Further Evidence for Co-Segregation between Pediatric Obsessive Compulsive Disorder and Attention Deficit Hyperactivity Disorder: A Familial Risk Analysis

Daniel Geller, Carter Petty, Fe Vivas, Jessica Johnson, David Pauls, and Joseph Biederman

Background: To examine the relationship between obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) in children and adolescents using familial risk analysis.

Methods: We assessed for ADHD and OCD in the 1057 first-degree relatives of three groups of index children: those with OCD and ADHD, those with OCD but no ADHD and matched controls with neither disorder.

Results: The age-corrected risk for OCD was similarly elevated in families of OCD youth with (14.8%) and without ADHD (17.5%) ($p = .78$), and both groups had significantly higher rates of OCD compared with controls (.5%) ($p < .001$). In contrast, the risk for ADHD was significantly elevated only among relatives of youth who had ADHD (15.3%) compared with controls (4.6%) ($p < .001$). Relatives affected with ADHD also had a significantly elevated risk for OCD compared to relatives unaffected by ADHD (20% *vs*. 4.9%, hazard ratio 4.8) ($p < .001$) and the two disorders occurred together with higher than expected frequency in affected relatives of OCD+ADHD probands ($p < .001$) suggesting co-segregation between these two disorders. There was no evidence of nonrandom mating between OCD- and ADHD-affected spouses.

Conclusions: These results extend previous findings regarding the familiality of both OCD and ADHD and provide further evidence of a familial relationship between ADHD and pediatric OCD which best fit the hypothesis of a unique familial subtype.

Key Words: Attention deficit hyperactivity disorder, child and adolescent, familial risk, genetic, obsessive-compulsive disorder

A consistent overlap between obsessive compulsive disorder (OCD) and attention deficit-hyperactivity disorder (ADHD) has been reported in both referred and nonreferred samples (Flament *et al.* 1988; Geller *et al.* 1996, 2000; Hanna 1995; Riddle *et al.* 1990; Swedo and Rapoport 1989; Thomsen and Mikkelsen 1993; Valleni-Basile *et al.* 1994). As many as 30% of children and adolescents with OCD, particularly boys with an early onset, also satisfy diagnostic criteria for ADHD (Geller *et al.* 2002a), while the rate of OCD among children with ADHD is estimated to be around 8% (Geller *et al.* 2000) and considerably higher than the estimated population prevalence of 2–3%. Several studies have also supported the stability of the ADHD and OCD phenotypes as well as the validity of each diagnosis when both conditions occur together in youth (Geller *et al.* 2002a, 2003c). For example, affected children with comorbid OCD+ADHD have additive clinical, psychosocial, and educational impairments and respond less well to standard OCD treatment (Geller *et al.* 2002a, 2003a, 2003b, 2003c) indicating that this comorbid status is clinically meaningful. Yet, despite the evidence of higher than expected co-occurrence of these two conditions, the reasons behind this overlap have yet to be fully understood.

Since OCD and ADHD are both familial conditions (Biederman *et al.* 1992, 1995, 1996; Pauls *et al.* 2002) family studies can help to clarify the nature of their association by examining patterns of aggregation in first-degree relatives. Such an approach has been extensively and successfully used to examine the familial relationship between several psychiatric disorders in youth including ADHD with Tourette's syndrome (TS) (Pauls *et al.* 1986a); ADHD with TS, learning disabilities (LD) and speech disorders (Pauls *et al.* 1993); ADHD with major depressive disorder, conduct disorder, and anxiety disorders (Biederman *et al.* 1992); ADHD with anxiety disorders (Braaten *et al.* 2003); ADHD with antisocial disorders (Faraone *et al.* 1998); ADHD with LD (Doyle *et al.* 2001) and bipolar disorder with conduct and substance use disorders (Biederman *et al.* 2000). In a recent study of 280 boys and girls with ADHD and their 1533 first-degree relatives, we found evidence of a familial relationship between ADHD with pediatric OCD which best fit the hypothesis of a unique familial subtype (Geller *et al.* in press). However, because this study included only subjects with ADHD, this novel finding needs further confirmation outside the context of ADHD.

If replicated, the finding that children with OCD and ADHD represent a distinct familial subtype could have scientific and clinical importance. Genetic studies that aim to identify genes responsible for these conditions could be informed by evidence of co-segregation in affected relatives. From a clinical perspective, children and their relatives affected with OCD plus comorbid ADHD may have differing treatment response and outcome compared with their noncomorbid counterparts and manifest more OCD spectrum disorders that involve greater degrees of impulsivity such as pathological gambling, trichotillomania, or binge eating disorders (Hollander 1993).

To this end, we aimed to replicate our previous findings of a unique familial subtype of pediatric OCD using familial risk

From the Pediatric Psychopharmacology Program (DG, CP, FV, JJ, JB), Department of Psychiatry (DG, DP, JB), and the Psychiatric and Neurodevelopmental Genetics Unit (DG, DP), Center for Human Genetics, Massachusetts General Hospital; Harvard Medical School, Boston, Massachusetts.

Address reprint requests to Daniel Geller, M.D., YAW 6A, Massachusetts General Hospital, Fruit Street, Boston, MA 02114; E-mail: dageller@partners.org.

Received June 1, 2006; revised September 7, 2006; accepted September 26, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.09.026

analysis methodology to examine the relationship between OCD and ADHD in children using a separately acquired sample of children and adolescents ascertained via an OCD diagnosis. By comparing the actual aggregation of OCD and ADHD in relatives to patterns predicted by different models of transmission (Pauls *et al.* 1986a), we aimed to determine the relationship of these two conditions. We examined four competing hypotheses regarding the relationship between OCD and ADHD in children.

