Familial and Sporadic Subtypes of Early-Onset Obsessive–Compulsive Disorder

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Background: *Family studies of Obsessive–Compulsive (OCD) indicate there is substantial heterogeneity in the familiality of the disorder. This study was done to determine whether there are differences between familial and sporadic probands with early-onset OCD in obsessive–compulsive (OC) symptom categories and comorbid psychiatric diagnoses.*

Methods: *We ascertained 50 OCD probands ranging in age from 10 to 19 years with an onset of OC symptoms before age 15 years. All probands were directly assessed with semistructured diagnostic interviews; their first-degree and second-degree relatives were directly or indirectly assessed with similar diagnostic instruments. Descriptive data were compared in 33 familial and 17 sporadic OCD probands using logistic regression to control for age, gender, and age at onset of OC symptoms.*

Results: *Ordering compulsions were significantly more common in the familial OCD probands. Aberrant grooming behaviors were significantly more frequent in the familial subgroup with skin picking contributing significantly to that difference. Anxiety disorders other than OCD were also significantly more frequent in the familial subgroup with phobic disorders contributing significantly to that difference.*

Conclusions: *The results indicate that familial and sporadic forms of early-onset OCD may be differentiated by ordering compulsions, aberrant grooming behaviors, and anxiety disorders other than OCD.*

Key Words: Obsessive-compulsive disorder, subtypes, family study, logistic regression, comorbidity

Obsessive–compulsive disorder (OCD) is a heterogeneous illness of unknown etiology that has been subtyped according to age at onset of obsessive–compulsive (OC) symptoms. Early onset has been associated with male preponderance (Hanna 1995), a higher incidence of compulsions without obsessions (Geller et al 1998), higher symptom severity ratings (Rosario-Campos et al 2001), and higher rates of OC symptoms unrelated to the duration of illness (Sobin et al 2000). Early onset has also been associated with higher rates of comorbid tic disorders (Eichstedt and Arnold 2001), attention-deficit/hyperactivity disorder (ADHD), simple phobia, agoraphobia, and multiple anxiety disorders (Geller et al 2001). The distinction between early-onset and late-onset OCD has received further support from pharamacotherapy (Rosario-Campos et al 2001) and imaging studies (Busatto et al 2001).

Controlled family studies using adult probands have found that an early age at onset of OC symptoms in case probands is strongly related to a more familial form of the disorder (Nestadt et al 2000; Pauls et al 1995). The initial genome scan of families with early-onset OCD yielded suggestive evidence for genetic linkage on chromosome 9 (Hanna et al 2002b). Furthermore, the finding on 9p24 was replicated by another research group (Willour et al 2004). Because of ongoing efforts to map and identify susceptibility genes for early-onset OCD, as well as to examine the validity of subtyping OCD according to family history, it is necessary to further characterize the clinical correlates of familial and sporadic (nonfamilial) forms of OCD.

There have been few comparisons of the clinical or biological characteristics of familial and sporadic OCD (Hanna et al 1991). A family study found that compared with familial OCD probands, somatic obsessions were more frequent in sporadic OCD probands and that life events prior to the onset of OCD were more common and severe in the sporadic subgroup (Albert et al 2002). However, only a minority of the OCD probands (22%) had onset before 18 years of age and there were only eight familial OCD probands, so the power of the study to detect significant differences between the two subgroups was limited. A complex segregation analysis of OCD determined in a subset of families with higher symptom-based factor scores for symmetry and ordering symptoms that the polygenic model could be rejected, indicating the involvement of a major locus in OCD (Alsobrook et al 1999). In contrast, analysis of the entire sample allowed rejection of only the no-transmission model. The relative risk of OCD was also higher in relatives of probands with higher factor scores for symmetry and ordering symptoms, suggesting these symptoms may identify a genetically significant form of OCD. In addition to specific OC symptom categories, some comorbid conditions in OCD probands may be associated with a more familial form of OCD. In particular, pathologic grooming behaviors, tic disorders, and certain anxiety disorders other than OCD may be part of a familial OCD spectrum that can be used to differentiate familial and sporadic OCD (Andrews et al 1990; Bienvenu et al 2000; Cullen et al 2001; Grados et al 2001; Nestadt et al 2001, 2003).

To further assess these two putative subtypes of OCD, we completed analyses with descriptive data from 33 familial and 17 sporadic early-onset OCD probands to determine whether there are differences between familial and sporadic OCD in 13 lifetime OC symptom categories and 5 lifetime psychiatric diagnostic groups consisting of aberrant grooming behaviors, attention-deficit/hyperactivity disorder, tic disorders, depressive disorders, and anxiety disorders other than OCD. Ordering and arranging compulsions, aberrant grooming behaviors, and anxiety disorders other than OCD were associated with a more familial form of early-onset OCD.

Methods and Materials

Subjects

The 50 OCD probands consisted of 33 male subjects and 17 female subjects ranging in age from 10 to 19 years (14.2 ± 2.6

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years). Age at onset of OC symptoms ranged from 3 to 14 years (8.2 ± 3.2 years). Only one of the probands (2%) was African American; all other probands (98%) were Caucasian. The probands were recruited between 1994 and 2001 for family genetic studies from clinics at the University of Michigan Medical Center and local chapters of the Obsessive-Compulsive Disorder Foundation. The first series of 34 OCD probands was ascertained for a family study of pediatric OCD in which first-degree relatives were directly interviewed blind to proband status. Of the first 34 probands, 22 had at least one first-degree relative with a diagnosis of definite or subthreshold OCD and 12 had no first-degree relatives with evidence of OCD. The second series of seven OCD probands was ascertained for a genetic linkage study of early-onset OCD in which at least one first-degree relative had a diagnosis of definite or subthreshold OCD based on direct interview. The third series of nine OCD probands was ascertained for a family-based association study of early-onset OCD in which four probands had at least one parent with a diagnosis of definite or subthreshold OCD and five probands had no first-degree relatives with evidence of OCD.

