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September 23rd, 2004

Richard I. Shader, MD
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Please find enclosed four copies of our manuscript, "Clinical features of refractory Obsessive-Compulsive Disorder: predictive factors of refractoriness" for submission as Original Contribution to the JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY .

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Dr Ygor Arzeno Ferrão will serve as the corresponding author (address in the first page).

We thank you for considering this work for inclusion in the JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY.

Yours Sincerely,

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Clinical features of refractory Obsessive-Compulsive Disorder patients.

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Clinical features of refractory Obsessive-Compulsive Disorder patients.

Abstract

Some patients with obsessive-compulsive disorder (OCD) do not respond to conventional treatments, including serotonin reuptake inhibitors (40 to 60%) and cognitive behavior therapy (20 to 40%). Although there are many efforts to describe the clinical features of these treatment refractory OCD patients, current findings are very inconsistent. In this study, we compared 23 patients with refractory OCD to 26 patients with OCD who have responded to conventional treatments. We found that higher severity, the presence of sexual/religious content of obsessive-compulsive symptoms, lower socio-economic status and higher scores of Family Accommodation Index were the most relevant factors associated to conventional treatment refractory OCD. Other factors associated to OCD refractoriness were: marital status (having no spouse), lower education level, unemployment, chronic course, worse quality of life according to SF-36, higher severity since the beginning of OCD according to Psychiatric State Rating. Further longitudinal studies are needed to investigate these variables prospectively.

Key words: Obsessive-compulsive disorder, Treatment, predictive factors of response.

Introduction

Despite the proven effectiveness of cognitive-behavioral therapy and serotonin reuptake inhibitors (SRIs) in the treatment of obsessive-compulsive disorder (OCD), as about 20% (1,2) to 40% (3-5) of patients do not respond to adequate trials with these treatment strategies respectively. These findings led to several studies trying to identify predictors of treatment response.

Factors that were already shown to be of potential value in predicting worse treatment response in OCD include: early Onset of OCS (6-9), lack of a partner (10), chronic course of obsessive-compulsive symptoms (OCS) (11,12), presence or high score on sexual/religious dimension (13,14), presence of Hoarding (15-18), Somatic obsessions (8,19), poorer insight (8,19), psychiatric comorbidity (e.g.: Bipolar Disorder, Eating Disorder and Schizotypal, Borderline and Paranoid Personality Disorders) (10,20-23), family history of tic disorder (10,24) , lack of family history (8), higher severity of OCD(24), and absence of sensory phenomena (10).

Jenike and Rauch (1994) termed "*treatment-resistant*" the individuals with OCD who do not respond satisfactory to any first line therapy trial, and "*treatment-refractory*" those patients with OCD who, despite being treated with all available therapeutic alternatives, do not show a satisfactory reduction in the severity of symptoms (4). Most current studies compare treatment resistant cases and responders (5,10,20,23-28). This study compares treatment refractory OCD cases with treatment responders with the aim of investigating which factors reported above are associated to refractoriness.

Early identification of socio-demographic and clinical predictors of treatment refractoriness may save patients lengthy trials that are unlikely to be effective and steer treatment toward modalities that have higher probabilities of succeeding.

METHODS

Patients

OCD patients (according to DSM-IV criteria) were consecutively recruited from three reference centers: 1) the obsessive-compulsive spectrum disorders clinic at *Hospital Presidente Vargas* (n=36), 2) the anxiety disorders clinic at *Hospital das Clínicas - Universidade Federal do Rio Grande do Sul* (n=6) [both centers located in the city of Porto Alegre], and 3)the OCD clinic (PROTOC), at the Institute of Psychiatry, *Hospital das Clinicas - Universidade de São Paulo* (n=7) [in the city of São Paulo]. Patients did not differ in terms of treatment refractoriness and response as to their origin of recruitment ($\chi 2$=4,229; p=0,121). Inclusion criteria comprised: (1) age between 18 and 65 years old, (2) OCD as the most significant current psychiatric diagnosis, (3) absence of general medical or neurological disease. All patients have provided a written informed consent before entering the study, approved by the local ethics committee.

We defined refractory OCD by the following criteria: 1) less than 25% decrease of the initial Y-BOCS scores or less than a minimal improvement on CGI, after treatment with first line drugs, 2) at least 3 therapeutic trials with first line drugs (clomipramine included necessarily), for 16 weeks each, with maximum recommended or tolerated doses, 3) at least one pharmacological augmentation strategy (including other SRIs or neuroleptics), 4) at least 20 hours of cognitive-behavioral therapy (exposure and response prevention). A given patient was considered a treatment responder if, after treated by any conventional therapy: 1) the patient displayed at least a 35% decrease in the initial YBOCS scores or 2) the patient was considered to be better or much better on the CGI, and 3) the improvement was

maintained for at least one year. The refractory group was composed by 23 patients and the responder group by 26.

