Obsessive-Compulsive Spectrum Disorders and Rheumatic Fever: A Family Study

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Background: *Obsessive-compulsive spectrum disorders (OCSDs) are more frequent in patients with active or prior rheumatic fever (RF), suggesting that OCSD and RF may share underlying etiologic mechanisms. Our objective was to estimate the frequency of OCSD in first-degree relatives (FDRs) of RF patients and controls to determine whether there is a familial relationship between OCSD and RF.*

Methods: *This is a case-control family study. Of the 98 probands included in this study, 31 had RF without Sydenham's chorea (SC) and had 131 relatives, 28 had RF with SC and had 120 relatives, and 39 were controls without RF. All probands, 87.9% of the RF FDRs and 93.7% of the control FDRs were assessed directly with structured psychiatric interviews and best-estimate diagnoses were assigned. Odds ratios of morbid risks were estimated using logistic regression by the generalized estimating equations (GEE) method and compared between groups.*

Results: *The rate of OCSDs was significantly higher among FDRs of RF probands than among FDRs of controls (*n*=37; 14.7% vs.* n*=10; 7.3%, i=.0279). A diagnosis of OCSDs in an RF proband was associated with a higher rate of OCSDs among FDRs when compared to control FDRs (*p-GEE*=.02). There was a trend for a higher rate of OCSDs among FDRs of RF probands presenting no OCSD, although the difference was not significant (*p-GEE*=.09).*

Conclusion: *The results are consistent with the hypothesis that a familial relationship exists between OCSD and RF, since an OCSD in the RF proband was found to increase the risk of OCSDs among FDRs. Additional neuroimmunological and genetic studies involving larger samples are needed to further elucidate this apparent familial relationship between RF and OCSD.*

Key Words: Family study, obsessive-compulsive disorder, rheumatic fever, tics, Tourette

Rheumatic fever (RF) is a systemic disorder triggered by group A beta hemolytic streptococcus pharyngeal infections. The most widely accepted pathophysiological theory postulates that antibodies against the bacteria cross-react with similar proteins in different organs in the body, a mechanism known as mimicry. In joints, RF is associated with arthritis, in the heart with carditis, and in the brain with choreiform movements, the last being a condition known as Sydenham's chorea (SC). Cellular mechanisms have been implicated in the origin and persistence of symptoms, most often in carditis. Recently, it has been demonstrated that anti-streptococcal antibodies extracted from sera of SC patients cross-react with caudate and putamen lysoganglioside receptors, activating intracellular signaling (Kirvan et al 2003).

In addition to these systemic and neurologic manifestations, a number of psychiatric disorders have been reported in individuals with RF (Freeman et al 1965; Hounie et al 2004; Mercadante et al 2005). In the last 15 years, the focus has been on OCD and related conditions. Several reports have described obsessions and compulsions in patients with RF both with (Asbahr et al 1998; Mercadante et al 2005; Swedo et al 1989; Swedo et al 1993) and without SC (Mercadante et al 2005). In some instances, the individuals met all DSM criteria for OCD. These initial studies were performed in patients experiencing acute phases of RF. However, more recent studies of RF patients who were not acutely ill (Alvarenga et al in press; Hounie et al 2004; Mercadante et al 2005) have also reported the presence of OCD and related disorders. These OCD-related conditions, which include disorders with similar phenotypes and putative genetic background (Kelsoe 2003), have been referred to as obsessive-compulsive spectrum disorders (OCSDs) (Hollander 1993). These OCSDs encompass a range of conditions including tic disorders such as Tourette syndrome (TS) and chronic tic disorder (CTD), as well as body dysmorphic disorder (BDD) and grooming behaviors (trichotillomania, onicophagia, and skin picking) (Bienvenu et al 2000; Grados et al 2001; Jaisoorya et al 2003; Pauls et al 1995). The disorders that comprise OCSD all present similar repetitive behaviors. In addition, data from family/genetic studies provide some evidence that these conditions might have some common etiological factors. For example, data from OCD family studies have demonstrated higher rates of tic disorders (Grados et al 2001; Pauls et al 1995), BDD (Bienvenu et al 2000) and grooming behaviors (trichotillomania, onicophagia, and skin picking) (Bienvenu et al 2000; Jaisoorya et al 2003) among first-degree relatives of OCD probands.

