Obsessive-Compulsive Spectrum Disorders in Rheumatic Fever With and Without Sydenham's Chorea

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Background: Recent findings suggest that acute-phase rheumatic fever (RF) patients present with higher frequencies of obsessive-compulsive disorder (OCD) and tic disorders. Until now, there have been no such studies in RF in non-acute phases.

Objective: To verify whether patients with a history of RF with or without Sydenham's chorea (SC) present with higher rates of OCD, tic disorders, and other obsessive-compulsive (OC) spectrum disorders (such as body dysmorphic disorder [BDD]) than controls.

Method: Between February 1999 and December 2002, 59 consecutive outpatients with non-acute RF (28 with and 31 without SC) from an RF clinic and 39 controls from an orthopedics clinic were blindly assessed for OC spectrum disorders using structured interviews to assign DSM-IV diagnosis. Data were analyzed with Fisher exact and χ^2 tests to compare frequencies of disorders, and Kaplan-Meier survival analyses were used to obtain age-corrected rates.

Results: The age-corrected rates of tic disorders were higher in patients with RF without SC (N = 3; 14.39%) (p = .003) when compared with controls. Age-corrected rates for OC spectrum disorders (OCD, tic disorders, and BDD) combined were higher both in RF without SC (N = 4; 20.65%) and RF with SC (N = 5; 19.55%) groups than in controls (N = 1; 2.56%) (p = .048).

Conclusions: RF, even in the non-acute phase, may increase the risk for some OC spectrum disorders, such as OCD, tic disorders, and BDD. These data, although preliminary, reinforce the idea that OC spectrum disorders may share common underlying pathophysiologic mechanisms and vulnerability factors with RF or that RF could trigger central nervous system late manifestations such as OC spectrum disorders.

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Rheumatic fever (RF) is an autoimmune disorder that occurs after infection by specific strains of group A β-hemolytic streptococci.[1] An initially normal immune response leads to the development of antibodies that cross-react with host tissues.[2] Specific subgroups of T cells are also activated and infiltrate various tissues, leading to damage of multiple organ systems, including heart valves and joints.[3] Symptoms may also progress to include the central nervous system (CNS), displaying the distinctive movement disorder known as St. Vitus' dance or Sydenham's chorea (SC).[4] The manifestation of SC is sufficient to warrant a diagnosis of acute RF, whereas arthritis, carditis, and evidence of a group A streptococcal infection, among other features, are required to establish an RF diagnosis in the absence of SC.[5,6]

Several studies report higher frequencies of obsessive-compulsive (OC) symptoms, obsessive-compulsive disorder (OCD),[7–9] and tics[10–13] in SC patients. There is also striking evidence of higher frequencies of OCD in patients with RF without SC.[14] Although several psychopathologic manifestations have been described in RF

patients over the years (for a comprehensive review, see references 13 and 15), they have all been described in acute-phase RF patients. The relationship between neuropsychiatric disorders and acute-phase RF suggests that immunologic mechanisms, such as those described in SC, would be implicated in the etiology of neuropsychiatric disorders.

These previous studies did not report the rates of other obsessive-compulsive (OC) spectrum disorders, such as body dysmorphic disorder (BDD).[16] At present, we are unaware of any studies examining the frequencies of OC spectrum disorders in either acute- or non–acute-phase RF patients. The finding of neuropsychiatric disorders in patients with non-acute RF is theoretically interesting and intriguing, as chronic sequelae have been described concerning the heart and joints, but not the central nervous system.[17]

It has been speculated that OCD, tic disorders, and BDD belong to the same spectrum of disorders, with common underlying genetic mechanisms.[18,19] Spectrum disorders may share clinical, psychopathologic, and pathophysiologic characteristics.[20] This study investigated the frequencies of some OC spectrum disorders, more specifically OCD, tic disorders, and BDD in patients with RF with (RF + SC) and without (RF – SC) SC compared with a control group. The main objective was to verify whether patients with a history of RF (non-acute phase) present higher frequencies of OC spectrum disorders. Our hypotheses were similar to the findings from a previous study of acute-phase patients.[14] We hypothesized that the frequency of OC spectrum disorders (specifically OCD, tic disorders, and BDD) would be increased in RF patients (with or without SC) when compared with control subjects. We also predicted that the frequency of OCD spectrum disorders would be higher among RF + SC patients than among RF – SC patients.

