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Predictors of Early Adult Outcome in Pediatric-Onset Obsessive-Compulsive Disorder

Brittany G. Craiglow
Yale University

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Brittany G. Craiglow

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ABSTRACT

PREDICTORS OF ADULT OUTCOME OF PEDIATRIC-ONSET OBSESSIVE-COMPULSIVE DISORDER. Brittany G. Craiglow, Michael H. Bloch, Angeli Landeros-Weisenberger, Philip A. Dombrowski, Kaitlyn E. Panza, Bradley S. Peterson, and James F. Leckman. Child Study Center, Yale University School of Medicine, New Haven, CT.

This study was conducted in order to determine childhood clinical predictors of early adult outcome in pediatric-onset obsessive-compulsive disorder (OCD). We specifically hypothesized that OCD symptom dimensions and comorbid tic disorders would be associated with persistence of obsessive-compulsive (OC) symptoms into early adulthood. The study followed a longitudinal cohort design in which 45 of 61 eligible children with OCD were reassessed in early adulthood an average of 9 years following a baseline childhood assessment. Main outcome measures included expert-rated OC symptom severity and time to remission of OC symptoms. Baseline clinical characteristics were evaluated in terms of their impact on early adulthood OC symptom severity and time to remission of OC symptoms.

Forty-four percent of subjects were determined to have subclinical OC symptoms at follow-up. Absence of a comorbid tic disorder and presence of prominent hoarding symptoms were associated with OC symptom persistence. In our best-fitting multivariate Cox Proportional Hazard model female gender, younger age at childhood baseline assessment, older age of OCD onset, more severe childhood OC symptoms, and comorbid oppositional defiant disorder were also independently associated with persistence of OC symptoms into early adulthood. Our results suggest that a significant

proportion of patients with pediatric-onset OCD will remit by early adulthood. The presence of comorbid tics was associated with a favorable outcome, while primary hoarding symptoms were associated with persistent OCD.

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INTRODUCTION

Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric condition characterized by intrusive thoughts or images (obsessions) and/or repetitive behaviors or mental rituals (compulsions) that are often aimed at preventing or alleviating anxiety generated by obsessions. Common obsessions include fears of causing harm to oneself or others, fears of contamination, and need for symmetry and exactness, while common compulsions include behaviors such as cleaning, ordering, or checking, and mental rituals such as counting or repeating words silently (1). To meet diagnostic criteria for OCD, a person's symptoms must not be due to a general medical disorder or substance, and he or she must experience recurrent obsessions or compulsions that are severe enough to be time-consuming or cause significant distress or impairment. In addition, the DSM criteria specify that for adults with OCD, at some point the person must recognize that his or her symptoms are excessive or unreasonable; in children, this criterion is often not met (2).

Obsessions and compulsions can be significantly disruptive to overall functioning, as they can take the place of productive and enjoyable behaviors. Many individuals with OCD avoid certain situations or objects that stimulate obsessions or compulsions, and such avoidance can become widespread and generalized. Additionally, because obsessions can be distracting, they may interfere with performance on certain cognitive tasks, such as reading or computation (2). Studies of OCD in children and adolescents have consistently reported substantial interference of symptoms with social, scholastic, and psychosocial functioning (3).

Epidemiology

The symptoms of OCD are similar across many cultures (4), and OCD affects an estimated 50 million people worldwide (5). In the United States the lifetime prevalence of OCD was found to be between 1.9% and 3.3% based on the Epidemiological Catchment Area study, which examined a representative sample of 18,500 people from five geographical areas (6). These results suggested that OCD is the fourth most common psychiatric disorder, following phobias, substance abuse, and major depression. In a cross-national study using similar methodology, lifetime prevalence was found to be remarkably consistent among seven countries: the United States, Canada, Puerto Rico, Germany, Taiwan, Korea, and New Zealand. The OCD annual prevalence ranged from 1.1/100 in Korea and New Zealand to 1.8/100 in Puerto Rico. The population of Taiwan, which has the lowest prevalence for other psychiatric disorders, was the least affected, with a prevalence of OCD of 0.4/100 (4).

More recently, an evaluation of OCD was included in the National Comorbidity Survey Replication (NCS-R), which is the most current large-scale epidemiological survey of the United States population to date. While the earlier NCS did not include OCD, the NCS-R assessed both lifetime experiences of OCD as well as nine types of common obsessions and compulsions, and also provided information regarding comorbidity, impairment, and treatment (7). Lifetime and 12-month prevalence estimates from this study were 2.3% and 1.2%, respectively. Although OCD is defined by obsessive-compulsive (OC) symptoms severe enough to be time consuming or cause significant distress or impairment (2), a wide range of less severe OC symptoms is common among the general and non-referred population. In the NCS-R, over one-quarter

of respondents (28.2%) reported experiencing obsessions or compulsions at some point in their lives, most commonly checking, hoarding, or ordering (7). Another recent community-based sample demonstrated similar prevalence rates of obsessions and compulsions, with 13-17% of patients without a psychiatric diagnosis experiencing obsessions or compulsions, and 31-49% of individuals with a psychiatric diagnosis other than OCD experiencing them (8). The cross-national variance in OCD noted above might in part be related to the relatively high frequency of obsessions and compulsions in community samples and differences in what is considered to be significantly time-consuming, impairing, or distressing.

Obsessive-compulsive disorder can be severely impairing and has been named by the World Health Organization as one of the top 10 causes of worldwide 'years lived with illness-related disability' (9). Nearly two-thirds of individuals with OCD assessed by the NCS-R reported severe role impairment, particularly within relationship and social functioning domains, and past-year OCD was associated with an average of 45.7 days out of role in the past 12 months. Notably, among the group of respondents with severe OCD, the average number of days out of role was significantly higher at 129.4 (7). Not surprisingly, the economic burden of OCD is also considerable – for instance, in 1990 the total cost of OCD in the United States alone was estimated to be upwards of $8.4 billion, and the indirect cost, which reflects loss of productivity from individuals suffering with OCD, was estimated at $6.2 billion (10).

Etiology and Pathogenesis

Genetics

Relatively little is known about the etiology and neurobiological origins of OCD (11). There is compelling evidence from twin, family, segregation, and linkage studies that genetic factors play an important role (12). A recent review that examined the literature of all twin studies for OCD published since 1929 concluded that OC symptoms are heritable in children, with genetic influences ranging from 45% to 65%. The genetic influence on OC symptoms in adults ranged from 27% to 47% (13). Results from a number of family studies of OCD also support the hypothesis that some forms of OCD are familial (12). A recent meta-analysis of five OCD family studies demonstrated that the unadjusted aggregate risk for OCD among proband relatives was 8.2%, as compared with 2.0% for control relatives (14). Segregation analyses, which are used to examine patterns of inheritance within families, have demonstrated that the pattern of transmission of OCD is consistent with one of genetic transmission (12).

Upwards of 60 candidate gene studies have been reported in the past decade (15), with mixed results. Some studies have suggested a genetic association between OCD and genes in the dopaminergic and serotonergic pathways, while others have failed to replicate such findings. None to date have reached genome-wide significance, which may in part be due to the clinical heterogeneity of OCD (12). Genetic linkage studies have also yielded somewhat varied results, but taken together studies suggest that there may be a susceptibility locus located on chromosome 9 (12, 16).