The presence of OCSDs in non-acute-RF patients suggests several possible mechanisms. First, acute changes related to RF might have persisted or triggered late pathophysiological changes that increase susceptibility to these neuropsychiatric disorders. Second, it is possible that OCSD and RF share a common familial/genetic etiology.

To our knowledge, this is the first family study designed to investigate a familial relationship between RF and the spectrum

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Received July 13, 2005; revised January 30, 2006; accepted February 6, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.02.021

of obsessive-compulsive (OC) behaviors by estimating the frequencies of OCSDs among relatives of RF probands. The hypothesis proposed is that there is a higher rate of OCSDs among relatives of RF probands than among relatives of controls.

Methods and Materials

Sample

Sample Selection. The ethical committee of the Clinical Hospital of the University of São Paulo approved this study. All subjects and their relatives gave their informed consent before entering in the study. Case probands were recruited from an RF outpatient clinic and control probands were recruited by research assistants from an orthopedic outpatient clinic at the University of São Paulo Medical School. Probands who agreed to participate and gave permission to contact their first-degree relatives (FDRs) were enrolled in the study. A total of 126 individuals were invited to participate. Twenty-eight subjects were excluded (11 refused, 3 had lost contact with relatives, 6 were under 5 years of age, and 8 were half-siblings). Therefore, the final sample consisted of 98 probands and their 389 FDRs (251 case relatives and 138 control relatives). All subjects gave their informed consent before the assessment. Of the 98 probands, 31 had RF without SC (RF–SC) and had 131 relatives, 28 had RF with SC (RF+SC) and had 120 relatives, and 39 were controls without RF.

Diagnostic Interviews. All individuals under the age of 16 were interviewed using the Kiddie Schedule for Affective Disorder and Schizophrenia for School-age Children–epidemiologic version (K-SADS-E) (Chambers et al 1985), revised in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (Kaufman et al 1997). Individuals over the age of 16 were interviewed using the non-patient version of the Structured Clinical Interview for DSM (SCID) (Spitzer et al 1992). All participants were also interviewed regarding the presence of TS, CTD, transient tic disorder, trichotillomania, onicophagia, compulsive gambling, kleptomania, pyromania, compulsive buying and skin picking. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al 1989) and the Yale Global Tic Severity Scale (YGTSS) (Leckman et al 1989) were used to assess the presence and severity of OC symptoms and tics. Information about severity and age-at-onset for each symptom was also collected. For the other disorders (trichotillomania, onicophagia, compulsive gambling, kleptomania, pyromania, compulsive buying and skin picking), separate modules designed by the authors and including questions that operationalized the DSM-IV criteria for each disorder were used (available upon request). The K-SADS-E, SCID, Y-BOCS and YGTSS are standard instruments with well-established psychometrics (Chambers et al 1985; Goodman et al 1989; Leckman et al 1989; Spitzer et al 1992). All psychiatric diagnoses were made according to DSM-IV criteria, through a best-estimate procedure (Leckman et al 1982).

Family History Interviews. In addition to the K-SADS-E and SCID, semi-structured family history interviews, in which each member of a nuclear family provided information regarding the other family members, were conducted. This instrument was an adaptation of the instrument used by Pauls et al (1995) and included questions about tics, attentional problems, OC symptoms, depression, anxiety disorders, mania, phobias and trichotillomania. Therefore, for each individual, direct interviews, family history data, and (when available) medical records were used to assign best-estimate diagnoses.

Interviewers. All interviewers were either psychologists or psychiatrists who were duly trained for reliability purposes. Training consisted of didactic classes regarding psychiatric disorders and their differential diagnoses, video sessions of recorded interviews, supervised interviews, and independent interviews with further evaluation. In all FDR interviews, the interviewers were blinded as to the diagnosis of the proband.