METHOD

Subjects

Patients studied were probands in a family study on RF (A.G.H., D.L.P., M.T.M., et al., manuscript submitted). One hundred eighteen consecutive RF patients and 156 control individuals and their families were invited to participate. Fifty-nine non–acute-phase RF patients (28 with and 31 without SC) from the Rheumatic Fever Outpatient Clinic of the Child Institute (children = 96.6% of the sample) and the Rheumatic Fever Service (adults over 18 years old = 3.4% of the sample) at the Medical School of the University of São Paulo, São Paulo, Brazil, and 39 controls (patients from the Orthopedics Institute who did not present autoimmune or neurologic diseases) agreed to participate in the study. Reasons for refusal included: (1) probands were in town only for treatment and relatives lived in other states and were not available; (2) probands and their families could not miss work or school; and (3) probands could not be brought to the hospital due to their medical conditions (e.g., bone fractures in the control group).

RF diagnosis was made according to modified Jones criteria[5,6] by a pediatrician with expertise in RF. RF was considered to be in the chronic phase when patients had no acute symptoms such as fever, arthritis, carditis, motor symptoms of SC, or positive acute-phase laboratory tests. RF and control probands were excluded from the study if they were (1) under 5 years of age, (2) adopted, (3) mentally retarded, or (4) a child without siblings. Written consent was obtained from all subjects after a detailed description of the study. Children under 18 years had consent given by their parents, and the children also assented to the study. This study was approved by the Ethical Committee of the Clinical Hospital of the University of São Paulo.

Obsessive-Compulsive Spectrum Diagnoses

Subjects under 16 years were interviewed by trained research assistants with the Kiddie-Schedule for Affective Disorders and Schizophrenia, Epidemiologic Edition (K-SADS),[21] and those 16 years and over were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-IV).[22] Subjects were also assessed with the Yale-Brown Obsessive Compulsive Checklist and Scale (Y-BOCS),[23] and their tics were assessed by the Yale Global Tic Severity Scale (YGTSS).[24] For the diagnosis of tic disorders, we used DSM-IV criteria with the adaptations for research discussed by Freeman et al.[25] and First et al.[26] Briefly, these authors propose that the diagnoses of tic disorders should be made even in the absence of interference and in patients with SC. In order to differentiate choreiform movements from tics, we emphasized the presence of vocal tics in making a diagnosis of tic disorders. When motor tics could not be distinguished from choreic movements, the diagnosis of tic disorders was not made.

The interviewers were trained by the first author to reliability and were blinded to the group to the diagnostic status of the proband. Best-estimate diagnoses[27] were assigned by expert psychiatrists (E.C.M., M.C.R.-C., and R.G.S.) who were also blinded to the diagnostic status of the proband. Three levels of diagnostic certainty were used: definite, probable, and possible. Only definite diagnoses were included in the statistical analyses. Subclinical OCD diagnoses were assigned when subjects met all criteria for OCD except that their symptoms (1) did not cause distress, (2) lasted less than 1 hour, or (3) did not cause significant interference.[27] The interrater reliability of the best-estimate diagnoses among psychiatrists in all probands was excellent for OCD and subclinical OCD (coefficient = .91) and for tic disorders (coefficient = .99). It was not calculated for BDD due to the small number of patients.

Table 1. Demographics of Case and Control Probands

Characteristic	Rheumatic Fever Probands (N = 59)	Control Probands (N = 39)
Gender, N (%)		
Male	26 (44.1)	24 (61.5)
Female	33 (56.9)	15 (38.5)
Male/female ratio	0.78	1.6
Single marital status, N (%)	54 (91.5)	39 (100)
Catholic religion, N (%)	31 (52.5)	24 (61.5)
Socioeconomic class, median[a]	4 (class "D")	3 (class "C")
Age at onset of RF, mean ± SD, y	8.6 ± 2.5	...
Age at onset of tics, mean ± SD, y	10.0 ± 2.5	...
Age at onset of OCS, mean ± SD, y	12.0 ± 1.4	6[b]

[a]Socioeconomic class measured using the Associacao Brasileira de Pesos e Medidas.
[b]True age of 1 control proband with OCS.
Abbreviations: OCS = obsessive-compulsive symptoms, RF = rheumatic fever. Symbol: … = no proband.

