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Research Article

MAJOR DEPRESSIVE DISORDER IN A FAMILY STUDY OF OBSESSIVE–COMPULSIVE DISORDER WITH PEDIATRIC PROBANDS

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Objective: *This study examined the comorbidity of obsessive–compulsive disorder (OCD) with major depressive disorder (MDD) in a family study of OCD with pediatric probands.* **Method:** *This study assessed the lifetime prevalence of MDD in 141 first-degree relatives (FDR) and 452 second-degree relatives (SDR) of pediatric probands with OCD and healthy controls, and identified variables associated with MDD in case FDR. All available FDR were directly interviewed blind to proband status; parents were also interviewed to assess the family psychiatric history of FDR and SDR. Best-estimate diagnoses were made using all sources of information. Data were analyzed with logistic regression and robust Cox regression models.* **Results:** *Lifetime MDD prevalence was significantly higher in case than in control FDR (30.4 versus 15.4%). Lifetime MDD prevalence was significantly higher in FDR of case probands with MDD than in FDR of case probands without MDD or control FDR (46.3 versus 19.7 versus 15.4%, respectively). MDD in case FDR was significantly associated with MDD in case probands and with age and OCD in those relatives. Lifetime MDD prevalence was similar in case and control SDR. However, lifetime MDD prevalence was significantly higher in SDR of case probands with MDD than in SDR of case probands without MDD or control SDR (31.9 versus 16.8 versus 15.4%, respectively).* **Conclusions:** *MDD prevalence was significantly higher in both FDR and SDR of case probands with MDD than in relatives of case probands without MDD or control relatives, suggesting that pediatric OCD comorbid with MDD is a complex familial syndrome. Depression and Anxiety 28:501–508, 2011.*

Key words: *anxiety; comorbidity; first-degree relatives; second-degree relatives; logistic regression; survival analysis*

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INTRODUCTION

Obsessive–compulsive disorder (OCD) is a heterogeneous psychiatric disorder usually associated with other psychiatric disorders.[1–5] Major depressive disorder (MDD) is the most common comorbid psychiatric disorder in studies of OCD in children and adults, with MDD prevalence estimates in clinical and epidemiological studies of OCD ranging from 40 to 80%.[1–5] Recurrent MDD in adults with OCD has been related to an early age at onset of OCD, more severe obsessive–compulsive (OC) symptoms, and family history of recurrent MDD.[6] However, only an early age at OCD onset was significantly associated with recurrent MDD in a multiple logistic regression model.[6]

Family studies have been used to examine models of psychiatric comorbidity.[7,8] Few studies, however, have examined the familiality of depressive disorders in the relatives of individuals with OCD (case relatives). An early OCD family study found the lifetime prevalence of psychiatric disorders was higher in case than control relatives, with the difference mainly due to an increase in depressive and anxiety disorders.[9] A later study found the relatives of adult probands with OCD and secondary MDD had no greater risk for MDD than relatives of OCD probands without MDD.[10]

A large OCD family study determined that recurrent MDD, generalized anxiety disorder (GAD), panic disorder, agoraphobia, and separation anxiety disorder were more common in case than control relatives.[2] However, only GAD was significantly more frequent in case relatives regardless of whether the relatives had OCD. The results suggested that recurrent MDD and some non-OCD anxiety disorders may emerge either as a consequence of OCD or as a more complex syndrome.

Another large OCD family study found the lifetime prevalence of MDD and non-OCD anxiety disorders were comparable in relatives of OCD probands and controls.[3] However, an early age at OC symptom onset in case probands was associated with higher prevalence of MDD and non-OCD anxiety disorders in case relatives with OCD. The occurrence of MDD and non-OCD anxiety disorders was independent of the same comorbid diagnosis in the OCD probands. The greater comorbidity in case relatives of early-onset compared to late-onset probands supported the hypothesis that age at OC symptom onset in probands is associated with specific affective and anxiety disorders among case relatives.

