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Perinatal Factors Affecting Expression of Obsessive Compulsive Disorder in Children and Adolescents

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Abstract

Objective: To examine whether adverse perinatal experiences of children are associated with obsessive compulsive disorder (OCD) in youth.
Methods: Subjects were 130 children and adolescents with OCD recruited from a family genetic study of pediatric OCD and 49 matched controls from a contemporaneous family case-control study of attention-deficit/hyperactivity disorder (ADHD). Subjects were comprehensively assessed in multiple domains of function. A systematic history of pregnancy, delivery, and infancy complications was obtained.
Results: Compared to normal controls, children with OCD had mothers with significantly higher rates of illness during pregnancy requiring medical care ($\chi^2 = 8.61$, $p = 0.003$) and more birth difficulties (induced labor, forceps delivery, nuchal cord, or prolonged labor) ($\chi^2 = 7.51$, $p = 0.006$). Among the OCD-affected children, we found several significant associations between adverse perinatal experiences and earlier age at onset, increased OCD severity, and increased risk for comorbid ADHD, chronic tic disorder, anxiety disorder, and major depressive disorder.
Conclusion: Although exploratory, our analyses found that children with OCD had higher rates of several adverse perinatal experiences compared with controls. Among OCD-affected children, comorbid psychopathology was predicted by specific perinatal risk factors. Prospective studies of perinatal adverse events that minimize potential recall bias and type I errors are needed.

Introduction

Despite substantial extant research documenting the importance of genetic and familial influences on expression of obsessive compulsive disorder (OCD) (Alsobrook II et al. 1999; Grados et al. 2001; Hanna et al. 2005; Nestadt et al. 2000; Pauls et al. 1995; Reddy et al. 2001; do Rosario–Campos et al 2005), scant information is available regarding environmental factors for the disorder. Such environmental factors could have important implications for prevention or management if they could be identified and manipulated. One approach to study unique environmental effects on the expression of psychiatric illness examines perinatal (intrauterine, birth, and postnatal) experiences of affected subjects. The intrauterine environment also includes exposure to potential teratogens such as alcohol and tobacco.An increase in various perinatal risk factors has been observed in several psychiatric disorders that onset in childhood including autism (Glasson et al. 2004; Juul–Dam et al. 2001), schizophrenia (Cannon et al. 2000; Geddes and Lawrie 1995; Hultman et al. 1999; Jones et al. 1998; Sacker et al. 1995) and attention-deficit/hyperactivity disorder (ADHD) (Bat-

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stra et al. 2003; Brookes et al. 2006; Knopik et al. 2005; Linnet et al. 2003; Mick et al. 2002) when compared with controls. Unfortunately, research examining the relationship between perinatal factors and OCD has been extremely limited. One exception is a study by Lensi et al. (1996) who collected perinatal histories from 263 patients (mean age 33 years) as part of a study on gender differences in OCD. Using a specially developed OCD questionnaire that included probes related to perinatal adverse events, the authors found a higher rate of perinatal trauma (defined by dystocic delivery, use of forceps, breech presentation, or prolonged hypoxia) in males with an earlier onset of OCD. In another study of 60 pediatric probands with Tourette's disorder (TD), Santangelo et al. (1994) examined the association between comorbid OCD status and pre- and perinatal complications and found that TD probands with comorbid OCD ($n = 33$) were almost 8 times as likely to have been delivered by forceps than those without OCD and 5 times more likely to have been regularly exposed to coffee, cigarettes, and alcohol in utero. A similar study by Mathews et al. (2006) also identified maternal cigarette exposure in utero as a significant predictor of increased tic severity and comorbid OCD status in a sample of 180 probands (ages 3 to 59) with TD. Recently, Vasconcelos et al. (2007) compared 68 adult OCD patients to 70 controls based on responses to a standardized questionnaire that evaluated environmental factors, including gestation, labor, birth, and early infancy. They reported significantly greater frequency of perinatal risk factors (edema, excessive weight gain, hyperemesis gravidarum, prolonged labor, preterm birth, and jaundice) in OCD patients than in controls.