Environmental Factors

In addition to genetic factors, environmental influences are likely to be implicated in the etiology of OCD; however, very little is known about environmental triggers for the

disorder (17). There is some evidence that traumatic or stressful events may be risk factors for developing OCD. One study demonstrated that children with OCD had significantly more total and negative life events in the year prior to onset of OCD than normal controls, and they also perceived these events as having more impact (18). It has also been reported that statistically significant covariation between lifetime post-traumatic stress disorder (PTSD) and OCD was attributable to cases in which a principal diagnosis of PTSD was followed by a secondary diagnosis of OCD (19), suggesting that precipitants or features of PTSD may act as causal factors in OCD (17).

Another study found that the only difference between patients with familial and non-familial OCD was that life events prior to the onset of OCD were more common and more severe in patients with non-familial OCD (20). Pregnancy and childbirth have also been associated with precipitation or exacerbation of OCD (21). Finally, the results of the NCS-R demonstrated that in adults OCD typically emerges following the onset of other psychiatric disorders and begins at a later age than most (79.6%) comorbid anxiety disorders. Earlier mental disorders predict the subsequent first onset of OCD, with the highest odds of subsequent OCD associated with preexisting bipolar disorder, agoraphobia, panic disorder, and alcohol dependence (7).

Neuroanatomy

The current dominant model of OCD suggests that the disorder is mediated by specific neuronal circuits, with emphasis on abnormalities in cortico-striatal circuitry, in particular orbitofronto-striato-thalamic circuits (16). Three neuroanatomical areas have been consistently implicated in a variety of types of neuroimaging studies of OCD – the

orbitofrontal cortex, the anterior cingulate cortex, and the head of the caudate nucleus (22). These areas are hyperactive at rest in adults with OCD as compared to healthy controls, become more active with provocation of symptoms, and are no longer hyperactive at rest following successful treatment with either pharmacological treatment or cognitive-behavioral therapy (22). Recent studies suggest the existence of other structural abnormalities in OCD, particularly within the parietal cortex (23, 24), generating evidence for a revised model for OCD in which the underlying pathology involves abnormalities in lateral and frontal parietal regions in addition to orbitofronto-striatal regions and their associated limbic structures (16).

Neurochemistry

The evidence that serotonin reuptake inhibitors are effective in the treatment of OCD led to the development of the serotonergic hypothesis (25), which although plausible has not been proven conclusively (26). The hypothesis suggests that there is an abnormality in the serotonergic system in OCD, presumably related to a reduction of function (26). The results from pharmacological, genetic, and imaging studies lend support for a role for serotonin in OCD, but to date no specific abnormality has been identified within the serotonin system (27). While it appears that serotonin does play some part in the disorder, its role may be secondary and modulatory rather than primary (26).

There is now growing evidence that the dopamine system may also be involved in the pathogenesis of OCD (28). The results of most studies that have examined the role of dopamine in OCD suggest an association between increased midbrain dopamine neurotransmission and the disorder (29), a hypothesis which is in agreement with the

hyperactive cortico-striatal-thalamic model of OCD (28). Finally, there is evidence that dysregulation of glutamate neurotransmission may also contribute to the pathophysiology of OCD, and preliminary studies of glutamate-modulating drugs such as riluzole, an antiglutamatergic agent, have achieved promising results in the treatment of OCD (30).

Neuroimmunology

There is a growing body of evidence to suggest that immune mechanisms may play a role in the pathophysiology of some subtypes of OCD (31). In particular, it has been hypothesized that some individuals develop OCD following infection with group-A beta-hemolytic streptococcal infections. The acronym 'PANDAS' (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) has been coined to describe patients who meet five inclusionary criteria: presence of OCD and/or tic disorder, pre-pubertal symptom onset, sudden onset or episodic course of symptoms, temporal association between streptococcal infections and neuropsychiatric symptom exacerbations, and associated neurological abnormalities (32). This putative subgroup of patients experiences a unique clinical course in which the onset of symptoms tends to be abrupt and dramatic, and which is temporally linked with streptococcal infections. Some patients with PANDAS have been shown to benefit from immunomodulatory therapies and long-term antibiotic therapy (33). In addition, children with PANDAS during the acute phase of illness have been shown to have larger caudate, putamen, and globus pallidus volumes when compared to healthy controls (34).

Perhaps the strongest evidence to support the notion that streptococcal infection may be related to the onset of OCD comes from a case-control study of 144 patients

reported by Mell and colleagues (35) who demonstrated that patients with OCD, Tourette Syndrome (TS), or tic disorder were significantly more likely than controls to have had prior streptococcal infection in the 3 months prior to onset. The risk was even higher among children with multiple streptococcal infections within 12 months of onset. Similar results were recently reported based on a national sample of OCD cases (36). Further research will be necessary to clarify the relationship between immune mechanisms and OCD; the results of current studies that are investigating the specific antineuronal antigens and antibodies that characterize members of the PANDAS subgroup will likely be of particular interest (31).

Comorbidity

Rates of comorbid psychiatric illness are high among individuals with OCD. In the NCS-R, fully 90% of respondents with OCD met criteria for another lifetime DSM-IV disorder. The most common comorbid conditions were anxiety disorders (75.8%), followed by mood disorders (63.3%), impulse-control disorders (55.9%), and substance use disorders (38.6%) (7). Comorbid psychopathology is also extremely common among children and adolescents with OCD – in one study of pediatric patients, only one participant out of 30 failed to meet criteria for at least one psychiatric diagnosis other than OCD (37). Rates of comorbid lifetime major depression are higher in adults (78%) than in adolescents (62%) or children (39%), whereas Tourette Syndrome is more prevalent among children with OCD (25%) than among adolescents (9%) or adults (6%) with OCD (38). While disruptive behavior disorders are not typically reported in adult populations, they frequently co-occur in children and adolescents with OCD. Rates of

attention deficit hyperactivity disorder have been reported at 51% among children and 36% among adolescents, and rates of oppositional defiant disorder are 51% and 47% among children and adolescents, respectively (38).

Treatment

Psychotherapy

Controlled clinical trials have consistently demonstrated that psychotherapeutic interventions for OCD, including exposure response prevention (ERP) and cognitive therapy, substantially reduce obsessive-compulsive symptomatology. ERP is based on the notion that classical conditioning is responsible for the development of obsessions, while operant conditioning perpetuates anxiety and maintenance behaviors, and therefore it consists of both exposure to the anxiety-provoking obsessions as well as prevention of responses aimed at reducing anxiety (39). In ERP patients create a hierarchy of feared situations that trigger anxiety and/or obsessions, and then sequentially move up the hierarchy following successful habituation to each OCD trigger. Importantly, effective ERP necessitates that each exposure be followed by response prevention, in which the patient neither avoids the trigger nor performs rituals to alleviate anxiety (40). Cognitive therapy is based on the cognitive theory of emotional disorders and attempts to modify dysfunctional beliefs or faulty appraisals of stimuli that generate obsessions (39, 40).

A recent meta-analysis that examined the results of 15 clinical trials of psychological therapy for OCD demonstrated that across all treatments about two-thirds of patients who completed treatment improved (range: 33–78%), and one-third met

recovery criteria (range: 27–47%). Findings were strongest for more behaviorally-oriented treatments, such as ERP, and for individual as opposed to group therapy (39).

