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Clinical features associated with treatment response in obsessive-compulsive disorder

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Abstract

Objective: This study aims to investigate the effect of sociodemographic and clinical features on the short-term response to pharmacological treatment in obsessive-compulsive disorder (OCD). We focused especially on investigating factors previously associated with poorer prognosis, such as comorbidity with tic disorders, early onset of symptoms, and sensory phenomena preceding compulsions, which have been described as common in both tic-related and early-onset OCD.

Method: The study involved 41 consecutive adult patients with OCD diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria and was conducted at the OCD Spectrum Disorders Clinic of the University of Sao Paulo School of Medicine in São Paulo, Brazil, between January of 2000 and December of 2001. All patients were treated exclusively with oral clomipramine for 14 weeks. Treatment response, measured for Yale-Brown Obsessive-Compulsive Scale score decrease from baseline, was assessed by an investigator blinded as to the variables of interest present.

Results: Linear regression analysis showed that having a partner and sensory phenomena preceding compulsions were associated with better response to clomipramine treatment ($P = .04$ and $P = .002$, respectively). Tic comorbidity and early onset of symptoms were not associated with poorer response.

Conclusions: In OCD, having a partner and sensory phenomena preceding compulsions seem to be associated with a favorable response to pharmacological treatment.

1. Introduction

Seen in the past as a disorder with a poor prognosis, it is currently accepted that most patients with obsessive-compulsive disorder (OCD) improve after conventional treatments [1]. The potentially devastating nature of this disorder, however, remains unchanged, threatening the social, academic, professional, and family lives of affected individuals.

Variability in OCD treatment outcome supports the notion that OCD is a heterogeneous condition. Efforts to identify homogeneous OCD subtypes have resulted in a variety of studies that have used varying criteria to characterize specific subgroups of patients. Some authors have attempted to determine the association between specific patient characteristics and treatment response. For instance, being single has been associated with a worse prognosis in a 5-year follow-up study [2]. Various studies have suggested that patients in whom hoarding is the main clinical feature present a worse response to treatment with clomipramine (CMI) or selective serotonin reuptake inhibitors (SSRIs) [3,4] and to cognitive behavioral therapy (CBT) [5]. Lack of response to the same pharmacological treatments was also observed in patients with OCD with poor insight [6,7]. On the other hand, being treatment-naive, having baseline Yale-Brown obsessive-compulsive scale (Y-BOCS) scores below 23, and low baseline levels of

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depression have been associated with a good treatment response [8]. Currently, a large body of evidence points to the existence of 2 main putative OCD subtypes: tic-related OCD [9,10] and early-onset OCD [10-12]. Both tic-related and early-onset OCD have been associated with a poorer response to antiobsessional agents [11,13].

Originally observed in patients with tic disorders, sensory phenomena can be described as uncomfortable sensations, feelings, or perceptions that are focal or general in nature and can precede compulsions in the absence of obsessions. Examples include the urge to count, a need to repeat a behavior to alleviate feelings of incompleteness or inner tension, and a need to arrange things until feeling "just right" [9,14,15]. Patients report that these phenomena precede the compulsions in the absence of any thought, fear, or worry, and that they are compelled to perform the behaviors until achieving a sense of relief. Clinicians have long observed such subjective experiences among patients with OCD. Leckman et al [16] found that, among the patients studied, the majority reported the occurrence of "just right" perceptions at some point in their illness. In a more recent study, two thirds of the patients studied reported repetitive behaviors preceded by "feelings of things not being 'just right'" [9]. Despite the absence of systematic evaluations using structured instruments to assess sensory phenomena, anecdotal reports suggest that patients with such symptoms could present a poorer response to CBT [15].

In the present study, we attempted to identify clinical features associated with the short-term response to pharmacological treatment in OCD. Such features include sociodemographic variables, type of obsessive-compulsive symptom (OCS), age at onset of symptoms, and patterns of comorbidity. Patients with tic-related and early-onset OCD have been shown to present a high frequency of sensory phenomena and a poorer treatment response [9,11]. In view of this, our hypothesis was that tic comorbidity and early onset of OCS, as well as sensory phenomena, are clinical features associated with poorer treatment response. This study is part of a larger investigation, which aims to identify, within the area of OCD phenomenology, more homogeneous subtypes of OCD and their relationship to particular genetic, immunologic, and therapeutic aspects [9,11,17-19].

