Changes in Caudate Volume after Exposure to Atypical Neuroleptics in Patients with Schizophrenia may be Sex Dependent

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ABSTRACT

Background

Changes in the volume of the caudate nucleus over time in patients with schizophrenia has been shown to be directly related to neuroleptic exposure. Few studies have evaluated caudate volume in subjects with schizophrenia who were neuroleptic naïve at intake and treated exclusively with atypical neuroleptics.

Methods

Fourteen patients were matched by gender to 14 healthy controls and were evaluated over time using MRI. The patients were neuroleptic naïve at intake and at follow-up had been treated exclusively with atypical neuroleptics. Difference scores were calculated for caudate volumes. Neuroleptic exposure was quantified using a dose-years formula.

Results

There was no difference between patients and controls in the amount of change over time in the volume of the caudate. However, there were significant gender differences in the relationship between drug exposure and change in volume over time, with female patients showing a negative correlation (r= -0.74), and male patients a positive correlation (r= 0.63).

Conclusions

The change in caudate nucleus volume over time with exposure to atypical neuroleptics may be sex dependent. Atypical neuroleptic expsoure was associated with volume increase over time in the males, while exposure in females was associated with volume decrement over time.

Key words: schizophrenia, caudate nucleus, atypical neuroleptics, MRI, sex effect

INTRODUCTION

The study of basal ganglia morphology in schizophrenia is important because of its role in cognitive and motor function control. However, the morphologic change in response to neuroleptic treatment has been a major focus of the most recent research in this brain region. Early studies of chronic patients with schizophrenia found the basal ganglia to be increased in volume when compared to controls (Heckers et al. 1991; Jernigan et al. 1991; Breier et al. 1992; Swayze et al. 1992; Elkashef et al. 1994; Frazier et al. 1996). This was initially interpreted as being due to abnormal neurodevelopmental factors such as "lack of pruning" (Jernigan et al. 1991; Swayze et al. 1992). However, later studies indicated that this enlargement appeared to be secondary to neuroleptic exposure (Chakos et al. 1994; Elkashef et al. 1994; Keshavan et al. 1994). In addition, there appeared to be differing structural effects based on the type of neuroleptics. That is, several studies indicated that initial treatment with *typical* neuroleptics increased the volume of basal ganglia, and that later treatment with ayptical neuroleptics *decreased* the volume of these brain regions (Chakos et al. 1995; Gur et al. 1998; Corson et al. 1999; Scheepers et al. 2001). These studies suggested that atypical drugs may reverse the effect of the typical neuroleptics on the basal ganglia volume, allowing for a return to baseline volume.

Whether or not the atypical drugs have a *direct effect* on reducing the volume of the basal ganglia has yet to be adequately studied. In a recent report, patients treated with risperidone showed no change in volume over time (Lang et al.

2001). No study has evaluated the effects of other atypical drugs on neuroleptic naïve patients.

Our group and others have reported on the differences in brain abnormalities in schizophrenia with regard to sex, with the most frequent finding being that male patients have more severe morphologic abnormalities compared to female patients (Nopoulos et al. 1997). There has also been a study showing gender differences in the distribution of dopamine D2 receptor binding in neuroleptic naïve patients (Schroder et al. 1997). However, no study has evaluated whether or not the change in basal ganglia structure after exposure to neuroleptic manifests differently in male compared to female patients.

The current study was designed to assess the effect of atypical neuroleptics on the volume of the caudate nucleus in neuroleptic naïve patients with schizophrenia. Our aim was to quantify the change in volume of the caudate nucleus over time in a group of patients who were neuroleptic naïve, then treated with atypical antipsychotics only. In addition, we explored gender differences in brain morphology in response to medication exposure.

METHODS AND MATERIALS

Subjects

Subjects were obtained from the Prospective Longitudinal Study of Schizophrenia and the Mental Health Clinical Research Center (MH-CRC) at the

University of Iowa (Flaum et al. 1992). The patients in this study were identified early in the course of their illness, and then followed over time. We studied 14 patients with a DSM IV diagnosis of schizophrenia, 7 males and 7 females.

Controls for the study consisted of 14 healthy subjects matched to the patient sample by sex. Exclusion criteria included a positive history of medical, neurological, or psychiatric illness. Individuals with a history of alcohol and substance abuse were also excluded. These control subjects were also followed over time and participated in follow-up MRI scanning.