The purpose of this study was to re-examine the association of adverse perinatal experiences as potential risk factors for OCD in children in general, and whether they would predict sporadic versus familial cases of pediatric OCD. We hypothesized that more frequent adverse perinatal experiences would predict sporadic (i.e., nonfamilial OCD), rather than the familial form. We also aimed to examine whether perinatal complications moderate the clinical picture of pediatric OCD. To this end we used data from a well-characterized cohort of children and adolescents with OCD that included substantial sample size, ascertainment close to illness onset, and systematic collection of obstetric, perinatal, and early developmental history.

Methods

Participants

Our sample included 130 children and adolescents recruited from a longitudinal family study (DG K08 MH01481) of pediatric OCD and 49 matched controls from a contemporaneous family study of ADHD. Briefly, the pediatric OCD study comprehensively assessed children with OCD in multiple domains using parent and child structured diagnostic interviews using the Kiddie–Schedule for Affective Disorders and Schizophrenia–Epidemiological version (K-SADS-E) (Orvaschel and Puig–Antich 1987), clinical assessment including the CY-BOCS, and best estimate diagnoses (Leckman et al. 1982). We screened a total of 194 youth and enrolled 130, most of whom were referred to the OCD clinical program, although 22 were ascertained directly through advertising and direct referral to the research study (methods are detailed fully in Geller et al. 2007). For comparison, a sample of non-OCD non-ADHD controls ascertained from a separately funded but contemporaneous family case-control study of Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R) ADHD was used. The same pool of identically trained raters interviewed controls with the same assessment battery, thus avoiding assessment bias. This study ascertained youth with and without ADHD from consecutive referrals to an outpatient psychiatry clinic at the same urban medical center and pediatric patients from a Health Maintenance Organization (HMO). Within each setting, non-ADHD controls were also selected. For this comparison we chose a random sample of siblings of non-ADHD control probands matched to the OCD baseline sample on age, gender, socioeconomic status (SES), and family intact status. Siblings of non-ADHD controls were selected (rather than controls themselves) because no diagnoses were excluded (including ADHD) in this group. This study was approved by the institutional review board (IRB) of the hospital. For all children, parents provided hospital IRB-approved written informed consent for themselves, while children and youth provided written assent to participate.

Assessments

Our sample was assessed along multiple domains including psychopathology, neuropsychological, and psychosocial functioning. Psychiatric assessments of probands and siblings were made using the K-SADS-E (Epidemiologic Version) (Orvaschel and Puig–Antich 1987) and were based on independent interviews with the mothers and direct interviews of probands and siblings. Raters who were blind to the clinical status of the subjects (probands or siblings) evaluated the subjects. A diagnostic review team blindly weighed each source of information from direct and indirect K-SADS-E to yield diagnoses using a best estimate method described by Leckman et al. (1982), and using clinical judgment based on the information provided in each report. Diagnoses were considered definite only if Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) criteria were met to a degree that would be considered clinically meaningful. We excluded potential participants if they had a diagnosis of autism or pervasive developmental disorder, psychosis, or schizophrenia, eating disorder, major sensorimotor handicaps (deafness, blindness), or inadequate English language.

The K-SADS-E, administered to mother as indirect informant, also included standardized questions about mother's pregnancy, including drug and alcohol use, delivery and obstetric information, perinatal history, and early developmental history, with further probes to quantify frequency, severity, amount, and duration where relevant. The recorded information was coded in a systematic fashion with operational definitions for items such as tobacco use, premature birth, low birth weight, etc (Table 1).