Best-estimate Diagnosis. Diagnoses of all subjects (probands and their FDRs) were made using the best-estimate procedure (Leckman et al 1982). Clinical vignettes including patients' age and a detailed description of their psychiatric symptoms were prepared by the first author. The vignettes did not state to which group they belonged or if they were probands or family members. The vignettes were evaluated by independent and experienced psychiatrists (ECM and RGS) who assigned best-estimate diagnosis. Both were blinded as to the diagnosis of the proband, the identity of the individual, and the relationship of the individual to the proband. 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 best estimates of the two raters were then compared, and in cases of disagreement, a third diagnostician was consulted (MCRC).

The inter-rater reliability of the best-estimate diagnostic procedure was estimated using intraclass correlation coefficients (ICCs). For OCD and TS, there was excellent agreement (ICC=.91 and ICC=1.00, respectively) and good agreement for body dysmorphic disorder (ICC=.85). Due to the small number of cases, reliability analysis was not performed for other diagnoses.

Several levels of diagnostic certainty were used. When an individual met all DSM IV criteria, a "definite" diagnosis was assigned. If symptoms were clearly present but the individual failed to meet either the duration/distress criterion or the interference criterion, a diagnosis of subthreshold disorder was given. Regarding OCD, an individual received a definite diagnosis when meeting the criteria for duration, distress and interference. If the subject met all criteria for definite OCD but OC symptoms occurred for less than 1 hour a day or did not cause interference or distress, a diagnosis of subthreshold OCD was assigned. For statistical analysis, definite and subthreshold diagnoses were included.

All probands (case and control) were interviewed directly, as were 219 (87.3%) of the case FDRs and 129 (93.5%) of the control FDRs. For all subjects not interviewed directly, family history data were collected from each of the other relatives. On average, there were 3 to 4 family history interviews completed for each person not interviewed. It has been shown that family history data collected from this many relatives is almost as reliable as direct interview data (Gershon et al 1984).

Measurement of Streptococcal Infection Exposure. To measure streptococcal exposure of the FDRs in both groups, antistreptolysin O (ASO) titers were obtained at the time of the interview. Of the sample of 389 FDRs, 278 (71.5%) gave blood at the time of the interview. Antistreptolysin-O (ASO) was analyzed by nephelometry in sera using the N Latex ASL kit (Dade Behring GmbH, Marburg, Germany). The analyses were performed in the Clinical Laboratory of the Heart Institute of the University of São Paulo. The sensitivity of the test allows the identification of ASO concentrations from 50 IU/ml to 1600 IU/ml. Values higher than 200 IU/ml were considered positive.

Data Analysis

Demographic characteristics in case and control probands and their respective FDRs were compared with chi-square or

Table 1. Demographic Characteristics of Case and Control Probands

Variable	RF Probands (n=59)	Control Probands (n=39)	Statistical Test
Gender	N (%)	N (%)	χ^2=2.9; df=1; p=.09
Male	26 (44.1)	24 (61.5)	
Female	33 (55.9)	15 (38.5)	
Current age (mean)	years ± SD	years ± SD	t-test (df=96)=3.33; p=.001
	14.36 ± 4.60	11.51 ± 3.29	
Direct interviews	N (%)	N (%)	N/A
	59 (100)	39 (100)	
Comorbidities	N (%)	N (%)	
OCD	2 (3.4)	1 (2.6)	Fisher's (p=1.0)[b]
Tic disorders	6 (10.2)	0 (0)	Fisher's (p=.078)[b]
BDD	2 (3.4)	0 (0)	Fisher's (p=.51)[b]
Trichotillomania	3 (5.1)	0 (0)	Fisher's (p=.27)[b]
Total (OCSDs)[a]	10 (16.9)	1 (2.6)	Fisher's (p=.046)

OCD, obsessive-compulsive disorder (clinical or subthreshold); Tic disorders, Tourette syndrome and chronic tic disorder (Fisher's exact test p=.003 if transient tic disorder is included); BDD, body dysmorphic disorder; OCSDs, obsessive-compulsive spectrum disorders (OCD, tic disorders, BDD and trichotillomania); N/A, not applicable.

