CHAPTER 6

LACK OF ASSOCIATION BETWEEN ANTIPSYCHOTIC-INDUCED PARKINSONISM OR ITS SUBSYMPTOMS AND rs4606 SNP OF RGS2 GENE IN AFRICAN-CARIBBEANS AND THE POSSIBLE ROLE OF THE MEDICATION

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ABSTRACT

Background: Recent studies demonstrate an association between antipsychotic-induced parkinsonism (AIP) and rs4606 SNP of RGS2 gene in Jewish and African-Americans. The current study investigates the association between rs4606 and AIP or its subsymptoms (rest-tremor, rigidity and bradykinesia) in 112 psychiatric inpatients of African-Caribbean origin.

Methods: Presence of AIP, rigidity, bradykinesia and rest-tremor was measured by the UPDRS. We applied Chi-square (or Fisher Exact) and logistic regression analyses in several models including rs4606, age, gender, dose of antipsychotics and anticholinergics, and 2 other putatively functional SNPs in DRD2 (-141CIns/Del) and HTR2C (Cys23Ser) genes.

Results and conclusions: In contrast to recent literature, we find no evidence for an association between rs4606 and AIP or any of its subsymptoms. We hypothesize that the observed lack of association is due probably to differences in serotonin 2A-receptor affinities of the antipsychotics utilized (in contrast to the other published studies, the majority of our patients utilized typical antipsychotics).

INTRODUCTION

Antipsychotic-induced parkinsonism (AIP) is an acute movement disorder with three cardinal features: rigidity, bradykinesia, and rest-tremor. Several risk factors have been suggested to predispose to AIP such as old age, female gender, high antipsychotic dose, and hereditary predisposition [Al Hadithy et al., 2008; Caligiuri et al., 1999; Hirose 2006; Jabs et al., 2003].

Various neurotransmitter receptors may be involved in the etiology of AIP. AIP may be caused by the antagonistic effects of antipsychotics on nigrostriatal dopamine D2 receptors (DRD2) [Reynolds 2004]. The effects of DRD2 antagonism are however modulated by serotonin 2A and 2C receptors (HTR2A and HT2C, respectively) [Alex et al., 2005; Haleem 2006]. Antagonism of muscarinic acetylcholine M1 and M3 receptors (CHRM1 and CHRM3, respectively) may also lead to alleviation of AIP symptoms [Reynolds 2004].

DRD2, HTR2A, HTR2C, CHRM1 and CHRM3 receptors are G-protein coupled receptors that utilize G-protein molecules for intracellular signaling and second-messenger activation. The intracellular signaling of these receptors is regulated by proteins belonging to the family of Regulators of G-protein Signaling (RGS), which modulate the intrinsic GTPase activity and hence the duration and intensity of the intracellular signaling of these receptors [Greenbaum et al., 2007].

RGS2, a member of the RGS family, is involved in the intracellular signaling of HTR2A [Ghavami et al., 2004] and CHRM1 and CHRM3 [Bernstein et al., 2004; Tovey and Willars 2004] receptors. Polymorphisms (SNPs) affecting RGS2 functionality may therefore predispose to AIP.

Greenbaum et al. [2007 and 2008] have recently reported an association between RGS2 gene and AIP in Jewish, Caucasians, and African-American patients and have also shown that among the polymorphisms studied, the rs4606 exhibits the strongest association with AIP. The samples studied by Greenbaum et al. included subjects that received atypical antipsychotics; 76% of the subjects in the African-American and Caucasian sample and 41% in the Jewish sample [Greenbaum et al. 2008 and 2007, respectively].

As opposed to typical antipsychotics, all of the atypical antipsychotics have strong HTR2A binding affinities [Nasrallah 2008]. Since RGS2 is involved in the intracellular signaling mediated by serotonin 2A receptor (HTR2A), but not in the signaling mediated by dopamine D2 receptors (DRD2) [Ghavami et al., 2004], it is pharmacologically plausible that the possible effects of rs4606 are expressed only in those patients subjected to strong HTR2A antagonism.

We endeavored to test this hypothesis by examining the association between rs4606 and AIP, rigidity, rest-tremor, and bradykinesia in African-Caribbean inpatients, chronically treated with predominantly typical antipsychotics.

METHODS

Subjects

In this study we utilized data previously obtained from predominantly African-Caribbean subjects (Negroid or Mixed) [van Harten et al., 1996]. All of the study subjects were inpatients from Dr. Capriles Clinic (Curaçao, Dutch Antilles) and had received almost all of their psychiatric care from that hospital. The study protocol was approved by the Curaçao institutional review board and informed consent was obtained from each patient after full explanation of the study.