Data analysis

Pregnancy, labor, and postnatal experiences of children with OCD were compared to those of controls. Within the OCD cohort, perinatal variables were also used to predict the likelihood of having an affected first-degree relative (familial OCD), clinical characteristics of OCD (earlier vs. later onset, severity, duration), presence of comorbid disorders, and gender. We also collapsed related variables into a smaller

TABLE 1. PERINATAL ADVERSE EVENTS IN CHILDREN WITH OCD AND CONTROL SUBJECTS

	OCD probands N *(%)*	*Matched controls* N *(%)*
PRENATAL COMPLICATIONS	98 (78)	39 (80)
Complications of pregnancy	89 (71)	38 (78)
Spotting/light bleeding	14 (12)	11 (22)
Heavy bleeding requiring bed rest	3 (2)	1 (2)
Excessive nausea/vomiting >3 months	17 (14)	8 (16)
Weight gain >25 lbs	66 (54)	26 (53)
Weight loss >10 lb	4 (3)	0 (0)
Infection requiring medical attention	14 (11)	3 (6)
High blood pressure and/or excessive fluid in body	16 (13)	6 (12)
Maternal convulsions (not due to previous epilepsy)	0 (0)	1 (2)
Prenatal complications not directly related to pregnancy	48 (39)	8 (16)
Accidents requiring medical care	4 (3)	1 (2)
Other illnesses requiring medical care	24 (20)	1 (2)
Emotional problems for which mother sought counseling	9 (7)	1 (2)
MEDICATIONS/DRUGS TAKEN DURING PREGNANCY	56 (45)	13 (27)
Prescribed medications	38 (31)	11 (22)
Smoke > or = 3 months	5 (4)	1 (2)
Alcohol consumption daily or binges	0 (0)	1 (2)
Drugs not prescribed by an M.D.	1 (0.8)	0 (0)
LABOR, DELIVERY, AND NEONATAL	97 (77)	30 (61)
Complications of labor	91 (72)	28 (57)
Breech delivery	8 (6)	2 (4)
Cesarean delivery	36 (29)	11 (22)
Other birth difficulties (post-term, prolonged labor, jaundice requiring phototherapy)	76 (62)	19 (39)
Postnatal complications	31 (25)	7 (14)
Incubator post-birth	10 (8)	5 (10)
Low birth weight <5 lbs	1 (0.8)	0 (0)
Infant remained in hospital after mother went home	9 (7)	2 (4)
Infant had surgery in first month of life	4 (3)	1 (2)
Switched milk formulas > or = 3 times	18 (15)	0 (0)
EARLY DEVELOPMENTAL PROBLEMS	9 (71)	8 (16)
Excessive crying (infant cried day and night, never satisfied)	23 (19)	6 (12)
Infant too quiet (did not seem to respond to care/attention)	2 (2)	1 (2)
Infant stiffened up when help or seemed to push away	4 (3)	2 (4)
Infant floppy or limp when help or did not cuddle	4 (3)	0 (0)
Other infant events (e.g. infection during infancy)	27 (22)	0 (0)

Percentages for probands vary due to differences in denominator data; range 122–126 for probands; 49 controls.

number of categories such as complications of pregnancy, medication and drug use during pregnancy, birth complications, and postnatal problems, as a means of improving power to examine broader clusters of perinatal events on outcomes. Outcomes were assessed using Pearson's chi-squared and Fisher's exact tests for binary variables and linear regression for continuous variables. Fisher's exact test was used in the event that one or more cells in the two-by-two table had an expected value less than five, thus violating the assumptions of Pearson's chi-squared test. All tests were two-tailed with alpha set at 0.01 to limit the number of type I errors that may arise in our exploratory analysis.