All probands were directly interviewed to determine whether they met DSM-III-R or DSM-IV criteria for OCD (American Psychiatric Association 1987, 2000). Exclusion criteria were: 1) chronic neurological disorder other than tic disorder; 2) mental retardation; 3) diagnosis of autistic disorder, schizophrenia, or bipolar disorder; and 4) adoption. Written informed consent or assent was obtained from each proband. Written informed consent was obtained from both parents if the proband was a minor. The study was approved by the Institutional Review Board for the University of Michigan Medical Center.

Diagnostic Procedures

The ascertainment and diagnostic procedures used in the family genetic studies have been described previously (Hanna et al 1998; 2002b). 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 (Orvaschel 1987, 1995). The interview was completed independently with a parent of the subject, as well as with the subject. It was supplemented with sections on OCD and tic disorders from the Schedule for Tourette and Other Behavioral Syndromes, so that information about specific OC symptoms was obtained from probands and siblings between 10 and 17 years of age and their parents (Pauls and Hurst 1991b). Probands and relatives 18 years and older were interviewed with the Structured Clinical Interview for DSM-III-R (Spitzer et al 1990) or the Structured Clinical Interview for DSM-IV (First et al 1998). It was supplemented with sections on OCD and tic disorders from the Schedule for Tourette and Other Behavioral Disorders (Pauls and Hurst 1991a).

The OCD sections included a series of screening questions that covered all criteria for a DSM-III-R diagnosis of OCD (Pauls et al 1995), a checklist from the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al 1989a, 1989b) modified to obtain information about the lifetime occurrence of obsessions and compulsions, and five questions assessing lifetime OC symptom severity. Hair pulling, skin picking, and nail biting were assessed as part of the modified Y-BOCS checklist. However, other questions were not added to assess these aberrant grooming behaviors as possible impulse control disorders. Categorizations of OC symptoms were made according to the checklist subheadings to standardize the recording of the symptoms (Hanna et al 2002a). Symptoms were assigned to only one obsession and/or compulsion category. Presence of a symptom category was scored as 1 and its absence was scored as 0. Symptom scores were not summed to provide a total score for each category.

Tics were assessed by examination and interview, and characterized using the DSM-III-R definition of "involuntary, sudden, rapid, recurrent, non-rhythmic, stereotyped" motor movements, or vocalizations (American Psychiatric Association 1987). In contrast, compulsions were defined as repetitive but intentional types of behaviors. Tics were distinguished from "tic-like" compulsions (such as repetitive touching or blinking) based on whether the patient attached a meaning or purpose to the behavior (Holzer et al 1994; Hanna et al 2002a). According to probands and their parents, OCD was the most important clinical problem in those with tics.

Additional information on relatives 18 years and older was obtained with the Family Informant Schedule and Criteria (FISC) (Mannuzza et al 1985). The mother of each affected offspring was interviewed with the FISC regarding her spouse, adult offspring, parents, and siblings. The father of each affected offspring was interviewed with the FISC regarding his spouse, parents, and siblings. Thus, two types of data were obtained on adult subjects: 1) information from direct structured interviews, and 2) personal history information from a biological relative and/or spouse.

A total of 50 probands and 186 first-degree and second-degree relatives were directly interviewed. Family history information was collected on another 302 first-degree and second-degree relatives. All interviews were audiotaped, as well as coded on paper to assess reliability, maintain quality control, and achieve diagnostic consensus. All interviewers had at least a master's degree and clinical training in either child or adult psychopathology. They were trained to at least 90% diagnostic agreement with the individual instruments. After completion of all interviews for an individual, all available materials (personal interview data, family history data, and clinical records) were collated.

Best estimate lifetime diagnoses were made independently by two investigators using DSM-III-R criteria for the first 34 families and DSM-IV criteria for the next 16 families. Definite OCD was diagnosed only if a subject met all diagnostic criteria. Subthreshold OCD was diagnosed if a subject met criteria for obsessions and/or compulsions but lacked compelling evidence for any of the following criteria: 1) marked distress, 2) duration of obsessive-compulsive symptoms for more than 1 hour a day, or 3) significant interference in the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships with others. If reviewers were uncertain about the presence or absence of a particular diagnosis, that diagnosis was coded as "unknown." If any required criterion was absent, the diagnosis was considered "not present." To avoid forcing closure on inadequate diagnostic information, subjects were reinterviewed if necessary to clarify incomplete or contradictory information. When major disagreements occurred between two diagnosticians, consensus diagnoses were reached with the assistance of a third diagnostician following procedures developed for the diagnosis of other psychiatric disorders (Roy et al 1997).

An OCD proband was classified as familial if a first-degree relative was diagnosed with definite or subthreshold OCD based on direct interview or detailed clinical records. Conversely, an OCD proband was classified as sporadic if there was no evidence of OCD in any first-degree relatives based on direct interview and family informant data. Of the 33 familial OCD probands, 6 had at