Patients were included in this study regardless the presence or absence of AIP and regardless the type or severity of their mental illness. Inclusion criteria were: (i) absence of organic and neurological disorders that could cause movement disorders, (ii) a history of neuroleptic use for at least three months, and (iii) informed consent.

Clinical data

AIP, rigidity, bradykinesia, and rest-tremor were measured with the motor examination part of the Unified Parkinson Disease Rating Scale (UPDRS) [Martinez-Martin et al., 1994]. All of the ratings were dichotomized in presence/absence of these symptoms. Since rest-tremor and rigidity are typical of AIP, a 'mild' involvement on one of these items led to AIP case definition [van Harten et al., 1996]. If no tremor or rigidity was present, then the cut-off point for the presence of AIP was at least one 'moderate' or two 'mild' scores on the other items [van Harten et al., 1996]. This more stringent criterion for items concerning bradykinesia and postural stability was chosen because these symptoms can also be caused by psychiatric syndromes or sedation.

Two medical doctors assessed patients' medical files for qualitative and quantitative information on the antipsychotic and anticholinergic medications used. The dose of the antipsychotic and anticholinergic medication was converted into chlorpromazine and benztropine equivalents, respectively [Davis 1976].

DNA genotyping

Genomic DNA was extracted from EDTA whole-blood and genotyping was conducted blind to the clinical status of the patients. Standard fluorogenic 5'-exonuclease TaqMan® assays were applied for the determination of rs4606 (+2971C>G; RGS2) and rs1799732 (-141CIns/Del; DRD2) polymorphisms. We have utilized the following primers and FAM/VIC probes for rs4606 (forward and reverse primers, TTT TAG TTT AGG ATT CAG TAA CAG TGA AGT GT

and GCA TTA CAT GAG ACA ACA GTA CTG ATG AT, respectively; NFQ probes, ACT ATG TGC AAG GGT ATT and CTA TGT GCA ACG GTA TT) and for -141C Ins/Del (forward and reverse primers; AAA ACA AGG GAT GGC GGA AT and CCC ACC AAA GGA GCT GTA CCT, respectively; TAMRA probes CCT ACC CGT TCA GGC CGGG and CCT ACC CGT TCC AGG CCGG). rs6318 (Cys23Ser, HTR2C) polymorphism was determined by a restriction fragment length polymorphism (RFLP) protocols, as previously described [Ebstein et al., 1997].

Statistics

Chi-square or, when appropriate, Fisher Exact tests were applied for the association analyses. These analyses were conducted twice: by genotype (C/C, C/G, or G/G) or by G-allele carriership status (carriers vs. non-carriers of the minor G-allele). Furthermore, step-wise logistic regression analyses were conducted for several models including age, gender, dose of antipsychotic and anticholinergic medication, as well as carriership status of rs4606 (+2971C>G; RGS2), rs1799732 (-141CIns/Del; DRD2) and rs6318 (Cys23Ser; HTR2C). Student's t-test was applied for analysis of continuous data.

Departure from Hardy-Weinberg Equilibrium was calculated for rs4606 and rs1799732 by the use of an online tool (http://www.tufts.edu/~mcourt01/Documents /Court%20lab%20-%20HW%20calculator.xls; accessed March 13th , 2008).
P-values <0.05 were regarded as significant.

RESULTS

Demographic and clinical features of the subjects

One hundred and twelve subjects (93 males and 19 females) met the inclusion criteria. Table 1 presents basic demographic and clinical features.

Table 1. Age, diagnosis (DSM-III-R), ethnicity, cocaine abuse, number and type of antipsychotics used, daily use of antipsychotics and anticholinergics (in mg/day chlorpromazine (CPZeq) and benztropine equivalents (BNZeq), respectively) on the day of assessment of the UPDRS, lifetime exposure to antipsychotics (kg CPZeq) and the frequency of subjects with concomitant anticholinergics, benzodiazepines, antidepressants, Antipsychotic-induced parkinsonism (AIP), rigidity (RIG), rest-tremor (TREM), and bradykinesia (BRAD).