Table 2. Distribution of Obsessive-Compulsive Spectrum Disorders Among Groups[a]

Diagnosis	RF – SC, N = 31, N (%)	RF + SC, N = 28, N (%)	Total RF, N = 59, N (%)	Controls, N = 39, N (%)
OCD	0	1 (3.57)	1 (1.69)	1 (2.56)
Sub OCD	0	1 (1.69)	1 (1.69)	0
OCD + subOCD	0	2 (7.14)	2 (3.38)	1 (2.56)
BDD	1 (3.22)	1 (3.57)	2 (3.38)	0

[a]The reported values are not age-corrected.
Abbreviations: BDD = body dysmorphic disorder, OCD = obsessive-compulsive disorder, subOCD = subclinical OCD, RF = rheumatic fever, SC = Sydenham's chorea, RF – SC = rheumatic fever patients without SC, RF + SC = rheumatic fever patients with SC.

Statistical Analysis

Comparisons of categorical variables among groups were performed using χ^2 or Fisher exact tests. Comparisons of continuous variables were done with analysis of variance and Student t test. For variables without a normal distribution, Kruskal-Wallis and Mann-Whitney tests were performed. Age-corrected rates were calculated for OCD, subclinical OCD, tic disorders, and BDD using Kaplan-Meier survival analysis.[28] Some patients had more than 1 disorder. In these cases, the age at onset for the aggregated age-corrected rates of OC spectrum disorders (necessary for the survival analysis) was the age at onset of the earliest disorder. The age-corrected aggregated rate of OC spectrum disorders excluded transient tic disorder. Statistical comparisons of the age-corrected rates were made by comparing the 95% confidence intervals (CIs) calculated by the formula age-corrected rate $\pm 1.96 \times$ SE. The SPSS 10.0 package (SPSS Inc.; Chicago, Ill.) was used for the statistical analyses.

RESULTS

The total sample comprised 98 individuals: 31 RF – SC patients (mean age = 14.55 years [SD = 5.66; range, 6–39]), 28 RF + SC patients (mean age = 14.14 years [SD = 3.15; range, 6–20]), and 39 controls (mean age = 11.51 years [SD = 3.28; range, 6–17]). Given the significant difference between the mean ages ($p = .005$) of RF patients and controls, the rates of OCD, subclinical OCD, tic disorders (including Tourette's disorder and chronic tic disorder), transient tic disorder, and BDD were age-corrected. There were no significant differences between the groups regarding gender ($p = .22$), socioeconomic class, ($p = .27$) marital status ($p = .11$), and religion ($p = .07$) (Table 1).

The age-corrected rate for OCD plus subclinical OCD in patients with RF + SC (8.65%; 95% CI = 8.54 to 8.76) was significantly higher than in controls (2.56%; 95% CI = 2.51 to 2.60). Similarly, the rates for OCD alone were slightly higher in RF + SC (3.85%; 95% CI = 3.7 to 3.9) than in controls (2.56%). BDD was more frequent in the RF – SC group than in the RF + SC group and also more frequent in the total RF group than in controls. Table 2 displays the frequencies of OC spectrum disorders among the groups.

The age-corrected rates for Tourette's disorder (7.17%; 95% CI = 7.10 to 7.23) and chronic tic disorder (6.26%; 95% CI = 6.17 to 6.34) were higher among the total RF group than among controls (0%). The risk for transient tic disorder was higher in the RF + SC group (19.62%; 95% CI = 19.47 to 19.77) than in the RF – SC group (3.33%; 95% CI = 3.26 to 3.36). The age-corrected rate for tic disorders (Tourette's disorder plus chronic tic disorder) was higher in the RF – SC group (14.39%; 95% CI = 14.23 to 14.55) than in RF + SC group (11.11%; 95% CI = 11.0 to 11.2) (Table 3). It is important to mention that the risk for tic disorders (Tourette's disorder + chronic tic disorder) in males (11.11%; 95% CI = 11.5 to 11.8) was higher than in females (7.26%; 95% CI = 7.16 to 7.31), although there were only 3 subjects with tics in each group. The age-corrected rates for Tourette's disorder were almost the same in males (4.85%; 95% CI = 4.78 to 4.91) and females (4.66%; 95% CI = 4.59 to 4.72).

The age-corrected rates for the combined OC spectrum disorders (OCD + tic disorders + BDD) are shown in Table 4. The age-corrected rate for OC spectrum disorders considered as a single entity was slightly higher in RF – SC patients than RF + SC patients. Of note, the age-corrected rate for OC spectrum disorders combined was 8 times higher in the total RF group (20.89%) than in controls (2.56%).