Assessment

The following instruments were employed for the evaluation of our patients with OCD:

1) Structured Clinical Interview for DSM-IV Axis I Disorders. A chapter on Impulse Control Disorders not otherwise classified was included (29),

2) Structured Interview for Personality Disorders of DSM-IV (30). It was applied by at least 2 interviewers at the same time, with a consensus drawn afterwards,

3) Yale-Brown Obsessive-Compulsive Scale (YBOCS) and Symptom Checklist for the assessment of Obsessions and Compulsions. Applied by a blind rater (31,32),

4) Dimensional Yale-Brown Obsessive-Compulsive Scale (DYBOCS). It includes a self-report and expert clinician ratings. This instrument measures the severity for each of six symptom dimensions (contamination/cleaning, hoarding, symmetry, aggressive, sexual/religious, and miscellaneous). Innovative features include the joint consideration of obsessions and compulsions in assessing the severity of each domain, separation of specific forms of checking, repetition and mental rituals into discrete dimensions, and inclusion of avoidance in measures of severity. The list of symptoms was self-reported, and confirmed later on with an interviewer (33),

5) Yale Global Tics Severity Scale (YGTSS) for the assessment of vocal and motor tics (34),

6) Brown Assessment of Beliefs Scale (BABS), which measure the patient's conviction and insight about the obsessions (35). Applied by a blind rater,

7) Family Accommodation Scale (36), constituted by questions on family accommodation to the patient's obsessive-compulsive symptoms, family distress, reaction of the patients when the family resists to accommodate. Applied by a blind rater,

8) Hamilton Anxiety (HAMA-14 items) and Depression Scales (HAMD-21 items) (37,38). Applied by a blind rater,

10) Structured Interview for Socio-demographic data of OCD Clinic (PROTOC-USP). It was developed to gather personal aspects of OCD patients, including identification data, marital status, occupation, educational status, psychiatric treatments, family history, socio-economic classification and epigenetic factors,

11) OCD course visual instrument, a self-report instrument that consists of 5 graphics with possible courses for OCS,

12) Psychiatric Status Ratings (PSR), which measures the severity of OCS for 4 periods of patients' life: sub-clinical, clinical, worse episode and current episode. It also collects information about the onset of the OCS (abrupt or insidious) (39),

13) Medical Outcomes Study 36 – Item Short-Form Health Survey (SF-36), a self-report instrument which consists of 36 questions, divided in 8 dimensions which reflect quality of life (40).

Whenever possible (3 patients had to be interviewed at home because of their symptoms severity), the raters were blind to the type of response exhibited by the patient.

Statistical analysis

Student's t test or Mann-Whitney test were used to compare continuous variables. Continuous variables were tested for its variance homogeneity. Chi-square test with Yates's correction or Fisher's exact test was used to compare categorical variables. A stepwise

logistic regression was employed to find factors associated to refractoriness, controlling confounding variables. Variables entered on the model were those with $p \leq 0,10$ on univariate analysis and that were intrinsic to OCD phenomenology or those considered relevant for clinical practice). The statistical significance level chosen was 5%. Statistical Package for Social Science for Windows, 10.0 version (SPSS 10.0) was used to analyze data.

Results

As expected based on the patient recruitment criteria, more patients of the refractory group: 1) have performed Cognitive Behavioral Therapy (all of the refractory group and 19(73,1%) of the responder group; Fisher's Exact Test, p=0,011); have been hospitalized (15(65,2%) patients of the refractory group and 6 (23,1%) of the responder group ($\chi 2=7,21$; p=0,007)); and have been submitted to eletroconvulsivetherapy (4 (17,4%) patients of the refractory group and 1(3,8%) patient of the responder group (Fisher's Exact Test, p=0,17)). The mean (SD) YBOCS total score of the refractory group was 27,82 (6,09) while for responder group it was 17,42 (7,74) (t=5,03; p<0,001), the mean (SD) YBOCS obsessions subscale score was 13,64 (2,98) for refractory group and 8,67 (4,47) for the responders (t=4,39; p<0,001), the mean (SD) YBOCS compulsions subscale score was 14,18 (4,00) for refractory group and 8,75 (4,29) for the responder group (t=4,43; p<0,001). The mean (SD) DYBOCS total score for the refractory group was 21,65 (4,26) and for the responder group it was 14,69 (4,42) (t=5,60; p<0,001).

The mean (SD) severity of anxiety and depression symptoms were higher for refractory group: HAMA=13,7 (5,37) for the refractory group versus 7,54 (4,72) for the

responder group (t=4,27;p<0,001), and HAMD=13,3 (5,21) for the refractory group versus 6,89 (3,77) for the responder group (t=4,98; p<0,001).

The quality of life measured by MOS SF-36 showed worse mean (SD) scores for refractory group on 3 dimensions: vitality=36,91 (21,99) for refractory versus 54,61 (18,27) for responder group (t=3,017; p=0,004); social aspects=37,50 (24,04) for refractory versus 68,85 (21,26) for responder group (t=4,74; p<0,001); and mental health=33,91 (16,13) for refractory versus 57,54 (16,08) for responder group (t=5,00; p<0,001).

In addition, comparing the groups according to the use of lifetime used psychiatric medication, it was observed that all the patients were treated at least once in their life with a serotonergic agent. Twenty-two (96%) patients of the refractory group and 12 (46%) of the responder group used antipsychotic agents (Fisher's Exact Test, p<0.001), 17 (74%) of the refractory group and 8 (31%) of the responder group used mood stabilizers ($\chi 2$=9,09; p=0,004), 14 (61%) of the refractory and 7 (27%) of the responder group used tricyclics ($\chi 2$=5,74; p=0,022). No differences were found on benzodiazepines and noradrenergic agents. These findings reflect the current severity of OCD and associated features and their impact on the patients' life, and provide further validity for the entry criteria used for the refractory group.