	Total sample (112)	Male (93)	Female (19)
Age, years (mean ± SD)	48.5±13.5	47.2±13.1	55.0±13.6
Diagnosis, n (%) [1]			
Schizophrenia [2]	78 (80.4)	-	-
Affective disorder	5 (5.2)		
Dementia or other	14 (14.4)		
Cocaine abuse, n (%) [3]	18 (16.8)	-	-
Ethnicity, n (%) [4]			
Negroid	72 (72.0)	-	-
Mixed	23 (23.0)		
Other	5 (5.0)		
Number of patients using:			
0 antipsychotics	10	-	-
1 antipsychotic	75		
2 antipsychotics	25		
3 antipsychotics	2		
Antipsychotics/day, mg CPZeq/day (mean ± SD)	687.0±744.2	702.1±681.3	613.0±1018.0
Lifetime antipsychotics use [5]**, kg CPZeq (mean ± SD)**	3.6±3.2	3.9±3.3	2.6±2.6
Anticholinergics/day, mg BNZeq/day (mean ± SD)	1.5±2.2	1.7±2.3	0.8±1.5
Subjects with concomitant anticholinergics, n (%)	46 (41.1)	41 (44.1)	5 (26.3)
Subjects with concomitant benzodiazepines, n (%)	25 (22.3)	23 (24.7)	2 (10.5)
Subjects with concomitant antidepressants, n (%)	7 (6.3)	3 (3.2)	4 (21.1)
AIP present, n (%)	37 (33.0)	30 (32.3)	7 (36.8)
RIG present, n (%)	11 (9.8)	9 (9.7)	2 (10.5)
TREM present, n (%)	18 (16.0)	16 (17.2)	2 (10.5)
BRAD present, n (%)	27 (24.1)	20 (21.5)	7 (36.8)

[1] Data from 97 patients;
[2] Includes 295.1, 295.2, 295.3, 295.4, 295.6, 296.7, 295.9;
[3] Data from 107 patients;
[4] Data from 100 patients;
[5] Data from 83 patients (69 males + 14 females).

Genotype distribution, Hardy-Weinberg Equilibrium (HWE), and allele-carriership frequency

The genotype distributions and allele-carriership frequencies are reported in Table 2. The genotype distributions of rs4606 (RGS2) and -141CIns/Del (DRD2) are in consistency with Hardy–Weinberg Equilibrium (χ^2=0.0020, p=0.964 and χ^2=0.0305, p=0.861; respectively).

Association between rs4606 and AIP, rigidity, tremor, and bradykinesia

Table 2 represents the case/non-case ratios of AIP and its subsymptoms per allele-carriership status. Genotype-wise and allele-carriership wise analyses did not provide evidence for an association between rs4606 and AIP or its subsymptoms even after correction for age, daily use of antipsychotics and anticholinergics, and allele-carriership status of -141CIns/Del (DRD2) and Cys23Ser (HTR2C) polymorphisms.

Table 2. Genotype distribution, allele-carriership frequencies, case/non-case ratios of antipsychotic-induced parkinsonism (AIP), rigidity (RIG), rest -tremor (TREM), and bradykinesia (BRAD) per allele-carriership status.

Genetic variation	N (%)	Allele-carriership, N (%)	AIP+ : AIP–	RIG+ : RIG–	TREM+ : TREM-	BRAD+ : BRAD-
RGS2 rs4606						
C/C	49 (43.8)	*G* -allele *non-carriers*	18 : 31 (36.7%)	3 : 46 (6.1%)	8 : 41 (16.3%)	13 : 36 (26.5%)
C/G	50 (44.6)	*G* -allele *carriers* N (%): 63 (56.2%)	19 : 44 (30.2%)	8 : 55 (12.7%)	10 : 53 (15.9%)	14 : 49 (22.2%)
G/G	13 (11.6)					
DRD2 -141CIns/Del						
Ins/Ins	48 (42.9)	*Del*-allele non-carriers	14 : 34 (29.2%)	1 : 47 (2.1%)	6 : 42 (12.5%)	9 : 39 (18.8)
Ins/Del	50 (44.6)	*Del*-allele carriers N (%): 64 (57.1)	23 : 41 (35.9%)	10 : 54 (15.6%)	12 : 52 (18.8%)	18 : 46 (28.1%)
Del/Del	14 (12.5)					
HTR2C Cys23Ser						
Cys23/Cys23	49 (43.8)	*Ser*-allele non-carriers	18 : 52 (25.7%)	6 : 64 (8.6%)	11 : 59 (15.7%)	12 : 58 (17.1%)
Cys23/Ser23	50 (44.6)	*Ser*-allele carriers N (%): 63 (56.2)	19 : 23 (45.2%)	5 : 37 (11.9%)	7 : 35 (16.7%)	15 : 27 (35.7%)
Ser23/Ser23	13 (11.6)					

Cases and non-cases are denoted by + and –, respectively.

