

## Brief Research Communication

# Obsessive–Compulsive Symptoms in Sibling Pairs Concordant for Obsessive–Compulsive Disorder

Priscila Chacon,<sup>1\*</sup> Maria Conceição Rosario-Campos,<sup>2</sup> David L. Pauls,<sup>3</sup> Ana Gabriela Hounie,<sup>1</sup> Mariana Curi,<sup>1</sup> Fernando Akkerman,<sup>1</sup> Fabiana Harumi Shimabokuro,<sup>1</sup> Maria Alice de Mathis,<sup>1</sup> Antonio Carlos Lopes,<sup>1</sup> Gregor Hasler,<sup>4</sup> and Euripedes Constantino Miguel<sup>1</sup>

<sup>1</sup>Department of Psychiatry, University of São Paulo School of Medicine, São Paulo, Brazil

<sup>2</sup>Federal University of Bahia, Salvador, Brazil

<sup>3</sup>Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

<sup>4</sup>Department of Psychiatry, University Hospital, Zurich, Switzerland

Obsessive–compulsive disorder (OCD) is a heterogeneous disorder of unknown etiology. Phenotypic studies of affected sib-pairs (SPs) may help to characterize familial components of the phenotype. To determine whether SPs affected with OCD are similar in age at onset of obsessive–compulsive symptoms (OCS), symptom dimensions and presence of tic disorders (TDs). Forty OCD siblings ranging from 13 to 59 years old were evaluated by expert psychiatrists or psychologists. Families with two or more siblings affected with OCD were recruited from several OCD clinics in Brazil. The Yale Brown Obsessive–Compulsive Scale Checklist was used to assess OCS and the severity of OCD. The OCD diagnoses were made according to the DSM-IV. The chi-square test was used to assess concordance of TD presence within SPs based on the TD frequency reported in the literature (30%). There were significantly more siblings with early-onset OCS than with late-onset OCS ( $P = 0.002$ ). Age at onset of OCS correlated positively and significantly between the two members of each SP ( $P = 0.005$ ). Fourteen patients (35%) were diagnosed with TDs. There was no concordance of the TD presence within the SPs. When both were male, there was a significant sibling correlation in the contamination obsessions/cleaning compulsions dimension (ICC = 0.74;  $P = 0.002$ ). Similarly, when both siblings were female, they were comparable in the hoarding obsessions/compulsions dimension (ICC = 0.76;  $P = 0.01$ ). Familial factors seem to

contribute to specific OCD phenotypic components such as age at onset of OCS and specific dimensions. The obvious influence of gender is as yet unexplained. © 2007 Wiley-Liss, Inc.

**KEY WORDS:** obsessive; factors; age at onset; gender

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Obsessive–compulsive disorder (OCD) is a genetically heterogeneous disorder [Pauls et al., 1995; Nestadt et al., 2000a; Fontenelle et al., 2005; Miguel et al., 2005], with lifetime prevalence of approximately 2% [Miguel et al., 2005; Torres and Lima, 2005]. The symptoms that characterize OCD vary from one patient to another and even from time to time in the same patient [Mataix-Cols et al., 2002]. The heterogeneity of OCD reduces the chances of finding specific genes related to the disorder [Mataix-Cols et al., 2005; Miguel et al., 2005]. Consequently, many studies have been conducted in attempts to identify phenotypic characteristics (more homogeneous genetic profiles) of patient subgroups. Some of those studies have used categorical approaches to define homogeneous OCD subtypes, whereas others have employed dimensional approaches, in which obsessive–compulsive symptom (OCS) dimensions are considered as quantitative traits [Miguel et al., 2005].

In the categorical approach, some of the putative subgroups are early-onset OCD [Rosario-Campos et al., 2001] and OCD comorbid with tics [Miguel et al., 2001, 2005; Diniz et al., 2006]. In both subgroups, males predominate [Rasmussen and Eisen, 1990; Fontenelle et al., 2002; Lochner et al., 2004], and the morbid risk for OCD is higher among family members [Pauls et al., 1995; Rosario-Campos et al., 2005].

The dimensional approach is derived from statistical methods used to reduce OCS into fewer clinically meaningful symptom dimensions [Mataix-Cols et al., 2005]. Despite the fact that different instruments and methods have been used [Hasler et al., 2005; Miguel et al., 2005; Mataix-Cols, 2006], three to five dimensions have been consistently identified as significant. These OCS dimensions have proved valuable in genetic studies [Alsobrook et al., 1999; Cavallini et al., 2002; Zhang et al., 2002; Leckman et al., 2003]. Among these, the hoarding obsessions/compulsions dimension has been

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\*Correspondence to: Priscila Chacon, B.S., Department of Psychiatry, University of São Paulo Medical School, Rua Dr. Ovídio Pires de Campos, s/n, 05403-010, São Paulo, SP, Brazil. E-mail: priscila@protoc.com.br

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considered a clearly distinct OCS dimension [Hasler et al., 2005] and has been shown to be familial [Alsobrook et al., 1999; Leckman et al., 2003; Fontenelle et al., 2004; Mataix-Cols et al., 2005].

