Psychological Medicine, 2001, **31**, 481–487. Printed in the United Kingdom

The relationship between obsessive–compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study

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ABSTRACT

Objective. This study investigates the relationship of specific anxiety and affective disorders to obsessive–compulsive disorder (OCD) in a blind, controlled family study.

Method. Eighty case and 73 control probands, as well as 343 case and 300 control first-degree relatives of these probands, participated in the study. Subjects were examined by psychologists or psychiatrists using the Schedule for Affective Disorder and Schizophrenia-Lifetime Anxiety version (SADS-LA). Two experienced psychiatrists independently reviewed all clinical materials, and final diagnoses were made according to DSM-IV criteria, by consensus procedure.

Results. Except for bipolar disorder, all anxiety and affective disorders investigated were more frequent in case than control probands. Substance dependence disorders were not more frequent. Generalized anxiety disorder (GAD), panic disorder, agoraphobia, separation anxiety disorder (SAD) and recurrent major depression were more common in case than control relatives. These disorders occurred more frequently if the relative was diagnosed with OCD. Only GAD and agoraphobia were more frequent in case relatives independent of OCD.

Conclusion. GAD and agoraphobia share a common familial aetiology with OCD. The other anxiety and affective disorders, when comorbid with OCD, may emerge as a consequence of the OCD or as a more complex syndrome.

INTRODUCTION

Obsessive–compulsive disorder (OCD) affects 2 to 3% of the population (Karno *et al*. 1988). The diagnosis is based on the presence of obsessions and/or compulsions that are impairing to the individual (APA, 1994). The course is usually persistent with a relatively young age of onset (Samuels & Nestadt, 1997). Individuals with OCD frequently experience additional diagnosable psychiatric disorders over the course of their lifetimes. Disorders reported to occur commonly include tic, 'OCD spectrum', affective, anxiety, substance use and personality disorders (Eisen & Rasmussen, 1989; Pigott *et al*. 1994; Black *et al*. 1995; Chen & Dilasaver, 1995; Pauls *et al*. 1995; Perugi *et al*. 1999; Bienvenu *et al*. 2000; Samuels *et al*. 2000; Yaryura-Tobias *et al*. 2000).

The nature of the relationship between these various disorders and OCD remains speculative, and several mechanisms are plausible. There may be a common underlying aetiology or pathophysiology for these disorders. Alternatively, having one disorder may predispose persons to develop others. Comprehension of the nature of these relationships will provide important insights into the aetiology, pathophysiology, treatment and prevention of these disorders.

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One approach to understand these relationships is to investigate whether the disorders occur more frequently in families of OCD probands than those of control probands, suggesting a common aetiology. We have previously reported that OCD was significantly more common in the first-degree relatives of OCD probands than in the first-degree relatives of controls, in the Johns Hopkins OCD Family Study (Nestadt *et al*. 2000). In the same study, we also found that body dysmorphic disorder and hypochondriasis, grooming disorders (trichotillomania, pathological skin picking and nail biting), and obsessive–compulsive personality disorder were more common in case relatives (Bienvenu *et al*. 2000; Samuels *et al*. 2000). Pauls *et al*. (1995) have reported that tic disorders were more common in the relatives of individuals with OCD. However, only one study has investigated the familial relationships of anxiety disorders to OCD. In that study, Black *et al*. (1995) reported evidence for an anxiety diathesis in the relatives of OCD cases.

The study examines the familial relationship between anxiety, affective, and substance use disorders and OCD. First, the co-occurrence of each of these disorders in probands with OCD is addressed. The objective is to identify conditions potentially related to OCD. The second objective is to establish which, if any, disorders occur more frequently among relatives of OCD probands, indicating a common familial aetiology. Finally, for those disorders that are more common in the families of OCD cases, we investigate whether this familial pattern is distributed only in relatives who also have OCD. The question is whether the disorders co-segregate with OCD, indicating either a causal link between the disorders or that the disorders are part of the same syndrome.