Comparison of age and the use of antipsychotics, anticholinergics and benzodiazepines

Mean age, chlorpromazine and benztropine equivalents, and the proportion of patients using anticholinergic medication did not differ significantly between carriers and non-carriers of the G-alleles or between subjects with and without AIP, rigidity, rest-tremor, or bradykinesia (data not shown). Furthermore, the frequency of patients using benzodiazepines did not differ significantly between cases and non-cases of bradykinesia or between carriers and non- carriers of the G-allele of rs4606 polymorphism (data not shown). Stratification by gender did not alter any of the abovementioned findings.

The vast majority (>90%) of the inpatients studied were using typical antipsychotics (classical neuroleptics) and as shown in Table 1, only 10 out of the 112 (8.9%) subjects did not use an antipsychotic on the day of UPDRS assessment.

We have also applied 2x2 contingency tables to evaluate the possible effects of polypharmacy ($\leq$ 1 antipsychotic versus $\geq$ 2 antipsychotics) on AIP, rigidity, rest-tremor, or bradykinesia. We have also evaluated the distribution of subjects with $\leq$ 1 or $\geq$ 2 antipsychotics in relation to G-allele carriership. The comparisons made did not reveal any significant differences in the utilization patterns (data not shown).

DISCUSSION

Greenbaum et al. [2007] have recently reported a significant association between rs4606 of RGS2 gene and AIP (as measured by the Simpson Angus Scale, SAS) in Jewish schizophrenic patients. In a replication study, Greenbaum et al. [2008] have examined the association between rs4606 with AIP (measured by SAS as well) in 184 U.S. patients with schizophrenia (115 African-American, 69 Caucasian). The results of Greenbaum et al. [Greenbaum et al., 2008] support the association in the overall sample as well as in the African-American subsample.

The rs4606 polymorphism is a C→G SNP (+2971C>G) in the 3' untranslated regulatory region of the RGS2 gene and is known to reduce RGS2 mRNA stability and expression [Semplicini et al., 2006]. Greenbaum et al. [2008] have fully sequenced RGS2 in Jewish patients with and without AIP but could not find relevant SNPs other than the rs4606 and have suggested that the association of rs4606 AIP is biologically meaningful and is not a consequence of linkage disequilibrium (LD) with another functional variant.

Since LD is ethnicity-dependent and since African-Caribbean subjects have similar ethnic roots to those of African-Americans and native Africans [Page 1997], we endeavored in the current study to replicate the findings of Greenbaum et al. [2008 and 2007] in African-Caribbean subjects from the Dutch Antilles.

The present study evaluates the association between rs4606 and AIP, rigidity, rest-tremor, or bradykinesia (all measured by UPDRS) in subjects with a history of chronic treatment with antipsychotics. The clinical part (UPDRS and medication assessment) of the present study was conducted before 1996 [van Harten et al., 1996]. Therefore, the majority of the inpatients were treated with typical antipsychotics (classical neuroleptics). Because all of the subjects were inpatients from the only psychiatric hospital in the Dutch Antilles (Dr. Capriles Clinic), and because the natural boundaries of these islands provide a well-defined catchment area, a good documentation of the medications prescribed to the subjects was possible. Although therapeutic compliance is often low in patients using antipsychotics [Schorr et al., 2007], our subjects were fully compliant inpatients.

In the present study we find no evidence or support for a significant association between rs4606 and AIP or its subsymptoms, even after controlling for age, pharmacotherapy, and 2 SNPs in DRD2 and HTR2C genes (-141CIns/Del and Cys23Ser, respectively). Correction for the possible effects of these SNPs is indicated in our study, because these SNPs have been associated with AIP, rigidity, and bradykinesia in the same African-Caribbean sample [Al Hadithy et al., 2008].

There were no differences in age or in the utilization patterns of antipsychotics, anticholinergics, and benzodiazepines and the lack of association is therefore not likely to be caused by these potential confounders.

Although there are other explanations possible for the observed lack of association, a possible explanation for the observed lack of association probably lies in the differences between the types of the antipsychotics utilized by our patients and those utilized by Greenbaum et al. [2008 and 2007] patients.