Phenotypic studies using the categorical and dimensional approach in affected sib-pairs may be particularly useful in identifying familial components of the phenotype. In this regard, Leckman et al. [2003] investigated OCS in sibling pairs affected with Tourette syndrome, simultaneously assessing the parents of those sibling pairs. The authors were interested in determining whether there would be correlations for OCS dimensions within families. Dimensions included: aggressive, sexual, religious and somatic obsessions, together with checking compulsions (collectively, Factor 1); symmetry, repeating, counting and ordering/arranging symptoms (Factor 2); contamination obsessions and cleaning compulsions (Factor 3); and hoarding symptoms (Factor 4). Factor scores were computed for each family member using an algorithm derived from item endorsements from the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) symptom checklist. The authors repeated all analyses using all possible siblings, also including an analysis of the two eldest siblings from sibships with three or more affected members, since the sib-pairs were not independent. These authors found that the siblings resembled each other significantly for Factor 1 and -2. Using the same data set, Zhang et al. [2002] conducted a simulation study and reported that, hoarding was more powerful in detecting linked chromosomal regions when it was considered a quantitative trait (symptom dimension) than when it was considered a binary trait.

Although studies of affected sib-pairs have shown promise in the search for familial components of the phenotypes of other disorders [Fouldrin et al., 2001; Leckman et al., 2003], no such studies have been conducted for OCD. Therefore, the present study was designed to investigate whether siblings affected with OCD resembled one another regarding age at onset of OCS, expression of tic disorders (TDs) and OCS dimensions. We hypothesized that, between siblings in a sib-pair, there would be a positive correlation in terms of age at onset of OCS, a significant concordance for the presence of TDs, and a positive correlation in terms of OCS dimensions, particularly for the hoarding factor.

All families were recruited from specialized OCD clinics where at least one sibling was being treated. All of the clinics involved belonged to the Brazilian OCD Research Consortium (<http://www.protoc.com.br/portal/ctoc/>). We included families with two or more siblings affected with OCD. A home visit was provided, during which informed consent was obtained and patients were interviewed. This study was approved by the Institutional Review Board for the University of São Paulo. Nine families refused to participate in this study prior to the home visit. Forty outpatient OCD siblings (from 18 families) accepted and were assessed. The siblings were diagnosed with OCD, according to DSM-IV criteria [American Psychiatric Association, 1994].

To ensure reliability, all interviewers were either psychologists or psychiatrists and were duly trained for the purposes of this study. Training consisted of classes on psychiatric disorders and their differential diagnoses, video sessions of recorded interviews, supervised interviews and independent interviews with further evaluation [see more detail in Hounie et al., 2004]. The diagnosticians were never given a complete family to evaluate at one time, and all diagnostic evaluations of probands were performed separately from those of the relatives.

The Y-BOCS checklist [Goodman et al., 1989] was used to assess lifetime OCS and the severity of current OCS. Through the use of separate modules designed by the authors [available upon request; Miguel et al., 1995, 1997, 2000; Rosario-Campos

et al., 2001; Diniz et al., 2004], all participants were also assessed regarding the presence of Tourette syndrome, chronic tic disorder and transient tic disorder.

Patients presenting alcohol abuse, substance abuse or head trauma with brain injury were excluded, as were those with any systemic or neurological disorder that would interfere with answering the questionnaires.

At the time of the interview patients ranged from 13 to 59 years old (mean: 29.65; SD: 11.497). We defined the age at onset of OCS as the age that the patient, or a family member, remembered as the beginning of the obsessive-compulsive symptoms [Rosario-Campos et al., 2001]. Early-onset OCD has been defined as the beginning of symptoms before 11 years of age, whereas patients first presenting symptoms after 17 years of age have been classified as having late-onset OCD [see Rosario-Campos et al., 2001 for detailed information].

For the analysis of TD concordance, we compared the number of families presenting each of the three possible situations—concordance of absence of TDs (0% of siblings from the same family presenting TDs), discordance of presence or absence of TDs (50% of siblings from the same family presenting TDs), and concordance of presence of TDs (100% of siblings from the same family presenting TDs)—taking into account the frequency of TDs reported in the literature (30% of OCD patients presenting TDs) [Miguel et al., 1995, 1997; Pauls et al., 1995]. A chi-square was obtained for the contribution of each partition: 0%, 50%, and 100%.