[a]Subjects diagnosed with more than one disorder were counted only once.

[b]Non-significant.

Fisher's Exact Test for categorical data and t-test for continuous data. All tests were two-tailed, with $\alpha \leq .05$. Age-corrected morbid risks were estimated using Kaplan-Meier survival analyses. To examine differences between morbid risks in case and control FDRs, odds ratios (ORs) were estimated using logistic regression by the generalized estimating equations (GEE) method, which accounts for within-family correlations among relatives. Aggregated risks for OCSDs, including OCD, subthreshold OCD, tic disorders, and BDD, were calculated. In our sample, grooming behaviors included only trichotillomania and onicophagia, as there were no cases of skin picking. However, we decided to exclude them from the concept of OCSDs due to the scarcity of supportive data. The SPSS 11.0 statistical package was used for all analyses. Therefore, the concept of OCSD utilized for the analyses described below included the following disorders: OCD, Tic Disorders (TS, CTD and transient tic disorder), and BDD.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the probands and relatives are shown in Tables 1 and 2, respectively. For a more detailed description of clinical features of the probands, see Hounie et al (2004).

The RF probands were more frequently affected with OCSD than were controls (Table 1). Table 3 shows the frequency and morbid risk of each OCSD in relatives of probands with and without RF. Although the frequency of each OCSD was not different in relatives of RF and controls, when these disorders are combined and the aggregated risks calculated, the relatives of RF probands had a significantly higher frequency of OCSD than did control relatives (n=37; 14.7% vs. n=10; 7.3%; *GEE* p=.0279; *OR* = 2.2101, 95%CI=[1.0898–4.4853]) (Table 4).

Of interest is that SC in the RF probands did not appear to have much effect on the rate of OCSDs among the FDRs. There were no significant differences in OCSD frequencies between the FDRs of RF+SC patients and of RF–SC patients. The rates of OCSDs among FDRs of RF+SC probands (n=20; 16.7%) and RF–SC probands (n=17; 13.0%) were both higher than the rate among FDRs of controls (n=10; 7.3%) albeit the difference between the rates among relatives of RF–SC and controls only reached borderline statistical significance (RF+SC vs. controls: *p-GEE* =.0247; *OR* = 2.5663; 95%CI=[1.1276–5.8430] and RF–SC vs. controls; *p-GEE*=.0907; *OR* = 1.9174; 95%CI=[.9020–4.0760]) (Table 4).

Seventeen percent of the case probands presented OCSDs (OCD, Tic disorders and BDD; [Table 1]). Therefore, rates of OCSDs in FDRs of probands with and without an OCSD were compared to determine if the presence of OCSDs in FDRs was associated with the presence of OCSD in the proband (Table 5).

The FDRs of probands with an OCSD had a significantly higher rate of OCSDs than did the FDRs of control probands (*p-GEE*=.02; *OR*=3.09; 95% *CI*=1.18–8.13). In addition, the rate of OCSDs among FDRs of case probands without an OCSD was higher than that seen among FDRs of controls, although the

Table 2. Demographic Characteristics of Case and Control First-degree Relatives

Variable	Case FDRs (n=251)	Control FDRs (n=138)	Statistical Test
Gender	N (%)	N (%)	χ^2=.201; df=1; p=.65
Male	126 (50.2)	66 (47.8)	
Female	125 (49.8)	72 (52.2)	
Current age (mean)	Years ± SD	Years ± SD	t-test (df=387)=.081; p=.936
	27.91 (14.35)	28.04 (14.69)	
Direct interviews	N (%)	N (%)	χ^2=3.66; df=1; p=.056
	219 (87.3)	129 (93.5)	

FDRs, first-degree relatives; SD, standard deviation.