Twin, family, and segregation studies provide evidence that OCD is a complex trait, with both genetic and environmental susceptibility factors.[11–17] Controlled family studies have demonstrated that the lifetime prevalence of OCD is significantly higher in case compared to control first-degree relatives (FDR), and that an early age at onset of OC symptoms is usually associated with a more familial form of OCD.[12–16] Although the relationship between OCD and MDD has been assessed in controlled family studies with adult probands, this relationship has not been examined in a controlled family study with pediatric probands. The primary goal of this study was to examine the lifetime prevalence of MDD in the FDR and second-degree relatives (SDR) of 35 pediatric probands with OCD and 17 controls with no psychiatric diagnosis. The secondary goal was to determine whether a lifetime diagnosis of MDD in case probands, age of case FDR, and lifetime diagnosis of OCD in case FDR are predictive of MDD in case FDR.[2,3]

METHOD

SUBJECTS

As described previously, we ascertained 35 case and 17 control families through probands between the ages of 10 and 17 years.[15] All probands were directly interviewed to determine whether they met *DSM-III-R and DSM-IV* criteria for OCD. The exclusion criteria for case probands were (1) a diagnosis of mental retardation, autistic disorder, schizophrenia, or bipolar disorder, (2) currently living away from both biological parents, and (3) adoption. The exclusion criteria for control probands were (1) any psychiatric disorder as well as (2) and (3) as above. Written informed consent was obtained from both parents and informed assent from the probands. The study was approved by the University of Michigan Institutional Review Board.

Direct diagnostic interviews were completed with 203 individuals (52 probands, 136 FDR, 15 SDR). The sample did not include four directly interviewed individuals because genotyping indicated nonpaternity within a family.[18] Diagnostic information was also collected from parents or spouses on 637 individuals (52 probands, 133 FDR, 452 SDR). This process provided diagnostic information on 5 FDR without direct interviews and 437 SDR without direct interviews for 442 relatives with only family informant data.

PROCEDURE

Probands and siblings between 10 and 17 years of age were interviewed with the Schedule for Affective Disorders and Schizophrenia for School Age Children-Epidemiologic Version.[19] The interview was completed independently with a parent of the subject as well as with the subject. Relatives 18 years and older were interviewed with the Structured Clinical Interview for DSM-III-R.[20] Both interviews were supplemented with sections on OCD and tic disorders from the Schedule for Tourette and Other Behavioral Syndromes.[12,21] The OCD section included a checklist from the Yale–Brown Obsessive Compulsive Scale,[22] modified to obtain information about the lifetime occurrence of obsessions and compulsions. Further information on relatives 18 years and older was obtained using the Family Informant Schedule and Criteria (FISC).[23] The mother of each proband was interviewed with the FISC regarding her spouse, adult offspring, parents, and siblings; the father of each proband was interviewed similarly regarding his spouse, parents, and siblings. Thus, two types of information were obtained on directly interviewed adults.

Interviews were audiotaped and coded on paper to assess reliability, maintain quality control, and achieve diagnostic consensus. The interviewers were limited to interviewing either probands and their relatives between 10 and 17 years of age or adult relatives. The interviewer for a proband was not involved with the interviews of other family members. After completing all interviews for an individual, all available materials including clinical records were collated. Information identifying the proband was removed, so that diagnostic ratings could be completed by raters blind to proband diagnosis. Diagnosticians were never given a complete family to

evaluate at one time. All proband diagnostic evaluations were done separately from those of their relatives.

BEST-ESTIMATE DIAGNOSES

Best-estimate lifetime diagnoses were made independently for directly interviewed subjects by two investigators using *DSM-III-R* and *DSM-IV* criteria following established procedures described previously.[15,17,18,24] To avoid forcing closure on inadequate diagnostic information, subjects were reinterviewed, if necessary, to clarify incomplete or contradictory information. When disagreement occurred between two diagnosticians, the case was discussed until either consensus was reached or a third diagnostician was consulted to reach a final diagnosis. There was good diagnostic agreement in the initial diagnoses, as evidenced by a $\kappa = 0.91$ for OCD, a $\kappa = 1.00$ for MDD, and an intraclass correlation coefficient of 0.94 for age at onset of OC symptoms. The diagnoses of OCD, MDD, and non-OCD anxiety disorders were made in subjects with only family history information available only if symptoms met definite FISC criteria for diagnosis. The non-OCD anxiety disorders consisted of overanxious disorder/GAD, panic disorder, and phobias.

