Serotonin Transporter Gene Status and Electroconvulsive Therapy Outcomes: A Retrospective Analysis of 83 Patients

Keith G. Rasmussen, M.D., and John L. Black III, M.D.

Background: The length of the promoter polymorphism of the serotonin transporter gene has been shown to have an impact on response to some selective serotonin reuptake inhibitor antidepressants. Carrier status for the long allele has been associated with a better response to serotonin reuptake inhibitor antidepressant medications in most studies.

Method: We retrospectively studied whether the allelic state was also associated with differential response to electroconvulsive therapy (ECT). Eighty-three ECT patients treated for unipolar or bipolar depression (based upon the treating psychiatrist's DSM-IV diagnosis) between July 2006 and September 2007 had allelic status testing at our facility. We determined whether serotonin transporter gene allelic status was associated with several aspects of ECT treatment, such as seizure length/threshold, number of treatments in a series, and depression scale ratings.

Results: We found no significant associations.

Conclusions: We conclude that currently available serotonin transporter gene long/short promoter polymorphism allelic status determination should not be used to guide clinical decisions about ECT.

J Clin Psychiatry 2009;70(1):92–94

Received Feb. 6, 2008; accepted April 30, 2008. From the Department of Psychiatry and Psychology (Drs. Rasmussen and Black) and the Department of Laboratory Medicine and Pathology (Dr. Black), Mayo Clinic, Rochester, Minn.

The authors report no financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Keith G. Rasmussen, M.D., Department of Psychiatry and Psychology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (e-mail: rasmussen.keith@mayo.edu).

Many studies have found an association between the long (L) allele of the serotonin transporter gene (SLC6A4; OMIM 182138) promoter length polymorphism (either long-long [LL] or long-short [LS]) and favorable response to serotonin reuptake inhibitor medications.[1–4] In Asian populations, the L allele has been associated with lesser antidepressant effects.[5,6] A recent meta-analysis revealed a strong association between serotonin transporter allelic status and outcome in antidepressant medication studies.[7]

On the basis of these studies and the clinical availability of serotonin transporter allelic status testing at our institution, several of the psychiatrists in our department have been ordering this testing as part of the routine care of their patients to help guide antidepressant medication choice. A review of records in our electroconvulsive therapy (ECT) practice revealed that over the approximately 1-year period since inception of this testing, 84 ECT patients had allelic status assessed. As an exploratory endeavor, we analyzed several aspects of the ECT patients' treatments, such as number of treatments, seizure threshold, seizure duration, and depression rating scale scores, to see if there was a correlation with serotonin transporter promoter length polymorphism genotype or allele carrier status.

METHOD

Study Design

This project was approved by the institutional review board at the Mayo Clinic. We searched the names of all ECT patients treated between July 2006 (when the genotyping was made available at our institution) and September 2007. All patients had been diagnosed (according to DSM-IV) with either unipolar or bipolar depression by their treating psychiatrists. Not all ECT patients had the genotyping; rather, testing was ordered at the discretion of the primary referring psychiatrist. Of all patients who received ECT, 84 underwent allelic status testing. In 1 case, the result was not for SL, SS, or LL; rather, the patient had 1 L allele and another which was interpreted as aberrantly long. This patient's data were not included in our analysis. Thus, our sample size was 83 patients. No aspects of ECT

Table 1. Demographic and Clinical Characteristics of 83 ECT Patients

Variable	Sample
Genotype, n	
LL	21
SL	48
SS	14
Gender, n	
Male	20
Female	63
Age, mean (SD), y	46.5 (10.3)
Seizure threshold, mean (SD), %[a]	20.9 (15.8)
Motor length, mean (SD), s	48.8 (28.6)
EEG length, mean (SD), s	75.4 (38.3)
Placement of electrode, n	
Bifrontal	9
Bitemporal	28
Right unilateral	46
Number of treatments, mean (SD)	8.0 (2.3)
Baseline HAM-D score, mean (SD)	32.3 (7.5)
Discharge HAM-D score, mean (SD)	10.0 (6.8)
Baseline BDI score, mean (SD)	37.5 (11.2)
Discharge BDI score, mean (SD)	14.7 (11.5)

[a]Seizure threshold expressed as a percentage of the maximum charge (504 millicoulombs) on the Thymatron System IV.
Abbreviations: BDI = Beck Depression Inventory, ECT = electroconvulsive therapy, EEG = electroencephalogram, HAM-D = Hamilton Rating Scale for Depression, L = long allele of the serotonin transporter gene, S = short allele of the serotonin transporter gene.

practice, such as choice of electrode placement or even the choice to do ECT, were affected by genotyping results. However, genotype results may have been used to determine choice of pharmacologic agents.