The mean age of the patient group was 26.3 years (SD=6.8) for patients and 26.7 years (SD=11.3) for controls. Mean length of follow-up period for the subjects was 30.2 months (S.D.=13.3) and 32.4 months (SD = 12.1) for the control subjects.

Each subject was evaluated using a structured interview, the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992), which has well-documented reliability. All patients were considered “first episode” as defined by their intake evaluation being their first psychiatric hospitalization. Prior exposure to neuroleptics was carefully assessed, and all of the subjects were neuroleptic naïve at the time of intake. The Iowa Prospective Longitudinal Study is a naturalistic study with no treatment protocol, and the patients are treated by their local care providers. Every six months the subjects return for

follow-up, and a detailed evaluation of medication is documented and confirmed by local medical records. The "Dose Year" formula (Miller et al. 1995) was used to measure neuroleptic exposure, which was calculated as cumulative dose between intake and follow-up time period (Miller et al. 1995). This requires conversion of neuroleptic medication to chlorpromazine equivalents (Davis 1974). The older equivalents have recently been extrapolated to atypical neuroleptics. Exposure is calculated over time, weighted for dose.

At follow-up, the patient sample had been treated with different atypical neuroleptic medications. Of the 7 male patients, two had been treated with Risperidone only, one with Olanzapine and later Quetiapine, three with a combination over time of Risperidone and/or Olanzapine, and one with Risperidone, Olanzapine, and finally Clozapine. The pattern of drugs was very similar for the 7 female patients: one treated with Risperidone only and one with Risperidone and/or Quetiapine; one treated with Olanzapine only, and three who had been treated with Risperidone and/or Olanzapine.

Image Acquisition and Processing

The multi-modal MRI scans given to the neural network were obtained using a 1.5 Tesla General Electric Signa scanner (GE Medical Systems, Milwaukee, WI). T1 weighted images, using a spoiled grass (SPGR) sequence, were acquired with the following parameters: 1.5 mm coronal slices, 40 degree flip angle, repetition time (TR)= 24 ms, echo time (TE)= 5 ms, number of excitations (NEX)=

2, field of view (FOV)= 26 cm, and a matrix of 256 x 256 x 192 cm. PD and T2 sequences were acquired as follows: 3.0 or 4.0 mm thick coronal slices, TR= 3000 ms, TE= 36 ms (for PD) and 96 ms (for TE), NEX= 1, FOV= 26 cm, matrix= 256 x 192.

In order to measure the volume of the caudate nucleus in a reliable manner, we used a neural network developed by our lab (Andreasen et al. 1992), from which volume measurements can be made (Magnotta et al. 1999) and reliably delineate the brain structure in question. Although mostly an automated method, it requires a certain amount of manual trimming in order to obtain the most anatomically valid volume (Corson et al. 1999). Complete tracing guidelines are available upon request.

Statistical Analysis

To represent change in volume over time, a difference score for the volume of the caudate was calculated as follows: difference = volume (in cc's) at time 2 - volume at time 1. A positive difference score would indicate enlargement in volume of the caudate over time, whereas a negative difference score would indicate decrease in volume of the caudate over time. Difference scores were calculated for right caudate, left caudate and total caudate volume.

A paired t-test was used to compare difference scores between patients and controls. As some variables such as dose-years were not normally distributed, a

non-parametric (Spearman's) correlation analysis was used to evaluate the relationship between change in volume over time and cumulative drug exposure.

RESULTS

The mean difference score for both patients and controls, right side, left side, and total caudate volumes all were positive indicating an enlargement in volume over time. Changes over time in volume of the caudate were positive for both groups indicating enlargement between time one and time two. These change values were very small and virtually identical between the two groups (see Table 1). Further, the standard deviation of the change score for both groups was very high. When the total sample was separated by sex, the males showed greater volume enlargement compared to females, though this was not statistically significant (total caudate change $t = 1.41$, $p = 0.172$)

When each group was separated by sex, the group with the most enlargement over time was the male patient group and the group with the least enlargement over time was the female patient group. However again, there were no significant differences between any of the groups (see Table 2).

Although the two groups as a whole were comparable in terms of mean age, there were significant differences in age among the patient group, divided by sex (mean female patient age = 31.5, s.d. 12.8, mean male patient age = 21.1, s.d. 7.64). In addition, using the entire sample, there was a significant relationship

between volume of caudate and age at both intake ($r = -0.335$, $p = 0.081$) and volume of caudate at time 2 ($r = -0.430$, $p = 0.024$). Therefore, when calculating the Spearman correlations between volume change and drug exposure between male and female patients, age was controlled for.

