Reviews

The Environmental Epidemiology of Primary Dystonia

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Abstract

Background: Dystonia is a movement disorder characterized by involuntary muscle contractions that cause twisting movements and abnormal postures. Primary dystonia is the most common form and is thought to be a multifactorial condition in which one or more genes combine with environmental factors to reach disease.

Methods: We reviewed controlled studies on possible environmental risk factors for primary early- and late-onset dystonia.

Results: Environmental factors associated with primary early-onset dystonia are poorly understood. Early childhood illnesses have been reported to be more frequent in patients with DYT1 dystonia than in subjects carrying the DYT1 mutation that did not manifest dystonia, thus raising the possibility that such exposures precipitate dystonia among DYT1 carriers. Conversely, several environmental factors have been associated with primary adult-onset focal dystonias compared to control subjects. Namely, eye diseases, sore throat, idiopathic scoliosis, and repetitive upper limb motor action seem to be associated with blepharospasm (BSP), laryngeal dystonia (LD), cervical dystonia (CD), and upper limb dystonia, respectively. In addition, an inverse association between coffee drinking and BSP has been observed in both case-unrelated control and family-based case-control studies. Additional evidence supporting a causal link with different forms of primary late-onset dystonia is only available for diseases of the anterior segment of the eye, writing activity, and coffee intake.

Conclusion: There is reasonable epidemiological evidence that some environmental factors are risk-modifying factors for specific forms of primary adult-onset focal dystonia.

Keywords: Primary dystonia, environmental risk factors

Citation: Defazio G, Gigante AF. The environmental epidemiology of primary dystonia. Tremor Other Hyperkinet Mov 2013; 3: http://tremorjournal.org/article/view/131

Introduction

Dystonia is characterized by involuntary, sustained, patterned contractions of opposing muscles that cause twisting movements and abnormal postures.[1] Traditionally, the etiologic classification divides dystonia into four main categories:[1] primary, secondary (dystonia occurring secondary to brain lesions or exposure to drugs), here-dodegenerative (dystonia associated with neurodegenerative syndromes like parkinsonism, spinocerebellar ataxia, etc.), and plus (e.g., dopa-responsive dystonia, rapid-onset dystonia-parkinsonism, alcohol-responsive myoclonus-dystonia).

In primary dystonia, the most common form, patients exhibit dystonia as the only clinical feature, with or without tremor, and there is no exogenous cause, associated degenerative disorder, dramatic response to levodopa, or structural abnormalities detectable on conventional brain imaging modalities. The anatomical distribution of primary dystonia is highly dependent on age of onset: in patients with dystonia manifesting before the age of 28 (early-onset), dystonia usually begins in a limb and then becomes generalized. Conversely, in patients that develop symptoms after the age of 28 (late-onset), dystonia tends to manifest in focal forms (blepharospasm [BSP] or oromandibular, cervical, laryngeal, and upper limb dystonia) or, less frequently, in segmental/multifocal forms.[1] According to methodologically robust studies, the crude prevalence of primary early-onset dystonia ranges from 24 to 50 cases per million in various populations, the peak age of onset is in the first to second decade of life, and there is no clear gender bias.[2] However, the crude prevalence of primary late-onset dystonia ranges from 101 to 430 cases per million in various populations, and age of dystonia onset and sex distribution differ

among the various focal forms: hand dystonia tends to develop between 30 and 40 years old and is male predominate, whereas craniocervical dystonia usually appears over the age of 40 and more frequently affects women.[2]

Primary dystonia etiology

Primary dystonia is thought to be a multifactorial condition, in which one or more genes combine with environmental factors to reach the threshold of disease.