Results

Our OCD sample consisted of 130 children and adolescents (OCD group). The mean age at onset of OCD in our subjects was 7.6 years (SD = 3.1), mean age at ascertainment was 11.5 years (SD = 3.1), and duration of OCD was 4.5 years (SD = 3.7). They showed 59% male preponderance and were moderately to severely impaired overall (past GAF 48 (SD = 5.9), current GAF 53 (SD = 5.7)). The mean CY-BOCS score was 21 (SD = 5.6), and most subjects had both multiple obsessions and multiple compulsions. Forty-one probands had a positive first-degree family history of OCD. There were 49 matched controls (control group) and no differences in age, gender, or socioeconomic status (SES) between the OCD and control group (Table 2). Lifetime rates of comorbid DSM IV disorders in OCD probands were as follows: ADHD 42%, Tourette's syndrome 22%, major depressive disorder 50%, bipolar disorder 4.6%, and generalized anxiety disorder 49%.

Raw perinatal data organized into several categories including pregnancy, medication and drug use, birth, postnatal, and "other" are shown in Table 1. Collapsed variables summarizing related categorical events such as prenatal complications, medication and drug use during pregnancy,

Table 2. Comparison between Demographic Variables of OCD and Control Subjects

	OCD N = *130*	*Controls* N = *49*	*Test statistic*	p-*value*
Age at ascertainment (yrs) (± SD)	11.5 ± 3.1	11.7 ± 3.1	$t = 0.38$	0.70
Gender (male)	79 (61)	26 (53)	$\chi^2_{(1)} = 0.9$	0.35
SES	1.7 ± 0.8	1.6 ± 0.8	$z = -1.3$	0.19
Intact family	72 (56)	41 (84)	$\chi^2_{(1)} = 11.9$	0.001
Lifetime GAF	48.5 (6.0)	64.9 (9.1)	$t = 14.1$	<0.001
Current GAF	53.4 (5.6)	69.3 (7.2)	$t = 15.6$	<0.001

GAF, Global Assessment of Functioning; SES, socioeconomic status.
OCD, obsessive compulsive disorder.

labor, delivery, and neonatal complications, and early developmental problems are denoted by capitalized headings in Table 1. Those tests that met the threshold Bonferroni-corrected *p*-value of 0.002 are indicated using italicized *p* values to highlight the strength of their association.

Compared to controls, mothers of children with OCD reported significantly

a. higher rates of illness during pregnancy requiring medical care ($\chi^2_{(1)} = 8.61$, $p = 0.003$)
2. more birth difficulties (such as induced labor, forceps delivery, nuchal cord, or prolonged labor) ($\chi^2_{(1)} = 7.51$, $p = 0.006$)
3. needed more formula changes in infancy (defined as more than three formula switches) ($\chi^2_{(1)} = 7.94$, $p = 0.005$)

Among the OCD children we found several significant associations including:

a. higher rates of illness requiring medical care in pregnancy in mothers of children with a positive immediate family history of OCD ("familial" OCD) ($\chi^2_{(1)} = 7.56$, $p = 0.006$)
b. accidents sustained by mother (defined as requiring medical care) during pregnancy ($F(1,121) = 6.52$, $p = 0.01$) and severe response to changes in infancy ($F(1,82) = 10.69$, $p = 0.002$) predicted earlier onset of OCD
c. medication and drug use during pregnancy (yes = 31, no = 25, $\chi^2_{(1)} = 7.9$, $p = 0.005$), need for an incubator in the postnatal period (yes = 9, no = 1, Fisher's exact test, $p = 0.001$), need to stay in hospital after mother was discharged (yes = 8, no = 1, Fisher's exact test, $p = 0.003$), and excessive crying in infancy (yes = 15, no = 8, $\chi^2_{(1)} = 7.27$, $p = 0.007$) were all associated with an increased risk for comorbid ADHD
d. perinatal jaundice in infancy requiring treatment predicted comorbid chronic tic disorder (yes = 14, no = 7, $\chi^2_{(1)} = 10.93$, $p = 0.001$)
e. sleeping problems in infancy predicted a later comorbid anxiety disorder (yes = 33, no = 3, $\chi^2_{(1)} = 6.94$, $p = 0.008$)
4. severe irritability in infancy predicted lifetime comorbid major depressive disorder (yes = 14, no = 7, $\chi^2_{(1)} = 7.65$, $p = 0.006$).