STATISTICAL ANALYSES

The demographic characteristics of case and control probands and of case and control relatives were compared using χ^2 or Fisher exact tests for categorical data and *t* tests for continuous data.[25] Unadjusted lifetime rates of MDD in case and control relatives were compared by χ^2 tests with one degree of freedom for 2×2 tables. The odds of MDD in case versus control relatives were estimated using logistic regression by the generalized estimating equation (GEE) method, which accounts for within-family correlations among relatives.[26] The odds of MDD in case versus control FDR were also estimated with adjustment for age and gender in a multivariable model. Three predictors of MDD in case FDR were examined separately using logistic regression by the GEE method, with a history of MDD in case probands, age of case FDR, and history of OCD in case FDR entered as independent variables.[2,3,6]

Age-corrected lifetime rates of MDD among relatives were compared by Cox proportional hazards (PH) regression.[27] Robust Cox regression was used to control for the familial dependency of observations in relatives, which may be more appropriate than logistic regression for analyzing data from subjects still at risk for developing MDD, in that it censors subjects who have not developed MDD by the interview age. Two potentially confounding covariates, age and gender of relative, were controlled by including terms for these variables in PH models. Age-corrected occurrence risks were estimated using Kaplan–Meier survival analyses of the time to onset of MDD.[28] Analyses were performed with SAS 9.13 software.[29] All tests were two-tailed with $\alpha = .05$.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

The total sample had 645 individuals, consisting of 35 case probands, 102 case FDR, 303 case SDR, 17 control probands, 39 control FDR, and 149 control SDR. Direct interviews were completed with all probands, 98 (96.1%) case FDR, 38 (97.4%) control FDR, 14 (4.6%) case SDR, and one (0.7%) control SDR, yielding a significant difference between the case and control SDR in the proportion of directly interviewed subjects ($\chi^2 = 4.86$, $df = 1$, $P = .027$). Family informant information was obtained for all case and control relatives without direct interviews. Table 1 describes the demographic and age at onset characteristics of the sample.

PREVALENCE OF MDD IN CASE PROBANDS BY CLINICAL CHARACTERISTICS

Age at onset of OC symptoms in the case probands ranged from 4 to 14 years. Fourteen case probands had a lifetime diagnosis of MDD, with age at onset of the first MDD episode ranging from 7 to 14 years. In those with both OCD and MDD, age at OC symptom onset was significantly earlier than age at MDD onset (7.6 ± 3.2 versus 11.2 ± 2.0 years, mean $\pm$ SD, paired $t = 4.49$, $df = 13$, $P = .0006$). Compared to case probands without MDD, a higher proportion of case probands with MDD had a lifetime diagnosis of a phobic disorder (57.1 versus 23.8%, $\chi^2 = 4.00$, $df = 1$, $P = .046$). There were no significant differences between case probands with and without MDD in age, gender, social class, age at OC symptom onset, or diagnoses other than phobias.

PREVALENCE AND ODDS OF MAJOR DEPRESSIVE DISORDER IN CASE AND CONTROL FIRST-DEGREE RELATIVES

The lifetime prevalence of MDD was higher in case than control FDR (30.4 versus 15.4%, respectively). In a logistic regression, the odds of MDD in case FDR was 2.5 times that in control FDR (odds ratio [OR] 2.49; 95% CI 0.99–6.23; $P = .050$), which was confirmed with univariate robust Cox regression (HR 2.42; 95% CI 1.09–5.37; $P = .030$). Table 2 indicates the odds of MDD between the two groups of FDR increased slightly to 2.72 while controlling for the age and gender of the relative, in a multivariable model ($P = .035$). Age of relative per 10-year increase also had a significant effect in this model ($P = .032$). Type of interview was not included because almost all FDR were directly interviewed; the results did not change substantially with type of interview included in the model (data not shown). The significant difference between case and control FDR while controlling for the age and gender of the relative, was confirmed with multivariable robust Cox regression (HR 2.40; 95% CI 1.07–5.39; $P = .034$). Gender of relative had no significant effect in that model ($P = .11$).