2. Methods

This study was approved by the Ethics Committee of the Hospital das Clínicas of the Faculdade de Medicina da Universidade de São Paulo (University of São Paulo School of Medicine). All subjects were given a full explanation of the study procedures, and all gave written informed consent. Ninety-eight consecutive outpatients were recruited from the community through radio and newspaper announcements and participated in a screening interview. Forty-three initiated and 41 completed the study carried out at the OCD Spectrum Disorders Clinic of the University of São Paulo School of Medicine (São Paulo, Brazil) between January 2000 and December 2001. Of the 41 subjects, 21 (51.2%) were men and 20 (48.8%) were women. The mean age was 30.5 ± 8.3 years. The inclusion criteria were *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis of OCD, symptom duration of at least 1 year, minimum baseline total Y-BOCS [20] score of 18 for the presence of obsessions and compulsions and 10 for the presence of only obsessions or only compulsions, and absence of appropriate previous treatment of OCD (CMI or SSRIs in adequate doses for at least 12 weeks or at least 20 hours of CBT). Exclusion criteria included any physical or mental condition that precluded the use of CMI, a current diagnosis of alcohol or substance abuse or dependence, risk of suicide, pregnancy, lactation state, or being a fertile woman not using effective contraceptive methods.

The OCD and *DSM-IV* Axis I psychiatric comorbidity were assessed through the Structured Clinical Interview for *DSM-IV* [21]. A current diagnosis referred to symptoms present during the preceding month.

The term *early–onset OCD* was used when the first noticeable symptom occurred before or at 10 years of age. This criterion is in agreement with former studies by Pauls et al [22], Geller et al [12], and some studies by our group [11,23] that suggest a more prominent participation of genetic factors in OCD for the group whose symptoms first appear before or at 10 years of age. After that age, the differences regarding genetic aspects and family history become less significant.

Patients were excluded for not meeting *DSM-IV* OCD criteria (n = 9), Y-BOCS score below 18 (n = 9), symptoms lasting less than 1 year (n = 1), previous appropriate treatment of OCD (n = 10), current psychosis (n = 2), preference for psychotherapy (n = 11), and for current use of and unwillingness to discontinue anxiolytics (n = 3). Nine patients could not be located after the screening interview and failed to report for the study.

Dropouts were due to loss of interest (n = 2) and CMI side effects (n = 1; this patient was included in the analysis—she presented a 55% reduction in Y-BOCS score by week 10).

The Y-BOCS and Yale Global Tic Severity Scale [24] were used to assess OCS and tics, respectively. As in our previous study [11], age at onset was the age at which the first symptom occurred, based on the recollection of the patient. Sensory phenomena were assessed through the USP-Harvard Repetitive Behaviors Interview [17] and were considered present when the patient reported at least 1 repetitive behavior preceded by a bodily or mental sensation in the absence of obsessions. This semistructured interview was developed by one of the authors (ECM) at the OCD clinic of the Massachusetts General Hospital and has been used in more than 300 patients, both at our OCD clinic in Brazil and at the Massachusetts General Hospital. The questions help patients describe the cognitions (thoughts, fears, and worries), autonomic anxiety

(tachycardia, sweating, shortness of breath, etc), and sensory phenomena that occur immediately before their repetitive behaviors. Sensory phenomena were classified as bodily sensations (focal or general), including the tactile (itching, etc), muscular (stretching, etc) and visceral (burning, etc) or mental sensations (general, uncomfortable feelings or perceptions that include urges to perform the behaviors, feelings of inner tension or pressure, mental energy that builds up and needs to be discharged, an inner sense of incompleteness, imperfection or insufficiency, and the general perception of not being "just right" that leads to the performance of behaviors until achieving that "just-right" feeling). To avoid discordance in the diagnoses of sensory phenomena, all data collected through the USP-Harvard Repetitive Behaviors Interview were submitted to a best-estimate procedure (as described in Leckman et al [25]). In addition, to date, this is the only instrument presented in the literature for the systematic assessment of these subjective experiences.

The intensity of depressive and anxiety symptoms were assessed using the Beck Depression Inventory [26] and the Beck Anxiety Inventory [27], respectively.

Twenty-three (56.2%) of the patients were treatment-naive, and 18 (43,8%) patients had previously received inadequate treatment with antiobsessional agents. After a 2-week washout period for those who were taking any kind of psychotropic medication, subjects received exclusive oral CMI treatment for 14 weeks, starting at 25 mg/d, and increased by 25 mg every 3 days as tolerated until reaching a maximum dose of 250 mg/d (mean, 230.5 ± 40.8 mg/d; range, 100-250 mg/d). We chose CMI as the treatment agent because it is the gold standard treatment of OCD. A test treatment with CMI is mandatory before a patient can be considered refractory to treatment or become a candidate for neurosurgery. Various meta-analyses [1,28-30] have suggested that CMI is more effective than SSRIs for the treatment of OCD.

Response, in percent reduction of the initial total Y-BOCS score, was considered a continuous variable. Evaluation of outcome was made by an investigator (CB, who also rated baseline Y-BOCS symptom severity) who was blinded as to the variables of interest present in any given patient (which were assessed by investigator RGS).

