RESEARCH PAPER

An evaluation of the role of environmental factors in the disease penetrance of cervical dystonia

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ABSTRACT

Background Adult onset primary torsion dystonia (AOPTD) is a poorly penetrant autosomal dominant disorder; most gene carriers are non-manifesting despite having reached an adequate age for penetration. It is hypothesised that genetic, epigenetic and environmental factors may exert protective or deleterious effects on penetrance of AOPTD. By examining environmental exposure history in cervical dystonia patients and their similarly aged unaffected siblings we aimed to determine the role of previous environmental exposures in relation to disease penetrance.

Methods A case-control study of 67 patients with cervical dystonia and 67 of their age-matched unaffected siblings was performed. Past environmental exposures were assessed using a detailed 124-question standardised questionnaire.

Results By univariate analysis, cervical dystonia patients, compared to their unaffected siblings, had an increased frequency of a history of car accidents with hospital attendance (OR 10.1, 95% CI 2.1 to 47.4, p = 0.004) and surgical episodes (OR 6.5, 95% CI 1.76 to 23.61, p = 0.005). Following multivariate analysis, car accidents with hospital attendance (OR 7.3, 95% CI 1.4 to 37.6, p = 0.017) and all surgical episodes (OR 4.9, 95% CI 1.24 to 19.31, p = 0.023) remained significantly associated with case status.

Conclusions Cervical dystonia patients had a history, prior to symptom onset, of significantly more frequent episodes of surgery and of car accidents with hospital attendance than their age-matched unaffected siblings. Soft tissue trauma appears to increase risk of development of cervical dystonia in genetically predisposed individuals.

INTRODUCTION

Dystonia is a movement disorder, characterised by sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures1; the commonest form of dystonia is adult onset primary torsion dystonia (AOPTD). Although most AOPTD patients appear to be sporadic cases, segregation analyses suggest that AOPTD is inherited as an autosomal dominant trait with a markedly reduced penetrance of 12–15%.2 3 In light of this reduced penetrance, it has been hypothesised that certain factors, including past environmental exposures, may exert either protective or deleterious effects in these individuals. Multiple environmental events have been implicated in influencing the penetrance of AOPTD including head, neck and limb trauma, upper respiratory tract infection, early childhood infection, eye disease and repetitive motor actions.4–9 Genetic predisposition may combine with these environmental triggers to reach a threshold at which disease manifests. Non-manifesting carriers of dystonia genes may be disease-free as a result of the presence of protective genetic or epigenetic factors, protective environmental influences, or the absence of exposure to a contributory environmental risk factor.10

There are few large case-control studies of environmental risk factors in cervical dystonia.11–13 We aimed to examine a broad range of environmental risk factors for disease penetrance in cervical dystonia patients compared to their unaffected matched siblings.

PARTICIPANTS AND METHODS

Cervical dystonia patients

Cervical dystonia patients were recruited in the period July 2011–July 2013 at dystonia clinics in three tertiary referral centres. Patients were diagnosed with adult onset primary cervical dystonia according to published standardised criteria by a consultant neurologist with expertise in movement disorders.3 Patients entering the study had to have similarly aged siblings (up to 10 years older or less than 5 years younger) who were willing to be included in the study. Exclusion criteria were a recent diagnosis (<1 year) of dystonia, other neurological abnormalities apart from tremor, use of dopamine receptor blocking agents within 6 months of onset of dystonia, and features suggestive of dystonia-plus, heredodegenerative or secondary dystonia.

Unaffected control siblings

For each cervical dystonia patient, we recruited one age-matched sibling who was, whenever possible, also gender-matched. Age-matching meant that the control sibling was within 10/–5 years of the proband’s current age at study entry. Six siblings were more than 5 years younger than their proband but each was older than the age of onset of dystonia in the proband and they were therefore included on this basis, as only events prior to age of onset of dystonia in the proband were included in the analysis. All siblings were assessed for the absence of dystonia using a standardised examination by one
of the research fellows (AM, IJW, OK); a videotaped examination was not performed.