A detailed account of the general socio-demographic data, patterns of comorbidity, types of OCD symptoms, and clinical aspects and severity scales is given in the Tables 1, 2, 3 and 4 respectively. Table 1 shows that the refractory group patients more frequently are single or have no spouse, are unemployed, belong to a lower social-economic class and have a tendency to have lower education level. Table 2 shows that there were no differences according to all Axis I and Axis II psychiatric comorbidities investigated

between the two groups. Frequency comparison of the content of obsessive-compulsive symptoms according to the YBOCS and DYBOCS are described in Table 3. The groups did not differ in frequencies of OCS according to YBOCS, but according to the DYBOCS the refractory patients showed more frequently sexual/religious content of OCS. Table 4 interestingly shows higher frequency of chronic course, earlier age of OCD treatment onset, and higher Family Accommodation Index for the refractory group. Surprisingly the period of time between the age of OCS onset and the treatment onset showed a tendency to be shorter for the refractory group.

Insert TABLE 1, TABLE 2, TABLE 3 and TABEL 4 about here.

According to Psychiatric State Rating, when OCS were sub-clinic (when OCS started, with no interference on functioning or discomfort to the patient) there was a tendency of a higher severity of OCS for refractory patients (t=1,75; p=0,086). When OCS become discomfortable and start to interfere on functioning, refractory patients have higher severity of the disease (t=3,879; p<0,001). At the worse period of OCS, there were no differences between groups (t=1,529; p=0,133). As expected, current severity of OCS is higher for refractory than respondent patients (t=8,669; p<0,001).

Analyzing the frequency of at least one sensory phenomena we found no differences between the refractory and the responder group (n=20 (86,9%) versus n=22 (88,0%), Fisher's Exact Test, p=0,57). No differences were also found when comparing the following specific sensory phenomena: autonomic anxiety (χ2Yates =0,99; p=0,32), mental sensation (χ2Yates=0,00; p=1,00), body sensation (χ2Yates=0,00; p=1,00), "just right"

(χ2Yates=0,00; p=0,96), emptiness (Fisher's Exact Test, p=0,70), energy (Fisher's Exact Test, p=0,45), and "urges" (χ2Yates=0,29; p=0,59).

To verify the association of the significant variables (p≤0,10) of the univariate analysis with refractoriness condition (dependent variable), we performed 2 stepwise logistic regression analysis (enter probability of 0,05 and exit probability of 0,10). For the first model we entered the following OCD intrinsic factors (intrinsic factors are those that exclusively depend on the phenomenology of OCD): OCS symptom severity according to YBOCS, period of time between OCD onset and treatment onset, course of OCS, and presence of sexual/religious dimension according to DYBOCS symptoms checklist. For the second model we entered the following OCD extrinsic factors (extrinsic factors are those that are not inherent to the phenomenology of OCD): marital status, education level, occupation, socio-economic level and Family Accommodation Index. Other variables were not included because of its colinearity with OCS severity and/or Family Accommodation Index. The table below (Table 5) presents logistic regression final analysis results, after 2 steps. As it can be seen, the severity according to YBOCS and the presence of sexual/religious dimension according to DYBOCS and lower socio-economic level and higher scores of Family Accommodation stayed at the regression model as the principal aspects related to OCD refractoriness.

Insert Table 5 here

Discussion

Different than previous studies, we used a more strict criteria for refractoriness, which in this study was partially validated by findings such as higher OCS severity according to

YBOCS or DYBOCS, higher severity of depressive and anxious symptoms, worse quality of life according to SF-36 found in the refractory group. Likewise, our responder group included only patients with at least one year of consistent measures of treatment improvement. This strategy may be more reliable in finding distinct subgroups in terms of treatment response. However, our attempt to find more divergent subgroups could not preclude the fact that current responders could change to refractory cases in the future. This study has also the merit of testing a vast array of variables associated to the OCD clinical expression, including some new symptom related instruments (e.g.: DYBOCS) and epigenetic factors which were not used before.

Our study found that higher severity according to YBOCS, the presence of sexual/religious content of OCS according to DYBOCS, lower socio-economic level and higher scores of Family Accommodation Index were the most relevant factors associated to conventional treatment refractory OCD. Other factors associated to OCD refractoriness were: marital status (having no spouse), lower education level, unemployment, chronic course, worse quality of life according to SF-36, higher severity since the beginning of OCD according to Psychiatric State Rating.

The sexual/religious dimension (according to the DYBOCS) found more frequently in our refractory group was also associated with worse response in previous studies (13,14). Mataix-Cols et al (2002) found that, after controlling for symptom severity, higher scores on the 'sexual/religious obsessions' factor predicted poorer outcome with behavioral therapy (14). Although our findings agree with the studies above, there are no evidences on literature on how sexual or religious content of OCS could explain refractoriness. The expression of religious obsessions seems not to be related to cultural influences (41).

Currently, there have been 11 factor-analytic studies published suggesting that these OCD symptom dimensions are valid and reliable constructs and fairly consistent and temporally stable (17,22,41-49). Furthermore, recent neuroimaging studies have provided additional support for the validity of these factors: different patterns of activation have been observed for different OC symptom dimensions (50), leading to the hypothesis that the heterogeneous phenomenology of OCD could be mediated by different neuroanatomical structures. According to this model, the different symptoms of OCD could be a consequence of particular forms and levels of involvement of cortico-striatal circuits. It would explain, for example, why distinctive symptoms occur alone or in combination to other symptoms at a same patient, why would be a correlation of certain sub-types of symptoms and comorbid disorders, and why patients with the same type of symptom could become refractory to treatment.