Table 3. Comparison of Frequencies and Morbid Risks of Obsessive-Compulsive Spectrum Disorders in Relatives of Probands with and without Rheumatic Fever

	FDR of RF Probands Age Corrected Morbid Risk (%; *n*=251)	Control FDR Age Corrected Morbid Risk (%; *n*=138)	P (GEE)
OCD	2.8%; *n* = 6	0%; *n* = 0	Na
Subclinical OCD	6.2%; *n*=11	5.3%; *n*=6	.92
TS	.8%; *n*=2	.8%; *n*=1	.99
CTD	4.6%; *n*=10	.7%; *n*=1	.18
TTD	1.9%; *n*=4	1.0%; *n*=1	.76
Tic disorders	7.6%; *n*=16	2.5%; *n*=3	.16
BDD	5.1%; *n*=9/188	1.0%; *n*=1/96	.28

Abbreviations: FDR, first-degree relatives; RF, rheumatic fever; OCD, obsessive-compulsive disorder; TS, Tourette syndrome; CTD, chronic tic disorder; TTD, transient tic disorder; Tic disorders, ST+CTD+TTD; BDD, body dysmorphic disorder; n/a, not applicable. GEE values are not calculated with zero values.

difference did not reach statistical significance (*p-GEE*=.09; *OR*=1.88; 95% *CI*=.91–3.91) (Table 5).

The above results were obtained by expanding the definition of OCSD to include OCD only, tic disorders and BDD. However, the same results were obtained when trichotillomania was also included. Among FDRs of RF probands presenting an OCSD (including trichotillomania), OCSDs were more common than among controls (*GEE, p* = .0077), although no difference was found between controls and case relatives of probands presenting no spectrum disorders (*GEE, p* = .13). In this new analysis, we included three RF probands identified as being cases of trichotillomania (Table 1). There were also three cases of trichotillomania among FDRs of RF probands (morbid risk = 4.6%), whereas the OCSD rate among control FDRs was unchanged.

Table 6 displays the individual rates of the disorders studied in FDRs of RF probands with and without an OCSD. The adjusted rate of tic disorders and BDD in FDRs of RF probands with an OCSD was higher than the rates in controls (*p, GEE*=.020 and *p, GEE*=.024, respectively).

To better describe the phenotypic features of OCD in our sample, we compared several variables (presence of tic disorders, age at onset of obsessive-compulsive symptoms and content of obsessions and compulsions according to the Y-BOCS) of the FDR of RF probands with subclinical or clinical OCD (*n*=17) and controls (*n*=6). There were no differences between the two groups regarding the frequency of tic disorders [1/17 (5.9%) in the FDR of RF vs. 0 of the controls; F=1] and age at onset of obsessive-compulsive symptoms [mean=13.76 (7.6) in the FDR of RF vs. mean=11.33 (2.7) of the controls; $t(df=21)=-1.124$; *p*: .274]. However, the relatives of RF probands with subclinical or clinical OCD reported higher number of aggressive obsessions [10/16 (62%) in the FDR of RF vs. 0 in the controls; *F*=.15). All the other types of obsessions and compulsions were not different between groups.

Table 4. Comparison of the Frequencies and Morbid Risks of Obsessive-Compulsive Spectrum Disorders in Relatives of Probands with and without Sydenham's Chorea

Subjects	OCSDs *n* (%)	Morbid Risk of OCSDs[a]
FDRs of RF+SC probands (*n*=120)	20 (16.6%) a	19.7 e
FDRs of RF-SC probands (*n*=131)	17 (12.9%) b	15.9 f
All RF relatives (*n*=251)	37 (14.7%) c	17.8 g
Control FDRs (*n*=138)	10 (7.3%) d	8.5 h
P (abd) (GEE)[b]	.0730	
χ(abd)^2	.0636	

RF, rheumatic fever; SC, Sydenham's chorea; FDR, first-degree relatives; OCSDs, obsessive-compulsive spectrum disorders.