Serum levels of CMI and desmethylclomipramine (DCMI) were determined in the eighth week (mean CMI, 193.3 ± 121.2 ng/mL; range, 24-588; mean CMI + DCMI, 298.5 ± 191.5 ng/mL; range, 59-750) to ensure that the doses taken were within the nontoxic range.

Severity of side effects was rated through the side effects section of the Clinical Global Impression scale [31].

Two-tailed *t* tests and correlation analyses were used as indicated. Variables with a *P* value of 0.10 or less in the univariate analysis were entered into the regression model. The stepwise linear regression model was used, and the level of significance was set at .05. The SPSS version 10.0 was used (SPSS, Chicago, Ill).

3. Results

The mean reduction in Y-BOCS scores for this sample was 47.9% ± 24.5. Approximately 66% (n = 27) of patients presented a reduction of at least 35% in the baseline Y-BOCS scores and a "better" or "much better" rating in the Clinical Global Impression. Among the responders, 54% were treatment-naive. There were no significant differences between the degrees of response of treatment-naive patients and those who had received previous inadequate treatments (such as CMI or SSRIs in lower doses and for shorter duration than those recommended for OCD), any type of psychotherapy, antipsychotics, anxiolytics, anticonvulsants, or other antidepressants (one-way analysis of variance, $P = .198$). As stated in the methods section, 10 patients previously receiving adequate treatment were excluded from the study to avoid any confusion created by including treatment resistant patients.

The main sociodemographic and clinical characteristics of the sample are described in Table 1.

Table 2 shows the categorical variables that were significant in the univariate analyses (P value $\leq .10$) and were entered into the regression model. The presence of tic disorders and early-onset OCD symptoms were not associated with a poorer response to CMI. Among the subjective experiences that preceded compulsions, sensory phenomena were associated with higher degrees of response to CMI (Table 2). Sensory phenomena were present in 9 (64.3%) of 14 patients with tic disorders and in 9 (50%) of 18 patients with early-onset OCD. Those *DSM-IV* Axis I diagnoses that showed an association with treatment response are listed in Table 2. Grooming behaviors (including skin picking, trichotillomania, and onychophagia, as defined by Bienvenu et al [32]), anorexia nervosa, and bipolar disorder were associated with lower degrees of response.

Table 1
Sociodemographic and clinical characteristics of the sample

Variable	
Sex	n (%)
Male	21 (51.2)
Female	20 (48.8)
Age (y)	30.6 ± 8.3
Age at onset of OCD (y)	12.5 ± 6.5
Marital status	n (%)
Single/divorced	28 (68.3)
Married/cohabiting	13 (31.7)
Baseline total Y-BOCS score	26.7 ± 6.8
% Decrease from baseline Y-BOCS score	47.9 ± 24.5
Tic disorder comorbidity	n (%)
Yes	14 (34.1)
No	27 (65.8)
Age at onset of OCD	n (%)
≤ 10 y	19 (46.3)
≥ 17 y	10 (24.4)
11-16 y	12 (29.3)

Except where otherwise indicated, results are expressed as mean ± SD.

Table 2
Categorical variables significant at the univariate analysis that entered the regression model

Variable	n (%)	Mean % reduction in Y-BOCS score	*t*	df	P[a]
Marital status					
Single + divorced	28 (68.3)	43.2 ± 23.3	1.868	39	.069
Married + cohabiting	13 (31.7)	58.1 (24.8)			
Family history of tics					
Yes	12 (29.3)	43.4 ± 11.7	1.797	35.997	.081
No	26 (63.4)	54.4 ± 25.8			
Sensory phenomena					
Yes	23 (57.5)	56.2 ± 27.2	−2.433	38	.020
No	17 (42.5)	38.2 ± 15.8			
Grooming behaviors (trichotillomania, skin-picking, onychophagia)					
Yes	10 (24.4)	35.5 ± 15.9	1.897	39	.065
No	31 (75.6)	51.9 ± 25.7			
Attention deficit hyperactivity disorder					
Yes	7 (17.1)	62.9 ± 29.9	−1.822	39	.076
No	34 (82.9)	44.8 ± 22.6			
Bipolar disorder I or II					
Yes	3 (7.3)	13.7 ± 18.3	2.653	38	.012
No	37 (90.2)	50.3 ± 23.2			
Anorexia nervosa					
Yes	3 (7.3)	22.0 ± 20.4	1.925	38	.062
No	37 (90.2)	49.6 ± 24.1			

[a] Student *t* test; comorbidities are lifetime.

Categorical variables that did not present an association with treatment response were sex, family history of OCD, and type of OCD symptoms. In fact, the variable type of OCD symptoms divided into cells with numbers too small to have reasonable power to look for a relationship to outcome. Hoarding symptoms were reported by 13 (31.7%) patients and were never the main complaint. When present, hoarding symptoms were seen in combination with other types of OCS belonging to other dimensions. Therefore, it was not possible to investigate the influence of hoarding on treatment response.