Our sample evinced significant differences for all scores of Calvocoresi's family accommodation scale (36). The participation of relatives on patients' symptoms and the family modification of functioning due to OCS compose what Calvocoresi called Family Accommodation Index (FAI). When the relative does a ritual together with the patient, it reinforces the patient's symptom. The Family Distress Index (FDI) refers directly to the distress that OCD offers to the relatives. In our study it is higher in the refractory group. The patients' reactions when relatives do not participate on compulsions and rituals contributes to accommodate family to OCS, and also for this factor, the refractory group had higher scores. Guedes (2002), evaluating 26 OCD patients, found that all their families had some degree of family accommodation. There was a positive correlation between FAI and severity of YBOCS scores ($r=0,41;p=0,003$) (52). This correlation was also found in our study ($r=0,709$; $p<0,001$).

Our study showed that relatives of patients of the responder group have mild family accommodation, and relatives of refractory patients have serious accommodation (U=64,5; p<0,001). In our sample, most (76,9%) families of responders were in the none/mild level of accommodation versus only 14,3% of the families of refractory patients. Contrasting, in the other extreme, we found half (52,4%) of families of refractory patients on the severe/extreme level, and only 3,8% of families of responders' patients.

The higher levels of FAI may lead to a worse performance on Cognitive-Behavioral Therapy techniques (53). The influence of family accommodation over CBT could be explained by the fact that the family members respond adaptively by engaging in problem solving with the patient or maladaptively by becoming over-involved or frustrated, angry, and rejecting. Maladaptive reactions provoke more stress in the patient, leading to more symptoms and eventual relapse. Some evidence supports a negative effect of hostility, emotional over-involvement, and criticism perceived by the patient on behavioral treatment outcome. Family accommodation, as mentioned above, predicted poorer family functioning and more severe OCD symptoms after behavioral treatment (53). Conversely, the phenomenon of accommodation could be also secondary of more severe and/or complex cases. Further well-designed studies are needed to better understand this association .

We found a trend to statistical difference between groups in terms of educational level (p=0,054). Patients of the refractory group came from a lower social-economic class than responders (p=0,015). Refractory patients, in general, have no spouses, comparing to responders (p=0,037). As Steketee et al. (1999) pointed out married OCD patients had twice a chance of presenting partial remission of symptoms in a five-year period,

comparing to singles (54). Those findings agree with initial results of our group, when being married or having a spouse is associated to a better improvement degree (10).

It seems thus that refractory OCD patients have reduced productivity, resulting in smaller wages, probably posing a huge economic burden to patients and their families, employers, and society. Our results agree with Stein et al (1996), suggesting that OCD (and specially refractory OCD) causes significant morbidity, leading to clear distress and interference with social, academic and occupational function (55). Lower social status is a consequence. Burden associated to refractory OCD should be better investigated.

In our sample, 42 (85,4%) patients, 21 refractory (90,9%) and 21 responders (80,8%), presented some kind of lifetime psychiatric comorbidity. These prevalences are comparable to the literature, where the most prevalent lifetime psychiatric comorbidities are major depression (57,1%), simple phobia (52,4%), social phobia (40,5%) and tics (19,0%) (56,57).

Eating disorders (ED) tended to be more prevalent in refractory patients (p=0,088). It must be stressed that we did not find any ED diagnosis at the respondent group, which makes an interpretation difficult. ED patients would be ego-sintonic, with OCS, more frequently, related to symmetry, order and arrangement (58), aggression obsessions and, less frequently, related to pathological doubts or cleaning/washing compulsions (59). OCD patients, otherwise, would present more wide and complex OCS dimensions (58). It could be argued that ED and OCD comorbidity could make OCD refractory due to poor insight or to overvalued ideas that ED offers to the person's cognitive process. Shavitt et al. (2003) confirmed that a higher number of comorbid psychiatric disorders was related to a worse response to clomipramine. She also found that the number of comorbid disorders has no parallelism with OCD severity (r=0,119; p=0,463) (10). Other way, our study evinces that

the presence and number of comorbidities did not seem to be related to refractoriness. Sample size probably was too small to evince the expected difference between groups (type II error).

Refractory patients had a more chronic course and responders, more frequently, an intermittent course. Hollander et al (2002) found that refractory OCD patients in 90% of the time have a chronic course of the disease (versus 70% of responders) (24). Ravizza et al (1997) concluded that chronic course was associated with earlier onset, longer duration of illness, male gender, more severe compulsions and more family history of psychiatric disorders (60).

Our results of Psychiatric State Rating suggest that refractory patients, beyond a more chronic course, have more severe OCS since the onset, even before meeting OCD criteria. The higher severity of OCD since the beginning turns the patients less productive on emotional, social and professional aspects as mentioned above, which may contribute for a worse treatment response.

In our sample, the mean age at the onset of the treatment is lower for refractory patients than responders (p=0,002). Responders had a trend to remain a mean of 5 years more without treatment (p=0,08) when compared to refractory patients. As opposed to what we expected, no differences were found between groups for the difference of age of first treatment and age of OCD onset. Maybe age of onset is not itself a refractoriness predictive factor. Its influence could be modulated by other variables (family history, OCS severity, OCD course and interaction with environmental aspects: family accommodation). Refractory patients may seek treatment earlier either because OCD itself starts more severe or due to secondary depressive and anxious symptoms.

Limitations of this study include the sample size and inherent bias of a case-control design. That is, several variables associated with the refractory group, such as lower economic status, lower education level, having no spouse and unemployment could be in fact secondary to the severity of the condition itself. Future prospective studies are necessary to investigate whether or not some of these variables are true risk factor for refractoriness. Nevertheless, the findings reported above corroborate for the importance of early treatment interventions in OCD associated with social and family approaches to avoid negative influences of the disease in the development of the individual (avoiding lower education, and difficulties in work) as well as maladaptative behaviors of the family in dealing with patients symptoms. In addition, symptoms such sexual/religious obsessions in OCD patients may consist of an alert for clinicians to establish a more comprehensive treatment to avoid future refractoriness.