Support for a genetic contribution comes mainly from the observed familial aggregation of primary dystonia patients (even though the condition may be sporadic)[3–10] and the identification of some genetic abnormalities. A single GAG deletion in the DYT1 gene is associated with a considerable proportion of early-onset dystonia cases (either familial or sporadic), particularly among Ashkenazi Jews,[11,12] and mutations in the DYT6 gene account for a minority of early-onset dystonia cases.[13] Genes associated with primary late-onset dystonia have not been identified, even though a disease-associated locus called DYT7 has been found in a few families with pure late-onset dystonia.[14,15] It is worth noting that genetic inheritance may explain, at least in part, the etiology of late-onset familial cases, whereas the role of genes is less clear in late-onset sporadic patients for whom a genetic contribution is suspected but not proven. Regardless of possible underlying genetic abnormality, the pattern of transmission in primary dystonia families is compatible with autosomal dominant inheritance; penetrance rates are 40–60% and 20% in early- and late-onset dystonia, respectively.[16–19] .These observations, along with the existence of intrafamilial differences in age of dystonia onset and disease severity[20] and the partial concordance of clinical characteristics in identical twins with primary dystonia[21,22] suggest that dystonia genes may be modified by other genes and/or epigenetic modifiers, including environmental influences.

To investigate possible environmental contributions to primary dystonia, we reviewed studies examining the frequency of environmental factors in patients and controls. In those that reported an association between exposure and dystonia, we further evaluated the time between exposure and dystonia development and the relationships among exposure intensity, risk of developing dystonia, and age of onset. This information may be important for assessing the cause-and-effect relationships between putative environmental exposures and dystonia and for separating risk factors from antecedent factors/early dystonia manifestation. Given the epidemiological and clinical features that distinguish early- and late-onset dystonia and suggest etiological differences, we reviewed controlled studies that dealt with environmental contributions to primary early- and late-onset dystonia separately.

Search strategy and selection criteria

Relevant articles were identified with a computer-assisted review of research articles (MEDLINE) published between January 1966 and June 2012 using the terms "dystonia," "epidemiology," and "environmental factor." The reference lists of all papers found in the search were reviewed to identify additional articles.

Environmental factors and primary early-onset dystonia

Evidence for possible contributions of environmental factors to primary early-onset dystonia is limited. An early hospital-based case-control study assessed the role of a number of possible risk factors in 71 patients and 71 age- and sex-matched. controls; no associations were found between dystonia and history of abnormal birth, neonatal disorders, autoimmune diseases, or exposure to toxic substances.[23] However, the relatively small sample size did not allow sufficient study for several of the investigated variables.

More recently, Saunders et al. postulated that DYT1 carriers who experienced childhood illnesses (e.g., varicella, mumps, and measles) had a greater rate of dystonia development.[16] Using a mailed semistructured interview, the authors found a greater frequency of early childhood illnesses occurring at age 6 or earlier in 55 patients with DYT1 dystonia than in 47 subjects carrying the DYT1 mutation that did not manifest dystonia (odds ratio [OR], 2.71; 95% confidence interval [CI], 1.2–6.2).[16] Early childhood illnesses occurred more than one year before the onset of dystonia.

Environmental factors and primary late-onset dystonia

Environmental factors that have been investigated for possible association with primary late-onset dystonia include age-related systemic diseases, psychiatric disorders, stressful life events, head trauma, peripheral injury, and life habits.

Age-related systemic disease, psychiatric disorders, and stressful life events

A large exploratory case-control study based on an Italian multicenter clinical series of 202 case patients with cranial and extracranial late-onset dystonia and 202 control subjects suffering from hemifacial spasms, sciatalgia, and non-neoplastic gastroenterological diseases found no association between dystonia and age-related medical diseases (diabetes mellitus and arterial hypertension), history of anxiety/depression, or stressful life events (severe disease or death of a person very close to the patient, separation and divorce, migration inside or outside of Italy, job loss, or severe financial problems).[24] Data collection was obtained by a standardized questionnaire, and information on medical history was supported by medical records or detailed reports of specific treatments. Although study power was unsatisfactory for diabetes, the other variables had >90% study power.