In the present study, we defined/included the following: aggressive, sexual, religious, and somatic obsessions, together with checking compulsions (collectively, Factor 1); symmetry, repeating, counting and ordering/arranging symptoms (Factor 2); contamination obsessions and cleaning compulsions (Factor 3); and hoarding symptoms (Factor 4). Factor scores were generated using an algorithm derived from the Leckman et al. [1997] study. In brief, the lifetime symptoms in 13 Y-BOCS checklist categories [Goodman et al., 1989] were entered, using their sums for each patient. Miscellaneous obsessions and compulsions were excluded from the analyses. Intraclass correlations (ICCs) were determined for the scores related to all four factors.

Since some families had more than two affected siblings (there were two families in which four siblings were affected with OCD), the following additional analyses were performed: only the two eldest siblings (ES, 18 pairs); only the two youngest siblings (YS, 18 pairs); and all possible sib-pairs (AS, 28 pairs). A similar strategy was used by Leckman et al. [2003].

Among the siblings evaluated, 52% were male, and the mean age at the time of the interview was  $29.65 \pm 11.49$  years. The mean age at onset of the OCS was  $11.83 \pm 7.56$  years. There were significantly more siblings presenting an early onset of OCS (<11 years of age; 57%) than presenting a later onset of OCS (>17 years of age; 15%) ( $P = 0.002$ ). The age of onset of OCS was positively correlated between the sib-pairs in all three analyses (ES: ICC = 0.52,  $P = 0.01$ ; YS: ICC = 0.54,  $P = 0.008$ ; AS: ICC = 0.47— $P = 0.005$ ). There were no differences regarding the gender of siblings with early-onset OCD.

Fourteen patients (35%) were diagnosed with TDs. The sib-pairs were not concordant for the presence of TDs (ES:  $P = 0.5238$ ; YS:  $P = 0.9089$ ; AS:  $P = 0.5894$ ), even when the analysis was adjusted for gender (sib-pairs concordant for the male gender:  $P = 0.4122$ ; sib-pairs concordant for the female gender:  $P = 0.4933$ ).

In sib-pairs that were concordant for gender, the siblings had significant correlations between the scores for Factor 3 (contamination obsessions and cleaning compulsions) and Factor 4 (hoarding obsessions and compulsions). A significant correlation for Factor 3 (contamination obsessions and cleaning compulsions) was found in sib-pairs concordant for the male gender (ICC = 0.74; 95% CI = 0.32–0.91) ( $P = 0.002$ ).

TABLE I. Correlations of OCS Dimensions

Factors	ICC	CI lower	CI upper	<i>P</i>
Factor 1—agressive/sexual/religious/somatic—eldest siblings	-0.2610	-0.6404	0.2208	0.8598
Factor 1—agressive/sexual/religious/somatic—youngest siblings	-0.3035	-0.6668	0.1764	0.8967
Factor 1—agressive/sexual/religious/somatic—all possible sib-pairs	-0.2473	-0.5634	0.1320	0.9020
Factor 2—symmetry—eldest siblings	-0.0377	-0.4849	0.4251	0.5609
Factor 2—symmetry—youngest siblings	-0.0194	-0.4708	0.4400	0.5314
Factor 2—symmetry—all possible sib-pairs	-0.1004	-0.4510	0.2771	0.6978
Factor 3—contamination/cleaning—eldest siblings	-0.1391	-0.5592	0.3378	0.7150
Factor 3—contamination/cleaning—youngest siblings	-0.1650	-0.5771	0.3142	0.7501
Factor 3—contamination/cleaning—all possible sib-pairs	0.0610	-0.3133	0.4189	0.3767
Factor 4—hoarding—eldest siblings	-0.2648	-0.6428	0.2169	0.8634
Factor 4—hoarding—youngest siblings	-0.3130	-0.6726	0.1662	0.9040
Factor 4—hoarding—all possible sib pairs	0.2399	-0.1397	0.5580	0.1050

ICC, intraclass correlation coefficient; CI, confidence interval.

Factor 4 (hoarding obsessions and compulsions) was significantly correlated in sib-pairs concordant for the female gender (ICC = 0.76; 95% CI = 0.13–0.95) ( $P = 0.01$ ). No other significant correlations were found (Tables I and II).

The use of categorical and dimensional approaches to identify common phenotypic features in affected sib-pair families may represent powerful strategies for detecting familial components of the OCD phenotype. The results of the present study suggest that some of the OCD phenotypic features, such as age at onset of OCS and some OCS dimensions, are familial. Although it is accepted that these features are influenced by the gender of the affected family member, the exact cause and nature of that influence remains unknown.

