Anxiety Disorders and Rheumatic Fever: *Is There an Association?*

By André Augusto Anderson Seixas, MD, Ana Gabriela Hounie, MD, PhD, Victor Fossaluza, BS, Mariana Curi, MSc, Pedro Gomes Alvarenga, MD, Maria Alice De Mathis, BS, Maria Eugênia De Mathis, BS, Homero Vallada, MD, PhD, David Pauls, PhD, Carlos Alberto de Bragança Pereira, PhD, and Eurípedes Constantino Miguel, MD, PhD

ABSTRACT

Introduction: Findings suggest that obsessive-compulsive disorder (OCD) and related disorders, referred to as obsessive-compulsive spectrum disorders (OCSDs), are more common in patients with rheumatic fever (RF).

Objectives: To determine whether RF or Sydenham's chorea increases the probability of anxiety disorders in the relatives of individuals with RF with and without SC.

Methods: This was a case-control family study in which 98 probands and 389 first-degree relatives (FDRs) were assessed using structured psychiatric interviews. A Poisson regression model was used to determine whether the presence of any disorder in one family member influences the rate of disorders in the remaining family members.

Results: Generalized anxiety disorder (GAD) occurred more frequently in the FDRs of RF probands than in those of control probands (P=.018). The presence of RF, GAD, or separation anxiety disorder in one family member significantly increased the chance of OCSDs in another member of the family.

FOCUS POINTS

- Generalized anxiety disorder occurred more frequently in the first-degree relatives of rheumatic fever probands than in those of control probands.
- Clinicians should be aware of the possible familial relationship between generalized anxiety disorder and obsessive-compulsive spectrum disorder in their rheumatic fever patients and their family members.
- Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders are more common in patients with rheumatic fever.

Drs. Seixas and Alvarenga are psychiatrists in the Department of Psychiatry at the University of São Paulo Medical School in Brazil. Dr. Hounie is postdoctoral student in the Department of Psychiatry at the University of São Paulo Medical School. Mr. Fossaluza is postgraduate student at the Mathematics and Statistics Institute at University of São Paulo. Ms. Curi is PhD Professor at Institute of Mathematics and Computer at Science, University of São Paulo, Campus São Carlos. Ms. M.A. De Mathis is postgraduate student in the Department of Psychiatry at the University of São Paulo Medical School. Ms. M.E. De Mathis is a psychologist in the Department of Psychiatry at the University of São Paulo Medical School. Drs. Vallada and Miguel are associate professors in the Department of Psychiatry at the University of São Paulo Medical School. Dr. Pauls is professor of psychiatry (genetics) at Harvard Medical School and director of the Psychiatric and Neurodevelopmental Genetics Unit at the Center for Human Genetic Research at Massachusetts General Hospital in Boston. Dr. Pereira is full professor at the Mathematics and Statistics Institute at University of São Paulo.

Faculty Disclosures: The authors do not have an affiliation with or finanical interest in any organization that might pose a conflict of interest. This study was based on a doctoral thesis and was supported by grants provided to Dr. Hounie (FAPESP grant no. 98/15013-9) and to Dr. Miguel (FAPESP grant no. 99/12205-7).

Acknowledgments: The authors thank the many families participating in the study, as well as Fernando Akkerman, Marcos Salem, Maria Claudia Bravo, Juliana Belo Diniz, Priscila Chacon, Sérgio Broto, Yara Garzuzi, Rosemar Prota, and Daniela Dourado for their assistance in conducting the clinical evaluations.

Authors' note: Drs. Seixas and Hounie contributed equally to the final manuscript.

Submitted for publication: April 24, 2008; Accepted for publication: November 19, 2008.

Please direct all correspondence to: Ana Gabriela Hounie, MD, PhD, Instituto de Psiquiatria da Faculdade de Medicina da Universidade de São Paulo, (CEAPESQ-PROTOC) Rua Dr. Ovídeo Pires de Campos, 785, Cerqueira César, CEP: 05403010, São Paulo, SP, Brasil; Tel: 55-11-30696972, Fax: 55-11-30880842; E-mail: anah@protoc.com.br.