1) The presence of ADHD is secondary to the symptoms of OCD. In that case we would expect no familial transmission of ADHD in the families of OCD probands with ADHD, although an increase in ADHD might be found among relatives themselves affected with OCD.
2) Both ADHD and OCD share underlying etiological risk factors. In that case, we would expect similar familial transmission of both ADHD and OCD in first-degree relatives of probands with either ADHD or OCD compared with controls.
3) Both ADHD and OCD are independently transmitted. In that case, we would expect equally high rates of OCD in first-degree relatives of probands with OCD with or without ADHD, while the prevalence of ADHD should be elevated only in the relatives of probands with ADHD.
4) Children with OCD and ADHD represent a distinct familial subtype. In that case, we would expect co-segregation of OCD and ADHD in affected relatives and no evidence of nonrandom mating.

Methods and Materials

Participants

Children and adolescents with OCD with or without ADHD (OCD ± ADHD) derived from a family genetic study of pediatric OCD (National Institute of Mental Health K08 MH01481; Private Investigator: DG). Our baseline sample consists of 130 children and adolescents and their 374 first-degree relatives (including 133 siblings and 241 parents).

As a comparison group (controls $n = 235$), we used children participating contemporaneously in large, case-control family studies of boys and girls with and without ADHD ascertained from psychiatric and pediatric settings using a design identical to that of the pediatric OCD study (Biederman *et al.* 1992, 1999, 2002). Briefly, these studies ascertained families on the basis of a "case" (ADHD) ($n = 140$ boys, $n = 140$ girls) or control (non-ADHD) ($n = 120$ boys, $n = 122$ girls) proband child aged 6-17 years at time of ascertainment. Detailed study methodology is reported elsewhere (Biederman *et al.* 2002; Rosenbaum *et al.* 2000). For this study, we included 235 control (non-ADHD) probands and their 714 first-degree biological relatives respectively. Potential probands were excluded if they were adopted or if their nuclear family was not available for study. Also excluded were probands who had major sensorimotor handicaps (paralysis, deafness, blindness), or a Full Scale IQ less than 80. Children with psychosis or autism were also excluded but other psychiatric diagnoses were not exclusionary. None of the control probands used in this study met lifetime diagnostic criteria for either ADHD or OCD. For all children, parents provided hospital institutional review board (IRB)-approved written informed consent for themselves while children and youth provided written assent to participate.

Assessment Measures

Our sample was assessed along multiple domains including psychopathology, neuropsychological, and psychosocial functioning. Psychiatric assessments of probands and siblings were made using the Kiddie SADS-E (epidemiologic version) (Orvaschel and Puig-Antich 1987) and were based on independent interviews with the mothers as indirect informant and direct interviews of probands and siblings. All children with OCD were interviewed directly while control children younger than 12 years of age were not. Raters who were blind to the clinical status of the subjects (probands or siblings) evaluated the subjects. Different interviewers met with mothers and children in order to maintain blindness and to prevent information from one informant influencing the assessment of the other.

A diagnostic review team of at least two board-certified child psychiatrists or Ph.D.-level licensed psychologists blindly weighed each source of information from direct and indirect Kiddie SADS-E to yield diagnoses using a best estimate method described by Leckman *et al.* (1982) and using clinical judgment based on narrative information provided in each report. Diagnoses were considered definite only if DSM IV criteria were met to a degree that would be considered clinically meaningful. Differences between parent's and children's structured interview reports of OCD symptoms and severity were resolved using both reports and direct clinical interview of children and adolescents by the lead author, who subsequently administered the Children's Yale-Brown Obsessive Compulsive Disorder Scale and symptom checklist (CY-BOCS) and the Yale Global Tic Severity Scale (YGTSS) where indicated, and resolved any discrepancies in favor of the informant deemed most reliable. During administration of the CY-BOCS, parents and children were asked when OC symptoms first appeared with efforts to link their appearance to specific life events such as birthdays or starting school. Next they were asked to say when OC symptoms were considered clinically impairing by asking when symptoms interfered with functioning, created significant distress, or took up more than one hour per day. This is reported as the age at onset of OCD. In order to be considered positive, the PI corroborated all diagnoses of OCD or tic disorder in any subject meeting full criteria on structured interview. Diagnostic assessments of parents were based on direct interviews with each parent using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer *et al.* 1992) supplemented with KSADS-E modules to cover childhood diagnoses. For every diagnosis, data were also gathered on ages of onset, treatment, and impairment (scored as a three-level ordinal variable: 1 = minimal, 2 = moderate, 3 = severe).

All raters had undergraduate degrees in psychology and were trained to high levels of inter-rater reliability. We computed kappa coefficients of agreement by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98. Kappa coefficients for individual diagnoses included: ADHD (.88), OCD (.87), oppositional defiant disorder (.90), major depressive disorder (1.0), generalized anxiety disorder (.95), and specific phobia (.95). These measures indicated excellent reliability between ratings made by the nonclinician raters and experienced clinicians.

Socioeconomic status (SES) was assessed with the Hollingshead four-factor scale (Hollingshead 1975). As a measure of overall functioning, we used the Global Assessment of Functioning (GAF) (Orvaschel and Puig-Antich 1987).

Statistical Analysis

Probands were stratified into three groups: control probands with no history of OCD or ADHD (controls, $n = 235$), OCD