Relationship Between the Age at Onset of Rheumatic Fever and Psychiatric Symptoms

Fifteen patients (25%) in the total RF group (N = 59) received at least 1 psychiatric diagnosis (OCD, subclinical OCD, tic disorders, or BDD). In 80% of these cases (N = 12), symptoms started at the same age or after the first RF episode, whereas in the remaining 3 patients (20%), symptoms started before the onset of RF. Among

Table 3. Rates for Tic Disorders in Rheumatic Fever Patients and Controls*

	Tourette's Disorder				Chronic Tic Disorder (CTD)				Transient Tic Disorder				Tourette's Disorder + CTD			
Patient Group	Raw Rate (%)	N	Age-Corrected Rate (%)	SE	Raw Rate (%)	N	Age-Corrected Rate (%)	SE	Raw Rate (%)	N	Age-Corrected Rate (%)	SE	Raw Rate (%)	N	Age-Corrected Rate (%)	SE
RF – SC (N = 31)	6.45	2	7.26	.05	3.20	1	7.14 **a**	.07	3.20	1	3.33 **c**	.03	9.67	3	14.39 **e**	.08
RF + SC (N = 28)	7.14	2	7.41	.05	3.57	1	3.85 **b**	.03	17.85	5	19.62 **d**	.08	10.71	3	11.11 **f**	.06
Total RF group (N = 59)	6.77	4	7.17	.03	3.38	2	6.26	.04	10.26	6	11.22	.04	10.16	6	13.43	.06
Controls (N = 39)		0				0				0				0		

*The comparisons **ab**, **cd**, **ef** and all the comparisons between the total RF group versus controls are significantly different according to the comparisons of their 95% CI.
Abbreviations: RF = rheumatic fever, SC = Sydenham's chorea, RF – SC = rheumatic fever patients without SC, RF + SC = rheumatic fever patients with SC, SE = standard error.

Table 4. Rates for Obsessive-Compulsive Spectrum Disorders Combined in Rheumatic Fever Patients and Controls*

Patient Group	Raw Rate (%)	N	Corrected Rate (%)	SE	95% CI
RF – SC (N = 31)	12.90	4	20.65	.09	20.5 to 20.8
RF + SC (N = 28)	17.85	5	19.55	.08	19.3 to 19.7
Total RF group (N = 59)	15.25 **a**	9	20.89 **c**	.07	20.7 to 21.0
Controls (N = 39)	2.56 **b**	1	2.56 **d**	.02	2.51 to 2.60

*Comparison **ab** is significantly different (p = .048) and comparison **cd** is significantly different according to the 95% CI.
Abbreviations: RF = rheumatic fever, SC = Sydenham's chorea, RF – SC = rheumatic fever patients without SC, RF + SC = rheumatic fever patients with SC, SE = standard error.

patients with SC, 9 (90%) had onset of OC spectrum symptoms at the same age or after the RF; only 1 (10%) had onset before the onset of the RF. Among the RF – SC probands, 2 (40%) had psychiatric symptoms before and 3 (60%) after the onset of the RF episode. Five of the 6 cases with transient tics belonged to the RF + SC group, and in all cases presenting transient tics, the tics started during or after the SC episode.

DISCUSSION

We investigated the frequencies of some OC spectrum disorders, more specifically OCD, tic disorders, and BDD, in non–acute-phase RF patients (with or without SC) compared with a control group. As hypothesized, RF + SC patients reported higher frequencies of OCD and subclinical OCD when compared with controls. Similarly, the total RF group (with or without SC) presented higher frequencies of tic disorders when compared with controls. These findings in non–acute-phase RF patients replicate findings from previous studies done with acute-phase patients.[7–9,14] In addition, our findings suggest that the incidence of BDD may also be higher in RF patients. The relative risk of OC spectrum disorders (OCD, tic disorders, and BDD) considered as a single entity[29] was 8 times higher in RF patients than in controls.

Regarding OCD, our findings that the age-corrected rates were higher in RF + SC patients when compared with controls are in accordance with previous studies.[7,8,14] Nevertheless, our rates may be underestimated, considering that in our sample, psychiatric symptoms that had remitted after the acute episode might not have been recalled by our patients (memory bias). In fact, some of our patients had also participated in the sample studied by Asbahr et al.[7] Reviewing their medical records, we confirmed that during the acute phase some patients had presented obsessive-compulsive symptoms that were not reported in our interview, which was completed 3 to 5 years after the acute phase of the illness (A.G.H. and F. Asbahr, M.D., Ph.D., unpublished data, February 2003).