Conclusion: We found familial aggregation among RF, GAD, and OCSDs. Clinicians should be aware of the possible familial relationship between GAD and OCSDs in their RF patients and their family members, which may suggest a genetic component between them. Further studies on OCD should include anxiety disorders to better define OCD spectrum.

CNS Spectr. 2008;13(12):1039-1042,1044-1046

INTRODUCTION

Rheumatic fever (RF) is an autoimmune disorder that occurs after infection with specific strains of group A β-hemolytic streptococci.[1] The disorder is highly prevalent in developing countries such as Brazil, where the prevalence is 3.6/1,000 inhabitants.[2] However, the prevalence of RF has been increasing in developed countries such as the United States,[3] resulting in renewed interest in RF research. A diagnosis of RF is made based on the presence of two major or one major and two minor Jones' criteria.[4] The major criteria are as follows: carditis; erythema marginatum; subcutaneous nodules; Sydenham's chorea (SC); and arthritis. The following are the minor criteria: fever; polyarthralgia; reversible prolongation of the PR interval on the electrocardiogram; rapid erythrocyte sedimentation rate; evidence of previous β-hemolytic streptococcal infection; and a history of RF. The only major criteria sufficient to confirm a diagnosis of RF is SC, which is the central nervous system (CNS) manifestation of RF.[5-8]

Although the exact physiopathology of RF remains unknown, molecular mimicry between streptococcal and human proteins constitutes the most widely accepted theory to explain the autoimmunity occurring in this disorder. In this mimicry process, T cells recognize self-antigens that have some degree of homology with streptococcal antigens and provide assistance to autoreactive B cells. In RF, the humoral and cellular arms of the immune response play a role in autoimmunity. In fact, the various manifestations of RF, such as arthritis, carditis, and SC, can be mediated by dominance of either B cells or T cells in the immune response.[9] In a recent study,[10] it was suggested that cross-reactivity between specific streptococcal surface antigens are implicated in the generation of cross-reactive immune responses and brain-derived ganglioside in individuals with SC. Therefore, antibody-mediated signal transduction (eg, transduction via calcium calmodulin-dependent protein kinase II), together with the subsequent disruption of neurotransmitter synthesis and release, might constitute one mechanism involved in the immunopathogenesis of SC and other CNS manifestations of RF.[10,11]

Over the centuries, various psychopathological manifestations, notably obsessive-compulsive disorder (OCD) and related disorders, have been described in RF patients.[8,12] These OCD-related conditions, which include disorders of similar phenotypes and with similar putative genetic backgrounds,[13-16] have been referred to as obsessive-compulsive spectrum disorders (OCSDs),[17] encompassing a range of conditions, including tic disorders (TDs), body dysmorphic disorder (BDD), and grooming behaviors (trichotillomania, onychophagia, and skin picking).[13,14,16-18]

A number of studies have reported higher frequencies of obsessive-compulsive symptoms (OCS), OCD, and TDs in pre-pubertal children with RF, with or without SC.[19-23] These studies focused primarily on patients in the acute phase of RF. Subsequent studies investigated the relationship between RF and OCSD in patients in the non-active phase of RF, assessing adult patients with a history of RF. In one controlled study[24] and two uncontrolled studies,[25,26] higher frequencies of OCS were reported for individuals with RF, with or without SC, although this was not found in another controlled study.[27] Two additional studies,[7,28] although not designed with this specific aim, reported elevated rates of OCSDs in patients who were no longer in the acute phase of RF.