METHOD

Subjects

Sample ascertainment and diagnostic procedures have been described elsewhere (Nestadt *et al*. 2000). In brief, 80 adult OCD probands meeting strict DSM-IV criteria for OCD were recruited from five speciality OCD treatment centres in the Baltimore/Washington, DC area. Control probands were ascertained through a random-digit dialling procedure and were matched to case probands on sex, race and age. The protocol called for probands to be excluded from the study if they were diagnosed with schizophrenia, mental retardation, dementia, or Tourette's disorder, or if OCD occurred exclusively during a major depressive episode; however, no proband met these exclusion criteria. Eighty case probands and their 343 first-degree relatives, and 73 control probands and their 300 first-degree relatives were examined. Of 99 identified case probands, 19 refused or could not be reached; the completed sample included 93% of all first-degree relatives of case probands and 71% of all first-degree relatives of the control probands older than 7 years of age.

Diagnostic procedures

After informed consent was obtained, a semi-structured interview was conducted by a clinician blinded to the subject's proband and case or control family status. The primary diagnostic instrument was the Schedule for Affective Disorders and Schizophrenia-Life Time Anxiety version (SADS-LA; Mannuzza *et al*. 1986), which was adapted for this study to include additional questions about OCD, tic disorders, and 'OCD spectrum' disorders. Children, aged 8 to 15 years, were evaluated using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman *et al*. 1997). The Family Interview Schedule and Criteria (FISC; Mannuzza *et al*. 1985) was employed to collect additional information from an informant regarding subjects directly interviewed, as well as persons who could not be directly interviewed. All this information, as well as all available hospital records, was made available to two psychiatrists, each of whom independently reviewed the materials and together arrived at consensus diagnoses under strict DSM-IV criteria.

The criteria for recurrent brief depressive disorder were modified for this study; having episodes less frequent than every month was permitted for the diagnosis. Recurrent, rather than single episode major depression, was employed in this study to increase the specificity of this diagnosis. For all disorders, if all the necessary criteria were met, a 'definite' diagnosis was given. If it seemed likely that the subject had the diagnosis, but the diagnosticians could not be certain of a criterion, then the diagnosis was

made at the 'probable' level. If the diagnosticians could not be sure of the presence or absence of a given diagnosis, then that diagnosis was recorded as 'unknown'. If any necessary criterion was absent, the diagnosis was considered 'not present'. In the current study, 'definite' diagnoses are employed for analyses involving probands, and 'definite' plus 'probable' for analyses involving relatives.

The inter-rater reliability of the diagnostic procedure was assessed in a sample of 24 subjects. There was good agreement for all diagnoses studied. The estimated kappa for OCD, major depressive disorder, dysthymia, generalized anxiety disorder (GAD), social phobia, specific phobia, panic disorder, recurrent brief depressive disorder, and alcohol dependence ranged from 0·64 to 1·0. The kappa could not be estimated for separation anxiety disorder (SAD), agoraphobia, and substance dependence; in these instances the percentage agreement between examiners ranged from 96% to 100%.

Statistical methods

The prevalence rates of the specific disorders in OCD and control probands, and in their first-degree relatives, were compared using χ^2 or Fisher's exact tests. Logistic regression with the Generalized Estimation Equations procedure for correlated data (Liang & Zeger, 1986) was used to estimate odds ratios in first-degree relatives. Gender and age of the relative and type of interview (direct or informant only) were included in the models to control for these variables. The logistic regression analyses were conducted sequentially. First, the prevalence of the specific disorders in the relatives of cases was compared to that of relatives of controls. Secondly, the additional diagnosis of interest, in the proband, was included in the model to adjust for possible independent transmission of the disorder. Thirdly, the presence of OCD in relatives was also included in the model to investigate whether these disorders are transmitted independently of OCD.

