A Family Study of Obsessive-compulsive Disorder

Gerald Nestadt, MD, MPH; Jack Samuels, PhD; Mark Riddle, MD; O. Joseph Bienvenu III, MD; Kung-Yee Liang, PhD; Michele LaBuda, PhD; John Walkup, MD; Marco Grados, MD; Rudolf Hoehn-Saric, MD

Background: The causes of obsessive-compulsive disorder (OCD) are as yet unknown. Evidence of familial aggregation is one approach for investigating the role of genetics in the etiology of this condition. The current study was conducted to determine if OCD is familial and to investigate possible familial subtypes.

Methods: Eighty case probands were identified in 5 specialty OCD clinics and 73 community control probands were identified by random-digit dialing. These probands and their first-degree relatives (343 case and 300 control relatives) were blinded to group and evaluated by psychiatrists and doctoral-level clinical psychologists using semistructured instruments. Final diagnoses were assigned by a blinded-consensus procedure. The results were analyzed using logistic regression by the method of generalized estimating equations.

Results: The lifetime prevalence of OCD was significantly higher in case compared with control relatives (11.7% vs 2.7%) (P<.001). Case relatives had higher rates of both obsessions and compulsions; however, this finding is more robust for obsessions. Age at onset of obsessive-compulsive symptoms in the case proband was strongly related to familiality (odds ratio, 0.92; confidence interval, 0.85-0.99) (P = .05); no case of OCD symptoms was detected in the relatives of probands whose age at onset of symptoms was 18 years or older. Probands with tics or obsessive-compulsive personality disorder were not more likely to have relatives with OCD than those without these features.

Conclusions: Obsessive-compulsive disorder is a familial disorder. Obsessions are more specific to the phenotype than are compulsions. Age at onset of OCD is valuable in characterizing a familial subtype.

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OBSESSIVE-COMPULSIVE disorder (OCD) is a psychiatric condition first described more than 100 years ago.1 The pathognomonic features of the disorder are persistent, intrusive, senseless thoughts and impulses (obsessions) and repetitive, intentional behaviors (compulsions). Patients with the disorder recognize that their thoughts and behaviors are excessive and unreasonable, and they struggle to resist them. The lifetime prevalence of OCD is estimated to be 1% to 3%, based on population-based surveys conducted in many communities nationally and internationally.2,3 Although the disorder affects individuals of all ages, the period of greatest risk is from childhood to middle adulthood.4,5 Patients experience a chronic or episodic course with exacerbations that can substantially impair social, occupational, and academic functioning; according to the World Health Organization, OCD is among the 10 most disabling medical conditions worldwide.6 The role of heredity in OCD has long been suspected by clinicians.7-11 Several twin studies have found that the concordance for obsessive-compulsive symptoms is substantially greater in monozygotic twin pairs (80%-87%) than dizygotic twin pairs (47%-50%).12,13 Many family studies of OCD have been conducted, although most had methodological limitations, such as failure to use structured or semistructured diagnostic instruments and noninclusion of control groups.5,14,17 The results from more recent controlled family studies, which used contemporary diagnostic criteria and assessment methods, have been inconsistent. Pauls et al18 found higher morbidity risks of OCD in first-degree relatives of OCD probands vs first-degree relatives of psychiatrically normal controls (10% vs 1.9%). However, Black et al19 did not find differences in the rates of OCD in case and control relatives, and they concluded that an anxiety diathesis rather than OCD per se may be inherited. Given the importance of this issue, additional research was warranted.
SUBJECTS AND METHODS

STUDY SAMPLE

In the family study, we selected 99 adult OCD probands (aged ≥18 years) from 3 specialty OCD treatment centers in the Baltimore, Md, and Washington, DC, area. All adult patients with a diagnosis of OCD who were first evaluated in these centers in the 3 years prior to the initiation of this study were rostered (N = 418). A sample from each site was randomly selected to participate in the study, and these patients were contacted by their treating clinician to request participation. Interviews were completed for 80 of these case probands and 343 of their first-degree relatives. Control probands were identified by a random-digit dialing procedure, conducted by a survey research contractor (Battelle Corp, Baltimore), which individually matched control to case probands on sex, race, and age (within 10 years) and on whether medical care had been received in the preceding 1 year. Recruitment staff then contacted the control probands and their first-degree relatives. Interviews were completed for 73 control probands and 300 of their first-degree relatives.

Case probands were included if they met DSM-IV criteria for OCD as diagnosed by the consensus procedure. They also needed to score greater than 15 on the Yale-Brown Obsessive Compulsive Scale during the worst episode. The protocol excluded probands diagnosed with schizophrenia, mental retardation, dementia, or Tourette disorder, or if OCD occurred exclusively during a major depressive episode. Control probands also were excluded if any of the above diagnoses were present. In addition, if no member of the family other than the proband consented to participate, that family was excluded.