These findings raise several possible hypotheses. In addition to SC, psychiatric symptoms are part of neuropsychiatric manifestations of RF. These psychiatric manifestations can occur in patients with RF independently of the presence of SC. RF activity is not necessary for the expression of psychiatric symptoms. After the end of the acute phase of RF, acute changes persist or trigger other alterations that increase the susceptibility to these disorders. OCSDs share a common genetic vulnerability with RF.[25]

To test this last possibility, Hounie and colleagues[7] performed a case-control family study assessing 250 first-degree relatives (FDRs) of RF probands and 138 FDRs of controls. They reported significantly higher rates of OCSDs among the FDRs of the RF probands than among

those of the controls, a finding that is consistent with the hypothesis that a familial relationship exists between OCSDs and RF.[8] The principal goal of this study was to report findings regarding the rates of anxiety disorders in the FDRs of patients in the aforementioned cohort in order to investigate a possible familial aggregation of anxiety disorders and RF.

METHODS

The data evaluated in the present study were derived from a previous case-control family study in which the study sample consisted of RF probands and their FDRs.[7] The study methodology has previously been described in detail.[7,8] In brief, case probands and control probands were recruited from two clinics at the University of São Paulo School of Medicine Hospital das Clínicas: the RF Outpatient Clinic and the Orthopedic Outpatient Clinic, respectively. Probands who agreed to participate and gave permission to contact their FDRs were enrolled in the study. A total of 126 individuals were invited to participate. The final sample consisted of 98 probands (31 RF probands without SC; 28 RF probands with SC; and 39 control probands without RF or SC) and 389 FDRs (251 FDRs of RF probands and 138 FDRs of control probands).

The Medical Ethics Committee of the University of São Paulo School of Medicine approved the study. All patients gave written informed consent only after the study had been thoroughly described to them. Minors gave their assent and their parents or legal guardians gave written informed consent for their participation.

Clinical Assessment

Demographic and clinical characteristics of 100% of the probands were obtained through direct interview. Face-to-face interviews were conducted with all probands and with the majority of their FDRs (face-to-face interviews in 83% of the relatives). If FDRs were unavailable for direct interview, they were interviewed by telephone if possible (4% of the cases). Otherwise, a family history questionnaire was applied to another relative (indirect interview, 13% of the cases). There was no statistically significant difference on the type of interview between the groups.

Socioeconomic classes were defined as A, B, C, D, or E, based on a structured interview for Brazilian standards, and marital status was classified as married, never married, divorced, or widowed. Educational level was assessed based on the number of years of schooling. All lifetime psychiatric diagnoses were made according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. The interviewers were either psychologists or psychiatrists trained in order to ensure consistency. The interviewers were blinded as to the group to which each proband pertained. In addition, in all FDR interviews, the interviewers were blinded as to the diagnosis/diagnoses of the proband. Subjects <16 years of age were interviewed by trained research assistants using the Kiddie Schedule for Affective Disorders and Schizophrenia, epidemiological version,[29] whereas those >16 years of age were assessed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders, patient edition.[30] Additional modules for the diagnosis of TDs (Tourette syndrome, chronic TD, and transient TD) and grooming behaviors (trichotillomania, onychophagia, and skin picking) were included. The Yale-Brown Obsessive Compulsive Scale and the Yale Global Tic Severity Scale were used to assess the presence and severity of OCS and tics.[31,32]

Data Analysis

All characteristics of and variables in case probands, control probands, and their respective FDRs were compared using the χ^2 test with Yates correction and Bayesian analysis for categorical data.[33,34] Bayesian analysis produces an e-value, which corresponds to the *P*-value of classical statistics. To determine whether the rates of generalized anxiety disorder (GAD) or other anxiety disorders were influenced by the presence of disorders (including RF) in other family members, Poisson regression analysis was performed.[35,36] In this method, each family is considered a sample unit. All family members, whether they are RF probands or the FDRs of those probands, are included in the analysis. In addition, the influence that the number of family members has on the rate of disorders found in each family (ie, whether the higher rates of disorders found in larger families are merely coincidental) was evaluated. In order to confirm or refute our previous findings,[7,8] we re-analyzed our data with this alternative method of analysis to determine whether the presence of OCSDs in the FDRs was influenced by the presence of other anxiety disorders or of RF (with or without SC) in the remaining family members. All tests were two-tailed, with α=0.05. The Statistical