Pharmacotherapy

While OCD is certainly influenced by learning principles, it is also a biologically-based disorder and consequently medication is an important component of treatment (40). Meta-analyses and reviews of pharmacologic treatment for OCD have consistently supported the use of antidepressants (41). In particular, evidence from randomized controlled trials shows that serotonin reuptake inhibitors (SRIs) are effective in OCD. SRIs include both non-selective serotonin reuptake inhibitors such as clomipramine, as well as selective serotonin reuptake inhibitors (SSRIs), such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. A recent Cochrane review of SSRIs in the treatment of OCD demonstrated that patients receiving SSRIs were nearly twice as likely as those receiving placebo to achieve clinical response, which was defined as a 25% or greater reduction in symptoms (26). Another meta-analysis of studies of the efficacy of both selective and non-selective serotonin reuptake inhibitors as well as tricyclic antidepressants demonstrated greatest effect sizes for clomipramine, suggesting that this nonspecific SRI may be more effective than SSRIs and tricyclics in targeting obsessive-compulsive symptoms. It is worth noting, however, that the largest effect sizes for clomipramine were found in early studies and have not been as clearly replicated in more recent studies comparing it with SSRIs. Furthermore, clomipramine tends to have a less favorable side effect profile than the SSRIs, causing many patients to stop taking it despite its positive effects (41). Recent reports indicate that children and adolescents

with OCD and comorbid tics are less likely to respond well to SSRIs (42).

For patients who do not respond to SRIs, several studies have demonstrated that augmentation with antipsychotic medication can be effective in some cases. In a recent meta-analysis of such studies it was found that approximately one-third of patients with treatment-refractory OCD show a meaningful treatment response to antipsychotic augmentation. The report suggests that there is sufficient evidence demonstrating the efficacy of haloperidol and risperidone but states that evidence regarding the efficacy of quetiapine and olanzapine is inconclusive (43). A Cochrane review on the same subject concluded that antipsychotic augmentation can be an effective and well-tolerated short-term treatment strategy for patients who do not respond to first-line pharmacotherapy for OCD (44). The results of such studies, along with the more favorable side effect profiles of newer generations of antipsychotics, are contributing to a growing consensus that antipsychotics are the pharmacotherapy augmentation of choice in SRI-refractory OCD (45). This appears to be particularly the case for patients with OCD and a personal history of tics (43).

Combined Treatment

Because neither psychological therapy nor pharmacotherapy alone has been effective for all patients with OCD, a combination is often recommended as treatment of choice (40). In fact, effect sizes for combined psychotherapy and pharmacotherapy have been shown to be higher than those for either treatment modality alone (41). In a meta-analysis of pharmacotherapy trials in OCD among children and adolescents Geller and colleagues (46) found that medications were significantly more effective than placebo, with an effect

size of 0.46. The Pediatric OCD Treatment Study (POTS) (47) compared sertraline, cognitive-behavioral therapy (CBT), combined sertraline and CBT, and placebo for the treatment of OCD. The clinical remission rate for combined treatment was 53.6%; for CBT alone 39.3%; for sertraline alone 21.4%; and for placebo 3.6%, leading the authors to recommend that children and adolescents with OCD should begin treatment with either CBT or the combination of CBT and medication.

OCD Symptom Dimensions

Obsessive-compulsive disorder is heterogeneous in its clinical presentation, with many possible subtypes (48, 49). It is not unusual for two patients with OCD to display completely different symptom patterns (50). Despite this variability, OCD continues to be regarded by standard diagnostic classifications such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) (2) and the *International Classification of Diseases, Tenth Edition* (51) as a unitary nosological entity (50). While experts acknowledge that this characterization has certain formal appeal, it also has the potential to be misleading (50). The psychiatric community has recognized this, and a majority of OCD experts worldwide agree that "OCD is heterogeneous, that symptoms are experienced with multiple potentially overlapping symptom dimensions, and that it will be important to document their presence as specifiers in the DSM-V" (52). As investigators have sought to understand and describe the heterogeneity of OCD, a growing body of evidence has emerged in favor of a multidimensional model of the disorder.

The multidimensional approach is based on the notion that the complex clinical presentation of OCD can be summarized with a few consistent, temporally stable clusters of symptoms, referred to as symptom dimensions or factors (50). Over 20 factor analytic studies conducted on large cohorts of patients with OCD have identified potential symptom dimensions (53). In addition, these OCD symptom dimensions have been associated with distinct patterns of comorbid psychiatric conditions (54), different patterns of heritability (55), and different responses to pharmacological treatment and behavioral therapy (56, 57). In particular, a number of studies have demonstrated that patients with prominent hoarding symptoms respond more poorly to SSRIs (56, 58, 59) and have poor compliance with and response to cognitive-behavioral therapy (60, 61). The results of these and similar studies suggest that adopting a multidimensional approach to OCD has the potential to broaden understanding of the disorder (62).

A recent study synthesized data from 21 factor analytic studies involving over 5,000 subjects and via stratified meta-analysis demonstrated a four-factor structure for OCD that was remarkably consistent over time (53). The four OCD factors that emerged were: Factor I/Forbidden Thoughts, consisting of aggression, sexual, religious, and somatic obsessions and checking compulsions; Factor II/Symmetry, consisting of symmetry obsessions and ordering, repeating, and counting compulsions; Factor III/Cleaning, consisting of contamination obsessions and cleaning compulsions; and Factor IV/Hoarding, consisting of hoarding obsessions and compulsions. A similar four-factor structure has been demonstrated by a confirmatory factor analysis of children, adolescents, and adults with OCD (63). Importantly, the results of a recent study that examined the structure of obsessive-compulsive (OC) symptoms in a large pediatric

sample also demonstrated that symptom dimensions are similar across the lifespan (62), indicating that the factor structure may be applied to both pediatric- and adult-onset OCD.

Tic-Related OCD

A dimensional approach does not exclude other methods of sub-classifying OCD. Currently tic-related OCD, familial OCD, and pediatric-onset OCD appear to be potentially useful categorical distinctions (38, 64). Perhaps the best-described subgroup is tic-related OCD, which has been defined as a condition in which tics are observed either in the patient or in at least one first-degree relative (64). Patients with tic-related OCD have an earlier age of onset (49, 65, 66) and are more frequently males (48, 65). In addition, patients with tic-related OCD tend to display symptoms within the Forbidden Thoughts, Symmetry, and Hoarding dimensions more often than symptoms within the Cleaning dimension (67-69). Similarly, tic-related OCD has been associated with higher frequencies of sensory phenomena that precede or accompany compulsions (48, 69, 70).

Some studies have reported that patients with tic-related OCD have higher rates of comorbid trichotillomania, body dysmorphic disorder, social phobia, mood disorders, and attention-deficit hyperactivity disorder when compared with patients with non-tic-related OCD (71, 72). The results of longitudinal studies have also demonstrated that the presence of comorbid tics may be associated with increased OCD severity (73, 74). Finally, patients with tic-related OCD may not respond as favorably to treatment with SSRIs when compared to patients with non-tic-related OCD (38, 47), and as noted above,

individuals with tic-related OCD are also more likely to benefit from augmentation with antipsychotic medication (43).