References

1. Piacentini J, Bergman RL, Jacobs C, McCracken JT, Kretchman J. Open trial of cognitive behavior therapy for childhood obsessive-compulsive disorder. J Anxiety Disord 2002, 16(2):207-19.

2. Benazon NR, Ager J, Rosenberg DR. Cognitive behavior therapy in treatment-naive children and adolescents with obsessive-compulsive disorder: an open trial. Behav Res Ther 2002, 40(5):529-39.

3. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, Pato M, Stein D, Zohar J. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol 2002, 5(2):181-91.

4. Jenike MA, Rauch SL Managing the patient with treatment-resistant obsessive-compulsive disorder: current strategies. J Clin Psychiatry 1994, 55 (Suppl):11-7.

5. DeVaugh-Geiss J, Katz R, Landau P, Goodman W, Rasmussen S. Clinical predictors of treatment response in obsessive compulsive disorder: exploratory analyses from multicenter trials of clomipramine. Psychopharm Bull 1990, 26(1):54-9.

6. Ravizza L, Barzega G, Bellino S, Bogetto F, Maina G. Predictors of drug treatment response in obsessive-compulsive disorder. J Clin Psychiatry 1995, 56(8):368-73.

7. Rosario-Campos M, Leckman J, Mercadante M, Shavitt RG, Miguel EC et al. Adults With Early-Onset Obsessive-Compulsive Disorder. Am J Psychiatry 2001, 158:1899–1903.

8. Erzegovesi S, Cavallini MC, Cavedinei P, Diaferia G, Locatelli M, Bellodi L. Clinical predictors of drug response in obsessive-compulsive disorder. J Clin Psychopharmacol 2001, 21(5):488-92.

9. Ackerman D L, Greenland S, Bystritsky A, Morgenstern H, Katz RJ. Predictors of treatment response in Obsessive-Compulsive disorder: multivariate analyses from a multicenter trial of clomipramine. Journal of Clinical Psychopharmacology 1994, 14, 247-254.

10. Shavitt RG. Fatores preditivos de resposta ao tratamento em pacientes com o transtorno obsessivo-compulsivo. São Paulo, 2002. 137p. Tese (Doutorado) –Universidade de São Paulo.

11. Moreno AC, Calo JJP, Pinero MV, Zaragoza CL, Navarro VF, Marsa MD. Evolución y respuesta terapéutica en el Transtorno Obsesivo-Compulsivo. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1995, 23(1):9-19.

12. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. Arch Gen Psychiatry 1999; 56(2):121-7.

13. Alonso P, Menchon JM, Pifarre J, Mataix-Cols D, Torres L, Salgado P, Vallejo J. Long-term follow-up and predictors of clinical outcome in obsessive-compulsive patients treated with serotonin reuptake inhibitors and behavioral therapy. J Clin Psychiatry 2001, 62(7):535-40.

14. Mataix-Cols D, Marks IM, Greist JH, Kobak KA, Baer L. Obsessive-compulsive symptom dimensions as predictors of compliance with and response to behavior therapy: results from a controlled trial. Psychother Psychosom 2002, 71(5):255-62.

15. Abramowitz JS, Schwartz AS, Moore KM, Luenzmann KR. Obsessive-compulsive symptoms in pregnancy and the puerperium: a review of the literature. J Anxiety Disord 2003, 17(4):461-78.

16. Saxena S, Maidment KM, Vapnik T, Golden G, Rishwain T, Rosen RM, Tarlow G, Bystritsky A. Obsessive-compulsive hoarding: symptom severity and response to multimodal treatment. J Clin Psychiatry 2002,63:21-27.

17. Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L: Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. Am J Psychiatry 1999, 156:1409-1416.

18. Black DW, Monahan P, Gable J, Blum N, Clancy G, Baker P. Hoarding and treatment response in 38 nondepressed subjects with obsessive-compulsive disorder. J Clin Psychiatry 1998, 59, 420-425.

19. Neziroglu FA, Stevens PK, Yaryura-Tobias JA. Overvalued ideas and their impact on treatment outcome. *Rev. Bras. Psiquiat* 1999, 21(4):209-216.

20. Minichello WE, Baer L, Jenike MA et al. Schizotypical personality disorder: a poor prognostic indicator for behavioral therapy in the treatment of obsessive-compulsive disorder. J Anxiety Disord 1987, 1:273-6.

21. Mundo E, Erzegovesi S, Bellodi L. Follow-up of obsessive-compulsive patients treated with proserotonergi agents. J Clin Psychopharmacol 1995,15(4):288-9.

22. Baer L. Factor analysis of symptom subtypes of obsessive-compulsive disorder and their relation to personality and tic disorders. J Clin Psychiatry 1994,55(suppl):18–23.

23. McDougle CJ, Goodman WK, Price LH, Delgado PL, Krystal JH, Charney DS, Heninger GR. Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 1990,147(5):652-4.

24. Hollander E, Bienstock CA, Koran LM, Pallanti S, Marazziti D, Rasmussen AS, Ravizza L, Benkelfat C, Saxena S, Greenberg BD, Sasson Y, Zohar J. Refractory

obsessive-compulsive disorder: state-of-the-art treatment. J Clin Psychiatry 2002, 63(Suppl 6):20-9.