Package for the Social Sciences, version 11.0, and the program R: A language and environment for statistical computing, version 2.2.1, were used in the analyses.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the probands and FDRs have been described elsewhere.[7,8] In brief, there were no significant differences between the two groups regarding mean age (cases: 14.36±4.60 years; controls: 11.51±3.29; *t*-test (*df*=96)=3.33; *P*=.001), gender (44% of males in the case group x 24% in controls; χ^2=2.9; *df*=1; *P*=.09), marital status, or religion. However, the frequency of OCSDs (Tourette syndrome, chronic TDs, transient TDs, and BDD) was higher in the RF probands than in the control probands.

Frequency of Anxiety Disorders in FDRs of RF and Control Probands

The FDRs of RF probands presented GAD more frequently than did those of the control probands (*P*=.018; e-value=0.0056). In comparison with the rate of GAD observed in the FDRs of control probands (0%), those found for the FDRs of RF probands with SC were higher (8%; *P*=.02499; e-value=0.0256), as were those found for the FDRs of RF probands without SC (7%; *P*=.0143; e-value=0.0153). The rate of GAD did not differ significantly between the FDRs of RF probands with SC and those of RF probands without SC (e-value=0.9589). In addition, there were no significant differences between the FDRs of RF probands and the FDRs of control probands, in terms of the frequencies of other anxiety disorders (Table 1).

The Role of RF and Psychiatric Disorders in the Expression of GAD

The risk of GAD in another family member was higher when at least one FDR of the proband presented RF (*P*=.0189), specific phobia (*P*=.0156), or BDD (*P*=.0182) (Table 2). The number of family members tended to influence the presence of GAD in an FDR (ie, the chance of one family member having GAD was found to be greater in families with more members than in families with fewer members [*P*=.0523]).

The Role of RF and Psychiatric Disorders in the Expression of OCSDs

Aggregated Risk of OCSDs

Table 2 shows that the variables having the greatest influence on the combined rate of OCD and TDs (Tourette syndrome, chronic TD, and transient TD) in one family member were the diagnoses (in another family member) of RF (*P*=.0041), SC (*P*=.0633), GAD (*P*=.0074), and separation anxiety disorder (*P*=.0382). The number of members per family did not influence the results (*P*=.4464).

When we expanded the analysis to include OCD, TDs, and BDD (Table 2), we found that the

TABLE 1.
Comparison of the Frequencies of Anxiety Disorders in FDRs of RF and Control Probands

Anxiety Disorders	FDRs of RF probands	%	FDRs of Control Proband	%	e-value*	P-value†
Panic	9	3.6	2	1.4	0.4537	0.3868
Agoraphobia	14	5.6	4	2.8	0.4654	0.3679
Specific phobia	32	12.7	23	16.7	0.5748	0.4437
Social phobia	23	9.2	16	11.6	0.7507	0.6076
SEPAD§	11/63	17.5	4/42	9.5	0.5045	0.4779
GAD¶	14/188	7.5	0/96	—	0.0056‡	0.0188‡

* χ^2 test with Yates correction.
† Bayesian analysis.
‡ Statistically significant.
§ Assessed only in subjects <16 years of age ("n" in the denominator).
¶ Assessed only in subjects ≥16 years of age ("n" in the denominator).

FDRs=first degree relatives; RF=rheumatic fever; SEPAD=separation anxiety disorder; GAD=generalized anxiety disorder.

Seixas AAA, Hounie AG, Fossaluza V, et al. *CNS Spectr.* Vol 13, No 12. 2008.

Continued on page 1044

Continued from page 1042

risk of TDs, OCD, or BDD (at least one present in a single individual) was elevated by the presence (in another family member) of RF (*P*=.0033), SC (*P*=.0307), GAD (*P*=.0021), or separation anxiety disorder (*P*=.0340). The risk for those disorders was not influenced by the number of members per family (*P*=.3032).