Continuous variables that were entered into the regression model were baseline total Y-BOCS scores (26.7 ± 6.8; range, 11-40; $r = -0.390$; $P = .012$, significant correlation for P value <.05, 2-tailed test) and number of psychiatric comorbidities (2.4 ± 1.9; range, 0-7; $r = -0.344$; $P = .030$, significant correlation for P value <.05, 2-tailed test). Continuous variables that presented no association with treatment response were serum levels of CMI and DCMI, side effect severity, educational level, socioeconomic status, illness duration, and baseline Beck Depression and Beck Anxiety Inventories score.

In the multivariate analysis, having a steady partner and the presence of sensory phenomena were associated with a better outcome (coefficient ± SE and P values for having a partner: −15.030 ± 7.190, $P = .044$; for sensory phenomena: 23.428 ± 6.789, $P = .002$). The other variables did not reach statistical significance.

4. Discussion

Contrary to our hypothesis, the presence of tics and the early onset of OCD were not associated with a poorer response to CMI.

Also unexpectedly, the presence of sensory phenomena was a clinical manifestation associated with greater decreases in baseline Y-BOCS scores after treatment with CMI.

Conventional treatment of tic disorders includes the use of noradrenergic agents such as guanfacine [33]. Previous studies reporting a poor treatment response among patients with tic-related OCD have used mainly SSRIs [13,34]. A possible explanation for the high response rate observed in patients with tic-related OCD in our sample could be the pharmacological profile of CMI. Indeed, there are reports of successful treatment of Tourette syndrome (TS) with CMI [35,36].

Nevertheless, these contrasting findings could also reflect the unique profile of our sample, in which all patients could be technically considered treatment-naive (18 patients had previously received inadequate treatment). In addition, there have been few treatment studies including patients with OCD and TS, which is, in fact, often an exclusion criterion in clinical trials involving OCD. Therefore, further studies are necessary to determine whether tic-related OCD actually has a worse prognosis [37]. Rates of response among patients with early-onset OCD may also have been higher than expected because of the fact that this was the first specific treatment they were given.

It has been proposed that patients with sensory phenomena preceding compulsions in the absence of obsessions may represent a subtype of OCD closer to the TS end of the OCD-TS spectrum [9,17,18,38,39]. The association between sensory phenomena and higher rates of response in our sample could, as in tic-related OCD, be secondary to the pharmacological profile of CMI, producing a significant noradrenergic and mild antidopaminergic effect. Finally, we cannot rule out the possibility that using a structured interview focused on such subjective experiences had a psychoeducational effect. Having greater awareness of these premonitory phenomena may have contributed, to some extent, to the positive therapeutic responses observed in these patients.

Having a spouse or a partner was also associated with a better response to treatment. Patients with severe OCD may, as a consequence of their disorder, have difficulties in establishing close relationships and thus remain unattached and rely mainly on their own judgment to decide whether and when they should seek professional help. In contrast, having a partner can encourage the patient to seek assistance and comply with treatment. In a study of predictive factors of the course of OCD, Steketee et al [2] found that the probability for married patients to achieve partial remission within a period of 5 years was double that of singles. The

authors found that married patients presented lower total baseline Y-BOCS scores, possibly reflecting less impairment in global functioning. Future studies should clarify whether the better response seen in married patients is a function of having a less severe form of the disorder from the onset or whether the presence of a partner per se contributes to a better outcome.

Although not significant in the multivariate analyses, patients with a greater number of comorbidities presented lower degrees of response ($P = .03$). This is in accordance with other findings in the literature [40] and suggests that these patients are vulnerable to a broader spectrum of psychiatric disorders. More specifically, our data suggest that future studies should actively investigate OCD spectrum disorders (such as trichotillomania and skin picking), anorexia nervosa, and bipolar disorder as possible predictors of a worse treatment response in OCD.

This is essentially a pilot study and should, for reasons of its limited sample size and uncontrolled nature, be viewed as preliminary. In addition, it was not possible to determine how meaningful it is to study sensory phenomena alone because these could be features of the more well-defined early-onset and tic-related subtypes. However, the systematic assessment of sensory phenomena using the USP-Harvard Repetitive Behaviors Interview [17] is unique. This interview also proposes a systematic definition of the sensory phenomena, which present significant heterogeneity in the literature [15]. Furthermore, standardization of treatment and blinded rating of improvement should have minimized the chance of obtaining biased results. The data presented suggest that sensory phenomena and having a partner seem indicative of a good response to CMI. Although further studies are warranted, this finding supports the notion that narrowing the phenotype within OCD might improve the ability to predict treatment response.

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