This study also confirms previous reports of higher rates of tic disorders in RF patients.[8,9,14] The most impressive result was that the age-corrected rate for tic disorders (Tourette's disorder + chronic tic disorder) was 13 times higher in the total RF group. Furthermore, the rate of tic disorders was higher in the RF – SC group compared with the RF + SC group. In contrast, the RF + SC patients more frequently reported transient tic disorder. Considering that all patients with transient tics had their symptoms occurring simultaneously with SC, these results reinforce the idea that some tics may be part of the SC symptomatic expression.[10,12,13] On the other hand, tic disorders such as Tourette's disorder and chronic tic disorder, reported more frequently in RF – SC, could represent alternative (CNS) manifestations of RF.

Consistent with the literature on tic disorders,[30] the age-corrected rates for tic disorders were higher in males than females. However, the age-corrected rate for Tourette's disorder was similar for males and females, suggesting that RF might increase the risk for Tourette's disorder in females, since Tourette's disorder is known to be 3 to 5 times more frequent in males.[31–33] In addition, considering that males are more prone to tic disorders and that our sample had fewer males, it would be possible to expect higher absolute numbers of tic disorders in RF patients if they had been sampled from the general RF popu-

lation (i.e., non-biased), which has higher rates of males. For instance, a recent article about RF patients in India found a male/female ratio of 1.15,[34] whereas ours was 0.78. The probable explanation for this difference is that our sample was selected to have 50% of RF patients with and 50% without SC, whereas most of the studies whose patients are selected randomly report higher ratios of males/females, with SC being 3 times more frequent in females. Thus, our results could be considered conservative, as we could have found higher figures of tic disorders.

The age-corrected rates for the combined OC spectrum disorders (OCD + tic disorders + BDD) were also higher in the total RF group than in controls. BDD has long been speculated to belong to the OC spectrum.[16,20] There has been one family study[19] reporting an association between BDD and OCD. Considering the reports that at least some types of OCD are genetically linked to tic disorders,[18,35] it is possible that the OC spectrum disorders investigated in this study could be different phenotypic manifestations of RF that share some underlying pathophysiologic mechanisms. In acute-phase RF patients, these manifestations could be the result of an abnormal immune process related to the activity of the disease. In the non–acute-phase RF patients, it is not possible to exclude the fact that the acute changes could have persisted or triggered other changes that are etiologically important. In fact, cardiac tissue changes continue to develop long after the initial episode of RF.[2] The same can be considered for arthritis, since mild arthritis is present in RF later in life. Finally, it is widely accepted that female patients with SC present the clinical picture chorea gravidarum, suggesting that even the CNS suffers long-lasting vulnerabilities.[36] Furthermore, Faustino et al.[37] found persistent changes, detected by MRI, in the caudate of 3 (16%) of 19 SC patients.

However, the fact that in some patients the OC spectrum disorders started before the onset of RF suggests alternative hypotheses. A plausible explanation is that these spectrum disorders might share a common genetic vulnerability with RF. If that were the case, then relatives of RF probands should have higher rates of OC spectrum disorders independent of whether the RF probands had any OC spectrum manifestation. A family study is needed to examine this possibility. Thus, RF patients bearing genetic susceptibility for idiopathic spectrum disorders could have them triggered by the RF episode, whereas patients without this putative genetic susceptibility would not.

Finally, a preliminary study suggests that the rates of RF in relatives of children who develop OCD and tics after a streptococcal infection are increased. These disorders have been named PANDAS after the eponym Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections.[38] These findings raise the possibility that some cases of PANDAS may be part of the RF spectrum of manifestations. If true, the findings of this study may represent additional evidence for an association between streptococcal infections and OC spectrum disorders such as OCD, tic disorders, and BDD.

Limitations of the Study

The major limitation of this study is its small sample size. In addition, patients were selected from a tertiary hospital, which receives more severe cases. Furthermore, we cannot exclude a sampling bias, as the patients who accepted to participate in the study could have been self-selected due to higher presence of psychopathology. Therefore, these results should be considered preliminary and should be replicated in larger samples before generalizations are made.

We used group matching for the selection of patients,[39] which may explain why the mean ages of RF and control probands were different. However, using survival analysis to obtain age-corrected rates of illness should have minimized this difference in age.

Clinical Implications and Conclusion

This is the first report of OCD, tic disorders, and BDD in patients with non-acute rheumatic fever. If these findings are confirmed, clinicians should be careful to investigate and recognize psychiatric symptoms in RF patients, allowing early diagnosis and treatment when necessary. Further neuroimmunologic and genetic studies should be performed to elucidate the mechanisms through which RF confers a higher risk for OC spectrum disorders in these patients. These studies may open new opportunities for the treatment of these disorders and the knowledge of their relationship with streptococcal infections.

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