When we further expanded the analysis to include grooming behaviors (trichotillomania or skin picking) in the spectrum concept (Table 2), we identified the following as risk factors (when present in another family member): RF (*P*=.0005); SC (*P*=.0464); GAD (*P*=.0028); and separation anxiety disorder (*P*=.0454). The number of family members did not influence the results (*P*=.2728).

DISCUSSION

We have investigated the frequencies of anxiety disorders (panic disorder, agoraphobia, specific phobias, social phobia, separation anxiety disorder, and GAD) in FDRs of patients with RF (with and without SC) and in FDRs of controls. The FDRs of RF probands (with or without SC) presented GAD more frequently than did those of control probands. The presence of GAD in a given family member was independent of the presence of RF in the same individual. If the FDRs had presented GAD only in comorbidity with RF, we could speculate that GAD is a direct consequence of RF. However, the fact that the frequency of GAD was higher in FDRs of RF probands without RF suggests familial aggregation. Familial aggregation can be a consequence of genetic or environmental factors, and family studies are not capable of distinguishing between the two in terms of their influence on the phenotype.

The frequencies of the other anxiety disorders assessed were not found to be higher in the FDRs of RF probands than in those of the control probands. It would have been interesting to investigate whether the higher frequency of GAD in FDRs was enhanced by the presence of GAD in probands. That analysis, however, would have been limited by the fact that children and adolescents, still at risk for developing GAD, accounted for a large proportion (n=37/59; 63%) of the proband sample. In fact, there were no cases of GAD in the control group. Therefore, we used an alternative statistical approach, Poisson regression analysis, which deals with rare events. We further investigated whether the rates of GAD were influenced by the presence of RF or other disorders in the other FDRs. We found that, when present in one family member, RF, as well as BDD and specific phobias, increases the risk of GAD in the remaining relatives.

We examined the influence that various disorders in a given family member have on the expression of OCSDs in other members of the same family. We found that RF, SC, GAD, or separation anxiety disorder in one family member significantly increased the risk of the expression of OCSDs in another member of the family

TABLE 2.
The Role of Rheumatic Fever, Sydenham's Chorea, and Psychiatric Disorders in One Family Member and the Expression of GAD, OCD, Tics Disorders, BDD, or OCSD in Their Relatives

Response	*Variable*	*Risk*	*P-value**
GAD	RF	1.7051	.0189†
	Phobia	0.6432	.0156†
	BDD	1.1385	.0182†
	n ind.	–0.5350	.0523
	Intercept	–2.2551	.011
OCD + TD	RF	0.6988	.0041†
	CS	0.4616	.0633
	GAD	0.4706	.0074†
	SEPAD	0.3449	.0382†
	n ind.	0.0537	.4464
	intercept	–1.8641	4.23–06
OCD + TD + BDD	RF	0.6704	.0033†
	SC	0.5015	.0307†
	GAD	0.4901	.0021†
	SEPAD	0.3353	.0340†
	n ind.	0.0664	.3032
	Intercept	–1.7956	2.03–06
OCD + TD + BDD + Grooming Behaviors‡	RF	0.7563	.0005†
	SC	0.4506	.0464†
	GAD	0.4776	.0028†
	SEPAD	0.3162	.0454†
	n ind.	0.0701	.2728
	Intercept	–1.8483	8.3–07

*Poisson regression analysis.
‡ Grooming behaviors=trichotillomania and skin picking.
† Statistically significant.

GAD=generalized anxiety disorder; RF=rheumatic fever; SC=Sydenham's chorea; BDD=body dysmorphic disorder; SEPAD=separation anxiety disorder; Phobia=specific phobia; OCD=obsessive-compulsive disorder; TDs=tic disorders; n ind.=number of individuals (per family).

Seixas AAA, Hounie AG, Fossaluza V, et al. *CNS Spectr.* Vol 13, No 12. 2008.