PREVALENCE AND ODDS OF MAJOR DEPRESSIVE DISORDER IN CASE AND CONTROL FIRST-DEGREE RELATIVES WITH REFERENCE TO MAJOR DEPRESSIVE DISORDER IN CASE PROBANDS

As noted in Table 3, the lifetime prevalence of MDD was higher in the FDR of case probands with MDD than in either the FDR of case probands without MDD or control FDR (46.3 versus 19.7 versus 15.4%, respectively). There was minimal difference in

TABLE 1. Demographic and age at onset characteristics of 52 probands, 141 first-degree relatives, and 452 second-degree relatives

	Case probands ($N = 35$)	Control probands ($N = 17$)	Test statistic[a]	P
Gender, N (%)				
Male	25 (71)	10 (59)	$\chi^2_1 = 0.83$	.363
Female	10 (29)	7 (41)		
Mean (*SD*) age, years	13.7 (2.4)	12.4 (1.8)	$t_{50} = 1.97$	.055
Caucasian, N (%)	34 (97)	16 (94)	$\chi^2_1 = 0.28$	.595
Social class N (%)[b]				
I and II, highest	20 (57)	10 (59)		
III	9 (26)	6 (35)	Fisher's exact test	.588
IV and V, lowest	6 (17)	1 (6)		
Mean (*SD*) age at onset of OCD symptoms, years	8.8 (3.2)			
	Case first-degree relatives ($N = 102$)	Control first-degree relatives ($N = 39$)	Test statistic[a]	P
Gender, N (%)				
Male	52 (51)	21 (54)	$\chi^2_1 = 0.09$	.761
Female	50 (49)	18 (46)		
Mean (*SD*) age, years	36.1 (13.4)	39.8 (11.8)	$t_{139} = 1.51$	.134
Type of relative, N (%)				
Parents with diagnostic data	69 (68)	34 (87)	$\chi^2_1 = 5.47$	.019
Siblings with diagnostic data	33 (32)	5 (13)		
Mean (*SD*) number first-degree relatives assessed in family	2.9 (1.1)	2.3 (0.5)	$t_{50} = 2.80$	.007
Mean (*SD*) age at onset of MDD symptoms, years	24.0 (12.6)	28.2 (8.2)	$t_{35} = 0.78$	.440
	Case second-degree relatives ($N = 303$)	Control second-degree relatives ($N = 149$)	Test statistic[a]	P
Gender, N (%)				
Male	153 (50.5)	78 (52.4)	$\chi^2_1 = 0.137$	.711
Female	150 (49.5)	71 (47.6)		
Mean (*SD*) age, years	53.8 (16.7)	53.6 (16.2)	$t_{450} = 0.107$	.915
Type of relative, N (%)				
Grandparents	127 (41.9)	64 (43.0)		
Uncles and aunts	171 (56.4)	84 (56.4)	$\chi^2_2 = 0.747$	.688
Half-siblings	5 (1.6)	1 (0.7)		
Mean (*SD*) number second-degree relatives assessed in family	8.8 (0.5)	8.8 (0.7)	$t_{50} = 0.008$	.993

OCD, obsessive–compulsive disorder; MDD, major depressive disorder.
[a]Degrees of freedom are presented as subscript figures.
[b]Hollingshead index (1965).

TABLE 2. Odds ratios for major depressive disorder in 141 first-degree relatives using a multivariable model

Characteristic of first-degree relative	Odds ratio (95% confidence interval)[a]	P
Group		
Case	2.72 (1.07–6.92)	.035
Control[b]	1.0	
Gender		
Male	1.60 (0.81–3.16)	.172
Female[b]	1.0	
Age at interview (per 10-year increase)	1.34 (1.02–1.74)	.032

[a]Determined using logistic regression by the generalized estimating equation method.
[b]Reference group.

the lifetime prevalence of OCD, however, in the FDR of case probands with and without MDD (26.8 versus 19.7%, respectively). In a logistic regression, the odds of MDD was 3.8 times as great in FDR of case probands with MDD as in FDR of case probands without MDD ($P = .012$), which was confirmed with univariate robust Cox regression (HR 2.45; 95% CI 1.12–5.35; $P = .025$). Moreover, the odds of MDD was 5.1 times as great in FDR of case probands with MDD as in control FDR ($P = .004$), which was confirmed with univariate Cox regression (HR 3.94; 95% CI 1.64–9.47; $P = .002$). However, the odds of MDD in the FDR of case probands without MDD and the control FDR was not significantly greater than 1 ($P = .54$), with a similar result using univariate Cox regression ($P = .40$).