Head trauma

The Italian case-control study described above also identified a significant association between antecedent head trauma with loss of consciousness and primary late-onset dystonia with varied localization (OR, 3.2; 95% CI, 1.0–10.1). The interval between head trauma and late-onset dystonia onset was 4.7 years on average (range, 1–10 years).[24]

Four additional case-control studies explored associations between head trauma and specific forms of primary late-onset dystonia, with mixed results. A study evaluating a large number of variables in 104 consecutive patients with writer's cramp (WC) and matched controls found a significant positive association between head trauma with loss of consciousness and WC (OR, 3.5; 95% CI 1.0–15.7).[25] Similarly, a study assessing several possible risk factors in 150 patients with laryngeal dystonia (LD) and 136 control subjects with other voice disorders observed a significant inverse association with head trauma and loss of consciousness.[26] Hall et al. did not find any association between head trauma and BSP, which may have been due to insufficient study power.[27] A well-powered ad hoc multicenter study also failed to identify differences in the frequency of vault or maxillo-facial trauma between 177 case patients with cranial dystonia and 217 controls with primary hemifacial spasm matched by age strata and sex.[28] Although trauma severity could not be rated owing to the retrospective assessment, sequelae that seemed potentially important in cranial dystonia development (e.g., loss of consciousness, bone fractures, or facial wounds) were equally distributed in both groups.[28] In addition, head trauma occurred long before dystonia onset (29 years on average), and did not modify the age onset.[28]

Peripheral injury

Acute harm to a body part, especially in an accident or as part of a surgical procedure, and minor injury resulting from repetitive movements or postures or from chronic local diseases have been hypothesized to play a role in the development of topographically related focal dystonia.[29,30]

Prior neck and trunk trauma were significantly associated with cervical dystonia (CD) in the exploratory Italian case-control study (OR, 11.2; 95% CI 1.3–95), even though a long interval (4.2 years on average) elapsed between trauma and CD onset.[24] Conversely, no significant association was observed between prior trauma in the upper limb and WC (OR, 1.9; 95% CI, 0.9–4.0),[25] although insufficient study power might have contributed to the negative finding. In the same study, the risk of WC was associated with an abrupt increase in writing time during the year prior to onset (OR, 5.7; 95% CI, 1.3–33.9), and the risk also increased with time spent writing each day.[25]

Two large, multicenter case-control studies found a significant association between BSP and prior diseases of the anterior segment of the eye (see Table 1 for details on the strength of the association).[24,31] Further supporting this association, a Japanese study reported the frequency of BSP among subjects suffering from dry eye as 8.1%,[32] which is higher than the estimated prevalence of primary BSP in the Japanese population.[33] The association between eye diseases and BSP was much stronger for diseases starting in the year before BSP. The association between eye diseases and was much stronger for diseases starting in the year before BSP onset. A recent family-based case-control study revealed a significant inverse relationship between prior eye diseases and age at BSP onset in both familial and sporadic patients.[34]

Patients with focal LD often have a history of a sore throat,[35] and one study comparing 150 patients with LD and 136 patients with other voice disorders (excluding vocal tremor) confirmed the observation (see Table 1 for details on the strength of the association).[26] However, the authors found no relationship between the number of sore throats per year and dystonia risk. Other environmental factors significantly associated with LD were dust exposure (OR, 1.6; 95% CI, 0.9–2.7) and frequent voice use (OR, 1.8; 95% CI 1.1–3.0).[26]

Two case-control studies also reported a higher frequency of idiopathic scoliosis in CD than in in control patients (Table 1).[36,37] One of these papers stated that the finding was specific because there was no association between CD and other spine diseases.[36] Idiopathic scoliosis, however, did not affect age at CD onset.[36]

Prior peripheral injury seems to be specific for each form of focal dystonia. Eye diseases were only associated with BSP (OR, 1.2; 95% CI, 0.2–5.6),[24] idiopathic scoliosis was not associated with cranial dystonia (OR, 0.85; 95% CI, 0.2–3.3)[38] or WC (OR, 1.1; 95% CI, 0.6–2.1),[25] and neck/trunk trauma was not associated with WC (OR, 1.6; 95% CI, 0.5–5.7).[25]

