalities in addition to dystonia (except tremor associated with dystonia), and patients with clinical, laboratory or imaging features suggesting dopa-responsive dystonia, myoclonus dystonia, as well as other established causes of secondary dystonia (including structural lesions affecting the basal ganglia, thalami or brain stem) were excluded. Consecutive outpatients with primary hemifacial spasm (HFS) were recruited as controls, matched for referral centre and frequency with cases based on 5-year age strata. Diagnoses were confirmed by the senior neurologist with long-standing experience in movement disorders at each centre. All suitable patients and controls were asked to participate voluntarily and were consecutively enrolled after obtaining informed consent. The study was approved by the local ethical committees.

Abbreviations: BSP, blepharospasm; HFS, hemifacial spasm; OMD, oromandibular dystonia

Data collection

The same medical interviewer at each centre recorded information on age, sex, age at disease onset, years of schooling and head trauma. The interviewers received training before the study. Interviewers were not blinded to case/control status, because medical examiners cannot be successfully blinded to blepharospasm (BSP)/HFS status. For each head trauma, the following detailed information was recorded: year and site (vault or maxillofacial region) of the head trauma, occurrence and duration of loss of consciousness, and occurrence of scalp/facial wounds or bone fractures secondary to the trauma. Information on trauma was always confirmed by an informed relative or by medical records, or both.

Analysis

Differences between groups were assessed by Mann–Whitney U test for continuous variables, and by χ^2 or Fisher's exact test for categorical variables. The relationship between a history of cranial vault and/or maxillofacial trauma occurring before disease onset, and case/control status was analysed by logistic regression models adjusting for age, sex, age at disease onset and years of schooling. A history of trauma was represented in the model by a single indicator variable (1, if the subject was exposed; 0, if not); age, age at disease onset and number of school years were analysed as continuous variables. A standard statistical package (Stata V.8) computed odds ratios (ORs), two-sided 95% confidence intervals (CIs) and p values; $p < 0.05$ was considered to be significant. To check for type II error, the study power for case–control studies with an unequal case: control ratio was calculated using the equation reported by Schesselman and Stolley,¹⁷ assuming threefold modification in the risk of developing cranial dystonia with $\alpha = 0.05$ (two sided).

RESULTS

Demographic and clinical features of cases and controls

The participation rate was 96% among cases and 95% among controls. A total of 177 cases and 217 controls met the eligibility criteria and were enrolled in the study. Demographic and clinical features showed that cases had a lower average number of school years than controls, whereas sex distribution, mean age at study and at disease onset, and mean disease duration were similar in both groups (table 1).

Among cases, 133 patients had focal blepharospasm (BSP), 5 had focal oromandibular dystonia (OMD), 22 had BSP with OMD, 8 had BSP associated with cervical dystonia, 6 had BSP

with OMD and cervical dystonia, and 3 had OMD associated with cervical dystonia. All cases reported cranial localisation as the site of onset of dystonia, including the 17 cases with cervical dystonia. None of the cases or controls had post-traumatic Bell's palsy before disease onset. None of the cases or controls had a pending litigation related to a possible post-traumatic origin of dystonia/HFS.

Frequency of head trauma

A vault or maxillofacial trauma before disease onset was reported by 45 cases and 53 controls (table 1). Five cases and nine controls reported two head traumas. There was a trend towards a higher frequency of vault/maxillofacial traumas in men than in women, both in cases (22/57 v 23/120) and in controls (25/97 v 30/134). In most cases (53.3%) and controls (62.2%) reporting head trauma, the trauma occurred before 40 years of age. Vault trauma was found in 27 cases and 32 controls, whereas maxillofacial trauma was found in 23 cases and 30 controls. None of the analysed post-traumatic sequelae secondary to vault or maxillofacial trauma differed significantly between cases and controls (table 1). Maxillofacial traumas were equally distributed among cases with and without OMD (4/36 v 19/141; Fisher's exact test = 1).