The current study was conducted to extend knowledge regarding the familial nature of OCD. It was designed to improve on those that preceded it, and provide as rigorous a test of the hypothesis as possible. Care was taken to study probands from multiple treatment sites to reduce potential selection bias. Community controls were selected carefully to be comparable with the probands. Comprehensive diagnostic assessments were performed by psychiatrists and doctorate-level clinical psychologists on adults and children using age-appropriate diagnostic methods. The primary goal of the study was to determine whether OCD is familial, and to investigate clinical characteristics that might influence the familial aggregation of the disorder.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

As presented in Table 1, 53% of the case probands and 60% of the control probands were female. All but 1 proband in each group were white; 1 case and 1 control proband was Hispanic. Case and control probands were of similar ages. In the case probands, the age range was 18 to 88 years (median, 36 years; mean, 37 years); in the control probands, the age range was 18 to 79 years (median, 36 years; mean, 39 years). Both groups were highly educated. Most were college graduates, and 24% of the case probands and 22% of the control probands had graduate training. Despite these similarities, however, the case probands were significantly less likely to have ever married and, if married, to have children. The number of siblings in case-proband families (examined and not examined) (mean [SD], 2.1 [1.5] siblings) was not significantly different than control proband families (mean [SD], 2.6 [1.8] siblings) (t151 = 1.77; P = .08); however, case probands had significantly fewer children (for case probands: mean [SD], 0.5 [0.8] children; for control probands: mean [SD], 1.3 [1.5] children) (t151 = 4.25; P < .001).

As presented in Table 2, case relatives were, on average, significantly older than control relatives; in case relatives, the age range was 9 to 94 years (median, 49 years; mean, 48 years); in control relatives, the age range was 8 to 91 years (median, 43 years; mean, 45 years). There was a slight preponderance of females in the control relatives. The distribution of type of relative was significantly different between the 2 groups; children com-
for the assessment of personality disorders. The Revised NEO Personality Inventory34 and Leyton Obsessional Inventory35 were used as self-report measures of normal personality and obsessional features, respectively. Children were evaluated in a parallel procedure using comparable instruments (the Kiddie-Schedule for Affective Disorders and Schizophrenia,36 the Children's Yale-Brown Obsessive Compulsive Scale,37 and Leyton Obsessional Inventory—Child Version).38 For every subject, a DSM-IV diagnostic assignment form was completed; this form was designed to record the presence of all necessary diagnostic criteria and guide the assignment of diagnoses according to DSM-IV criteria.

The interrater reliability of the examiners' diagnostic procedure was studied in a sample of 30 subjects. There was good diagnostic agreement, as evidenced by a k = 0.81 for OCD and k = 1.0 for major depression; the intraclass correlation coefficient was 0.78 for compulsive personality disorder traits.

All available diagnostic materials (evaluation by the clinical examiner, informant interview, clinical case summary, medical records, and audiotapes) were reviewed independently by 2 expert psychiatrists (G.N., M.R., J.B., R.H.-S., M.G., or J.W.). The diagnosticians were blind as to whether the subject was a proband or relative and whether they were from a case or control family. All psychiatric diagnoses were made according to strict DSM-IV criteria.29 If all the criteria required for having the disorder were met, then a “definite” diagnosis was given. If any necessary criterion was absent, then the diagnosis was considered “not present.” If it seemed likely that the subject had the diagnosis, but the diagnosticians could not be certain of a given criterion (required for definite diagnosis), 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.” Obsessions and compulsions (but not OCD) were diagnosed if these symptoms were present but did not meet the impairment criteria required for OCD.

DATA ANALYSIS

Subjects with unknown diagnoses for the phenotypes of main interest in this article (OCD, obsessions, and compulsions) were excluded from both the numerator and the denominator in the analyses. Cases with probable diagnoses were treated in 2 ways: (1) when analyzing definite outcomes, these cases were considered as not present and excluded from the numerator but included in the denominator and (2) when analyzing definite and probable outcomes, these cases were considered as probable and included in the numerator and denominator. Although not reported here, we also reanalyzed the data considering the probable cases as “missing” and excluding them from both numerator and denominator; the magnitudes of the estimated odds ratios (ORs) were marginally stronger than the first method and considerably stronger than the second method described above.

Demographic characteristics in case and control probands and case and control relatives, were compared with χ2 or Fisher exact tests for categorical data30 and t or median tests for continuous data. All tests were 2-tailed, with α = .05. The odds of OCD, obsessions, and compulsions in case vs control relatives were estimated using logistic regression by the method of generalized estimating equations, which accounts for within-family correlation among relatives.31 Specifically, ignoring within-family correlation may lead to substantially incorrect SE calculations for logistic regression coefficient estimates. This method provides correct SE estimates using conventional methods while acknowledging that part of the model (within-family correlation in this case) may be misspecified. Potential confounding factors (age of relative, sex of relative, and type of interview [direct or informant-only]) were controlled by including terms for these variables in the regression models.