TABLE 3. Prevalence of major depressive disorder in 141 first-degree relatives and 452 second-degree relatives

	First-degree relatives					
	Of case probands without MDD (1) ($N = 61$)	Of case probands with MDD (2) ($N = 41$)	Of control probands (3) ($N = 39$)	Odds ratio (95% confidence interval)[a]		
Diagnosis	*N* (%)	*N* (%)	*N* (%)	Group 1 versus 3	Group 2 versus 3	Group 2 versus 1
MDD	12 (19.7)	19 (46.3)	6 (15.4)	1.36 (0.50–3.72)	5.13 (1.69–15.51)[b]	3.76 (1.34–10.57)[c]
OCD	12 (19.7)	11 (26.8)	1 (2.6)	9.33 (1.19–73.28)[d]	14.60 (1.91–112.13)[e]	1.56 (0.71–3.44)
Other anxiety disorders	19 (31.1)	9 (22.0)	6 (15.4)	2.41 (0.74–7.84)	1.56 (0.49–4.99)	0.65 (0.26–1.62)
	Second-degree relatives					
	Of case probands without MDD (1) ($N = 184$)	Of case probands with MDD (2) ($N = 119$)	Of control probands (3) ($N = 149$)	Odds ratio (95% confidence interval)[a]		
Diagnosis	*N* (%)	*N* (%)	*N* (%)	Group 1 versus 3	Group 2 versus 3	Group 2 versus 1
MDD	31 (16.8)	38 (31.9)	23 (15.4)	1.05 (0.49–2.24)	2.16 (1.10–4.25)[f]	2.06 (1.12–3.78)[g]

MDD, major depressive disorder; OCD, obsessive–compulsive disorder; Other Anxiety Disorders, overanxious disorder/generalized anxiety disorder, panic disorder, and phobic disorders.
[a]Determined using logistic regression by the generalized estimating equation method.
[b]$P < .005$, first-degree relatives of case probands with MDD significantly different from control first-degree relatives.
[c]$P < .05$, first-degree relatives of case probands with MDD significantly different from first-degree relatives of case probands without MDD.
[d]$P < .05$, first-degree relatives of case probands without MDD significantly different from control first-degree relatives.
[e]$P < .01$, first-degree relatives of case probands with OCD significantly different from control first-degree relatives.
[f]$P < .05$, second-degree relatives of case probands with MDD significantly different from control second-degree relatives.
[g]$P < .05$, second-degree relatives of case probands with MDD significantly different from second-degree relatives of case probands without MDD.

Figure 1 presents the Kaplan–Meier survivor functions comparing the ages at onset of the first MDD episode in the three groups of FDR, in which the FDR of control probands are compared with the FDR of case probands with and without MDD.

DISTRIBUTION OF MDD IN CASE FIRST-DEGREE RELATIVES WITH OCD OR WITH NON-OCD ANXIETY DISORDERS

To examine the extent of comorbidity with MDD, the prevalence of MDD was compared in case FDR with and without OCD and case FDR with and without a non-OCD anxiety disorder. First, the lifetime prevalence of MDD was higher in case FDR with OCD than in case FDR without OCD (60.9 versus 21.5%, respectively). In a logistic regression, the odds of MDD was 5.7 times as great in case FDR with OCD as in case FDR without OCD (OR = 5.67; 95% CI 2.14–15.87; $P < .0006$). In the 14-case FDR with both OCD and MDD, the age at OC symptom onset of was earlier than the age at MDD onset (12.9 ± 7.5 versus 20.7 ± 8.9 years, mean $\pm$ SD, paired $t = 2.88$, $df = 13$, $P = .013$). Second, the lifetime prevalence of MDD was higher in case FDR with a non-OCD anxiety disorder than in case FDR without one of those disorders (46.4 versus 24.3%, respectively). In a logistic regression, the odds of MDD was 2.7 times as great in