Pediatric-Onset OCD

Obsessive-compulsive disorder was previously thought to be very rare among pediatric populations; however, over the past two decades research has emerged identifying OCD as one of the more common psychiatric illnesses affecting children and adolescents (75). Epidemiological studies have documented roughly equivalent prevalence rates for pediatric and adult OCD (6, 76-78), and studies of children and adolescents with OCD have reported similarities with adult OCD (79). Importantly, however, several meaningful differences between pediatric- and adult-onset OCD have been identified, causing pediatric-onset OCD (including children and adolescents with OCD as well as adults with an early onset of symptoms) to be hypothesized to represent a distinct developmental subtype of OCD (66, 79).

Perhaps the most apparent distinction between pediatric- and adult-onset OCD relates to age of onset data, which demonstrates a bimodal distribution with one peak in childhood and another in adulthood (79). Pediatric-onset OCD has been associated with a mean age of onset around 10 years (79) in contrast to adult-onset OCD, which has been reported to have a mean age of onset of around 21 years (6, 80). In some studies pediatric-onset OCD has also been associated with a male preponderance (79), as compared to adult studies of OCD that have demonstrated slight female predominance or equal gender distribution (6). In addition, pediatric-onset OCD has been associated with

a higher rate of comorbid tic disorders (81), greater familial loading for OCD as demonstrated by family studies (9, 82), and poorer response to medications (66).

Course and Long-term Outcome of Pediatric-Onset OCD

Earlier studies of pediatric-onset OCD indicated that the disorder typically follows an unremitting, debilitating course (76, 83-85), a notion that has been perpetuated by clinical lore (75). This idea is also upheld by the DSM-IV-TR, which states that OCD follows a chronic course in the majority of individuals (2). Recent data calls these teachings into question, however, and as a result a shift in the understanding of the course and long-term outcome of pediatric-onset OCD has begun to occur (75).

The prevalence of OCD among adults is relatively equivalent to that among children and adolescents (6, 76, 78), and given that a significant portion of cases of OCD develop following adolescence, the similar prevalence rates in these two age groups suggests that many cases of pediatric-onset OCD remit prior to adulthood. Indeed, the results of a recent review and meta-analysis of previous long-term outcome studies of pediatric-onset OCD support this premise, suggesting that as many as 40-59% of cases remit by adulthood (75). This first systematic review of pediatric-onset OCD demonstrated that rates of persistence are lower than previously believed and outlined in the DSM-IV, with two-thirds of studies analyzed demonstrating that OCD did not persist as a full syndrome into adulthood for a majority of patients.

In addition to examining rates of persistence, this review examined predictors of outcome of pediatric-onset OCD. Meta-analysis regression demonstrated that earlier age of OCD onset, longer duration of OCD prior to treatment, and inpatient hospitalization

for OCD were predictive of OCD persistence (75). Selected longitudinal studies have reported presence of a comorbid tic (73, 74) or mood disorder (73), family psychiatric history, and poor initial response to pharmacologic treatment (73) as additional predictors of greater OCD severity at follow-up.

Many of the studies that have examined long-term outcome of pediatric-onset OCD were conducted prior to the widespread use of effective evidence-based treatments for OCD, such as SSRIs and cognitive-behavioral therapy, and before the introduction of validated clinical rating scales for OCD, suggesting that many of them may no longer be applicable to current patients. In addition, most of these studies had follow-up intervals that ranged from only 1-5 years and thus had a limited ability to assess adult outcome, or they were retrospective in character and therefore prone to recall bias (75). For these reasons, further investigation into the early adult outcome of pediatric-onset OCD is warranted.

Current Study

In light of the limitations of previous longitudinal studies examining outcome of pediatric-onset OCD and the emerging body of evidence in support of a multidimensional model of OCD, we conducted this prospective, longitudinal study in order to evaluate the course and early adult outcome of pediatric-onset OCD. Given the prevalence, morbidity, and functional impairment associated with OCD, a better understanding of its progression is important and will undoubtedly be helpful for clinicians and patients alike (75). The goals of this current study were to (1) determine childhood clinical predictors of early adult outcome in pediatric-onset OCD and (2) determine whether specific OCD

symptom dimensions are associated with outcome of pediatric-onset OCD as assessed in early adulthood. We hypothesized that OCD symptom dimensions and comorbid tic disorders would be associated with persistence of OC symptoms into early adulthood.

The first hypothesis was generated in large part because of the results of prior studies that have suggested that a dimensional approach may prove to be a valuable means for identifying predictors of outcome (86). As noted above, patients with hoarding symptoms have been shown to respond less favorably to both SSRIs (56, 58, 59) and cognitive-behavioral therapy (60, 61). Other studies have demonstrated that the presence of other symptoms, especially sexual obsessions, may predict non-response to SSRIs (87, 88). These data suggest that there may be fundamental differences among symptom dimensions in terms of the clinical course and outcome of OCD, and we speculated that we would identify one or more symptom dimensions that carried with it a poorer prognosis. The hypothesis that patients with OCD and tics would have a less favorable outcome was based on the results of selected longitudinal studies that have reported that the presence of a comorbid tic disorder may predict worse long-term outcome (73, 74) and poorer response to treatment with SSRIs (38, 47).

PATIENTS AND METHODS

Participants

All participants were recruited through the Yale Tourette Syndrome (TS)/OCD Clinic, a multidisciplinary specialty clinic at the Yale Child Study Center. Eligible participants were required to (1) have a childhood diagnosis of OCD, (2) have participated in magnetic resonance imaging or neuropsychological testing studies prior to 16 years of

age (these were prerequisites for having a detailed clinical research evaluation at that time), and (3) be older than 16 years at the time of potential follow-up interview. Early adulthood follow-up interview took place an average of 9 years after the initial childhood evaluation. Exclusionary criteria included a history of seizure, head trauma with loss of consciousness, ongoing or past substance abuse, or an IQ lower than 80. Parental written informed consent and subject assent were performed at childhood baseline assessment, and subject informed consent was performed at follow-up. Compensation for participation was provided at both time points under the guidelines of the Yale Human Investigations Committee.

From an eligible sample of 62 subjects evaluated at the baseline interview, 46 (74%) elected to participate. Reasons for nonparticipation included subject refusal to participate in a follow-up interview (n = 2) or inability to locate subjects (n = 14). At the follow-up interview, it was found that one participant had since been diagnosed with Asperger's disorder. He and his mother were re-interviewed by an expert clinician (Dr. Michael Bloch), and it was determined that he met criteria for Asperger's disorder rather than OCD in childhood, and he was therefore excluded from subsequent analyses. Demographic data as assessed at childhood baseline did not differ significantly between participants and non-participants, except for age at baseline evaluation (Table 1).