Data collection
Following enrolment, all participants were asked to fill out a 124-question questionnaire on the exposure variables of interest. In AOPTD patients and their siblings, only exposures prior to the index age (the age onset of dystonic symptoms in AOPTD patients) was assessed. Data were only included if participants included age at event where appropriate. If age at event was unknown, it was coded as missing in order to ensure that all data referred to events prior to the index date. This Environmental History Questionnaire had been developed for a similar study in DYT1 dystonia. Participants completed the questionnaire at home and either returned it by post or by hand to the outpatient clinic. The questions included basic demographic information (age, gender, marital status). Probands completed an extra section pertaining to onset and diagnosis of dystonia, dystonia-related medications and complementary therapies. The questionnaire explored perinatal adversities with questions relating to preterm birth and birth complications; history of childhood infections including measles, mumps, varicella, glandular fever and whooping cough; general anaesthesia; surgical procedures including appendicectomy, tonsillectomy, tooth extraction and other surgical procedures; and physical trauma including limb trauma and head trauma. The study received ethical approval from the St Vincent’s University Hospital, Cork University Hospital and Beaumont Hospital Ethics Committees.

Statistical analysis
A standard statistical package, SPSS V.20, was used for statistical analyses. Exposure variables were represented in the model by a single indicator variable (1 if present, 0 if not). Continuous variables (eg, age) were compared across groups using the Mann-Whitney U test. Categorical variables including gender, and binary responses including presence or absence of various variables of interest were compared using the χ² test. Binary univariate logistic regression was used to assess association of each variable with case status. All variables with p values <0.1 on univariate analysis were entered into a multivariate logistic regression model which was fitted with forward stepwise selection and the model was adjusted for age and gender. The threshold for statistical significance was set at p<0.05. For variables significantly associated with case status on multivariate analysis, we evaluated the direction of the association with age at onset of dystonia with parametric and non-parametric regression modelling if appropriate. One-way analysis of variance (ANOVA) was used to assess differences in means between cases and controls in relation to variables of interest where appropriate.

RESULTS
A total of 67 cervical dystonia patients (69% women) and 67 age-matched siblings (57% women) met the eligibility criteria and were enrolled in this study; 13 sibling pairs were male-male, 32 sibling pairs were female-female, and 22 sibling pairs were gender discordant. Mean age of cases was 39.8 years (SD: 10.5, range 38–82 years) and mean age of siblings was 60.2 years (SD: 10.5, range 37–81 years). Mean age of onset of cervical dystonia in the patients was 43 years (SD 12.2 years, range 10–71 years); in the controls in relation to variables of interest where appropriate.

Environmental questionnaire
All 67 pairs of sibling completed the questionnaire but, mainly because of recall difficulty, not all questions were answered. Thus, total responses to any one question were less than 67. Hospital attendance was defined as presentation to the Accident and Emergency Department for medical assessment as a direct result of an insult (eg, car accident).

Frequencies of analysed variables
Significant differences in proportions (cases vs controls) were noted in: all surgeries (94.5% vs 72.9%, p=0.002); car accidents (41.1% vs 15%, p=0.002); car accident with hospital attendance (23.2% vs 3.3%, p=0.001) (table 1). None of the various subtypes of surgery were significantly more frequently associated with case status.

In a univariate binary logistic regression analysis all surgeries (OR 6.45; 95% CI 1.76 to 23.61) and car accidents with hospital attendance (OR 10.05; 95% CI 2.13 to 47.41) were significantly associated with case status (table 2, figure 1).

A number of variables were examined by χ² testing and subsequently by univariate binary logistic regression analysis, and no significant differences in frequencies between cases and controls were noted (table 1, see online supplementary tables e-1 and e-2): all perinatal adversities; any developmental delay; any childhood infection; any limb injury; all anaesthetics; depression; and all vaccines. The frequency of neck/torso injury was 23.1% in cases and 13.9% in siblings which was notable, but this did not reach significance (p=0.308). Similarly, there was a higher proportion of head injury reported by cases, but this was not significant (28.3% vs 17%, p=0.181).

Multivariate analysis
A multivariate model was fitted with forward selection. Due to the large number of candidate variables, only variables with a significance level of p<0.1 on univariate analysis were included. Age and gender were included as covariates in addition to car accidents and surgical procedures. After multivariate analysis, all

<table>
<thead>
<tr>
<th>Table 1</th>
<th>χ² Frequencies of surgeries, car accidents in cases versus siblings</th>
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<tbody>
<tr>
<td>Reported exposure</td>
<td>Cervical dystonia patients n/N (%)</td>
</tr>
<tr>
<td>All surgeries</td>
<td>52/55 (94.5)</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>14/56 (25)</td>
</tr>
<tr>
<td>Appendicectomy</td>
<td>12/55 (21.8)</td>
</tr>
<tr>
<td>Wisdom tooth extraction</td>
<td>11/47 (23.4)</td>
</tr>
<tr>
<td>Other tooth extraction</td>
<td>23/37 (62.2)</td>
</tr>
<tr>
<td>All other surgery</td>
<td>30/59 (50.8)</td>
</tr>
<tr>
<td>All car accidents</td>
<td>23/56 (41.1)</td>
</tr>
<tr>
<td>Car accidents/no hospital attendance</td>
<td>10/56 (17.9)</td>
</tr>
<tr>
<td>Car accidents/hospital attendance</td>
<td>13/56 (23.2)</td>
</tr>
</tbody>
</table>