Contrary to our expectation, we found no associations between "familial" versus nonfamilial occurrence of OCD and complications of pregnancy, delivery, and immediate postnatal course, and drug or medication use, and no effect of gender on frequency of perinatal adverse events. We found no differences between OCD and controls in birth order or season of birth.

Discussion

Our analyses of systematically collected information on perinatal and early developmental complications yielded significant differences between children affected with OCD and controls in rates of illness during pregnancy requiring medical care, birth difficulties (such as induced labor, forceps delivery, nuchal cord, or prolonged labor) and needing more formula changes in infancy than did mothers of controls. We also found significant associations between familial (versus sporadic) OCD and age of onset with perinatal risk factors such as accidents and illnesses during pregnancy requiring medical care. Complications during labor, delivery, and the postnatal period also predicted higher frequency of comorbid disorders, including ADHD, chronic tics, anxiety, and major depressive disorder.

Our findings documenting that perinatal complications contribute to the risk of pediatric OCD are consistent with data from genetic studies suggesting that a considerable proportion of the variance in the occurrence of OCD can be explained by nongenetic environmental factors. For example, in a meta-analysis of family studies, Hettema et al. (2001) found only modest estimated heritability coefficients for OCD of 30%–40%. In a cross-cultural sample of 4246 twin pairs, Hudziak et al. (2004) used structural equation modeling using an 8-item Obsessive Compulsive Scale (OCS) from the Child Behavior Checklist as a proxy for OCD to examine the influence of both genetic (45%–58%) and unique environmental (42%–55%) factors and concluded that both were about equally important. Even lower estimates of heritability of OCD were reported by Jonnal et al. (2000) in a population sample of 527 female twin pairs using items from the Padua Inventory. Even if such estimates are inflated due to measurement errors and gene–environment interactions that are not accounted for in the models, these studies support the role of environmental risk factors that could influence the expression of OCD or of symptoms that exist along a dimension of an OC spectrum disorder.

Our results showing that children with OCD differed from controls in rates of several risk factors during pregnancy, birth, and infancy are consistent with the limited literature on this subject. Our findings showing that maternal accidents requiring medical care during pregnancy (perhaps a proxy

for prenatal insult) predicted earlier onset of OCD are consistent with those of Lensi et al. (1996) who also found a significantly greater history of perinatal trauma in males who had an early onset of OCD. Although the reasons for this association are not entirely clear, perinatal insults may disrupt development or migration of neuronal elements in cortical–striatal–thalamic circuits known to be involved in OCD (Fitzgerald et al. 1999; Rauch and Savage 1997). In view of the critical importance of the perinatal period as a time of neural growth, it is not surprising that this developmental phase should be an area of scientific interest regarding putative environmental risk factors for psychiatric illness (Burd et al. 1999a; Burd et al. 1999b; Klug et al. 2003).

Several significant group differences between OCD and control subjects such as "maternal illnesses requiring medical care," "frequent switching of milk formulas," and "other infant events (e.g., infection during infancy)" could also suggest a genetic immune vulnerability in both mother and child as another possible etiological mechanism. This hypothesis is supported by the finding of higher rates of illness requiring maternal medical care with familial OCD.

Our hypothesis that perinatal complications would be more in evidence in sporadic cases was not supported by our data. In fact, many if not most cases of OCD arise *without* a positive family history of the disorder—so-called "sporadic" cases (Pauls et al. 1995). Although sporadic occurrences do not rule out a genetic etiology (for example, due to spontaneous mutations), familial and sporadic "subtypes" of OCD have repeatedly been identified (Albert et al. 2002; Hanna et al. 2005; Nestadt et al. 2000; Pauls et al. 1995), leading to speculation about the differing impact of environmental and genetic factors on familial and sporadic forms of the disorder. It is generally assumed that sporadic cases have less genetic loading (and perhaps more environmental risk factors) than familial cases. However, no perinatal risk factors that we assayed predicted this "subtype" of pediatric OCD.