The significant positive correlations found between the siblings in terms of age at OCS onset replicate previous findings [Rosario-Campos et al., 2005]. Rosario-Campos et al. [2005] found significant positive correlations in terms of age at onset not only between siblings but also between siblings and their affected first-degree relatives. The higher frequency of siblings with early-onset OCD found in our sample of affected sib-paired is consistent with previous reports of higher familial aggregation in probands with early-onset OCD [Pauls et al., 1995; Nestadt et al., 2000a; Hanna et al., 2005; Rosario-Campos et al., 2005].

The fact that the correlations found between the siblings for Factor 3 (contamination obsessions and cleaning/washing compulsions) scores and Factor 4 (hoarding obsessions and compulsions) scores were only significant when there was gender concordance (male and female, respectively) suggests that the OCD phenotype may be partially influenced by the gender of the affected relative. Previous studies have reported gender-related phenotypic differences in OCD patients, although these findings are often inconsistent. For instance, some authors have found more contamination obsessions and

cleaning compulsions in males with OCD than in females with OCD [Fischer et al., 1997; Mataix-Cols et al., 1999; Sobin et al., 1999; Denys et al., 2004; Hasler et al., 2005], whereas others have found the opposite [Castle and Groves, 2000; Lochner et al., 2004]. Hanna et al. [2005] found that contamination obsessions and washing compulsions were among the most prevalent OCS in early-onset familial OCD, differently from what was found for early-onset sporadic OCD probands. However, this familiarity was not investigated in function of the gender of the patients. Likewise, previous studies have also reported higher rates of hoarding obsessions and compulsions in males in addition to find evidence for hoarding as a familial trait in OCD [Samuels et al., 2002].

Contradictory gender differences are also reported for the presence of aggressive obsessions and checking rituals [Rachman and Hodgson, 1980; Rasmussen and Eisen, 1988; Minichiello et al., 1990; Castle et al., 1995; Cavallini et al., 2002; Lochner et al., 2004]. It has also been shown that, among males, the age at onset of OCS is earlier [Fontanelle et al., 2002; Lochner et al., 2004; Samuels et al., 2006], the frequency of tics is higher [Lochner et al., 2004; Samuels et al., 2006], and the response to serotonin reuptake inhibitors is limited [Mundo et al., 1999]. The gender differences in the familiarity of OCS dimensions found in the current study are also inline with the findings of a previous study showing etiologic heterogeneity between families, as ascertained through evaluation of male and female probands [Nestadt et al., 2000b].

In contrast with what had been expected, the sib-pairs in the current study were not concordant for TDs, perhaps as a function of our small sample. However, the prevalence of TDs was similar to what has been reported in the literature [Miguel et al., 1995, 1997; Pauls et al., 1995].

Further studies involving larger samples are needed in order to confirm our results. The assessment of age at onset of OCS is problematic, specifically when an significant part of the sample

TABLE II. Correlations of OCS Dimensions According to Gender

Factors	ICC	CI lower	CI upper	<i>P</i>
Factor 1—agressive/sexual/religious/somatic—female	-0.4182	-0.8683	0.4096	0.8488
Factor 2—symmetry—female	-0.6327	-0.9256	0.1339	0.9539
Factor 3—contamination/cleaning—female	-0.1251	-0.7643	0.6380	0.6161
Factor 4—hoarding—female	0.7681	0.1342	0.9559	0.0130*
Factor 1—agressive/sexual/religious/somatic—male	0.1066	0.6229	0.4743	0.6356
Factor 2—symmetry—male	0.0455	-0.5205	0.5838	0.4413
Factor 3—contamination/cleaning—male	0.7462	0.3290	0.9197	0.0017*
Factor 4—hoarding—male	0.1635	-0.4282	0.6570	0.2968

ICC, intraclass correlation coefficient; CI, confidence interval.

\*Significant correlations.

are adults. Another important limitation concerns the measurement of the OCS dimensions. We used an algorithm—derived from the Leckman et al. [1997] study—that generates four factor scores for each patient. This four-factor solution has been shown consistent in several other recent studies [Mataix-Cols et al., 1999, 2005; Leckman et al., 2001; Cavallini et al., 2002]. Future study using a recently developed instrument especially designed to evaluate these dimensions [Rosario-Campos et al., 2006] will likely produce data that is more robust. Finally, the design of our study precluded the determination of whether the familial contribution identified was of genetic or environmental origin.

In conclusion, our findings suggest that age at onset of OCS and OCS dimensions of contamination/cleaning and hoarding features seem to be familial and to depend on the gender of the affective relative. Therefore, they represent relevant phenotypic characteristics, advancing the search for OCD subgroups that are more homogeneous.

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