The frequencies of environmental exposures reported by 67 cervical dystonia patients and their 67 age-matched unaffected siblings. The number of responses was less than 67 to each question because not all 67 patients or siblings could remember whether an exposure had occurred or, more commonly, were unable to date the exposure. Comparison of the frequencies by χ² yielded a number of significant results (marked with asterisk) including all car accidents, car accidents requiring hospital attendance, and all surgical procedures.
surgeries (OR 4.89; 95% CI 1.24 to 19.31, p=0.023, Nagelkerke r² 0.196) and car accidents with hospital attendance (OR 7.34; 95% CI 1.43 to 37.62, p=0.017, Nagelkerke r² 0.196) remained significant variables.

We performed further analyses on the variables that were significant on multivariate analysis (surgery and car accidents).

### All surgeries

There were no significant differences on one-way ANOVA testing in: mean age of first surgery (cases: 16.4 years, SD 10.1, range 2–42) (controls 19.7 years, SD 11.6, range 2–50) (ANOVA F(1,91)=2.31, p=0.132), mean age of last surgery (cases: 25.6 years, SD 14.7, range 2–53) (controls 28.1 years, SD 13.9, range 4–58) (ANOVA F(1,91)=0.72, p=0.40), mean age of onset of dystonia in patients who did, or did not, have surgery (ANOVA F(1,53)=0.018, p=0.89). Linear regression showed a positive relationship between age at first surgery and age at onset of dystonia in patients who did, or did not, have surgery (r=0.52, 95% CI 0.23 to 0.63, p<0.001). First surgery occurred an average of 26.1 years pre-dystonia onset (SD 14.5, range 2–58 years); last surgery occurred an average of 17.7 years prior to dystonia onset (SD 13.4, range 1–49) (see online supplementary graphs e-3 and e-4).

### All car accidents

Mean age at first car accident was 29.5 years (SD 11.9, range 12–57) in cases and 24.9 years (SD 8.3, range 10–41 years) in controls. There was no significant difference in means between the two groups (ANOVA F(1,30)=0.11, p=0.31). Mean age of last car accident was 30.7 years in cases (SD 11.8, range 12–57) and 25.2 years in controls (SD 8.3, range 10–41); difference in means was not significant (ANOVA F(1,30) 0.16, p=0.22). There was a significant association between age of onset of dystonia in the proband and age of first car accident on linear regression analysis (r=0.57; 95% CI 0.17 to 0.86, p=0.005).

Age of last car accident was likewise associated with age of onset (r=0.55; 95% CI 0.14 to 0.86, p=0.009). The mean time from first car accident to development of dystonia was 16.4 years (SD 10.57, range 0–32 years) and the mean time from last car accident to development of dystonia was 15.3 years (SD 11.1, range 0–32) (see online supplementary graphs e-3 and e-4). Average number of car accidents was 1.5 in cases and 1.1 in controls, but this difference was not significant (ANOVA F(1,30)=0.9, p=0.35) on one-way ANOVA testing. When the number of car accidents and number of surgical procedures in cases and controls were combined, the mean number of events in cases was 2.6 (SD 1.7, range 1–8), and in controls was 2.0 (SD 1.3, range 1–7), but this difference was not significant (ANOVA F(1,85)=2.0, p=0.16). Of note, there was a significant correlation between neck/torso injuries and car accidents (Phi correlation coefficient p=0.003).