Our finding that medication use during pregnancy and post-birth complications (incubator post-birth, hospital stay after mother returned home, and excessive crying during infancy) were significantly associated with the presence of comorbid ADHD and are consistent with other studies of both TD and ADHD. For example, Mathews et al. (2006) found associations between subject's birth weight and a comorbid ADHD diagnosis in their TD cohort. Reports detailing in utero exposure to alcohol (Brookes et al. 2006; Knopik et al. 2006), smoking (Mick et al. 2002; Rodriguez and Bohlin 2005; Thapar et al. 2003), and other complications of pregnancy, delivery, and infancy (Batstra et al. 2003; Linnet et al. 2003; Milberger et al. 1997; Sato et al. 2004; Sprich-Buckminster et al. 1993) have been repeatedly shown to be associated with ADHD. Perinatal complications may also influence the trajectories of certain disorders (moderators) through the development of comorbid disorders.

The inclusion of early developmental factors in our analysis, a unique aspect not uniformly assessed in other studies of this nature, yielded several interesting links with comorbidity in our sample. Although not well operationalized, maternal reports of "sleeping difficulties" and "severe irritability in infancy" predicted later anxiety and depressive disorders. An inability to adapt to changes in the environment is often viewed as one indicator of a rigid, "difficult" temperament that could be a precursor for later behavioral symptoms. Developmental markers such as these, if operationalized and quantified, could create opportunities for early intervention.

While these results indicate the relevance of perinatal complications in the study of nongenetic influences in the expression of OCD, they also demonstrate the difficulties inherent in this type of study. Despite the burgeoning evidence for early environmental triggers of neurodevelopmental disorders, reconciling research findings between studies is frequently limited by their nonuniform characteristics that include selection and publication bias, as well as variable measures, sample sizes, and methods (Glasson et al. 2004).

Our results need to be viewed in light of some methodological limitations. Although the retrospective nature of this study could lead to inaccurate or biased recall and reports from mothers, this risk is reduced by collecting information close to illness onset and from mothers rather than subjects. It is possible that greater rates of perinatal complications in children with OCD versus control children could stem from other differences that do not necessarily arise from OCD per se, since our findings do not prove causality but rather show an association. Such evidence would require a prospective study that controlled for all possible factors. Nonetheless, a controlled retrospective analysis such as this may be helpful in identifying particular perinatal events as risk factors worthy of further study. Although most definitions were operationalized (e.g., illness or accidents requiring medical care, weight gain greater than 25 pounds, caffeine intake greater than one cup per day), for some risk factors there is a lack of specificity that may make interpretation of the risk difficult. This is especially so for those early developmental and temperamental behaviors that involve great subjectivity on the part of mothers such as severe irritability in infancy that cannot be easily operationalized, yet may provide useful information. It is plausible that mothers of children with OCD are more anxious than their control counterparts and would report perinatal events as "adverse" more often than mothers of controls. Without prospective data and no corroborating medical information, the predictive value of these items is low.

We also report on some perinatal risk factors that occurred at very low rates making statistical analysis of limited value. Further, if the effect size of a specific risk factor is low, then only larger studies will have sufficient power to detect these as significant. Finally, consistent with the exploratory nature of this study, we tested many relationships increasing the chance for type I errors (false positives). Despite these concerns, our focus on both perinatal and early developmental periods make this study, which is the first to examine links between perinatal factors and pediatric OCD as *primary* diagnosis, more comprehensive than several other similar efforts.

Despite these considerations, this study shows a significant association between adverse perinatal experiences and the onset and expression of OCD occurring in children and points to the need for further study of nongenetic etiological factors in the development of OCD in youth with attention to familial and sporadic forms of the disorder, age at onset, and comorbid status. Future research that employs prospective methods is needed to better study nongenetic factors in the etiology of OCD and other psychiatric disorders, particularly those with a developmental onset.

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