[a]Age-corrected rates.

[b]GEE, *p*(comparison ad)=.0247; OR=2.566; 95% CI=[1.1276–5.8430]; GEE *p*(comparison bd)=.0907; OR=1.9174; 95% CI=[.9020–4.0760]; GEE *p*(comparison cd)=.0279; OR=2.2101, 95% CI=[1.0898–4.4853] log-rank, *p*(gh)=.0383.

Rheumatic Fever in First-Degree Relatives

Among the FDRs included in the study, 4 (1.6%) were previously diagnosed with RF. None of the FDRs of controls presented RF. This rate is four times higher than the rate of RF in the general Brazilian population (3.6/1000) (Alves-Meira et al 1995), in other words, it is significantly higher (*p*=.01), supporting the hypothesis that RF is familial. Of the 4 RF-affected FDRs, 3 presented an OCSD. Given the potential bias of these affected relatives in increasing the rate of OCSDs among FDRs, the data were reanalyzed after removing them from the sample, and there was no significant change in any of the results reported above.

Antistreptolysin-O Results in Probands

Blood was collected from 77% (76/98) of the probands. Positive values were found more frequently in control probands (68%, 19/28) than in case probands (27%, 13/48) (*p*=.001). This may reflect the fact that most case probands were under antibiotic

Table 5. Comparison of the Frequencies and Morbid Risks of Obsessive-Compulsive Spectrum Disorders in Relatives of Rheumatic Fever and Control Probands Divided According to the Presence of a Spectrum Disorder in the Proband

Subjects	OCSDs *n* (%)	Morbid Risk of OCSDs[a]
FDRs of RF+OCSD probands (*n*=44)	9 (20.5%) a	22.7 d
FDRs of RF−OCSD probands (*n*=207)	28 (13.5%) b	16.7 e
FDRs of control-OCSD probands (*n*=130)	10 (7.7%) c	9.0 f
P (abc)(GEE)[b]	.0614	
χ^2(abc)	.0625	
Log-Rank (def)	.0584	

OCSD, obsessive-compulsive spectrum disorder (includes OCD, tic disorders and BDD); FDR, first-degree relatives; RF, rheumatic fever; SC, Sydenham's chorea; FDRs of RF+OCSD probands, relatives of RF probands presenting at least one OCSD; FDRs of RF−OCSD, relatives of RF probands presenting no spectrum disorders; Control FDRs−OCSD, relatives of controls presenting no spectrum disorders.

[a]Age-corrected percentages.

[b]GEE log-linear (comparison ac), *p*=.02; OR(ac)=3.09; 95% CI: 1.18–8.13; log-rank, (ac) *p*=.02; GEE log-linear (bc), *p*=.09; log-rank (bc), *p*=.12; OR (bc)=1.88; 95% CI: .91–3.91.

Table 6. Morbid Risks for Individual Obsessive-Compulsive Spectrum Disorders in Relatives of RF and Control Probands According to the Presence of an Obsessive-Compulsive Spectrum Disorder in the Proband

	FDR of RF+OCSD (*n*=44)	%	FDR of RF−OCSD (*n*=207)	%	Controls −OCSD (*n*=130)	%	*p*
OCD	0	0%	6	2.9%	0	0%	.10 (F)
Subclinical OCD	2	4.5%	9	4.3%	6	4.6%	.99 (χ^2)[a]
OCD+subcOCD	2	4.5%	15	7.2%	6	4.6%	.55 (χ^2)[b]
TS	1	2.3%	1	.5%	1	.8%	.35 (F)
CTD	2	4.5%	8	3.9%	1	.8%	.14 (F)[c]
TTD	2	4.5%	2	1%	1	.8%	.15 (F)
TS+CTD	3	6.8%	9	4.3%	2	1.5%	.16
TS+TCD+TTD	5 a	11.4%	11	5.3%	3 b	2.3%	.055 (χ^2)[d]
BDD	4/32 a	12.5%	5/156 b	3.2%	1/92 c	1.1%	.019 (F)[e]

OCSD, obsessive-compulsive spectrum disorder (includes OCD, tic disorders and BDD); FDR, first-degree relatives; RF, rheumatic fever; OCD, obsessive-compulsive disorder; TS, Tourette syndrome; CTD, Chronic tic disorder; TTD, transient tic disorder; BDD, body dysmorphic disorder; χ^2, chi-square test; F, Fisher test.