**Table 3** Findings in previous case-control studies in adult onset primary torsion dystonia

<table>
<thead>
<tr>
<th>Environmental factor associated with case status</th>
<th>Study participants</th>
<th>OR; 95% CI; p value</th>
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<tbody>
<tr>
<td>Neck/trunk trauma12</td>
<td>202 AOPTD patients</td>
<td>11.2 (1.3 to 95)</td>
</tr>
<tr>
<td></td>
<td>202 unrelated hospital controls</td>
<td>p=0.03 (59 CD patients)</td>
</tr>
<tr>
<td>Head trauma with LOC12</td>
<td>202 AOPTD patients</td>
<td>3.2 (1.04 to 10.1)</td>
</tr>
<tr>
<td></td>
<td>202 unrelated hospital controls</td>
<td>p=0.042 (whole group)</td>
</tr>
<tr>
<td>Head trauma11</td>
<td>177 cranial dystonia patients</td>
<td>1.2 (0.73 to 1.95)</td>
</tr>
<tr>
<td></td>
<td>217 hemifacial spasm controls</td>
<td>p&lt;0.049 (whole group)</td>
</tr>
<tr>
<td>Prior childhood/adolescent scoliosis13</td>
<td>72 cervical dystonia patients</td>
<td>6.8 (1.5 to 29.7)</td>
</tr>
<tr>
<td></td>
<td>144 unrelated hospital controls</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

Published case-control studies of significant environmental exposures in adult onset primary torsion dystonia cohorts which have included a proportion of cervical dystonia patients. Significant associations with adult onset primary torsion dystonia included neck/torso trauma, prior childbirth or adolescent scoliosis (not explored in our study), and head trauma with loss of consciousness (superscript indicates references in text).

*APTD: adult onset primary torsion dystonia; CD: cervical dystonia; LOC: loss of consciousness.*
cervical dystonia that we are aware of. It is hypothesised that asymptomatic carriers of gene mutations for AOPTD are liable to develop dystonia once an environmental exposure threshold is reached, and that approximately 50% of the unaffected siblings in this study carry gene(s) conferring a risk for dystonia.

We included prevalent cervical dystonia cases and their siblings who had been attending our service for over a year in this study. The reason for not including incident/new cases was that diagnostic uncertainty sometimes exists with cervical dystonia; we wished to be sure that cervical dystonia cases did not have another underlying neurological condition that might manifest over the course of the first year. The use of siblings as control participants strengthens the relevance of this study because approximately half will carry potentially causative genes. Although a case-sibling study design is at risk of over-matching because matched siblings share environmental exposures, such matching would obscure weak associations and highlight more influential associations. A case-sibling study is immune to population stratification bias and, for rare genes, it can lead to improved efficiency in the estimation of a gene-environment interaction.

Car accidents are a common cause of soft tissue injury, in particular to the neck. The European Transport Safety Council states that soft tissue neck injury (‘whiplash’) accounts for 65% of all injuries to persons in road traffic. That neck injury is a cause of secondary (post-traumatic) cervical dystonia is well recognised, but certain features differentiate it from idiopathic or primary dystonia. In our study, all cases had typical, sporadic isolated adult-onset cervical dystonia and did not have features of post-traumatic dystonia. Mild and transient soft tissue injury to the neck that might be sustained in a road traffic collision may serve as a trigger for dystonia in later life. The positive correlation between neck injuries and car accidents in our study was interesting, and supports a link between neck injury and car accidents overall. The time interval between car accidents and onset of symptoms separates our findings from those of studies on post-traumatic secondary dystonia.

An Italian case-control study in 1998 examined 202 AOPTD patients and 202 age-matched and gender-matched unrelated controls; the dystonia phenotypes were mixed but were mainly blepharospasms and other cranial dystonias; all neck or trunk trauma was significantly associated with cervical dystonia on multivariate analysis. In another Italian case-control study of 177 adult-onset cranial dystonia patients and 217 controls with primary hemifacial spasm, there were no significant associations between case status and the presence of prior vault/maxillofacial trauma.

When combined as a single group, ‘all surgical procedures’ was a significant risk factor for cervical dystonia; there were trends for tonsillectomy (OR 1.5), appendicectomy (OR 1.57), wisdom tooth extraction (OR 1.57) to be associated with case status compared to other surgical procedures (OR 1.12). Reporting bias may have meant that prolonged, painful procedures were more frequently reported, whereas minor procedures, such as tooth extractions may have been under-reported. The associations between cervical dystonia and car accidents with possible minor neck trauma, and with surgical procedures that involve injury to soft tissue around the neck, such as tonsillectomy and tooth extraction, are perhaps more plausible than an association with procedures such as appendicectomy. Given that none of these surgical procedures were individually significant, a more detailed analysis with a greater number of participants ought to be performed to investigate this finding further.

Reports of surgical procedures as risk factors for dystonia are few and include anecdotal reports of oromandibular dystonia occurring after faciobuccal surgery. We noted that there was no significant difference in proportions of probands and siblings who reported ever having had a general anaesthetic (p=0.4), arguing against hypotheses that intubation or that induction anaesthesia were possible confounding factors between surgery and dystonia.