Time interval between trauma and disease onset

The median time elapsed between trauma and disease onset was 29 (range 1–67) years in cases and 27 (range 1–61) years in controls. Stratification by the duration of the interval yielded no significant difference in the distribution of vault and maxillofacial trauma between cases and controls (table 2).

This finding remained unchanged regardless of the presence or absence of loss of consciousness, bone fractures or facial wounds (data not shown).

Logistic regression analysis

Logistic regression analysis adjusted for age, sex, age at disease onset and years of schooling failed to establish significant associations between case status and the presence of prior vault/maxillofacial trauma (table 3).

When the analysis was repeated separately for vault and maxillofacial trauma, it showed no significant association with dystonia for either localisation (table 3). The study had an estimate of 94% chance of detecting threefold modifications in the risk of developing cranial dystonia, with $\alpha = 0.05$ (two sided) for head trauma overall. Study power estimates related to the subgroups were 94% for all vault traumas, 89% for vault

Table 1 Demographic and clinical features of cases and controls

	Cases (n = 177)	Controls (n = 217)	p Value*
Age, mean (SD)	65.85 (10.16)	64.16 (11.13)	0.12
Sex, female/male	120/57	138/79	0.38
Age of disease onset, mean (SD)	57.19 (12.15)	55.48 (11.75)	0.16
Disease duration, mean (SD)	8.54 (6.63)	8.69 (6.54)	0.83
Education level (number of school years), mean (SD)	6.28 (3.9)	7.32 (4.51)	0.02
Vault or maxillofacial trauma (all)	45 (25.4%)	53 (24.4%)	0.82
Vault trauma			
All traumas	27	32	0.89
Traumas with loss of consciousness or skull fractures or both	8	14	0.41
Maxillofacial trauma			
All traumas	23	30	0.81
Traumas with facial wounds or maxillofacial bone fractures or both	18	22	0.99

Five cases and nine controls reported two head traumas.

*Mann–Whitney U test or χ^2 , as appropriate.

Table 2 Frequency distribution of trauma in cases and controls according to the time period elapsed between trauma and disease onset

Time elapsed from trauma to disease onset (years)	Vault trauma*		Maxillofacial trauma†	
	Cases (n = 177) (%)	Controls (n = 217) (%)	Cases (n = 177) (%)	Controls (n = 217) (%)
≤1	2 (1.1)	3 (1.4)	2 (1.1)	3 (1.4)
1–5	4 (2.2)	4 (1.8)	1 (0.55)	4 (1.8)
>5	21 (11.9)	25 (11.5)	20 (11.3)	23 (10.6)

*Fisher's exact test: $p = 1$; †Fisher's exact test: $p = 0.77$.

traumas with loss of consciousness and/or skull fractures, 94% for all maxillofacial traumas, and 92% for maxillofacial traumas with facial wounds and/or bone fractures.

Relationship with age of disease onset

Mean (SD) age of cranial dystonia onset did not significantly differ in cases with and without any type of head trauma (56.7 (12.5) ν 57.3 (12.1) years; $p > 0.05$). Similarly, age of cranial dystonia onset was not significantly different either between case patients with and without vault trauma (58.55 (9.01) ν 56.94 (12.66) years; $p > 0.05$) or between those with and without maxillofacial trauma (55.43 (14.83) ν 57.46 (11.8) years; $p > 0.05$). Stratification by the presence or absence of loss of consciousness/skull fractures and of facial wounds/maxillofacial bone fractures yielded no significant difference in age at cranial dystonia onset among the various subgroups of cases (data not shown). Similar to cases, the age of HFS onset did not significantly differ between controls with and without any type of head trauma (55 (11.1) ν 53.9 (13) years; $p > 0.05$).