Life habits

The exploratory Italian case-control study on primary late-onset dystonia also assessed wine drinking and cigarette smoking as possible risk factors. Despite satisfactory study power, wine drinking was not associated with dystonia (OR, 0.78; 95% CI, 0.51–1.20), whereas an inverse, possibly protective association was observed for cigarette smoking (OR, 0.51; 95% CI, 0.29–0.89).[24] However, the study did not examine the effects of potential confounders, such as coffee intake. A subsequent ad hoc case-unrelated control study[39] and a family-based case-control study raised doubts about the association between smoking and BSP but strongly supported coffee consumption as a protective factor.[32] Interestingly, the strength of the inverse association between coffee and dystonia increased with the amount consumed,[39] and there was also an inverse relationship between coffee intake and age at BSP onset.[32,39] Coffee exerted a similar influence on age of BSP onset in familial and sporadic patients.[32]

Discussion

The possibility of an environmental contribution to primary dystonia has been tested in several case-control studies, but given the methodological limitations of that design, prospective surveys may be more suitable for investigating the pathogenetic role of putative environmental risk factors. However, addressing this issue in a sufficiently powered prospective study is difficult due to the low reported incidence of primary dystonia.[2]

Existing case-control studies found no association between primary dystonia and age-related medical diseases like arterial hypertension, life habits such as wine drinking, psychiatric illnesses including anxiety and depression, and stressful life events.[24] The lack of association between late-onset dystonia and a history of psychiatric illnesses or emotionally relevant life events contributes to the large body of

Table 1. Environmental Factors Associated with Dystonia

Environmental factor Type of dystonia [ref.]	Association Strength OR (95% CI)	Time Between Exposure and Dystonia Onset	Exposure Intensity and Risk of Dystonia/ Age at Onset
Early childhood illnesses			
DYT1 dystonia[16]	2.71 (1.2–6.2)	> 1 year	Not done
Head trauma			
Cranial/extracranial dystonia[24]	3.2 (1.0–10.1)	4.7 years (range, 1–10)	Not done
CD[28]	1.2 (0.7–1.9)	29 years (range, 1–67)	No correlation with age at dystonia onset
WC[25]	3.5 (1.0–5.7)	17 years (SD, 13)	The more head trauma the greater the risk of dystonia
LD[26]	0.5 (0.3–0.9)	Not done	Not done
Eye diseases			
BSP[24]	4.5 (1.6–12.5)	3.2 years (range, 1–5),	Not done
BSP[31]	5.53 (2.7–11.4)	<1 year	Not done
BSP[34]	2.5 (1.1–6.1)	1.8 years (SD, 0.7)	Inverse correlation with age at dystonia onset
Sore throat			
LD[26]	Significant association1	Not done	No relationship between no. throat/year and risk of dystonia
Idiopathic scoliosis			
CD[36]	6.8 (1.5–29.5)	Not done	Not done
Repetitive motor action			
WC[25]	5.7 (1.3–33.9)	≤1 year	OR increased with the writing time
LD[26]	2.3 (1.2–4.4)	Not done	Not done
Neck and trunk trauma			
CD[24]	11.2 (1.3–95)	4.2 years (range, 1–7)	Not done
Upper limb trauma			
WC[25]	1.9 (0.9–4.0)	Not done	Not done
Smoke			
Cranial/extracranial dystonia[24]	0.5 (0.3–0.9)	Current smokers	Not done
BSP[39]	0.77 (0.4–1.3)	Never smokers	Not done
WC[25]	1.0 (0.5–1.8)	Not done	Not done
Coffee			
BSP[39]	0.44 (0.2–0.8)	Not done	Increasing of the inverse association with the amount
BSP[34]	0.23 (1–0.8)	Not done	consumed/delayed age at dystonia onset

Abbreviations: BSP, blepharospasm; CD, cervical dystonia; LD, laryngeal dystonia; OR, odds ratio; WC, writer's cramp.
1Authors provided the OR stratified by 1–2 sore throats per year (OR, 2.9; 95% CI, 1.4–5.7) and 3 sore throats per year (OR, 2.1; 95% CI, 1.0–4.1).

evidence refuting the once commonly held view that psychological factors are important in the etiology of this disorder.