RESULTS

Demographic characteristics of the sample

Fifty-three per cent (42) of the case probands and 60% (44) of the control probands are female. All but one proband in each group are Caucasian; one case and one control proband is Hispanic. Case and control probands are of similar ages; in the case probands, the mean age is 37 years, and the age range is 18–88 years. In the control probands, the mean age is 39 years, and the age range is 18–79 years. The majority of case and control probands are college graduates (66% *v.* 53%, respectively). Case probands are significantly less likely than control probands to have married (53% *v.* 73%; $\chi^2_{(1)} = 6{\cdot}55$, $P < 0{\cdot}01$).

Demographic characteristics of the first-degree relatives of case and control probands are shown in Table 1. Males comprise a greater proportion of case than control relatives. There is a greater proportion of college graduates among case relatives (Nestadt *et al.* 2000).

Psychiatric disorders in case and control probands

The lifetime prevalence rates of definite DSM-IV anxiety disorders, recurrent major depression, bipolar disorder and the substance use disorders in the case and control probands are shown in Table 2. The rates of five anxiety disorders are significantly higher in the case probands than the controls, while marginal for specific phobia ($\chi^2 = 3{\cdot}62$, $P = 0{\cdot}057$). For agoraphobia, panic disorder, and generalized anxiety disorder (GAD) there is more than a ten-fold difference. Recurrent major depression and recurrent brief depressive disorder are also significantly more frequent among the case probands, whereas bipolar disorder, dysthymia and the alcohol and substance dependence disorders are not. In females, dysthymia is significantly more frequent in case than control probands (16% *v.* 0%; $\chi^2_{(1)} = 10{\cdot}0$, $P = 0{\cdot}007$), whereas in males the prevalence of dysthymia is not different between case and control probands (0% *v.* 3%). In contrast, in males specific phobias are more frequent in case than control probands (23% *v.* 4%; $\chi^2_{(1)} = 5{\cdot}5$, $P = 0{\cdot}04$), but this is not the case for female probands compared to controls (38% *v.* 26%).

Psychiatric disorders in case and control relatives

The same disorders are compared among the first-degree relatives of the OCD and control probands in Table 3. GAD, agoraphobia, panic disorder, SAD and recurrent major depression are significantly more common in the relatives of

https://doi.org/10.1017/S0033291701003579 Published online by Cambridge University Press

Table 1. *Demographic characteristics of case and control first-degree relatives*

	Case relatives ($N = 343$)		Control relatives ($N = 300$)		Test statistic (df)	P
	N	(%)	N	(%)		
Sex						
Male	178	(51·9)	135	(45·0)	$\chi^2_{(1)} = 3{\cdot}1$	0·08
Female	165	(48·1)	165	(55·0)		
Age (years)						
8–20	28	(8·2)	33	(11·0)	$\chi^2_{(3)} = 4{\cdot}6$	0·20
21–40	98	(28·6)	101	(33·7)		
41–60	122	(35·6)	97	(32·3)		
$\geqslant 61$	95	(27·7)	69	(23·0)		
Education						
College grad.	153	(44·6)	108	(36·1)	$\chi^2_{(2)} = 6{\cdot}4$	0·04
HS grad.	131	(38·2)	143	(47·8)		
Not HS grad.	59	(17·2)	48	(16·1)		

Table 2. *Lifetime prevalence of DSM-IV disorders (definite) in OCD case and control probands*