Table 3 shows the results of the correlation analysis between drug exposure and change in caudate volume and reveals a significant difference between the sexes. Female patients had a robust negative correlation between drug exposure and change in volume over time. The greater the amount of drug exposure, the greater the decrement in volume. For men, the correlation was in the opposite direction. In this case, the greater the drug exposure, the greater the enlargement in volume. None of the correlations was statistically significant due to lack of power with such small sample size. However, the difference in correlations between male and female patients was significant for all three measures (see Table 3).

DISCUSSION

As a group (men and women combined), patients with schizophrenia and a group of matched controls showed a negligible increase in volume of the caudate nucleus over a time period of approximately 2 years. This suggests that, unlike typical neuroleptics, exposure to atypical neuroleptics does not affect the volume of basal ganglia structures such as the caudate. This also suggests that as a

class, these medications may pose less risk for long-term motor abnormalities such as tardive dyskinesia.

An important caveat, however, is that there were significant sex differences in the response of the volume of the caudate to exposure to atypical medications. In female patients, atypical drugs appeared to decrease the volume of the caudate over time. In males, there was a tendency for these drugs to increase the volume over time. As these subjects were neuroleptic naïve and then exposed only to atypical antipsychotics, these findings suggest that atypical neuroleptics do indeed have a *direct* effect on the morphology of basal ganglia. This is in contrast to the previously held hypotheses that decrement in volume over time with exposure to atypicals (after treatment with typicals) was due to a "removal" of the high dopamine receptor blockade of the typical class, and that the atypical neuroleptics had no direct effect on morphology (Chakos et al. 1995; Corson et al. 1999; Lang et al. 2001; Scheepers et al. 2001; Scheepers et al. 2001).

Gender differences in response to neuroleptics have been well studied in both animals and humans, but most studies have focused on treatment with typical neuroleptics. These studies show females having both a higher degree of symptom improvement (Seeman 1986; Angermeyer et al. 1990), but also a higher rate of extrapyramidal symptoms (Seeman et al. 1990; Szymanski et al. 1995). In humans, biologic measures such as plasma prolactin levels, plasma homovanillic acid (HVA) levels, and methylphenidate infusion activation are

higher among females with schizophrenia, suggesting greater pharmacologic responsivity of the female patient (Szymanski et al. 1995). Animal studies show fewer striatal dopamine receptors and higher affinity of striatal cholinergic receptors in females compared to males (Miller 1983). How this information translates to support the findings of the current study is still unclear. It is also unclear whether or not the gender difference shown in this study is also seen in treatment with typical neuroleptics as none of the previous studies evaluated a sex effect. Our previous study of basal ganglia volume change over time was limited to a male only sample (Corson et al. 1999).

Limitations of this study include the small sample size. The raw means suggest that the group that enlarged the most was male patients and the group that changed the least was female patients. However, most likely due to lack of power, the difference between these two groups was not significant ($t = 1.42$, $p = .14$). Another limitation is that the groups are not "clean" with regard to medication. This is a naturalistic study whereby medications are prescribed by local physicians. Therefore, many subjects had been treated over time with several medications making it difficult to discern any drug-specific changes. As we continue to collect subjects in this prospective study, in the future we will be able to create larger data sets that will not only allow more power and provide a chance to replicate the current findings, but may provide the opportunity to study more drug-specific effects.

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Table 1: Change in Volume of Caudate Over Time (cc's).

	Patients	SD	Controls	SD
Right	0.0976	0.2104	0.0798	0.1714
Left	0.0928	0.1765	0.1114	0.3547
Total	0.1904	0.3647	0.1913	0.3632

Table 2: Gender Difference Observed in Change in Volume of Caudate Over Time.

	Female Patients	Female Controls	Male Patients	Male Controls
Right	0.013	0.071	0.181	0.088
Left	0.043	0.067	0.142	0.155
Total	0.057	0.139	0.323	0.243

Table 3: Spearman Correlations Between Cumulative Neuroleptic Exposure and Change in Caudate Volume Over Time*

	Female patients		Male Patients			
	r	p	r	p	z**	p
Right	-0.627	0.182	0.564	0.243	1.94	0.051
Left	-0.577	0.229	0.631	0.179	1.98	0.047
Total	-0.741	0.091	0.631	0.179	2.39	0.016

* Controlling for age.

** Test for comparing correlations.

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