25. De Hann E, van Oppen P, van Balkom AJLM, Spinhoven P, Hoogduin KAL, Van Dyck R et al. Prediction of outcome and early vs. Late improvement in OCD patients treated with cognitive behavior therapy and pharmacotherapy. Acta Psychiatr Scand 1997, 96:354-61.

26. Alarcon RD, Libb JW, Spitler D. A predictive study of obsessive-compulsive disorder response to clomipramine. J Clin Psychopharmacol 1993, 13(3):210-3.

27. McDougle CJ, Goodman WK, Leckman JF, Barr LC, Heninger GR, Price LH. The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder. J Clin Psychopharmacology 1993, 13(5), 354-358.

28. McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 1994,51(4):302-8.

29. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders: clinical version (SCID-CV). Washington, DC: American psychiatric Press, 1997.

30. Pfohl B, Blum N, Zimmerman M. Structured Interview for DSM-IV® Personality (SIDP-IV). Washington, DC: American psychiatric Press, 1997.

31. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale: development, use and reliability. Arch Gen Psychiatry 1989, 46:1006-1001.

32. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale: validity. Arch Gen Psychiatry 1989, 46:1006-1001.

33. Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao YA, Findley D, Scahill L, King R, Woody S, Tolin D, Hollander E, Kano Y, Leckman JF. The Dimensional Yale-Brown Obsessive Compulsive Scales (D-YBOCS): development and initial testing of a new instrument for assessing the severity of obsessive-compulsive symptom dimensions. (submitted).

34. Leckman JF, Riddle MA, Hardin MT. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989, 28:566-73.

35. Eisen JL, Phillips KA, Baer L, Beer DA, Atala KD, Rasmussen SA. The Brown Assessment of Beliefs Scale:reliability and validity. Am J Psychiatry 1998, 155:102-108.

36. Calvocoressi L, Lewis B, Harris M, Trufan S, Goodman W, Mcdougle C, Price L. Family accommodation in obsessive-compulsive disorder. Am J Psychiatry 1995,152: 441-3

37. Hamilton, M. The assessment of anxiety states by rating. Brit J Med Psychol 1959, 32: 50-55.

38. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967,6(4):278-96.

39. Keller MB, Lavori PW, Friedman B et al. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychioatry 1987,44:540-48.

40.Ware JE, Gandek B. IQOLA Project Group: The SF-36 health survey: development and

use in mental health research and the IQOLA project. Int J Ment Health 1994, 23:49-73.

41. Tek C, Ulug B. Religiosity and religious obsessions in obsessive-compulsive disorder. Psychiatry Res 2001, 104:99-108.

42. Hantouche EG, Lancrenon S. Modern typology of symptoms and obsessive-compulsive syndromes: results of a large French study of 615 patients. Encephale 1996,22 (1):9-21.

42. Leckman JF, Grice DE, Boardman J, Zhang H, Vitale A, Bondi C, Alsobrook J, Peterson BS, Cohen DJ, Rasmussen AS, Goodman WK, McDougle CJ, Pauls DL. Symptoms of obsessive-compulsive disorder. Am J Psychiatry 1997,154:911-917.

43. Summerfeldt LJ, Richter MA, Antony MM, Swinson RP. Symptom structure in obsessive-compulsive disorder: a confirmatory factor-analytic study. Behaviour Research Therapy 1999, 37(4), 297-311.

44. Mataix-Cols D, Rauch SL, Baer L, Eisen JL, Shera DM, Goodman WK, Rasmussen SA, Jenike MA. Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. Am J Psychiatry 2002, 159(2):263-8.

45. Cavallini MC, Di Bella D, Siliprandi F, Malchiodi F, Bellodi L. Exploratory factor analysis of obsessive-compulsive patients and association with 5-HTTLPR polymorphism. Am J Med Genet 2002,114(3):347-53.

46. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, Salkovskis PM. The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol Assess 2002,14(4):485-96.

47. Feinstein SB, Fallon BA, Petkova E, Liebowitz MR. Item-by-item factor analysis of the Yale-Brown Obsessive Compulsive Scale Symptom Checklist. J Neuropsychiatry Clin Neurosci. 2003,15(2):187-93.

48. Leckman JF , Pauls DL , Zhang H , Rosario-Campos MC , Katsovich L , Kidd KK , Pakstis AJ , Alsobrook JP , Robertson MM , McMahon WM , Walkup JT , van de Wetering BJ , King RA , Cohen DJ. Tourette Syndrome Assocation International Consortium for Genetics. Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. American Journal of Medical Genetics 2003,116B(1):60-8.

49. Mataix-Cols D, Fullana M.A, Alonso P, Menchon JM, Vallejo J. Convergent and discriminate validity of the Yale-Brown Obsessive-Compulsive Scale Symptom Checklist. Psychotherapy Psychosomatics. (In press).

50. Rauch SL, Dougherty DD, Shin LM, Alpert NM, Manzo P, Leahy L *et al*. Neural correlates of factor-analyzed OCD symptom dimensions: a PET study. CNS Spectrums 1998;3, 37-43.

51. Mataix-Cols D, Cullen S, Lange K, Zelaya F, Andrew C, Amaro E, Brammer MJ, Williams SC, Speckens A, Phillips ML. Neural correlates of anxiety associated with obsessive-compulsive symptom dimensions in normal volunteers. Biol Psychiatry 2003, 53(6), 482-493.

52. Guedes ML. Transtorno Obsessivo-Compulsivo: um estudo do processo de acomodação familiar. São Paulo, 1997. 80p. Dissertação (Mestrado) – Escola Paulista de Medicina, Universidade Federal de São Paulo.