	Male relatives				Female relatives				Total			
	Case		Control		Case		Control		Case		Control	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Generalized anxiety disorder	3	(9·7)	0	(0·0)	6	(15·8)	1	(2·4)	9	(13·0)	1	(1·4)**
Panic disorder	7	(18·9)	0	(0·0)	9	(22·5)	0	(0·0)**	16	(20·8)	0	(0·0)***
Agoraphobia	5	(13·5)	0	(0·0)	8	(19·5)	1	(2·3)*	13	(16·7)	1	(1·4)**
Separation anxiety disorder	5	(13·5)	0	(0·0)	8	(21·6)	3	(7·0)	13	(17·6)	3	(4·2)*
Social phobia	15	(44·1)	6	(21·4)	12	(29·3)	9	(20·9)	27	(36·0)	15	(21·1)*
Specific phobia	8	(22·9)	1	(3·6)*	15	(37·5)	11	(26·2)	23	(30·7)	12	(17·1)
Alcohol dependence	7	(18·9)	5	(17·2)	5	(11·9)	6	(14·3)	12	(15·2)	11	(15·5)
Substance dependence	4	(10·3)	3	(10·7)	2	(4·9)	3	(7·0)	6	(7·7)	6	(8·5)
Major depression, recurrent	18	(52·9)	1	(3·6)***	22	(55·0)	7	(16·7)	40	(54·1)	8	(11·4)***
Bipolar disorder	0	(0·0)	0	(0·0)	1	(2·5)	0	(0·0)	1	(1·3)	0	(0·0)
Dysthymia	0	(0·0)	1	(3·4)	6	(16·2)	0	(0·0)**	6	(8·0)	1	(1·4)
Recurrent brief depressive disorder	5	(16·7)	2	(6·9)	8	(22·2)	2	(4·8)*	13	(19·7)	4	(5·6)*

* $P < 0{\cdot}05$; **$P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

cases. One-third of the relatives with panic disorder also had agoraphobia. Agoraphobia is significantly more common among the relatives of OCD probands with panic disorder than control relatives with panic disorder (46% *v.* 11%, $\chi^2 = 4{\cdot}01$, $P < 0{\cdot}05$) (not in Table 3). The prevalence of social and specific phobias, bipolar disorder, recurrent brief depression, dysthymia, alcohol dependence, substance dependence and schizophrenia are not significantly different between the two relative groups.

Table 4 shows the relative odds and 95% confidence intervals for those disorders which occur significantly more frequently in case relatives than control relatives. The results are adjusted for the age and gender of the relatives, and type of examination (direct *v.* informant). The odds ratios from the first series of logistic models, are significant for all the disorders presented in Table 4.

The second series of logistic models, presented in Table 4, also adjusts for the presence of the specified disorder in the proband (i.e. whether the proband has the diagnosis in question), to control for the potential that the disorders are transmitted independently from OCD. After this adjustment, GAD, agoraphobia, and SAD, but not panic disorder and recurrent major depression, are significantly more frequent in case relatives.

The third series of models controls for the presence of OCD in the relatives, as well, to

https://doi.org/10.1017/S0033291701003579 Published online by Cambridge University Press

Table 3. *Lifetime prevalence of DSM-IV disorders (probable and definite) in first-degree relatives of OCD case and control probands*

	Male relatives				Female relatives				All relatives			
	Case		Control		Case		Control		Case		Control	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
OCD	27	(16·0)	3	(2·3)***	26	(16·6)	14	(8·5)*	53	(16·3)	17	(5·7)***
Generalized anxiety disorder	22	(13·4)	0	(0)***†	28	(17·9)	14	(8·8)*	50	(15·6)	14	(4·8)***
Panic disorder	13	(7·8)	3	(2·3)**	16	(10·2)	7	(4·3)	29	(9·0)	10	(3·4)**
Agoraphobia	5	(3·0)	0	(0)	9	(5·6)	2	(1·2)*	14	(4·3)	2	(0·7)**
Separation anxiety disorder	9	(8·8)	4	(4·3)	18	(16·1)	8	(5·8)*	27	(12·6)	12	(5·2)*
Social phobia	35	(21·0)	19	(14·3)	40	(25·0)	39	(23·6)	75	(22·9)	58	(19·5)
Specific phobia	31	(18·7)	20	(15·2)	51	(31·5)	42	(25·8)	82	(25·0)	62	(21·0)
Schizophrenia	3	(1·7)	2	(1·5)	1	(0·6)	0	(0)	4	(1·2)	2	(0·7)
Alcohol dependence	35	(21·5)	19	(14·5)	10	(6·2)	19	(11·8)	45	(13·9)	38	(13·0)
Substance dependence	15	(8·9)	14	(10·6)	5	(3·1)	5	(3·1)	20	(6·1)	19	(6·5)
Major depression, recurrent	20	(12·1)	8	(6·3)*	27	(18·1)	19	(11·8)	47	(15·0)	27	(9·3)*
Bipolar disorder	1	(0·6)	0	(0)	4	(2·5)	3	(1·8)	5	(1·5)	3	(1·0)
Dysthymia	6	(3·5)	3	(2·3)	7	(4·4)	7	(4·3)	13	(4·0)	10	(3·4)
Recurrent brief depressive disorder	5	(3·4)	0	(0)	2	(1·5)	5	(3·2)	7	(2·5)	5	(1·8)