TABLE 1:

Demographic	Participants	Non-Participants
N	45	16
Age at Evaluation*	12.1 ± 2.1	9.9 ± 1.6
Gender (N, % male)	37 (82%)	12 (75%)
TS	18 (40%)	11 (69%)
ADHD	18 (40%)	6 (38%)
CY-BOCS	11.6 ± 8.1	14.2 ± 9.8
YGTSS	8.0 ± 10.8	14.2 ± 10.8

TABLE 1. Demographic Comparison of Participants and Non-participants. Participants differed significantly from non-participants only in that non-participants were younger at the baseline evaluation than non-participants. *= $p<0.001$

Interview Procedure at Childhood Baseline Assessment

Childhood baseline assessment occurred prior to age 16 years and included current and worst-ever measures of obsessive-compulsive (OC) symptom severity using the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), a widely-used and well-validated instrument that rates symptom severity on the basis of time spent, distress, and impairment (89). The Yale Global Tic Severity Scale (YGTSS) was used to assess current and worst-ever tic severity (90). The Schedule for Tourette and Other Behavioral Syndromes was used to survey other psychiatric illnesses (91). Neuropsychiatric diagnoses were established through a best-estimate consensus procedure performed by two child psychiatrists (Drs. Bradley Peterson and James Leckman) following a review of all available materials (92). Participants were then classified based on these diagnoses on their diagnosis status (yes/no) for Tourette syndrome (TS), chronic tic disorder (CTD), Attention-Deficit Hyperactivity Disorder (ADHD), Major Depressive Disorder (depression), comorbid anxiety disorder other than OCD (anxiety), and Oppositional Defiant Disorder (ODD). Participants and their families were also asked about the participant's age of onset of OC symptoms.

Interview Procedure at Early Adulthood Follow-Up

Evaluations during follow-up in early adulthood included current and worst-ever ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and YGTSS (90, 93). Screening for comorbid psychiatric conditions was conducted with the *Structured Clinical Interview for* DSM-IV *Axis I Disorders*, and a standardized medication history was obtained (94). In addition, an interview of a parent or "close cohabitating adult" was performed to verify symptom severity when possible. All subjects who had improved significantly were also asked to provide the age at which their OC symptoms "remitted," which was defined in the interview as the age that "the age your OC symptoms improved substantially."

DATA ANALYSIS

All statistical analyses were performed using SAS version 9.1. The primary outcome variable for analysis was time to remission of OC symptoms from the initial childhood assessment. A participant was considered remitted if the Y-BOCS< 8 at follow-up. A Y-BOCS score of <8 was chosen as criteria for remission because the anchor point of 8 demarcates subclinical (YBOCS 0-7) from clinical OC symptoms (YBOCS≥8) (93). Age of OCD remission was determined by patient self-report at follow-up, and time to remission was calculated by subtracting age of baseline childhood assessment from age of remission.

The Kaplan-Meier method (implemented with SAS proc lifetest) was used to plot the overall survival function of the data and to test whether the a priori childhood clinical variables influenced the overall survival curve. Subjects were stratified by comorbid

CTD and by primary OCD symptom dimension (Symmetry, Cleaning, Forbidden thoughts, or Hoarding). The Wilcoxon test was used to compare survival curves, as this method places greater weight on time points that are associated with more observations. Bonferroni correction was used to set the threshold for statistical significance at $p<0.025$ to account for the two a priori hypotheses.

The Cox Proportional Hazards model of survival analysis (proc phreg command in SAS) was then employed to construct the best fitting exploratory model of the data. In the model the following variables of interest were examined: age of onset, OCD severity at baseline childhood assessment, age at baseline assessment, depression, anxiety, TS, CTD, ADHD, conduct disorder, ODD, gender, and worst-ever OCD severity. The best fitting model was built using the following steps: (1) all univariate variables that were significantly associated with time to OCD remission were identified, (2) all significant univariate terms were entered into the same model, and individual terms were identified based on the least significant p-value and then removed if they did not significantly improve the fit of the model based on Log-Likelihood Test, and (3) all non-significant univariate predictors of time to remission were added back into the model and kept if they improved fit of the model based on the Log-Likelihood Test (with a $p<0.05$ threshold). The dimensional measures of OCD were then added to the best fitting model with traditional clinical data to determine if this approach improved fit of the model. Dimensional OC symptoms were measured using factor scores for OCD dimensions computed in a previously published study; OC symptoms in each dimension were rated as 0=absent, 1=present, or 2=severe; and participants were categorized as primarily having hoarding symptoms or not. These dimensional approaches were only included in

the final best fitting model if they improved the goodness of fit based on the Log-Likelihood Test.

In post hoc analysis baseline characteristics of subjects classified as remitters were compared to non-remitters at early adulthood follow-up. All continuous variables were examined using a student t-test and categorical variables with the Fisher's exact test.

RESULTS

Childhood baseline interview took place at an average age of 12.1 ± 2.0 years (range 8.0 - 15.8). Additional demographic characteristics are provided in Table 1. The average age at early adulthood follow-up was 21.1 ± 3.1 years (range 16.0 – 27.0). The average duration between initial and follow-up interviews was 9.0 ± 2.9 years.

Clinical Course of Obsessive-Compulsive Symptoms

The average age of onset of OC symptoms was 8.0 ± 2.5 years (range 4-13). At follow-up, the average Y-BOCS score was 10.2 ± 8.6 compared to 25.6 ± 7.1 at worst-ever (age 11.3 ± 2.4 years). Twenty subjects (44%) had minimal OC symptoms at follow-up and were classified as remitted (Y-BOCS <8) (Table 2). Fourteen subjects (31%) had mild OC symptoms (Y-BOCS score 8-15) at follow-up, while 6 subjects (13%) had moderate OCD (Y-BOCS score 16-23), and 5 subjects (11%) had severe OC symptoms (Y-BOCS score 24-40).

Remitting Participants Compared to Non-Remitting Participants

Table 2 compares the characteristics of children whose OC symptoms remitted by the time of the early adult assessment to those who did not. Lesser OCD severity at childhood assessment, presence of a comorbid tic disorder, and absence of hoarding symptoms were associated with remission in adulthood. Male gender and lesser worst-ever childhood OCD severity were associated with OCD remission at trend levels.

TABLE 2:

Demographic	Remitted (N=20)	Non-Remitted (N=24)
Age at Childhood Baseline	12.1 +/- 2.1	12.1 +/- 2.1
Gender -- males^	18 (90%)	16 (67%)
Age of Onset	7.6 +/- 2.5	8.4 +/- 2.6
Duration of Symptoms	4.5 +/- 2.1	3.7 +/- 3.5
OCD Severity at Childhood Assessment*	8.4 +/- 4.7	14.3 +/- 9.4
Worst-Ever Childhood OCD Severity^	23.7 +/- 8.4	27.8 +/- 6.0
Comorbid Conditions		
Tourette Syndrome	10 (50%)	7 (29%)
Chronic Tic Disorder*	16 (80%)	10 (42%)
Attention-Deficit Hyperactivity Disorder	10 (50%)	8 (33%)
Depression	6 (30%)	7 (29%)
Oppositional Defiant Disorder	6 (30%)	7 (29%)
Primary OCD Symptom Dimension		
Cleaning	7 (35%)	5 (21%)
Forbidden Thoughts	6 (30%)	5 (21%)
Symmetry	6 (30%)	5 (21%)
Hoarding*	1 (5%)	9 (38%)
Medication Use		
Childhood Baseline Assessment		
Serotonin Reuptake Inhibitors	19 (95%)	22 (92%)
Antipsychotics	11 (55%)	12 (50%)
Alpha2-agonists	7 (35%)	6 (25%)
Adulthood Follow-up Assessment		
Serotonin Reuptake Inhibitors	11 (55%)	16 (67%)
Antipsychotics	3 (15%)	4 (17%)
Alpha2-agonists	1 (5%)	1 (4%)

TABLE 2. Characteristics of Remitting and Non-remitting Participants. Participants whose OC symptoms remitted in adulthood were less likely to have primary hoarding symptoms and more likely to have a comorbid chronic tic disorder when compared to non-remitters. *=$p<0.05$ and ^=$p<0.1$. Table courtesy of Dr. Michael Bloch.