53. Steketee G, VanNoppen B. Family approaches to treatment for obsessive-compulsive disorder. Rev Bras Psiquiatr 2003; 25(1):43-50.

54. Steketee G, Eisen J, Dyck I, Warshaw M, Rasmussen S. Predictors of course in obsessive-compulsive disorder. Psychiatry Res 1999; 89(3):229-38.

55. Stein DJ, Roberts M, Hollander E, Rowland C, Serebro P. Quality of life and pharmaco-economic aspects of obsessive-compulsive disorder. A South African survey. Afr Med J 1996; 86(12 Suppl):1579, 1582-5.

56. Rasmussen SA, Eisen JL. Treatment strategies for chronic and refractory obsessive-compulsive disorder. J Clin Psychiatry 1997; 58(Suppl) 13:9-13.

57. Vallejo J. Relación de los transtornos obsesivos con otras patologías psíquicas. In: Vallejo J and Berrios GE, Eds. Estados Obsesivos, 2ª. Ed. Madrid: Masson, 1995. p-71-90.

58. Thiel A, Zuger M, Jacoby GE, Schübler G. Thirty-month outcome in patients with Anorexia or Bulimia Nervosa and concomitant obsessive-compulsive disorder. Am J Psychiatry 1998;155(2):244-9.

59. Thiel A, Broocks A, Ohlmeier M, Jacoby GE, Schübler G. Obsessive-compulsive disorder among patients with anorexia and bulimia nervosa.Am J Psychiatry 1995;152:52-5

60. Ravizza L, Maina G, Bogetta F. Episodic and chronic Obsessive-compulsive Disorder. Depression and anxiety 1997;6:154-8.

Table

Table 1 - Socio-demographic variables possibly associated to OCD refractoriness.

	Refractory (N=23)	Responder (N=26)	Analysis	
	N(%)	N(%)	χ2 Yates	p
Male	12(52,2)	10(38,5)	0,456	0,499
Caucasian	21(91,3)	24(92,3)	*	1,00
Marital status				
(no spouse)	18(78,3)	5(19,2)	6,62	0,037
Occupation				
(unemployed)	14(60,9)	6(23,1)	5,04	0,025
Socio-economic classification				
Class A	1(4,3)	2(7,7)		
Class B	5(21,7)	13(50,0)	7,09**	0,069
Class C	14(60,9)	11(42,3)		
Class D	3(13,0)	0(0,0)		
	Mean (SD)	**Mean (SD)**	**t**	**p**
Current age	35,22(10,74)	41,35(11,45)	1,918	0,061
Education level	4 (2;4;6)	6 (4;6;7)	***	0,054

* Fisher's Exact Test; ** Pearson χ2; ***Mann-Whitney Test (U=204,5)- Median level and quartiles are presented; SD, Standard Deviation; OCD, Obsessive-compulsive Disorder.

Table 2- Comparison of Axis I and II psychiatric comorbidities between refractory and responder OCD groups of patients.

	Refractory (n=23)	Responder (n=26)	Analysis	
	N(%)	N(%)	χ2Yates	p
Substance use and abuse	5 (21,7)	4 (15,4)	*	0,716
Schizophrenia	2 (8,7)	0 (0)	*	0,215
Bipolar Disorder	0 (0)	1 (3,8)	*	1,00
Major Depression	17 (73,9)	17 (65,4)	0,11	0,737
Anxiety Disorders	9 (39,1)	12 (46,2)	0,04	0,836
Social Phobia	3 (13,0)	4 (15,4)	*	1,00
Simple Phobia	1 (4,3)	5 (19,2)	*	0,194
Panic/Agoraphobia	2 (8,7)	4 (15,4)	*	0,67
Generalized Anxiety	3 (13,0)	2 (7,7)	*	0,655
Pos-Traumatic Stress Disorder	2 (8,7)	1 (3,8)	*	0,594
Eating Disorders	3 (13,0)	0(0)	*	0,096
Tricothilomania / Skin Picking	4 (17,4)	4 (15,4)	*	1,00
Attention Deficit/Hyperactivity Disorder	0 (0)	1 (3,8)	*	1,00
Tourette Disorder	4 (17,4)	1 (3,8)	*	0,173
Tics Disorder	1(4,3)	3(11,5)	*	0,608
Personality Disorders	7(31,8)	8(30,8)	0,08	0,775
Cluster A	3(13,05)	4(15,3)	*	1,00
Paranoid	1(4,35)	3(11,5)	*	0,612
Schizoid	2(8,70)	1(3,8)	*	0,594
Cluster B	1(4,35)	1(3,8)	*	1,00
Hystrionic	1(4,35)	0	*	0,469
Narcisist	0(0)	1(3,8)	*	1,00
Cluster C	10(43,5)	8(30,8)	0,39	0,533
Evitative	4(17,4)	3(11,5)	*	0,692
Dependent	3(13,04)	1(3,8)	*	0,33
Anancastic	3(13,04)	4(15,4)	*	1,00
Till 1 psychiatric comorbidity	17(77,3)	14(53,8)	1,93	0,165
	Mean (SD)	**Mean (SD)**	**t**	**p**
Number of Axis I comorbidities	2,41(1,26)	1,92(1,20)	1,372	0,177

Legend: * Fisher Test; SD, Standart Deviation.

Table 3- Frequency comparison of obsessive-compulsive symptoms sub-types according to YBOCS and DYBOCS.

