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Obsessive-Compulsive Disorder is not a Clinical Manifestation of the DYT1 Dystonia Gene

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Abstract

Prior studies suggest that obsessive-compulsive symptoms (OCS) and disorder (OCD) are comorbid with dystonia. We tested if OCS/OCD is a clinical manifestation of the DYT1 dystonia mutation by interviewing members of families with an identified DYT1 mutation, and classifying by manifesting carriers (MC), non-manifesting carriers (NMC), and non-carriers (NC). We found that OCD/OCS are not increased in DYT1 mutation carriers compared with NC, nor is OCD associated with manifesting DYT1 dystonia.

Keywords

dystonia; obsessive-compulsive disorder; psychiatric manifestations; variable expressivity; pleiotropy

INTRODUCTION

Primary dystonia is a rare neurological condition involving involuntary sustained muscle contractions that can produce twisting and repetitive movements or abnormal postures [Fahn, 1988]. While the true prevalence is unknown, it has been estimated to affect about 32.9 per 100,000 individuals [Nutt et al., 1988]. A single mutation, an in-frame GAG deletion, in the *DYT1* gene on chromosome 9q34 is a major cause of early onset primary dystonia. The GAG deletion results in the loss of a glutamic acid residue in the encoded protein TorsinA [Ozelius et al., 1997], and is the only DYT1 mutation identified that is unequivocally associated with dystonia [Leung et al., 2001; Klein et al., 2002; Kabakci et al., 2004; Clarimon et al., 2005; Hague et al., 2006]. Penetrance is estimated at only 30%;

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thus most mutation carriers are clinically normal, or at least unaffected with overt signs of dystonia [Kramer et al., 1994].

Previous studies of primary dystonia have reported an increase of psychiatric symptoms, including depression and obsessive-compulsive disorder (OCD) or symptoms (OCS), in individuals with dystonia [Bihari et al., 1992a,b; Broocks et al., 1998; Wenzel et al., 1998; Wenzel et al., 2000; Cavallaro et al., 2002; Moraru et al., 2002; Saunders-Pullman et al., 2002]. Most of the previous studies involved patients with adult-onset of symptoms and were not restricted to a single genetic etiology. We previously investigated psychiatric symptoms in a large sample of families segregating the DYT1 mutation and found an increased rate of early-onset recurrent major depressive disorder in mutation carriers compared to non-carriers [Heiman et al., 2004]. Gene carriers both with and without symptoms of dystonia had similarly increased rates of depression and the severity of dystonia was not associated with a higher rate of recurrent depression. These results suggest that early-onset recurrent depression is a clinical expression of the DYT1 mutation [Heiman et al., 2004]. We now report our analysis of OCD and OCS in this same study population.

SUBJECTS AND METHODS

Participants

Subjects were recruited from families participating in previous genetic studies of dystonia and found to have the DYT1 GAG deletion [Kramer et al., 1994]. The study was approved by Institutional Review Boards; all subjects gave informed consent to participate. The recruitment and methods have been described previously [Kramer et al., 1994; Heiman et al., 2004]. Briefly, families were drawn from a computerized database of patients with dystonia seen by members of the Movement Disorders Group at the Neurological Institute of Columbia Presbyterian Medical Center, Beth Israel Medical Center, and Mount Sinai School of Medicine. Only families segregating the DYT1 mutation were selected. Subjects were classified as having “definite dystonia,” “probable dystonia,” “possible dystonia,” “no dystonia,” or “unrateable.” These classifications were made blinded to genotype [Bressman et al., 1989, 2002]. Subjects were classified as manifesting dystonia if they had definite or probable dystonia. We included “probable” because this category includes signs consistent with mild dystonia that could be symptomatic. Non-manifesting dystonia included possible and no dystonia. We excluded subjects under 18 years and those categorized as “unrateable” and only “at risk” family members were included (i.e., none were married-in and all were mutation carriers or first-degree NC relatives of mutation carriers). We divided the sample into “manifesting carriers” (MC), “non-manifesting carriers” (NMC), and non-carriers (NC) of the DYT1 mutation. Among MC, we rated dystonia as severe if it was generalized or multifocal in distribution and mild if it was segmental or focal [Bressman et al., 2000]. Four hundred fifteen individuals met criteria for inclusion in this study (187 MC, 125 NMC, and 103 NC). The interviewers were blind to genetic status and to study hypotheses.

Measures

Independent variable—Methods for DYT1 mutation carrier status were described previously [Heiman et al., 2004].

Dependent variables—OCD was assessed via the computerized lifetime version of the Composite International Diagnostic Interview (CIDI)—WHO version (http://wwwlive.who.ch/msa/cidi/computerizedcidi.htm) via telephone [Andrews and Peters, 1998]. The CIDI is a comprehensive, fully standardized diagnostic interview used to assess psychiatric symptomatology in epidemiologic studies and has good reliability and adequate validity [Andrews and Peters, 1998].