DISCUSSION

To the best of our knowledge, this is the first ad hoc controlled study exploring the association of head trauma with primary late-onset cranial dystonia. We analysed the effect of post-traumatic sequelae on the risk of developing cranial dystonia, and found no association between vault/maxillofacial trauma and cranial dystonia. In addition, none of the main clinical features of head trauma altered the chance of developing cranial dystonia, nor did head trauma modify the age at onset of cranial dystonia.

This study has several strengths. The demographic and clinical features of our case population were consistent with those typically observed in patients with primary adult-onset cranial dystonia.⁴ The history of head trauma reported by our controls was consistent with the distribution of exposure within the general population,¹⁸ with men presenting a higher frequency of vault/maxillofacial trauma than women, and with >60% of the control population reporting head trauma before

the fifth decade. Although the retrospective assessment prevented us from rating the severity of trauma, we checked for sequelae that seemed potentially important in the development of primary cranial dystonia. The satisfactory study power achieved for the examined exposure variables made a statistical type II error unlikely.

Our study was potentially susceptible to biases inherent to retrospective case-control studies.¹⁹ We corrected for a bias in case selection by consecutively recruiting patients who met the eligibility criteria during the study period. If our control population had a higher probability of being exposed to head trauma than the general population, this difference might have introduced a selection bias masking a true positive association between dystonia and the exposure. According to Rothman and Greenland,²⁰ this bias can be minimised by recruiting cases and controls from the same frame. Therefore, we compared a hospital-based case population with a hospital-based control population from the same services. Moreover, controls had a condition which strongly resembles cranial dystonia, even in the degree of medical surveillance required, and which is thought to be unrelated to trauma²¹—that is, primary HFS. A differential recall between cases and controls might have hindered the identification of a true association between case status and trauma. To minimise this risk, the historical data provided by subjects were always double checked with an informed relative or with available medical records; case and control patients were matched according to age strata and sex; and estimates were always adjusted for educational level, an established general confounder of retrospective observations. The observation that most traumas reported by both cases and controls occurred long before the disease onset is against a recall bias.

Our data showing the absence of an association between dystonia and any type of head trauma do not support discrete brain damage induced by trauma in “sensitive” areas, such as the basal ganglia, as a possible trigger for dystonia. Likewise, the lack of association between dystonia and any type of maxillofacial trauma argues against prior traumatic injuries to the face as a major and adequate peripheral “hit” for inducing topographically related cranial dystonia.

Considering the limitations of our retrospective study, mainly its service-based design, a prospective study would have been more suitable for investigating the link between head trauma and cranial dystonia. An adequately powered prospective observation study dealing with this problem is difficult to conduct owing to the lower reported prevalence of dystonia than trauma affecting the cranial region. Nevertheless, albeit retrospective, our case-control study was well powered, and was supported by a representative case population and an appropriately matched control population. Both measures presumably reduced the likelihood of bias inherent to this study design.

In conclusion, in this case-control study, we found no evidence favouring a role of head trauma in the development of primary late-onset cranial dystonia. If applied to patients with

Table 3 Logistic regression analysis of the association between head trauma and cranial dystonia

	OR	p Value	95% CI
Vault or maxillofacial trauma (all)	1.19	0.49	0.73 to 1.93
Vault trauma			
All traumas	1.17	0.58	0.66 to 2.08
Traumas with loss of consciousness or skull fractures or both	0.89	0.8	0.36 to 2.21
Maxillofacial trauma			
All traumas	1.11	0.75	0.60 to 2.06
Traumas with facial wounds or maxillofacial bone fractures or both	1.3	0.47	0.64 to 2.64

OR estimates were adjusted for age, sex, age at disease onset and years of schooling.

cranial dystonia reporting a prior traumatic accident, our findings might in theory also be of medical-legal interest. Yet, none of our subjects reported a pending litigation related to the case or control diagnoses. This adds value to our findings in respect of medical-forensic issues. Future studies evaluating the relationship between other forms of adult-onset dystonia and head trauma, involving populations of different ethnicity, are needed to confirm our findings and to verify whether this lack of association is common to all subtypes of primary adult-onset dystonia.

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