Severity and Timing of Worst-Ever Obsessive-Compulsive Symptoms

The mean worst-ever Y-BOCS score was 25.6 ± 7.1, which occurred at a mean age of 11.3 ± 2.4 years. For the majority of the participants (N = 30; 66.7%), the timing of their worst-ever OC symptoms occurred prior to their evaluation at childhood baseline assessment. Figure 1 presents a box plot showing the progression of OC symptom severity at worst-ever, childhood baseline assessment, and follow-up.

FIGURE 1:

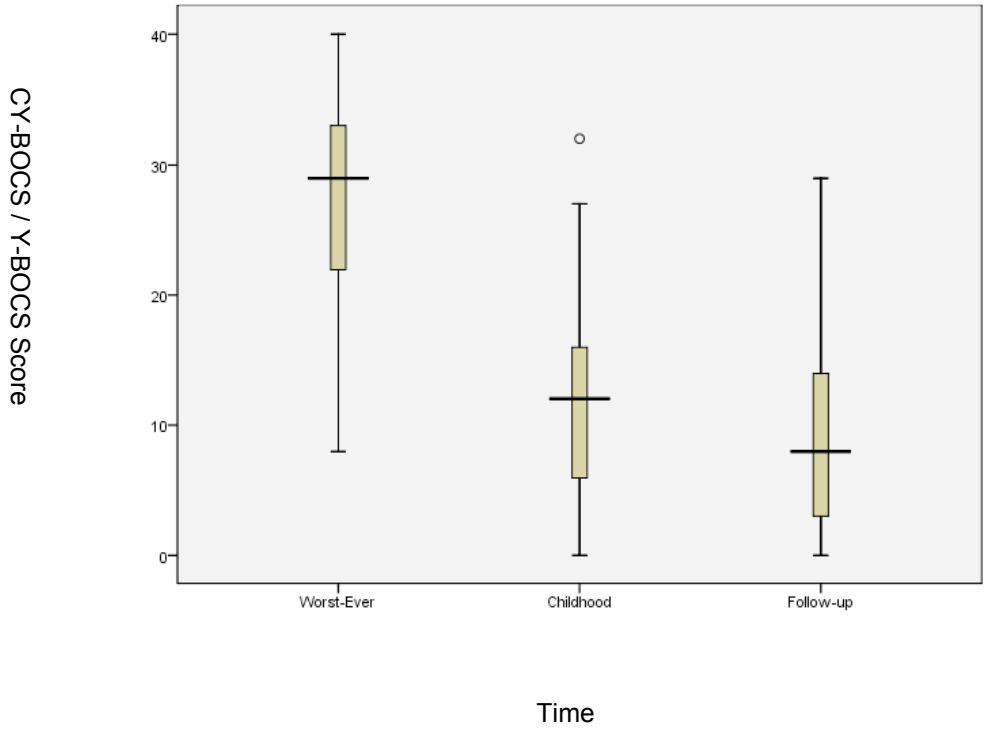

Figure 1. Box plot showing progression of OC symptom severity over time. Time is represented on the x-axis and CY-BOCS or Y-BOCS score is represented on the y-axis. Plot displays Y-BOCS score at the worst-ever time period, CY-BOCS score at time of the initial assessment in childhood, and Y-BOCS score at follow-up in early adulthood. Worst-ever severity is depicted first, as the majority of participants experienced their peak severity of symptoms prior to the baseline evaluation.

Comorbid Conditions at Follow-Up

At the time of the follow-up interview, 13 participants (29%) had a history of major depressive disorder, while two participants (4%) currently met criteria for major depression. One participant had been diagnosed with a psychotic disorder and another with bipolar disorder during the follow-up interval. No subjects had bipolar disorder or psychotic symptoms at the childhood assessment. Seven participants (16%) met criteria for alcohol abuse, three of whom also met criteria for substance abuse. Two additional subjects were using substances in the absence of alcohol abuse, making five (11%) the total number of participants who met criteria for substance abuse at follow-up.

Medication Use at Follow-Up

At the baseline childhood evaluation, 41 participants (91%) were taking selective serotonin reuptake inhibitors (SSRIs). At follow-up, 27 (60%) patients continued to take SSRIs, while 14 (31%) patients had stopped using them. Only four participants (9%) had never used SSRIs. Two subjects (4%) were using alpha2-agonists at adulthood follow-up, compared to 9 (20%) at childhood baseline evaluation. Seven participants (16%) were taking antipsychotic medications at adulthood follow-up as compared to 22 subjects (49%) who were taking them at childhood evaluation. There were no significant differences between remitted and non-remitted OCD subjects in terms of medication use at the time of the baseline childhood evaluation or at the adulthood follow-up.

Kaplan-Meier Model for A Priori Predictors of Time to OCD Remission

Kaplan-Meier survival plots demonstrated a reduced time to remission of OC symptoms for subjects with comorbid tic disorders (χ^2=6.0, df=1, p=0.02) (Figure 2). Primary OCD symptom dimension was also associated with likelihood of remission at trend levels (χ^2=6.6, df=3, p=0.09) (Figure 3). This result appeared to be primarily due to a significantly decreased likelihood of remission among individuals with primary hoarding symptoms compared to other children with OCD and primary symptoms in other dimensions (χ^2=5.4, df=1, p=0.02).

FIGURE 2:

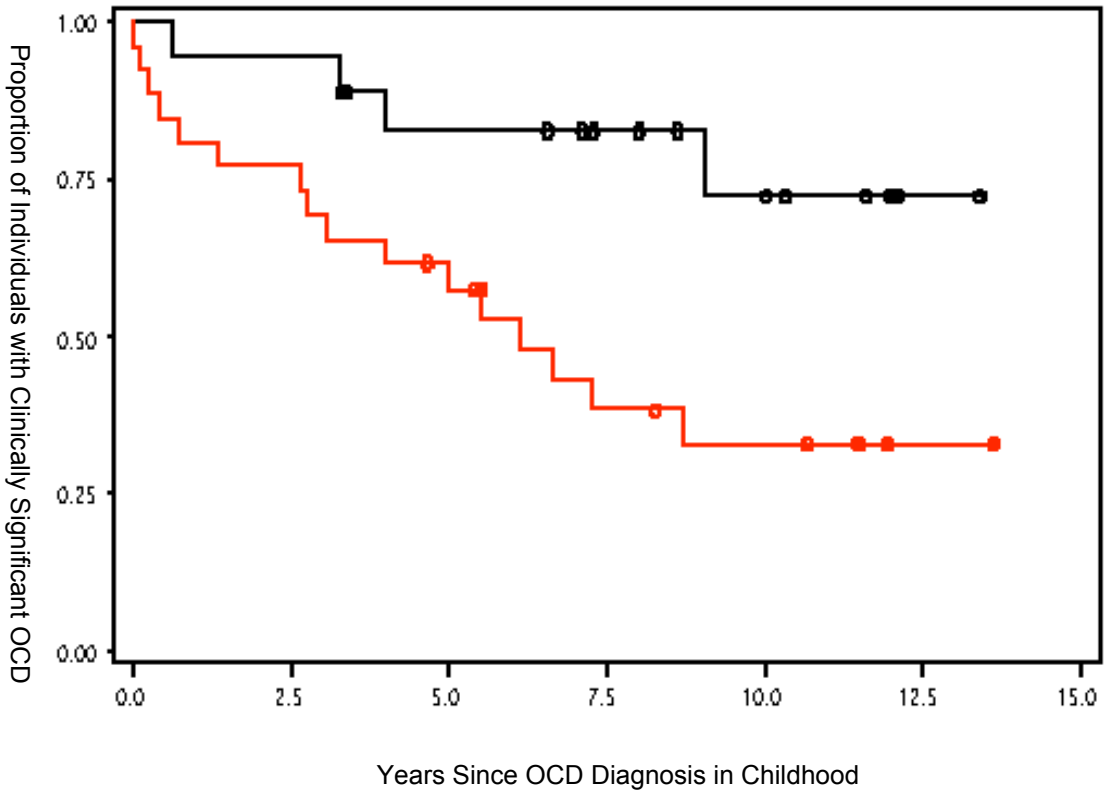

Figure 2: Survival curve comparing patients with OCD with and without comorbid chronic tic disorders. (Comorbid chronic tic disorder (red) and without (black); circles represent censored observations). Proportion of patients whose OCD remitted is displayed on the y-axis and time since childhood baseline assessment is displayed on the x-axis. Patients with a comorbid chronic tic disorder experienced a decreased time to remission of OC symptoms (χ^2=6.0, df=1, p=0.02). Figure courtesy of Dr. Michael Bloch.

FIGURE 3:

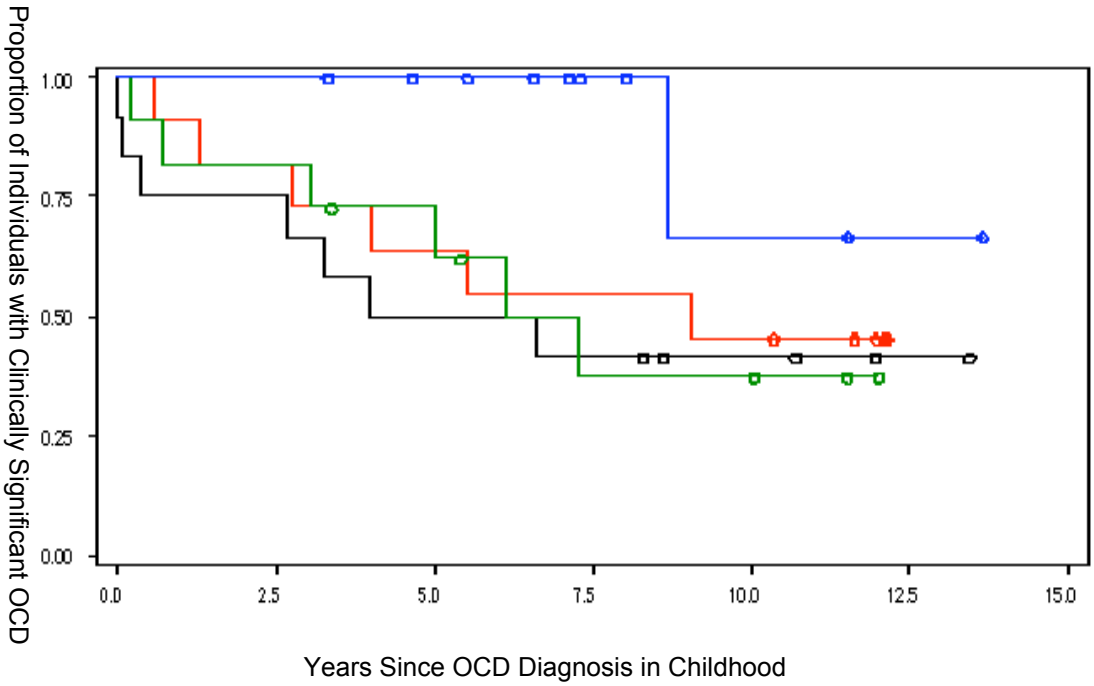

Figure 3. Survival curve comparing patients by primary symptom dimension. (Symmetry (red), Cleaning (green), Forbidden thoughts (black) and Hoarding (blue), circles represent censored observations). Proportion of patients with OCD who remitted is displayed on the y-axis and time since childhood baseline assessment is displayed on the x-axis. OCD symptom dimensions were associated with differences in likelihood of remission at trend levels (χ^2=6.6, df=3, p=0.09). Primary hoarding symptoms were associated with a significantly decreased likelihood of remission (χ^2=5.4, df=1, p=0.02) compared to non-hoarding OCD symptoms. Figure courtesy of Dr. Michael Bloch.

Cox-Proportional Hazard Model for Time to OCD Remission

The best fitting model by the Likelihood Ratio test is depicted in Table 3. Female gender, absence of comorbid tic symptoms, more severe initial OC symptoms, younger age at childhood assessment, older age of onset, comorbid ODD, and primary hoarding symptoms were associated with increased time to remission of OCD symptoms. Using patient factor scores for OCD symptom dimensions and classifying OCD severity in each dimension did not improve the overall fit of our model compared to the clinical variables alone (the best fitting model without the primary hoarding symptom variable).

TABLE 3:

Parameter	HR	95% CI	p
Gender (male=0, female=1)	0.06	0.02-0.15	0.002
Childhood CY-BOCS	0.89	0.85-0.94	0.018
Age at baseline assessment	2.00	1.64-2.43	<0.001
Chronic Tic Disorder	4.50	2.15-9.42	0.042
ODD	0.17	0.08-0.35	0.014
Age of OCD onset	0.77	0.70-0.84	0.004
Primary Hoarding symptoms	0.09	0.03-0.25	0.023

TABLE 3. Cox-Proportional Hazards Model of Time to Remission of Pediatric-Onset OC symptoms. A lower hazard ratio indicates an increased time to remission of OC symptoms. Female gender, more severe initial OC symptoms, younger age at initial assessment, later age of onset, comorbid ODD, absence of comorbid tic symptoms and primary hoarding symptoms were associated with increased time to remission. Overall model fit statistics: Likelihood Ratio χ^2=38.0, df=7, p<0.0001. Abbreviations: HR=hazard ratio, CY-BOCS=children's Yale-Brown Obsessive-Compulsive Scale, ODD=Oppositional Defiant Disorder, OCD=Obsessive-Compulsive Disorder. Table courtesy of Dr. Michael Bloch.

DISCUSSION

The results of this follow-up study examining the early adult outcome of patients with pediatric-onset OCD indicate that a significant proportion of children with OCD will remit by early adulthood. Depending on the criteria used for OCD remission, the percentage of children who remitted ranged from 44% (Y-BOCS <8) to 58% (Y-BOCS <10). This result is remarkably consistent with the results of a recent meta-analysis of previous studies of pediatric-onset OCD that reported rates of remission between 40-59% (75), but it is in stark contrast to outcome studies of adults, which report significantly lower rates of remission (95). The results also provide valuable information regarding the course and progression of pediatric-onset OCD.