OCS was assessed via the Maudsley Obsessive-Compulsive Inventory (MOCI) [Hodgson and Rachman, 1977]. The instrument yields total obsessionality score and four subtotal scores: checking, cleaning, slowness, and doubting. The MOCI has adequate reliability and the total score is significantly correlated with other OCD assessments [Hodgson and Rachman, 1977; Richter et al., 1994].

Analysis

We first compared carriers (both MC and NMC) with NC. Then, to exclude a difference related to symptoms of dystonia, we compared NMC to NC, thus restricting the comparison to individuals without dystonic symptoms. We also compared MC with NC. Finally, we compared MC with NMC to determine whether, among mutation carriers, OCD/OCS is associated with dystonic symptoms or severity of dystonic symptoms.

Since more than one member of a family was included, we used generalized estimating equation (GEE) models rather than conventional regression models to control for the non-independence of individuals within the same family [Zeger and Liang, 1986]. Analyses of the CIDI OCD categorical diagnosis were carried out with logistic regression using GEE techniques with STATA statistical software [StataCorp, 2003]. However, many of GEE regression analyses for the MOCI symptom scale did not converge using STATA possibly due to unbalanced families. Therefore, all of the MOCI analyses were conducted using a random effects model within generalized least squares regression which gives similar results.

RESULTS

Two hundred twenty-one (96 MC, 60 NMC, and 65 NC) of 415 (53%) individuals meeting inclusion criteria participated. Recruitment rates were as previously described [Heiman et al., 2004].

The three comparison groups did not differ significantly in refusal rates or in the proportion unreachable after numerous attempts. Table I shows the demographic characteristics of the participating groups. Compared with NC, the NMC were older, more likely to be Jewish, less likely to have a college education, and had smaller families with fewer affected family members. The MC also had smaller families and fewer family members with dystonia than the NC. Carrier status was not related either to gender or to genetic distance from an affected relative. Among the MC, 63 (66%) were rated as having severe dystonia, 25 (26%) had mild dystonia, and 8 (8%) had probable dystonia.

Only seven subjects, three MC (3%), one NMC (2%), and three NC (5%), met criteria for OCD as assessed by the CIDI (Table IIA) and therefore, were compared using Fisher exact test. Compared with NC, the prevalence of a lifetime history of OCD did not differ for either MC (Fisher exact *P*-value = 0.69), NMC (Fisher exact *P*-value = 0.62), or MC and NMC combined (Fisher exact *P*-value = 0.42). Prevalence did not differ, either, in MC versus NMC (Fisher exact *P*-value =1.00).

MOCI scores did not differ between NC and carriers, regardless of which group of carriers was examined (Table IIB). These results did not change after adjusting for ethnicity, age, education, the number of affected in the family, and family size (results not shown). However, the MOCI slow subscale was significantly higher in MC than in NMC (mean = 2.63 (SD = 0.94) vs. 2.30 (SD = 0.62), OR = 1.38, 95% CI = 1.06–1.81). This difference could be attributed to the physical difficulties dystonia imposes on individuals. For example, the three questions from the MOCI slow subscale with the highest absolute percent difference (questions 4, 16, 29) focus on either being late or the amount of time it takes to

accomplish various tasks (areas in which individuals exhibiting dystonia symptoms would be expected to have difficulty). To determine whether or not the increased rates of the slow subscale in MC were due to the symptoms of dystonia, we assessed the association of the MOCI slow subscale with severity of dystonia symptoms restricting the analysis to only MC. Severity was related to risk for the MOCI subscale (OR = 1.79, 95% CI =1.22–2.61) suggesting that the increase in the slow subscale in MC versus NMC was due to dystonia symptoms.

DISCUSSION

Unlike our previous findings relating to early-onset recurrent depression, [Heiman et al., 2004], we found no evidence to suggest that OCD or OCS is an expression of the DYT1 mutation. Our findings differ with previously reported increases of OCD/OCS in individuals with dystonia [Bihari et al., 1992a,b; Broocks et al., 1998; Wenzel et al., 1998, 2000; Cavallaro et al., 2002; Moraru et al., 2002; Saunders-Pullman et al., 2002]. This inconsistency probably reflects differing subject groups; that is, previous studies focused on subjects with etiologies other than DYT1, including families with myoclonus dystonia linked to DYT11 [Saunders-Pullman et al., 2002] and individuals with focal dystonia [Bihari et al., 1992a,b; Broocks et al., 1998; Wenzel et al., 1998, 2000; Cavallaro et al., 2002; Moraru et al., 2002]. The etiopathogenic and phenotypic differences between DYT1 dystonia and other dystonias, especially distinct involvement of fronto-striatal circuitry may explain the differences in OCD frequency among dystonia subtypes. Imaging and other functional studies may help shed light on the relationship between psychiatric and motor dysfunction for specific dystonia subtypes [Eidelberg et al., 1998; Carbon et al., 2004]. In the current study, few subjects met CIDI criteria for OCD, and the rate of OCD was not higher in gene carriers (either for the combined group of MC and NMC, or for either group alone) than in NC. Also, NMC and MC did not have higher rates of OCS than NC as measured by the MOCI symptom scale.