The mean (SD) number of first-degree relatives assessed (in addition to the proband) was 4.3 (1.8) for case families and 4.1 (2.2) for control families (t151 = 0.55; P = .59).

PREVALENCE AND ODDS OF OBSESSIONS, COMPULSIONS, AND OCD IN RELATIVES

As presented in Table 3, the prevalence of definite OCD was substantially higher in case than control relatives (11.7% vs 2.7%). The prevalence of definite and probable OCD also was higher in case relatives (16.3% vs 5.7%). The prevalence of definite obsessions was 10.4% and 2.4% and 15.1% and 3.8% for definite and probable obsessions in the case and control relatives, respectively. Similar differences are found for the compulsions: 18% of the case relatives vs 6.1% of the control relatives were diagnosed with definite compulsions, and 25% of case relatives vs 12% of the control relatives had definite and probable compulsions.

The odds of definite OCD is nearly 5 times greater in case relatives than control relatives (OR, 4.7; 95% confidence interval, 2.2-10.3) (P = .001) (Table 3). In addition, significant ORs were found for all definitions of the affected phenotype, indicating that first-degree relatives of cases met criteria for OCD-related phenotypes significantly more often than first-degree relatives of controls. In general, using more stringent criteria for affected status (ie, definite as opposed to definite and probable) resulted in larger ORs. Although there is a lower frequency of obsessions than compulsions in both case and control relatives, the magnitude of the association for obsessions is larger than that for compulsions.

As described earlier, case and control relatives were different with respect to age (case relatives were older), sex of relatives interviewed (a larger proportion of case relatives were male), and the type of interview conducted (a greater proportion of case relatives had informant-only interviews). Moreover, the prevalence of OCD was inversely related to current age and was greater in relatives who were directly interviewed than in those who had informant-only interviews (data not shown). We therefore controlled for these potential confounding variables in the regression models. The OR of OCD was higher after adjusting for these factors (Table 4); adjustment also increased the ORs for obsessions and compulsions (data not shown).
PREVALENCE OF OCD IN CASE RELATIVES BY PROBAND CLINICAL CHARACTERISTICS

The age at onset of obsessive-compulsive symptoms in the 80 case probands ranged from 5 to 41 years. As shown in the Figure, the median age at onset of symptoms was about 11 years; more than 75% of the probands had onset by age 14 years, and 90% by age 17 years. The mean (SD) age at onset in males (11.5 [5.6] years; range, 5-30 years) was similar to that in females (12.0 [7.4] years; range, 5-41 years). As shown in the Figure, the median age at onset of symptoms was about 11 years; more than 75% of the probands had onset by age 14 years, and 90% by age 17 years. The mean (SD) age at onset in males (11.5 [5.6] years; range, 5-30 years) was similar to that in females (12.0 [7.4] years; range, 5-41 years). (t151 = 0.98; P = .33).

Age at onset in case probands was dichotomized into early onset (5-17 years) and late onset (18-41 years) groups. The prevalence of OCD in the relatives of probands with early vs late onset was 38 (13.8%) of 276 and 0 (0%) of 49, respectively (P = .006 by Fisher exact test); thus, no cases of OCD were found in the case relatives of probands with late onset of obsessive-compulsive symptoms. In addition, the association between age at onset of obsessive-compulsive symptoms in the case probands and the prevalence of definite OCD in their relatives was examined by including this characteristic as a quantitative variable in a generalized estimating equation model. There was a significant inverse relationship between age at onset and the odds of OCD (OR, 0.92; 95% confidence interval, 0.85-0.99) (P = .02) (Table 5).
Tics (single or multiple vocal or motor tics) were diagnosed in 8 (10.4%) of 77 case probands but no control probands ($P = .008$ by Fisher exact test). The prevalence of definite OCD was nonsignificantly lower in the relatives of probands with tics (6.7%) compared with the relative of probands without tics (12.3%) ($P = .33$). The prevalence of definite OCD was similar in relatives of case probands with obsessive-compulsive personality disorder (OCPD) (10 [11%] of 91) and without OCPD (25 [13.1%] of 191) ($P = .83$) (Table 5).

This study reports 3 main findings. First, OCD is familial. The first-degree relatives of probands diagnosed with OCD had a nearly 5-fold higher lifetime prevalence of OCD. This finding is more robust for a definite diagnosis of OCD (ie, meeting all the DSM-IV criteria); however, the results are significant if probable diagnoses are included. The difference in rates between case and control relatives should be considered from the vantage point of prevalence rates of OCD in the general population; the estimated lifetime prevalence rate in the control relatives should be considered from the vantage point of estimating equation and controlling for relatives’ age, sex, and type of interview.