(Table 2). Therefore, using an alternative statistical approach, we confirmed the finding of our previous study: that there is a familial association between RF and OCSDs.[8] It is noteworthy that the familial association of GAD and OCSDs in the FDRs of RF probands reported here parallels previous findings of higher rates of GAD and OCSDs in relatives of OCD probands,[16,37] although those rates were higher among the FDRs of OCD probands than among the FDRs of the RF probands evaluated in the present study.[16,37]

Nestadt and colleagues[16] found the frequency of GAD and agoraphobia to be higher among the relatives of individuals with OCD, regardless of whether any of those relatives had OCD. Interestingly, no significant difference was found between the relatives of OCD probands and those of controls, in terms of the rates of specific phobia. Black and colleagues,[38] in a family study of OCD, found the frequency of anxiety disorders to be higher in the relatives of individuals with OCD than in those of control individuals (30% vs 17.1%). This difference was primarily attributable to the frequency of GAD in those same two groups (21.7% and 12.4%, respectively). Data from previous OCD family studies[13,14,18] demonstrate that the rates of TDs, BDD, and grooming behaviors (trichotillomania, onychophagia, and skin picking) are higher among the FDRs of OCD probands than among those of controls.

We also found that, in addition to RF and SC, GAD or separation anxiety disorder in one family member significantly increases the chance of the expression of OCSDs in another family member. Black and colleagues[38] also found that the offspring of individuals with OCD were significantly more likely to have certain anxiety disorders, including separation anxiety disorder, than were the offspring of control individuals, suggesting that separation anxiety disorder has a strong relationship with the OCD phenotype.[39] Therefore, it seems that RF, GAD, and OCSDs share common vulnerability genes. Following this line of research, we found association between two polymorphisms in the promoter region of the tumor necrosis alpha gene and OCD,[40] polymorphisms that have been also associated with RF.[41] Further molecular genetic studies should be performed in this type of samples. Possible limitations of the present study include the small sample size and the fact that all probands were recruited from a tertiary-care hospital, which affects the external validity of the study.[8] Another potential limitation is the fact that all psychiatric diagnoses were determined from retrospective data and part of the sample, although a minority, was interviewed by phone and from family history questionnaire, and might therefore represent underestimates of the true rates of illness. Although interviews were extensively trained for diagnostic procedures, we had no reliability analysis for GAD diagnoses. Finally, children and adolescents still at risk for developing GAD and OCSDs accounted for a large proportion (63%) of the proband sample. In addition, regarding the diagnosis, we did not assess overanxious disorder in children, which is the equivalent of GAD in adults. Since the percentage of children and adolescents was similar in the RF and control FDRs groups (25% and 30%, respectively), it is improbable that the investigation of this diagnosis would have altered the results. Future studies of this nature should involve samples with a wider age range and should assess all anxiety disorders that affect children. Another intriguing fact is that we found no GAD cases in the control group. This may have occurred due to mere chance, as interviewers and instruments were the same for both groups. In order to understand the finding, we revised all diagnoses of GAD, in both groups. When we looked for subclinic diagnoses of GAD, the difference is still the same, adding only one subclinic diagnosis of GAD in FDRs of the RF group and two subclinic cases in the FDRs of controls.

In view of the fact that the rates of other psychiatric disorders (depression, bipolar disorder, schizophrenia, specific phobias, social phobia, and attention-deficit/hyperactivity disorder) assessed in our previous study[8] (data non-published) were not significantly higher in the FDRs of RF probands than in those of controls, there seems to be some specificity in the relationship between RF and the disorders under study (GAD and OCSD).

Repetitive behaviors (cleaning compulsions, tics and grooming behaviors) that occur as part of the normal repertoire can become exaggerated and behaviorally dominant in individuals with OCSDs or in those exposed to infectious agents. Excessive worries, which are dominant in GAD, can also direct individuals towards adaptive behaviors in threatening situations, possibly including infections. It is tempting to speculate that, as result of its evolutionary heritage, the immune system has developed a pathway to control such behaviors by activating worries, specific

thoughts or rituals as an adaptive process. In this context, our finding of an association between GAD and OCSD and RF might represent a dysfunctional relationship between the immune system and the CNS. However, the elevated frequency of GAD in these families could be secondary to the presence of a chronically ill family member (the RF proband) and therefore due to environmental influences. Since family studies are incapable of distinguishing the effects of genetic factors from those of environmental factors, adoption studies or molecular genetic studies are warranted in order to confirm our findings.