Why soft tissue injury sustained in a car accident or in a surgical procedure relates to dystonia in later life is not clear. Sensory input, including trauma, can lead to maladaptive plasticity and reorganisation of cortical and subcortical circuits, resulting in motor dysfunction. Patients with limb amputations have larger motor-evoked potentials with transcortical magnetic stimulation in muscles ipsilateral and proximal to the amputated limb. Peripheral injuries can cause pain and immobilisation, and this in turn might induce reorganisation in the central nervous system. The basal ganglia are thought to be involved in the processing of painful stimuli, and positron emission tomography (PET) studies have shown increased blood flow in the contralateral putamen and globus pallidus during painful thermal stimulation of the hand. They contain a high concentration of opioid receptors, and studies have shown that changes in encephalin levels in the basal ganglia occur after thermal injury; this may be relevant to dystonia given the integral role that the basal ganglia (in particular the putamen) plays in dystonia pathophysiology. It is of interest that there was a long gap between last car accident (mean 15.3 years), and last surgery (mean 17.7 years), and dystonia onset. It is unclear why this is the case, but changes in brain plasticity may develop over a number of years. Age of first and last car accident, and age of last surgery were associated with age of onset in this study which further supports a link between cervical dystonia and these exposures.

Limitations of the study include the retrospective nature of the questionnaire. It is possible that there was recall bias with probands attributing their cervical dystonia to certain preceding events or exposures, clearly not a factor in unaffected siblings. This was an unblinded study, the examiners knew the proband and sibling status. However, certain questions pertained only to probands, and issuing a questionnaire (with that section included) to siblings would have been confusing for participants. We did not record the time taken to fill out the questionnaires; many of the questions, particularly about early life exposures may have required time to answer; the participants completed it in their own time. It is possible that certain individuals, for example those whose parents were still alive, may have had more information available in relation to early life exposures including birth and development. A case-sibling analysis such as this is not immune to type II error. One issue with missing data in questionnaire-based studies is that it may affect power to detect positive associations, and this may have been the case in this analysis. On this basis, no definite conclusions can be drawn on variables that were not associated with risk for cervical dystonia at this time. In future studies, to increase study power, we would suggest enrolment of more than one sibling per proband. As our findings were restricted to 67 sibling pairs, further confirmatory studies need to be carried out in order to confirm or refute our results in a larger group, with particular emphasis on a number of different surgical procedures, and car accidents alone.

To summarise, this work suggests that factors which may contribute to disease penetrance in an individual who carries gene(s) for dystonia include car accidents with hospital attendance and surgical procedures. No other variable was significantly associated with increased risk of dystonia in this study. We have examined temporal discrimination threshold (TDT) as a medianational endophenotype, a subclinical marker of gene expression,
for adult-onset primary dystonia.28 The power and specificity of studies of environmental factors in AOPTD would be considerably increased by comparing affected patients with their siblings of similar age or older who have abnormal TDTs (non-manifesting gene carriers) in order to determine various potential causal or protective environmental agents in individuals who share genetic risk factors for development of AOPTD; we plan to explore this in future studies.

Contributors Author Roles: AM was involved in the organisation and execution of the research project, execution and critique of the statistical analysis; writing of the first draft of the manuscript, review and critique of the manuscript. OK was involved in the conception, organisation and execution of the research project, review and critique of the statistical analysis. LW was involved in the execution of the research project; review and critique of the statistical analysis; review and critique of the manuscript. JG was involved in the execution of the research project; review and critique of the statistical analysis; review and critique of the manuscript. NB was involved in the execution of the research project and review and critique of the manuscript. FM was involved in the organisation of the research project, recruitment of participants, and review and critique of the manuscript. TL was involved in the organisation of the research project, recruitment of participants and review and critique of the manuscript. HM was involved in the organisation of the research project, recruitment of participants and review and critique of the manuscript. DGH was involved in the organisation of the research project, recruitment of participants and review and critique of the manuscript. MIE was involved in the conception of the research project and review and critique of the manuscript. OW was involved in the organisation of the research project; review and critique of the statistical analysis; review and critique of the manuscript. RBR was involved in the conception and organisation of the research project and review and critique of the manuscript. SO’R was involved in the conception and organisation of the research project; design, review and critique of the statistical analysis; review and critique of the manuscript. MH was involved in the conception and organisation of the research project; design, review and critique of the statistical analysis; review and critique of the manuscript.

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Patient consent Obtained.

Ethics approval St Vincent’s University Hospital, Beaumont Hospital, Cork University Hospital Ethics Committees.

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