Second, obsessions are more specific to the familial aspect of the disorder than are compulsions. Relatives of case probands are at greater risk for both obsessions and compulsions than the relatives of controls; however, the magnitude of the association is substantially stronger for obsessions than compulsions. It should be noted that the frequency of compulsions in both case and control relatives is relatively high. This may indicate substantial heterogeneity for compulsions (ie, they may be, in some instances, innocuous behaviors unrelated to an OCD diathesis, or they may be difficult to distinguish clinically from behaviors that are similar in form). These latter behaviors may be associated with other medical conditions and ought not be classified in the same group as compulsions. If there is heterogeneity, then compulsions alone perhaps should not be included in the phenotype for studies of OCD. Additionally, the specification for the definition of compulsions in the DSM-IV may benefit from refinement.

Third, earlier age at onset of the symptoms of OCD indicates a more familial subgroup. The relationship between younger ages at onset and familiality of medical conditions is a well-recognized phenomenon. Previous studies have found that OCD occurs more frequently in the families of those with Tourette disorder, and it has been suggested that the presence of comorbid tics defines a familial subtype of OCD. This finding has been reported previously for OCD, and the association was extremely significant in our sample; indeed, we found no occurrence of OCD in the relatives of probands who had an age at onset of OCD older than 17 years. This suggests that cases of OCD with early age at onset are more likely to yield information about the genetic origins of this disorder. Conversely, cases with older ages at onset, whose numbers are not inconsequential, may have different origins.

There has been a long-standing clinical impression that OCD symptoms may emerge as neurotic manifestations in individuals with OCPD. We hypothesized that the presence of OCPD distinguishes a subgroup of cases of OCD with a higher risk of OCD in their relatives. However, the results do not substantiate this hypothesis: there was no difference in the familial risk of OCD based on the presence of OCPD in the case probands.

Previous studies have found that OCD occurs more frequently in the families of those with Tourette disorder, and it has been suggested that the presence of comorbid tics defines a familial subtype of OCD. Our findings are generally in accord with the most recent family study of OCD. We acknowledge several methodologic limitations of our study. First, all case probands were in treatment. A community sample of OCD cases would have been more desirable; however, given our own experience in epidemiologic studies of OCD, we would have had to screen thousands of subjects to obtain a sufficient number of OCD probands to conduct this study. To minimize selection bias, subjects were rostered and randomly selected from each of the 5 treatment centers. In the sampling frame, we included all probands who presented for treatment during a specified period; subjects who dropped out of treatment were as eligible for selection as those who did not.

Second, only adult probands were selected. This may have reduced the estimate of familial risk, given that our results indicate that younger age at onset is associated with greater familial risk. In addition, few Hispanic and no African American subjects participated in the study. The low frequency of African American cases in the participating centers is compatible with the clinical experience of other centers and with epidemiologic studies.

Third, control probands may have agreed to participate based on their personal or family concerns about emotional difficulties. Although unaware that this was a study of OCD, control probands knew they were being
asked to participate in a family study of psychological difficulties. The effect of such a bias would be to reduce the likelihood of differences in rates of psychopathology between case and control relatives, making comparisons between the 2 groups more conservative. Furthermore, the control probands were identified by a stringent sampling method within the community in which the case probands resided. Every effort was made to ensure that the control probands were similar to the cases in all respects other than the presence of a diagnosis of OCD.

Thus, control relatives were not a “supernormal” control group but were representative of persons residing in the communities in which the cases lived.

Fourth, not all the interviews in the study were direct and in person. We conducted most interviews in subjects’ homes; however, in a minority of cases, a telephone interview was unavoidable. We maintained the same protocol for telephone interviews, including audiotaping and accessing informants; the rates of disorders did not differ between the in-person and telephone interviews. Some relatives could not be interviewed at all because of death or refusal to participate. We strove to include these relatives by conducting family informant interviews with 2 individuals knowledgeable about the subject in each instance. Overall, 71% of the relatives were directly interviewed.

The finding that OCD is familial is a necessity, albeit not sufficient, condition for genetic etiology. The estimated λ (ie, the ratio of the rates of definite OCD in case and control relatives, respectively) of 4.33 is within the range of that for other psychiatric disorders, such as bipolar disorder and panic disorder, although substantially lower than others, such as autism.33 The results, together with those from previous twin studies, encourage a molecular genetic approach to identify a genetic etiology for OCD. Clarification of the range of psychopathology that is transmitted in these families, as well as identification of etiologically homogeneous clinical subtypes, will increase the ability of association studies and genome-wide searches to detect genes involved in the pathogenesis of OCD.

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Reprints: Gerald Nestadt, MD, MPH, Johns Hopkins Hospital, Meyer 4-181, 600 N Wolfe St, Baltimore, MD 21287-7228 (e-mail: gnestadt@mail.jhmi.edu).

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