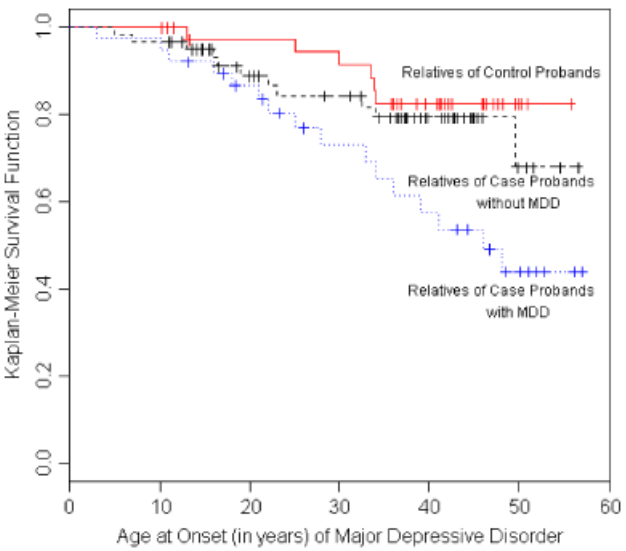

Figure 1. Age at onset in years of major depressive disorder (MDD) in first-degree relatives (FDR) of control probands, FDR of case probands without MDD, and FDR of case probands with MDD. The difference in the proportion of MDD between the two groups of case FDR was significant with univariate robust Cox regression (HR 2.45; 95% CI 1.12–5.35; $P = .025$). The difference in the proportion of MDD between FDR of case probands with MDD and control FDR was also significant with Cox regression (HR 3.94; 95% CI 1.64–9.47; $P = .002$).

FDR with a non-OCD anxiety disorder as in case FDR without one of those disorders (OR 2.70; 95% CI 1.08–6.78; $P = .033$). In the 13-case FDR with both MDD and a non-OCD anxiety disorder, however, there was no significant difference in the age at onset between these disorders ($P = .65$). Furthermore, when case proband history of MDD was considered, there was no significant difference in lifetime prevalence of the non-OCD anxiety disorders between the FDR of the case probands with and without MDD (see Table 3).

PREVALENCE OF MDD IN CASE FIRST-DEGREE RELATIVES BY CLINICAL CHARACTERISTICS

Three predictors of MDD in case FDR were assessed with logistic regression. MDD in probands (OR 4.09; 95% CI 1.45–11.54; $P = .008$), age of relative (OR per 10-year increase = 1.39; 95% CI 1.03–1.89; $P = .033$), and OCD in FDR (OR 5.74; 95% CI 2.66–12.38; $P < .0001$) were all significant predictors of MDD in case FDR. There was no evidence for an interaction between MDD in probands and OCD in FDR ($P = .39$). Multivariable robust Cox regression confirmed that MDD in probands (HR 2.59, 95% CI 1.20–5.61, $P = .016$) and OCD in case FDR (HR 4.12; 95% CI 2.22–7.66; $P < .0001$) were significant predictors of MDD in case FDR. Again, there was no evidence for an interaction between MDD in probands and OCD in relatives ($P = .51$).

PREVALENCE AND ODDS OF MAJOR DEPRESSIVE DISORDER IN CASE AND CONTROL SECOND-DEGREE RELATIVES

The lifetime prevalence of MDD was slightly higher in case than in control SDR (22.8 versus 15.4%, respectively), which was not significant with logistic regression ($P = .28$). However, as shown in Table 3, the lifetime prevalence of MDD was higher in SDR of case probands with MDD than in either SDR of case probands without MDD or control SDR (31.9 versus 16.8 versus 15.4%, respectively). In a logistic regression, the odds of MDD was 2.1 times as great in SDR of case probands with MDD as in SDR of case probands without MDD ($P = .020$). Furthermore, the odds of MDD was 2.2 times as great in SDR of case probands with MDD as in control SDR ($P = .025$). In contrast, the odds of MDD in SDR of case probands without MDD and control SDR was not significantly greater than 1 ($P = .90$).