Early childhood illnesses, head trauma and peripheral injury were found to be more frequent. Whereas coffee drinking was reported to be less frequent in dystonic patients. To further assess possible causal links between these factors and primary dystonia, we examined the time from exposure to dystonia onset and investigated the relationship between exposure intensity and the risk of developing dystonia or the age at dystonia onset (Table 1).

DYT1 mutation carriers who have early childhood diseases may be more prone to developing dystonia.[16] However, the observation that early childhood illnesses occurred more than one year before the onset of dystonia raised doubt regarding the cause-and-effect relationship between the two conditions.

Head trauma with loss of consciousness was significantly associated with primary late-onset dystonia in three studies. One assessed a mixed sample of patients with both cranial and extracranial dystonia,[24] the second investigated patients with WC alone,[25] and the third focused on LD.[26] Notably, the first two studies reported a greater frequency of head trauma in dystonic patients than control subjects, whereas the third study found an inverse association between head trauma and LD.[26] Because they employed multiple testing, these studies might have had false positives; two additional studies did not find any association between head trauma and BSP.[27,28] Although one was insufficiently powered,[27] the second study was well powered and still failed to identify any sequelae that seemed potentially important in the development of primary CD (e.g., loss of consciousness, bone fractures, or facial wounds) in case and control subjects. Of note, head trauma occurred long before dystonia onset,[24–28] and did not modify the age of dystonia onset.[28] Overall, these findings raise doubt regarding head trauma as a risk factor for primary late-onset dystonia. The widespread occurrence of acute injury and the paucity of reported cases of focal dystonia following such an event would suggest that they are only coincidentally associated.

The concept of peripheral injury inducing topographically related focal dystonia fits with our current understanding of dystonia neurophysiology. Minor peripheral injury, its consequences (painful symptoms and/or immobilization procedures), or repetitive motor actions might induce plastic reorganization of cortical and sub-cortical structures, leading to changes in motor excitability and sensorimotor cortical representation maps as observed in dystonia.[40–42] Controlled studies have documented a significantly greater frequency of neck/trunk trauma in CD,[24] of work or leisure activities requiring repetitive and accurate motor tasks in WC[25] and LD,[26] of eye diseases in BSP, of sore throat in LD, and of idiopathic scoliosis in CD.[31,33–38] However, evidence supporting a causal link between peripheral injury and topographically related focal dystonia is only available for working activity and WC and eye diseases and BSP. In patients with WC, the risk of dystonia was associated with an abrupt increase in writing time the year before dystonia onset and also increased with greater time spent writing each day.[25] Likewise, the association of eye diseases and BSP was much stronger for eye diseases starting the year before BSP onset, and there was also a significant inverse relationship between prior eye diseases and age at BSP onset.[28]

The reported association of BSP with coffee consumption seems biologically plausible given that adenosine receptors, a major site of action for caffeine in the central nervous system,[43] are thought to affect dopaminergic activity in the basal ganglia, a brain area that is probably involved in dystonia pathophysiology.[44] The reported significant inverse relationship between coffee intake and age of BSP onset strengthens the conjecture that coffee is a risk-modifying factors for BSP.[32,39] It is possible that coffee consumption also influences the development of other late-onset dystonias, but these relationships have not been explored.

Conclusions

Exposures to several environmental factors have been found to be more frequent in patients with primary dystonia than in control subjects. However, additional evidence supporting a causal link between environmental exposure and different forms of primary late-onset dystonia is available only for writing activity and WC, diseases of the anterior segment of the eye and BSP, and coffee intake and BSP. It remains to be seen whether acting on these conditions may reduce the risk of developing focal dystonia in predisposed subjects. We observed in a recent retrospective survival study[45] that prior occurrence of eye symptoms in first-degree relatives of adult-onset dystonia patients was significantly associated with later development of BSP. Therefore, assessing and treating eye diseases in this population at risk for BSP development might be recommended.

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