[a]GEE log-linear, p=.99; Log-Rank, p=.99.

[b]GEE log-linear, p=.56; Log-Rank, p=.5845.

[c]GEE log-linear, p=.25.; Log-Rank, p=.2070.

[d]GEE log-linear, p=.04; GEE log-linear (ab), p=.01, Log-Rank, p=.0512.

[e]BDD was assessed only in subjects over 15 years old ("*n*" in the denominator); GEE log-linear, p=.03. GEE log-linear, p(ac)=.0247, OR=12.56; 95% CI: 1.38–114.43; GEE Log-linear, p(ab)=.0452; OR=3.53; 95% CI: .42–28,95.

prophylaxis (IM penicillin regimen). Within RF probands, there was no association between OCSD and positive ASO values.

Antistreptolysin-O Results in First-Degree Relatives

The frequency of positive ASO titers did not differ between case and control FDRs at the time of the interview (RF relatives: 67/173—38.7%; Controls 43/105—41%, p=.7). In addition, OCSDs were not found to correlate with ASO positivity.

Discussion

This is the first family study investigating psychiatric disorders in FDRs of RF probands. The results reported herein support the hypothesis that a familial relationship exists between RF and OCSDs. The rate of OCSDs among FDRs of RF probands was significantly higher than the rate among FDRs of controls. The rate of OCSDs was highest among FDRs of RF+OCSD probands. However, the rate of OCSD was also higher among FDRs of RF probands without an OCSD, although the difference was not statistically significant. These results were obtained by expanding the definition of OCSD to include OCD only, tic disorders, and BDD. However, the same results were obtained when trichotillomania was also included.

The higher frequency of OCSDs in the FDRs of probands with an OCSD could lead to various interpretations. First, the higher frequency of OCSDs in FDRs could be merely due to a genetic vulnerability associated to the presence of the OCSD in the probands and thus be independent of RF. However, the same trend was found in FDRs of RF probands without an OCSD. In addition, OCSDs have been consistently found more frequently in RF patients (Hounie et al 2004; Mercadante et al 2005; Swedo et al 1989; Swedo et al 1993) than in non-RF controls. Alternatively, these findings could suggest that some individuals with RF represent a subgroup comprising individuals presenting both RF and OCSD symptoms, which would confer on the FDRs a higher familial vulnerability for developing OCD related disorders. The small rates of OCSDs are compatible with a multifactorial model, in which many genes of small effect interact with environmental factors.

It is also possible that the results of the present study are due merely to chance. However, this is less likely in view of the fact that the rate of other psychiatric disorders such as depression, bipolar disorder, schizophrenia, specific phobias, and social phobia were not statistically different between the groups. Therefore, it appears that there may be some specificity in the relationship between RF and OCSD.

The higher frequency of RF in case-proband FDRs than in control FDRs suggests that RF is familial as well. However, the increased rate of OCSDs is not due merely to the increased RF among FDRs since, when these RF-affected relatives were omitted from the family analyses, none of the OCSD recurrence patterns changed.

The ASO titers were high in both case and control FDRs. Although this is a cross-sectional study, and there are many different strains of group A beta hemolytic streptococcus, it is likely that the exposure to streptococcal infections was similar for the FDRs in both groups. Therefore, the differences observed between the FDRs of RF probands and those of controls cannot be explained by differential exposure to strep.