CONCLUSION

The repercussions of our findings are two fold. In addition to the familial relationship between OCSDs and RF, there might be familial aggregation of GAD and RF. Clinicians should systematically investigate and obtain information regarding GAD and OCSDs in their RF patients and in the family members of those patients. Given the additional evidence from OCD family studies, we speculate that RF, OCSDs, and GAD either are components of the same phenotypic spectrum or share some of the same liability. ***CNS***

REFERENCES

1. Stollerman GH. Rheumatic fever. *Lancet.* 1997;349:935-942.
2. Alves Meira ZM, de Castilho SR, Lins Barros MV, et al. Prevalence of rheumatic fever in children from a public high school in Belo Horizonte. *Ar Qbras Cardiol.* 1995;65:331-334.
3. Kaplan EL. The resurgence of group A streptococcal infections and their sequelae. *Eur J Clin Microbiol Infect Dis.* 1991;10:55-57.
4. Dajani AS, Ayoub E, Bierman FZ, et al. Guidelines for the diagnosis of rheumatic fever: Jones criteria, updated 1992. *Circulation.* 1993;87:302-307.
5. Mercadante, MT. Transtorno obsessivo-compulsivo: aspectos neuroimunológicos. *Rev Bras Psiquiatr.* 2001;23(suppl):31-34.
6. Mercadante MT, Hounie AG, Diniz JB, Miguel EC, Lombroso PL. The basal ganglia and immune-based neuropsychiatric disorders. *Psychiatric Annals.* 2001;31:534-540.
7. Hounie AG, Pauls DL, Mercadante MT, et.al. Obsessive-compulsive spectrum disorders in rheumatic fever with and without Sydenham's chorea. *J Clin Psychiatry.* 2004;65(7):994-999.
8. Hounie AG, Pauls DL, Rosário-Campos MC, et al. Obsessive-compulsive spectrum disorder and rheumatic fever: a family study. *Biol Psychiatry.* 2007;61:266-272.
9. Guilherme L, Fae K, Oshiro SE, Kalil J. Molecular pathogenesis of rheumatic fever and rheumatic heart disease. *Expert Rev Mol Med.* 2005;7:1-15.
10. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham's chorea. *Nat Med.* 2003;9:914-920.
11. Kirvan CA, Swedo SE, Kurahara D, Cunningham MW. Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. *Autoimmunity.* 2006;39:21-29.
12. Dale RC. Autoimmunity and the basal ganglia: new insights into old diseases. *Q J Med.* 2003;96:183-191.
13. Bienvenu OJ, Samuels JF, Riddle MA, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. *Biol Psychiatry.* 2000;48:287-293.
14. Grados MA, Riddle MA, Samuels JF, et al. The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study. *Biol Psychiatry.* 2001;50:559-565.
15. Miguel EC, Coffey BJ, Baer L, Savage CR, Rauch SL, Jenike MA. Phenomenology of intentional repetitive behaviors in obsessive-compulsive disorder and Tourette's disorder. *J Clin Psychiatry.* 1995;56:246-255.
16. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD family study. *Psychol Med.* 2001;31:481-487.
17. Hollander E. *Obsessive-Compulsive Related Disorders.* Washington, DC: American Psychiatry Press; 1993.
18. Pauls DL, Alsobrook JP 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. *Am J Psychiatry.* 1995;152:76-84.
19. Asbahr FR, Negrão AB, Gentil V, et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. *Am J Psychiatry.* 1998;155:1122-1124.
20. Asbahr FR, Ramos RT, Negrão AB, Gentil V. Case series: increased vulnerability to obsessive-compulsive symptoms with repeated episodes of Sydenham chorea. *J Am Acad Child Adolesc Psychiatry.* 1999;38:1522-1525.