* $P < 0·05$; **$P < 0·01$; *** $P < 0·001$.
† Fisher's Exact Test.

Table 4. *Odds ratios of DSM-IV disorders (definite and probable) in first-degree relatives of OCD case compared with control probands controlling for age, gender and type of examination*

	Unadjusted	Adjusted for proband diagnosis	Adjusted for proband diagnosis and OCD in the relative
Diagnosis	OR (95% CI)	OR (95% CI)	OR (95% CI)
Generalized anxiety disorder	3·5 (1·8–6·9)***	3·4 (1·7–6·9)***	2·9 (1·4–6·0)***
Agoraphobia	6·9 (1·5–31·3)*	5·3 (1·1–25·1)*	4·0 (0·9–18·9)
Panic disorder	3·2 (1·5–6·9)**	2·3 (0·9–5·6)	1·8 (0·7–4·3)
Separation anxiety disorder	3·0 (1·4–6·5)**	2·5 (1·2–5·4)*	1·6 (0·7–3·5)
Major depression, recurrent	1·9 (1·2–3·3)*	1·8 (0·9–3·8)	1·5 (0·7–3·0)

* $P < 0·05$; **$P < 0·01$; *** $P < 0·001$.

determine whether the disorders co-segregate with OCD. Of all the disorders, only GAD (OR = 2·9; 95% CI = 1·4–6·0) is significantly more frequent in case relatives independent of OCD. Although not statistically significant, the odds ratio remains high for agoraphobia (OR = 4·0; 95% CI = 0·9–18·9).

DISCUSSION

Co-morbidity in OCD probands

The results from this study indicate that individuals with OCD frequently experience additional psychopathology. Specifically, life-time anxiety disorders (GAD, agoraphobia, panic disorder, SAD, and social and specific phobias) and affective disorders (recurrent major depression and recurrent brief depressive disorder) are frequently present. The pattern of co-morbidity identified in this study is in agreement with the several published studies that examined these relationships (Angst, 1993; Pigott *et al.* 1994; Black *et al.* 1995). In contrast to previous reports of frequent co-morbidity between bipolar disorder and OCD (Chen & Dilsaver, 1995; Perugi *et al.* 1999), bipolar disorder occurred in only one OCD proband in this study. In addition, alcohol and substance dependence were not more prevalent in OCD than control probands, in contrast to previous reports (Eisen & Rasmussen, 1989). These findings may reflect differences in case ascertainment between studies. In our study, case probands were identified in OCD speciality services. It is

https://doi.org/10.1017/S0033291701003579 Published online by Cambridge University Press

plausible that patients with OCD and these other conditions are treated in other treatment settings.

Disorders in the relatives of OCD probands

We found that five anxiety/affective disorders occur significantly more frequently in case than control relatives – GAD, agoraphobia, SAD, panic disorder and recurrent major depression. However, the latter three disorders occur more frequently only in case relatives with OCD. These conditions may emerge as a direct psychological consequence of the OCD. For instance, patients with OCD may have an increased liability for depression due to the demoralizing effects of the disorder; or anxiety, already present as part of the OCD syndrome, may progress into a full-blown disorder such as panic disorder or social phobia. Alternatively, the pathophysiology of OCD may render the brain more vulnerable to the development of additional pathology manifesting in the comorbid conditions. If, as our findings suggest, these disorders occur as a complication of the OCD (i.e. secondarily), then early recognition and treatment of OCD is important and could reduce the risk of patients developing additional symptoms, reducing the potential for added disablement.