	Refractory (N=23)	Responders (N=26)	Analysis	
	N(%)	N(%)	χ2Yates	p
YBOCS - Obsessions of: [a]				
Agressivity	20(95,2)	19(76,0)	*	0,11
Contamination	16(76,2)	17(68,0)	0,08	0,775
Sexual content	8(38,1)	9(36,0)	0,03	0,87
Hoarding	5(23,8)	9(36,0)	0,33	0,566
Religiosity	11(52,4)	15(60,0)	0,05	0,825
Symmetry	15(71,9)	14(56,0)	0,6	0,44
Somatic content	9(42,9)	11(44,0)	0,05	0,825
Other contents	21(100)	21(84,0)	*	0,11
YBOCS – Compulsions of: [a]				
Cleaning/washing	17(80,9)	17(68,0)	0,43	0,51
Checking	16(76,2)	23(92,0)	*	0,22
Repetition	18(85,7)	18(72,0)	*	0,31
Counting	9(42,9)	7(28,0)	0,55	0,457
Ordering/arrangement	9(42,9)	13(52,0)	0,10	0,747
Hoarding	5(23,8)	9(36,0)	0,33	0,566
Other contents	20(95,2)	21(84,0)	*	0,36
DYBOCS [b]				
Agressivity dimension	18(81,8)	15(57,7)	1,269	0,26
Sexual/religious dimension	16(72,7)	10(38,5)	4,112	0,043
Simetry/order dimension	18(81,8)	19(73,1)	0,000	1,00
Contamination/cleaning dimension	19(86,4)	16(61,5)	*	0,202
Hoarding dimension	5(22,7)	10(38,5)	0,341	0,559
Other contents dimension	20(90,9)	20(76,9)	*	0,472

Legend- * Fisher Test; a-Refractory=21 and Responder=25; b-Refractory=22 and responders=26; YBOCS, Yale-Brown Obsessive-compulsive Scale; DYBOCS, Dimensional Yale-Brown Obsessive-compulsive Scale.

Table 4- Results of comparison of clinical features, epigenetic variables and clinical scales between refractory and respondent groups

	Refractory (n=23)	Responder (n=26)	Analysis	
	N(%)	N(%)	χ2Yates	p
Chronic Course [a]	10(47,6)	1(4,2)	*	0,0027
Familial History of OCD [b]	9 (40,9)	10(38,5)	0,05	0,82
Familial History of Psychiatric Disorders [b]	17 (77,3)	22 (84,6)	*	0,58
Familial History of Tic Disorders [b]	6 (27,3)	6 (23,1)	0,01	0,93
Epigenetic factors [b]				
Pregnancy related events	8 (36,4)	6 (23,1)	0,22	0,64
Pregnancy smoking	1(4,5)	2 (7,7)	*	1,00
Pregnancy alcohol use	0 (0)	1 (3,8)	2,523	0,471
Pregnancy exaggerated coffee consumption	3 (13,6)	6 (23,08)	*	0,46
Pregnancy illicit drugs use	4 (18,18)	3 (11,54)	*	1,00
Childbirth site (hospital)	16 (72,7)	16 (61,54)	0,203	0,904
Childbirth type (eutocic)	17 (77,3)	21 (80,8)	*	0,403
Forceps use	2 (9,09)	0 (0)	2,321	0,509
Childbirth medical occurrence	8 (36,4)	6 (23,08)	0,20	0,659
Premature childbirth	2 (9,09)	1 (3,8)	*	0,607
Post-childbirth medical occurrence	4 (18,18)	2 (7,7)	*	0,39
Mother with emotional problems on pregnancy	8 (36,4)	8 (30,8)	0,04	0,85
	Mean (SD)	Mean (SD)	t	p
BABS[d]	7,45(4,44)	6,67 (5,24)	0,547	0,587
Family Accommodation Index [b]	20 (11,5;20;27)	6,5 (3;6,5;9,25)	**	<0,001
Obsessive-compulsive age at onset [b]	13,5 (6,46)	17,0 (8,82)	1,524	0,135
OCD duration [b]	22,27 (10,55)	25,46 (12,63)	0,924	0,361
Age of treatment onset [b]	23,95 (7,04)	32,17 (9,42)	3,324	0,002
Period of time to start treatment [b]	10,32 (7,88)	15,17 (10,45)	1,764	0,085

Legend- * Fisher's Exact Test; ** Mann-Whitney Test (U=64,5)-Median rate and quartiles are presented; a-Refractory=21 and Responder=24; b-Refractory=22 and responder=26; c-Refractory=23 and responder=25; d-Refractory=21 and responder=26; SD, Standard Deviation; OCD, Obsessive-compulsive Disorder; OCS, Obsessive-compulsive Symptoms; BABS, Brown Assessment of Beliefs Scale.

Table 5 – Logistic regression analysis results of variables associated to OCD refractoriness.

Variable	Coefficient (SE)	p	Odds Ratio	95% Confidence Interval
OCD intrinsic Factors *				
Sexual/religious dimension	1,66 (0,824)	0,044	0,19	(0,038 – 0,954)
YBOCS sores of severity	0,198 (0,058)	0,001	1,22	(1,087 – 1,367)
OCD extrinsic factors**				
Socio-economic class	3,03(1,37)	0,027	20,72	(1,42 – 303,32)
Family Accommodation Index	0,423(0,162)	0,009	1,527	(1,111 – 2,097)

Legend: SE- Standard Error; OCD-Obsessive-compulsive disorder; YBOCS-Yale-Brown Obsessive-compulsive Scale; *Variable entered in step 1: YBOCS scores of severity; variable entered in step 2: Sexual/religious dimension; ** Variable entered in step 1: Family Accommodation Index; variable entered in step 2: socio-economic class