21. Maia DP, Teixeira AL Jr, Quintao Cunningham MC, Cardoso F. Obsessive compulsive behavior, hyperactivity, and attention deficit disorder in Sydenham chorea. *Neurology.* 2005;64:1799-1801.
22. Mercadante MT, Filho GB, Lombroso PJ, et al. Rheumatic fever and co-morbid psychiatric disorders. *Am J Psychiatry.* 2000;157:2036-2038.
23. Swedo SE , Rapoport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am J Psychiatry.* 1989;146:246-249.
24. Alvarenga PG, Hounie AG, Mercadante MT, et al. Obsessive-compulsive symptoms in heart disease patients with and without history of rheumatic fever. *J Neuropsychiatry Clin Neurosci.* 2006;18:405-408.
25. Alvarenga PG, Floresi AC, Hounie AG, Petribu K, Franca MF. Obsessive- compulsive symptoms in non-active rheumatic fever. *Rev Bras Psiquiatr.* 2006;28:161.
26. Rahaman AU, Reddy YCJ, Prabhavathi, Pal PK. Obsessive-compulsive disorder in adults with rheumatic heart disease. *Acta Neuropsychiatrica.* 2007;19:118-121.
27. Asbahr FR, Ramos RT, Costa AN, Sasi RB. Obsessive-compulsive symptoms in adults with history of rheumatic fever, Sydenham's chorea and type I diabetes mellitus: preliminary results. *Acta Psychiatr Scand.* 2005;111:159-161.
28. Mercadante MT, Diniz JB, Hounie AG, et al. Obsessive- compulsive spectrum disorders in rheumatic fever patients. *J Neuropsychiatry Clin Neurosci.* 2005;17:544-547.
29. Orvaschel H, Puig-antich J. Kiddie-SADS-E: Schedule for affective disorder and schizophrenia for school-age children–epidemiologic. 4th ver. Ft. Lauderdale, Fl: Nova University, Center for Psychological Study; 1987.
30. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders-patient edition (SCID-I/P, Version 2.0). New York, NY: New York State Psychiatric Institute, Biometrics Research Department; 1995.
31. Goodman WK, Price LH, Rasmussen AS, et al. The Yale-Brown obsessive-compulsive scale: I. development use and reliability. *Arch Gen Psychiatry.* 1989;46:1006-1011.
32. 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;28:566-573.
33. Everitt BS. *The Analysis of Contingency Tables.* London, UK: Chapman & Hall; 1977.
34. Madruga MR, Pereira CA de B, Stern JM. Bayesian evidence test for precise hypotheses. *Journal of Statistical Planning and Inference.* 2003;6:345-362.
35. Nelder JA, McCullagh P. *Generalized Linear Models.* 2nd ed. London, UK: Chapman & Hall/CRC; 1989.
36. Paula GA. *Modelos de regressão com apoio computacional.* São Paulo, Brazil: Instituto de Matemática e Estatística–USP; 2004.
37. Miguel EC, Leckman JF, Rauch S, et al. Obsessive-compulsive disorder phenotypes: implications for genetic studies. *Mol Psychiatry.* 2005;10:258-275.
38. Black DW, Goldstein RB, Noyes R Jr, Blum N. Psychiatric disorders in relatives of probands with obsessive-compulsive disorder and co-morbid major depression or generalized anxiety. *Psychiatric Genetics.* 1995;5:37-41.
39. Black DW, Gaffney GR, Schlosser S, Gabel J. Children of parents with obsessive-compulsive disorder–a 2-year follow-up study. *Acta Psychiatr Scand.* 2003;107:305-313.
40. Hounie AG, Cappi C, Cordeiro Q, et al. TNF-alpha polymorphism is associated with obsessive-compulsive disorder. *Neurosci Lett.* 2008 Jul 12. [Epub ahead of print].
41. Ramasawmy R, Faé KC, Spina G, et al. Association of polymorphism within the promoter region of the tumor necrosis factor-alpha with clinical outcomes of rheumatic fever. *Mol Immunol.* 2007;44:1873-1878.