In contrast to the disorders mentioned above, GAD and agoraphobia occur more frequently among the OCD relatives regardless of the presence of OCD in these relatives. This finding suggests that there is a common familial aetiology for OCD and GAD and agoraphobia in these families. Although we suspect that this is genetic in origin, the study design cannot exclude other possible familial causes. This finding is consistent with a report published by Black *et al.* (1995), who suggested that there is an anxiety diathesis transmitted in the families of OCD probands.

The fundamental phenomenological difference between GAD and OCD is that the former is characterized by uncontrollable worry, and the latter by obsessions. Although distinct phenomena, there are commonalties in these mental events. Both are painful bouts of exaggerated and persistent thoughts and concerns; albeit, obsessions are typically egodystonic, unbidden, and are usually responded to by vigorous unsuccessful attempts at resistance. The additional emotional accompaniments vary among patients with either disorder, but do not distinguish between disorders. The independence of obsessions and worry has not been satisfactorily established in clinical studies (Steketee *et al.* 1987; Wells & Papageorgia, 1998). OCD and GAD have similar ages of onset, a persistent waxing and waning course (Rickels & Schweitzer, 1990), and respond to many of the same pharmacological interventions (Ballenger, 1999). Furthermore, reports associate both disorders with the serotonin transporter gene (Ohara *et al.* 1999). Therefore, both the clinical and empirical perspectives provide credence to the conclusion that these disorders are part of the same phenotypic spectrum.

The propensity to develop agoraphobia in subjects with panic disorder may be increased in relatives of OCD probands. Individuals with panic disorder may be differentially likely to develop agoraphobic behaviours. The tendency to worry and ruminate could be a risk factor in individuals who progress to develop agoraphobia. This tendency could be the diathesis, common to OCD, GAD and agoraphobia, transmitted in these families.

Implications

These findings have both clinical and research implications. Relatives of patients with OCD often experience considerable personal burdens, and this may be aggravated substantially if they also have an anxiety disorder. It is important to evaluate family dynamics when treating patients with OCD. Given the findings of this study, genetic and neuropsychiatric studies of OCD should include GAD as an alternate phenotype.

Limitations

This research is limited in two important ways. First, only probands with OCD were identified, limiting potential comparisons between relatives of OCD probands with those of the other disorders. Also, it would have been advantageous to have selected certain probands with exclusively one disorder and others with more than one disorder. Investigators have employed this strategy productively for disorders other than OCD (Merikangas *et al.* 1998). Secondly, the diagnostic information is exclusively cross-sectional, increasing the possibility of retrospective recall bias. Longitudinal or even 'high-

risk' research strategies may minimize this bias. Nevertheless, care was taken by the examiners and diagnosticians to establish lifetime diagnoses for each disorder independently.

In summary, several anxiety and affective disorders frequently co-occur with OCD. These co-morbidities may arise as a result of a common aetiological pathway or as a complication of OCD. The results from this study suggest that the process differs depending upon the disorder. GAD and agoraphobia share a common underlying familial origin with OCD. The other disorders, when co-morbid with OCD, may emerge as a consequence of the OCD or as a more complex syndrome.

This study was supported by NIH grants R01 MH50214 and by NIH, NCRR, OPD-GCRC RR00052.

The authors thank: the many families participating in the study; Drs Jennifer Hahn, David Wellen, Ruth Zitner, Dan McLeod and Malgorzata Lamacz for conducting clinical evaluations; Drs Dennis Murphy, Ben Greenberg, Sally Winston, Ms Donna Burns and Ms Dorinda Schultz for access to their clinic patients; Drs David Pauls, Kathleen Merikangas, Abby Fyer and Salvatore Mannuzza for consultation on this study; and, Ms Dorothy Carpenter, Ms Krista Vermillion, Ms Margaret Dees and Ms Sandra Hensley for their efforts in conducting the study.

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