DISCUSSION

INCREASED AGGREGATION OF MDD IN THE FIRST- AND SECOND-DEGREE RELATIVES OF PEDIATRIC OCD PROBANDS WITH MDD

The lifetime prevalence of MDD in our family study was higher in FDR and SDR of pediatric OCD probands with MDD than in the relatives of case probands without MDD or control relatives. In both case probands with MDD and case FDR with comorbid OCD and MDD, age at onset of OC symptoms was significantly earlier than age at onset of the first MDD episode. A previous family study found a higher lifetime prevalence of MDD in FDR with comorbid OCD in which the probands had early-onset but not late-onset OCD, and that the occurrence of MDD in those relatives was independent of the same diagnosis in case probands.[3] In contrast, we found that MDD in case probands and OCD in case FDR were both significant predictors of MDD in case FDR. The results from these two studies, as well as from the study of recurrent MDD in individuals with OCD,[6] indicate that an early age at onset of OC symptoms is a significant risk for MDD in individuals with OCD.

The lifetime MDD prevalence of 46.3% in the FDR of case probands with MDD in our study is higher than the lifetime MDD prevalence of 33.9% in the FDR of probands with MDD reported in a large family study of adolescents with MDD, anxiety disorders, or substance use disorders.[30] The difference perhaps reflects increased familial aggregation of MDD in families ascertained through probands with both early-onset OCD and MDD. An increased prevalence of MDD in the case SDR of probands with both OCD and MDD has not been reported previously to our knowledge. Family studies have demonstrated that early-onset OCD is highly familial.[12,13,15,16] The results from this study indicate that MDD is also highly familial when comorbid with pediatric OCD.

The higher prevalence of MDD in the relatives of case probands with MDD compared to relatives of case probands without MDD provides further evidence for the heterogeneity of early-onset OCD.[31] Because the increased risk for MDD occurred only in relatives of probands with early-onset OCD and MDD, there is evidence for a model of correlated liabilities in which risk factors for the two disorders are correlated, rather than for a direct causal model in which one disorder is a cause of the other.[8] The higher prevalence of MDD in the FDR of case probands with MDD was not associated with a higher prevalence of non-OCD anxiety disorders in those relatives, indicating that the increase in MDD prevalence is not mediated by another anxiety disorder. Instead, a nonsignificantly higher prevalence of non-OCD anxiety disorders was observed in the FDR of the case probands without MDD.

LIMITATIONS

Several limitations of our family study require comment. Case probands were recruited through a tertiary medical center, which possibly attracted more comorbid psychopathology; hence, the case probands and relatives in our sample may not be representative of families with pediatric OCD in the general population.[32] The number of directly interviewed subjects was low, so that the statistical power in comparisons of case and control FDR was

modest and the significance level was not adjusted for multiple comparisons. The lifetime prevalence of MDD in FDR was based primarily on direct interviews, whereas that estimate in control SDR was based primarily on family history interviews. Both interviewing strategies yielded a lifetime MDD prevalence of 15.4% in the two groups of control relatives, which is comparable to the lifetime prevalence of MDD in the general population of 16.6%.[33] Similar prevalence estimates in the two groups of control relatives suggest the different interviewing strategies did not contribute substantially to the differences in lifetime MDD prevalence estimates between case and control relatives.

This study did not include an MDD without OCD proband group. Thus, we could not fully examine (1) whether OCD is transmitted in relatives of MDD probands to further assess whether OCD and MDD share a common diathesis and (2) whether OCD with MDD had an effect on the familial transmission of MDD compared with MDD alone. However, the three proband groups allowed us to address the effect of MDD in pediatric OCD probands on the familial transmission of MDD and its comorbidity with non-OCD anxiety disorders.

CLINICAL IMPLICATIONS

The results of the study are significant for reasons extending beyond our understanding of the familial relationship between OCD and MDD. Specifically, clinicians evaluating and treating children with OCD should routinely screen for comorbid mood and non-OCD anxiety disorders. Children with OCD who have a first- or second-degree relative with MDD seem to be at high risk for developing MDD themselves. Both OCD and MDD cause substantial distress and impairment, often requiring sustained treatment to improve long-term outcome.[34] Further research is warranted on the etiology, course, and treatment of comorbid OCD and MDD.

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