In the replication study of Greenbaum et al. [2008], which included 115 African-Americans and 69 Caucasians, atypical antipsychotics were prescribed to at least 75.6% of the patients (25.0% risperidone, 27.2% olanzapine, and 23.4% clozapine) while only 24.4% of the patients were utilizing typical antipsychotics. The original study of Greenbaum et al. [Greenbaum et al., 2007] consisted of 121 patients, of whom 40.5% were treated with an atypical antipsychotic (risperidone in all cases) plus a typical antipsychotic. In our study population, more than 90% of the patients were using typical antipsychotics only.

This finding might be of considerable importance, since RGS2 has no effects on signaling mediated by dopamine D2 receptors (DRD2) [Ghavami et al., 2004], the major targets for the antipsychotic action of typical antipsychotics. RGS2 is however involved in the intracellular signaling mediated by serotonin 2A receptor (HTR2A) [Ghavami et al., 2004]. All of the atypical antipsychotics (and particularly risperidone) have strong HTR2A binding affinities [Nasrallah 2008]. Therefore, it is pharmacologically plausible that the effect of rs4606 on the biological functionality of RGS2 gene is translated to neurological effects only in those patients subjected to strong HTR2A antagonism.

AIP can be alleviated by antagonists of muscarinic M1 and M3 receptors (CHRM1 and CHRM3, respectively) and certain atypical antipsychotics (particularly

olanzapine and clozapine) are associated with low AIP incidence, partially due to their strong antimuscarinic affinities [Raedler et al., 2000; Raedler et al., 2003]. Since RGS2 is directly involved in CHRM1 and CHRM3 intracellular signaling [Bernstein et al., 2004; Tovey and Willars 2004], a second possible explanation may lie in the involvement of enhanced functioning of CHRM1 and CHRM3 due to the polymorphism. However, the proportion of subjects on concomitant anticholinergics was in our sample very similar to that of Greenbaum et al. [2007] (41.1% versus 40.9%, respectively).

A third possible explanation may be related to differences in LD patterns. Although such differences can not be excluded, our African-Caribbean subjects are ethnically similar to African-Americans and may hence have similar LD patterns to the African-Americans studied by Greenbaum et al. [2008].

A limitation of our study, next to the sample size, is that we did not correct for variation in the psychopathology of the patients. However, our study sample can be considered as homogenous, since the majority of the patients was of Afro-Caribbean origin and had schizophrenia. Additionally, the presence of organic and neurological disorders that may cause movement disorders was a stringent exclusion criterion. Since we followed our patients for ten years [van Harten et al., 2006], neurological diseases such as Morbus Parkinson would have been detected [Hausner 1983]. Furthermore, factors other than genetic polymophisms may also cause the parkinsonian symptoms. Tremor for example may be an essential tremor or may be induced by other drugs (e.g., antidepressants). However, antidepressants were used by only a few patients (6.3%). In addition, such tremors are predominantly postural and action tremors, whereas our trained rates examined the patients for rest tremor, which is more specifically related to antipsychotics and AIP.

Since bradykinesia might be caused by psychiatric symptoms or sedation, we utilized a more stringent cut-off point for case-definition (see Experimental Procedures, Clinical Data). Additionally, we evaluated the utilization of benzodiazepines in our sample and found that the number of patients using benzodiazepines does not differ significantly between bradykinesia cases and non-cases or between carriers and non- carriers of the G allele of rs4606 polymorphism.

In contrast to Greenbaum et al. [2008 and 2007] who measured AIP by SAS, we utilized UPDRS for the assessment of AIP, rigidity, rest-tremor, or bradykinesia. Although it is not specifically developed to measure AIP, several studies have utilized UPDRS for AIP measurement [Hassin-Baer et al., 2001; Jamora et al., 2007; Lera and Zirulnik 1999; van Harten et al., 1996; van Harten et al., 2006] and UPDRS is far more comprehensive and balanced than SAS, which has been criticized for overemphasizing rigidity (6 out 10 items measure rigidity, while only 1 item measures tremor) [Loonen and van Praag 2007].

In conclusion, the present study does not support an association between rs4606 and AIP or any of its subsymptoms. Although differences in LD patterns can not be excluded, a possible explanation lies more likely in the type of antipsychotics utilized. Our findings do not undermine the significance of RGS2 as a promising

candidate gene for AIP but plausibly underline the importance of integrating pharmacology into pharmacogenetics. Future studies in larger samples of patients receiving uniform antipsychotic and anticholinergic treatment are warranted to support our hypothesis.

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