For each of these patients, we recorded age, gender, allelic status (SL, SS, or LL), electrode placement for the first ECT treatment, motor and EEG seizure duration at the first treatment session, seizure threshold, number of treatments in the acute series, and baseline and day-of-discharge 24-item Hamilton Rating Scale for Depression (HAM-D)[8] and Beck Depression Inventory (BDI)[9] scores, which were usually but not always performed on the inpatients in this sample. The HAM-D was administered by nurses trained by staff who had extensive research experience with this instrument. The patients filled out the BDI themselves. Of note, many patients continued their acute course of ECT treatments as outpatients, so that the day-of-discharge HAM-D and BDI scores do not reflect end-of-treatment scores in those patients. These 2 depression scales are not administered routinely in the outpatient ECT practice. That is why day-of-discharge scores are used as posttreatment scores in this analysis.

ECT electrode placement was right unilateral, bitemporal, or bifrontal and was individually chosen for each patient by the ECT clinician in concert with the referring psychiatrist. We recorded motor seizure duration with the "cuff" technique and EEG duration with a 1-lead EEG channel on the machine, which was a Thymatron System IV (Somatics, LLC, Lake Bluff, Ill.). At the first session, seizure threshold was determined by stimulus titration utilizing the following settings on the Thymatron: 5%–10%–20%–40% for those patients under age 50; for those patients aged 50 years and over, we started at 10%. After the first session, stimulus charge was given at 1.5 times threshold for the 2 bilateral placements and 5 to 6 times threshold for unilateral placement.

Serotonin transporter length was determined by polymerase chain reaction followed by sizing analysis similar to that described by Kim et al.[5] using a method that was developed by the Nucleotide Polymorphism Laboratory at the Mayo Clinic Department of Laboratory Medicine and Pathology.

Data Analysis

Data were analyzed using analysis of covariance in which the independent variable of interest was the 3-level genotype. Analyses were repeated assuming dominant, recessive, and additive genotypes. In other words, analyses were repeated asking the following 3 questions: Is presence versus absence of the S allele, presence versus absence of the L allele, or number of S alleles better associated with the outcome variables than merely assuming 3 separate genetic groups? Age, gender, and electrode placement were included as covariates in all models. Response variables consisted of seizure threshold, motor and EEG seizure duration, number of treatments in the acute series, and the 2 depression rating scale outcome scores. For the latter 2 response variables (i.e., posttreatment BDI and HAM-D scores), baseline values were also included as covariates. p Values less than .05 were considered statistically significant.

RESULTS

Table 1 presents means and standard deviations for continuous variables and distributions for categorical variables. As can be appreciated, ours was a middle-aged, predominantly female cohort. All of the patients were of white race/ethnicity. Bifrontal electrode placement was used relatively infrequently in this cohort. Both the HAM-D and BDI scores showed robust improvement.

Table 2 presents the results of the statistical analyses. As noted, there were 4 models for assessing the possible relationship of genotype with the 6 outcome variables. No significant relationship existed for any of the models for any of the outcome variables.

DISCUSSION

Over time, one can expect more data to shed light on the relationship of serotonin transporter allelic status and depression outcomes. On the basis of the current pharmacology literature, a clinician may wish to select antidepressant medication according to serotonin transporter

Table 2. Significance Values From Statistical Analyses of Outcome Variables

Model	Motor Duration[a]	EEG Duration[a]	No. of Treatments[b]	Seizure Threshold[c]	HAM-D Score[d]	BDI Score[e]
LL[f]	.9528	.6579	.1590	.6446	.7541	.3664
LS[f]	.3183	.8900	.0885	.3987	.1819	.6756
S allele[g]	.3934	.4443	.7463	.1424	.5752	.4118
L allele[h]	.4741	.9387	.0824	.6843	.2465	.5320
Additive[i]	.8682	.5691	.2271	.4408	.6793	.3646