The relationship between RF and OCSDs in the probands and their FDRs could involve several different mechanisms. First, it is possible that both RF and OCSDs are attributable to a dysfunctional immune response. Second, it is possible that RF and OCSDs could be related to an abnormal expression of some regulatory genes associated with the immune response (e.g., abnormal regulation of cytokines) (Leckman et al 2005; State et al 2003). Despite the speculative nature of the hypothesis that a relationship exists between immune response and psychopathology, some data has suggested an intriguing relationship between the immune system and the central nervous system (e.g., the SC patient monoclonal antibodies with signaling properties) (Kirvan et al 2003). Observations, both in humans and in experimental animals, have pointed to abnormalities in cortico-basal ganglia circuits as primary neural correlates of repetitive behaviors found in OCSDs (Graybiel and Rauch 2000; Saka et al 2004). Therefore, immune mediated reactivity against the brain could contribute to these OCSD behaviors inducing circuit-level neuroplasticity in cortico-basal ganglia circuits (e.g., differential activation of the striosomal system of the striatum).

Repetitive behaviors (cleaning compulsions, tics and grooming behaviors) which occur as part of normal repertoire

can become exaggerated and behaviorally dominant in OCSDs) (Leckman et al 2000). It is tempting to speculate that the close relationship between OCSDs behaviors and dysfunctional immune response to infections such as RF could be due to an adaptive process, as part of the phylogenic evolution. The health of subjects would be related with some habits (i.e., assembled routines including cleaning compulsions, tics and grooming behaviors) (Leckman et al 2000), which are more prominent when they are exposed to infectious agents. As result of an evolutionary heritage, the immune system would have developed a pathway to control such behaviors by activating specific striatal neurons, and our findings would show a dysfunctional relationship between the immune and central nervous systems.

Strengths and Limitations of the Study

The greatest limitation of this study is the small sample size. This may explain why we did not find statistical differences between relatives of RF and controls for the frequencies of individual OCDS disorders (Type II error). To confirm our results, further studies involving larger samples are warranted. In addition, since all of the probands were recruited from a tertiary hospital, it is possible that the RF probands represent the most severe and complex RF cases, which are more likely to present comorbidities that could have been inherited. It should be noted, however, that control probands were recruited from the same hospital. The control patients selected from the orthopedic clinic may also represent more severely ill patients. Forty percent of the control probands presented chronic disorders (e.g., bone cancer) or congenital disorders that could potentially expose their relatives to a considerable degree of chronic stress, resulting in a higher frequency of psychiatric disorders and also leading to a type II error. Another potential limitation is the fact that the proband assessment was retrospective. All were non-acute RF cases. Therefore, all psychiatric diagnoses were determined from retrospective data and could thus be underestimates of the true rates of illness. Considering that OC symptoms in children are usually egosyntonic, it is possible that OCD was underdiagnosed. Furthermore, the secretive nature of OC symptoms is well documented and could also have contributed to a possible underestimation of the OCD frequency. Finally, a great proportion (n=200; 41%) of the sample was composed of siblings, that is, children and adolescents still under risk of developing OCSDs. Although all of the rates were corrected for age, it will be important to replicate this study in a sample with a wider age range.

Conclusions

The present findings suggest a familial relationship between RF and OCSDs. If these findings are replicated, clinicians should systematically obtain information about OCSD symptoms in their RF patients and family members. Similarly, the investigation of RF might be included in the psychiatric evaluation of OCSD patients. Further neuroimmunological and genetic studies are needed in order to confirm the present findings and to elucidate the mechanisms through which RF confers a high risk of OCSD in individuals with RF and in their FDRs.

This research was supported by Grants from the Research Foundation of the state of São Paulo (FAPESP) 98/15013-9 and 99/12205-7 and by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ), Brasil (Grant#521369/96-7) (AH).

We thank Dr. James Leckman, who has followed several steps of this project and has made insightful comments for the final version of this paper. We also thank Dr. Milton de Arruda Martins and Dr. Christina Gonzalez, who have reviewed and made important contributions regarding this paper.

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