In this study, children with OCD and chronic tic disorder had a decreased time to remission of OC symptoms when compared to participants without tics – 62% of patients with pediatric-onset OCD and tics remitted by early adulthood, whereas only 22% of patients without a tic disorder remitted (Table 2). This finding goes against our hypothesis that the presence of tics would be associated with persistence of OC symptoms into early adulthood. It is also in contrast to the results of other longitudinal studies of OCD, which have demonstrated that the presence of tics is associated with increased OCD severity at follow-up (73, 74). One reason for this discrepancy may be that a larger proportion of participants in this study had tics when compared to other study populations.

When compared to patients with OCD without tics, patients with OCD and tics have been shown to have a comparable response to cognitive behavioral therapy but a worse short-term response to sertraline treatment (42), as well as a more favorable

response to antipsychotic augmentation (43). In studies of the course of tics in patients with Tourette Syndrome, tic symptoms typically reach their peak severity between 10-12 years of age and then improve during the course of adolescence (96, 97). The developmental changes that are responsible for improving tics in children during the adolescent years may also help to ameliorate OC symptoms in these children.

Participants with primary hoarding symptoms appeared to have a poorer long-term outcome when compared with other children with OCD whose primary symptoms were within other dimensions – rates of remission were 10% and 54%, respectively. Some experts have suggested that the Hoarding symptom dimension should be used as a specifier in the next version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), and a strong case can be made that compulsive hoarding in the absence of OCD should be listed as a separate diagnostic entity (98, 99). Results from several studies suggest that patients with OCD and primary hoarding symptoms are different from those without hoarding symptoms. As compared to patients with OCD without hoarding symptoms, patients who exhibit hoarding behavior have been reported to display more severe obsessions and compulsions (93), have a higher prevalence of comorbid personality disorders (100-102), and respond less favorably to SSRIs and cognitive-behavioral therapy (56, 58, 59, 103). In addition, neuroimaging studies have demonstrated differences in glucose metabolism, brain activation patterns (104, 105), and grey matter (106) among patients with compulsive hoarding symptoms when compared to other patients with OCD. The results of a recent genetic study suggest that a region on chromosome 14 is linked with compulsive hoarding behavior in families with OCD (107). These data suggest that patients with OCD and compulsive hoarding symptoms

are clinically and perhaps etiologically different from those without hoarding behavior and may indeed represent a distinct subtype of the disorder.

The results of multivariate, exploratory survival analyses demonstrated that increased OCD severity at baseline was associated with longer time to remission. Given that a Y-BOCS score of less than 8 was required to meet criteria for remission, this is not especially surprising since patients with more severe OCD would need a greater degree of improvement to achieve this metric. Initial severity of OCD has been reported to predict increased severity at follow-up in some but not all longitudinal studies of pediatric-onset OCD (75). A later age of onset and younger age at baseline evaluation were also found to be associated with increased time to remission of OC symptoms. This result is in contrast to those of previous long-term outcome studies that have demonstrated that earlier age of onset and increased duration of illness are associated with greater OCD persistence (75). The longer interval between baseline evaluation and follow-up, higher proportion of participants with comorbid tic disorders, and the use of multivariate as opposed to univariate analysis may in part explain this difference. Comorbid ODD was also associated with poorer long-term prognosis. While there are little data examining the relationship between OCD and comorbid ODD, other comorbid externalizing disorders such as ADHD have been associated with increased functional impairment among children with OCD (108).

Finally, female gender was associated with increased time to remission of OC symptoms. While there are little data available regarding gender differences in OCD, it has been suggested that gender may provide useful insight into the clinical and biological heterogeneity of the disorder (109). Some studies have demonstrated differences in

symptomatology, with females exhibiting more washing rituals and contamination fears (110, 111) and males displaying more checking and symmetry compulsions (111). Comorbidity studies have demonstrated increased prevalence of eating disorders (112) and depression (112, 113) among females with OCD, while investigations of the role of gender in genetic studies of OCD have yielded mixed results (109). In selected previous follow-up studies of pediatric-onset OCD female gender has predicted an episodic course (74, 114), while male gender was predictive of a more chronic course (74). Future studies of long-term outcome in pediatric-onset OCD will be necessary to elucidate the role of gender in the disorder.

This study has several limitations. First, the participation rate for all eligible participants in the follow-up portion of the study was 74%. While the only significant demographic difference between participants and non-participants was age at baseline assessment, it is possible that there were other systematic differences between the groups that would have emerged at the follow-up interview. In addition, the study relied on retrospective reporting of age of remission. Because multiple clinical and dimensional variables were tested in the multivariate Cox survival models, there exists a higher likelihood for Type I error, and therefore findings from these models should be regarded as hypothesis-generating. Further studies will be necessary to confirm these results. Finally, participants underwent treatment with both pharmacological and cognitive-behavioral therapies throughout the interval between baseline assessment and follow-up, so the outcomes and predictor variables identified are indicative of the clinical course of OCD rather than its natural history.

Despite these limitations, this study provides important data regarding the course and early adulthood outcome of pediatric-onset OCD. It substantiates the results of previous longitudinal studies that suggest that a majority of patients who experience onset of OCD in childhood will remit by the time they have reached early adulthood. Further, it provides information regarding the course of OC symptoms - in this group of patients, most children experienced an onset of symptoms around 8 years of age and most severe symptoms around 11 years. This information will be especially important for children and families who are receiving a new diagnosis of OCD and are interested in what to anticipate in terms of course and prognosis. Given that OCD can be significantly debilitating, clinicians, patients, and families will likely welcome the degree of optimism that comes with these results.

In this study comorbid tics were associated with improved long-term outcome in pediatric-onset OCD, suggesting that the presence of tics may indicate a clinical course of OCD that follows a trajectory similar to that of Tourette Syndrome, in which symptoms are more likely to remit during adolescence. In addition, this study identified subgroups of patients, particularly those with primary hoarding symptoms, that may have worse outcomes than other patients with OCD. This finding contributes to the growing body of evidence in support of a multidimensional model of OCD and suggests that compulsive hoarding may represent a discrete clinical entity. Moreover, it underscores the importance of early characterization of symptoms and comorbidities in patients with pediatric-onset OCD in order to identify patients at higher risk. It also emphasizes the need for development of improved pharmacological and cognitive-behavioral therapies for children, especially for those who display compulsive hoarding symptoms.

AUTHOR CONTRIBUTIONS

Ms. Craiglow conducted the majority of interviews with study participants, researched the background literature on related subject material, assisted with data analysis, primarily through organizing data and calculating means and frequencies, and wrote and coordinated the manuscript. Dr. Bloch participated in the follow-up study design, and was primarily responsible for biostatistical analyses, plotting survival curves, comparing them, and constructing the best-fitting model for the data. The description of the data analysis, along with the corresponding results, tables, and figures, were therefore in large part prepared by Dr. Bloch. Dr. Landeros-Weisenberger assisted with data analysis, particularly in terms of assessing the impact of symptom dimensions on long-term outcome. Ms. Panza and Mr. Philip Dombrowski served as research assistants who helped with the coordination of the study and who were instrumental in data compilation. Dr. Peterson participated in the initial study design. Dr. Leckman participated in the study design at both time points, oversaw the study as it was being carried out, and helped to coordinate the manuscript.

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