[a]Motor or EEG duration of first seizure in series.
[b]Number of treatments in the acute ECT series.
[c]Seizure threshold at first session of ECT.
[d]Discharge HAM-D score adjusted for baseline score.
[e]Discharge BDI score adjusted for baseline score.
[f]p Values correspond to comparisons with the SS genotype.
[g]p Values correspond to SS and SL genotypes combined compared to LL genotype.
[h]p Values correspond to LL and LS genotypes combined compared to SS genotype.
[i]p Values correspond to 0 vs. 1 vs. 2 S alleles.
Abbreviations: BDI = Beck Depression Inventory, ECT = electroconvulsive therapy, EEG = electroencephalogram, HAM-D = Hamilton Rating Scale for Depression, L = long allele of the serotonin transporter gene, S = short allele of the serotonin transporter gene.

allelic status. However, we find no basis for making clinical decisions in ECT practice based on these alleles. Furthermore, allelic status does not seem to predict speed of ECT response.

One might predict that because of selection bias, that is, reporting data only on patients referred for ECT, the allelic frequencies might be different from population norms. According to Lesch et al.,[10] we would expect the frequencies of LL, LS, and SS to be 0.32, 0.49, and 0.18, respectively. In our data set, the respective frequencies were very close, at 0.25, 0.58, and 0.17. Thus, we conclude that Hardy-Weinberg equilibrium is adequately reflected in our patient sample.

Limitations of this study include the fact that we did not test other polymorphisms known to exist in the serotonin transporter that might have an effect upon response. This choice was made because we wanted to focus upon the most-reported genotypes associated with antidepressant response and because of the clinical availability of the testing. It is possible that other genotyping techniques, such as LA/G, may yield different results. We also lack standardized information on other psychopathologic aspects of the patients, for example, more precise diagnostic subtyping of depressive states (e.g., dysthymia, personality disorders, unipolar or bipolar depression) or medication resistance data.

The study was not designed to rule out an association of ECT response and genotyping. Additionally, the timing of the assessments was not standardized across patients, nor was ECT technique (such as electrode placement or number of treatments). Thus, our claims of lack of an association between genotype and the various outcomes are modest at best.

Another limitation is the small sample size, especially of patients with the SS genotype. Furthermore, not all ECT patients received genotyping, so some type of selection bias is possible. We doubt that this is the case, as referring psychiatrists rotating on the inpatient units ordered the testing at their discretion. It has become something akin to "common wisdom" that this genotyping is relevant to antidepressant medication selection and not to ECT decision-making, at least in our institution. Thus, we strongly doubt that there was any significant difference between those ECT patients who had genotyping and those who did not. Finally, it is possible that patients' receiving serotonin transporter genotyping changed prescribing behaviors of the clinicians caring for these patients and that this change had some effect on recovery time, although that result was not apparent from this research.

In conclusion, this research found no evidence of an association between any of the measures studied, including treatment response as assessed by the depression rating scales, and the serotonin transporter promoter length polymorphism. Thus, use of this genotyping to inform ECT practice is not recommended. We do recommend that this research be extended to other genes and other serotonin transporter polymorphisms that are associated with antidepressant response.

REFERENCES

1. Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenomics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry 2004;9:442–473
2. Rausch JL, Johnson ME, Fei YJ, et al. Initial conditions of serotonin transporter kinetics and genotype: influence on SSRI treatment trial outcome. Biol Psychiatry 2002;51(9):723–732
3. Smeraldi E, Zanardi R, Benedetti F, et al. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998;3:508–511
4. Yu Y, Tsai S, Chen T, et al. Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. Mol Psychiatry 2002;7(10): 1115–1119
5. Kim DK, Lim SW, Lee S, et al. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport 2000;11(1):215–219
6. Yoshida K, Ito K, Sato K, et al. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2002 Feb;26(2):383–386
7. Seretti A, Kato M, De Ronchi D, et al. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry 2007;12:247–257
8. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
9. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, Tex: Psychological Corporation; 1996
10. Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996;274:1527–1530