MC did have a significantly higher MOCI slow subscale score than NMC and this difference is probably due to physical limitations imposed by the dystonic contractions. This subscale pertains to the slow repetitive behavior [Hodgson and Rachman, 1977] and the greatest differences on the MOCI slow scale between MC and NMC were in questions related to the time it takes to accomplish various tasks. Further, the MOCI slow subscale was associated with the severity of dystonia symptoms suggesting that score differences were a direct effect of motor disability.

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TABLE I

Comparison of Demographic Variables Between Manifesting Carriers, Non-Manifesting Carriers, and Non-Carriers

	Manifesting carriers (n = 96)	Non-manifesting carriers (n = 60)	Non-carriers (n = 65)
	Number (%)	Number (%)	Number (%)
Gender			
Male	49 (51.0)	24 (40.0)	28 (43.1)
Female	47 (49.0)	36 (60.0)	37 (56.9)
Ethnicity			
Jewish	59 (61.5)	44* (73.3)	37 (56.9)
Non-Jewish	37 (38.5)	16 (26.7)	28 (43.1)
Education			
<College graduate	47 (49.0)	35* (58.3)	31 (47.7)
College graduate	49 (51.0)	25 (47.7)	34 (52.3)
Genetic distance from affected relative			
>First-degree relative		11 (18.3)	9 (13.8)
First-degree relative		49 (81.7)	56 (86.2)
Age at interview[a]			
<49 years old	52 (54.2)	22* (36.7)	38 (58.5)
≥age 49	44 (45.8)	38 (63.3)	27 (41.5)
Number affected in family[a]			
<5 affected members	67* (69.8)	39* (65.0)	33 (50.8)
≥5 affected members	29 (30.2)	21 (35.0)	32 (49.2)
Family size			
<7 members	62* (64.6)	34* (56.7)	25 (38.5)
≥7 members	34 (35.4)	26 (43.3)	40 (61.5)

[a] Variables categorized as bivariate for table clarity but are included as continuous in analyses.

* Significantly different from non-carrier group ($P < 0.05$, from logistic regression).

TABLE II

Results of Univariate Analyses for Lifetime Rates of DSM-IV Obsessive-Compulsive Disorder (OCD) and MOCI Scores Using Random Effects Model Within Generalized Least Squares Regression

(A) Score and percents of each MOCI scale in manifesting carriers, non-manifesting carriers, and non-carriers

		Manifesting carriers (n = 96)	Non-Manifesting carriers (n = 60)	Non-carriers (n =65)
Diagnosis	**MOCI score***	**No. (%)**	**# No. (%)**	**No. (%)**
OCD		3 (3.13)	1 (1.70)	3 (4.60)
MOCI-total	Score ≥ 3	48 (50.0)	34 (56.7)	32 (49.2)
	Score M < 3	48 (50.0)	26 (43.3)	33 (50.8)
MOCI-check	Score = 0	50 (52.1)	37 (61.7)	34 (52.3)
	Score > 0	46 (47.9)	23 (38.3)	31 (47.7)
MOCI-wash	Score = 0	42 (43.8)	28 (46.7)	27 (41.5)
	Score > 0	54 (56.3)	32 (53.3)	38 (58.5)
MOCI-slow	Score ≤ 2	58 (60.4)	44 (73.3)	40 (61.5)
	Score > 2	38 (39.6)	16 (26.7)	25 (38.5)
MOCI-doubt	Score ≤ 1	40 (41.7)	25 (41.7)	25 (38.5)
	Score > 1	56 (58.3)	35 (58.3)	40 (61.5)

(B) Results of univariate analyses for MOCI scores

	All carriers vs. non-carriers	Non-manifesting carriers vs non-carriers	Manifesting carriers vs non-carriers	Manifesting vs non-manifesting carriers
Diagnosis	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
MOCI-total	0.67 (0.21–2.16)	0.41 (0.10–1.59)	0.92 (0.25–3.48)	2.27 (0.63–8.11)
MOCI-check	0.97 (0.65–1.44)	0.81 (0.51–1.29)	1.06 (0.67–1.65)	1.33 (0.86–2.07)
MOCI-wash	0.88 (0.54–1.41)	0.75 (0.44–1.29)	0.97 (0.57–1.66)	1.29 (0.75–2.22)
MOCI-slow	1.02 (0.80–1.31)	0.84 (0.65–1.09)	1.16 (0.87–1.54)	1.38 (1.06–1.81)[a]
MOCI-doubt	0.87 (0.57–1.35)	0.82 (0.49–1.37)	0.91 (0.56–1.46)	1.10 (0.68–1.80)

*MOCI scores categorized as bivariate for table clarity but are included as continuous in analyses

[a]Significantly different ($P < 0.05$).