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EFFECTS OF ANTI-OBSESSIONAL TREATMENT ON PITUITARY VOLUMES IN OBSESSIVE-COMPULSIVE DISORDER

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SUMMARY

Background: *We aimed to examine the effct of anti-obsessional drugs on pituitary gland volumes in the patients with obsessive-compulsive disorder (OCD).*

Subjects and methods: *A group of patients with OCD and of healthy controls were evaluated by using pituitary gland magnetic resonance imaging (MRI) at baseline and after twelve weeks of treatment with selective serotonin re-uptake inhibitors or clomipramine.*

Results: *Pituitary gland volumes were found to be statistically significantly smaller in the patients with OCD compared to healthy control subjects at the beginning of the study. We found that pituitary volumes significantly increased throughout twelve weeks of treatment.*

Conclusions: *This study provides an evidence of the effect of anti-obsessional treatment on the volumes of pituitary gland in OCD patients.*

Key words: *anti-obsessional – OCD - pituitary gland - SSRI*

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INTRODUCTION

Obsessive compulsive disorder (OCD) is a psychiatric disorder that has been classified in anxiety disorders until the release of the Diagnostic and Statistical Manual of Mental Disorders Fifth Eversion (DSM 5) which has placed OCD in a new category, named Obsessive Compulsive and Related Disorders (APA 2013).

Limbic–hypothalamic–pituitary–adrenal (LHPA) axis abnormality has been reported in the patients with OCD (Altemus et al. 1992, Catapano et al. 1992, Monteleone et al. 1997). On the other hand, an increased activity of the HPA axis in OCD has been reported both indirectly by the finding that corticotropin-releasing hormone (CRH) levels in cerebrospinal fluid (CSF) were significantly higher in patients with OCD than in healthy controls (Altemus et al. 1992) and directly by the finding that Kluge et al. (2007) examined the blood of patients and controls every 20 min between 23:00 and 7:00 h during sleep using a long catheter for later ACTH and cortisol analysis. In this context, in the patients with OCD, pituitary volumes was previously evaluated by our study group (Atmaca et al. 2009). In that study, we found statistically significant smaller volumes of pituitary gland of the patients with OCD compared to those of healthy controls (age and ICV as covariates). Narayanaswamy et al. (2015) compared 50 patients with obsessive-compulsive disorder without any comorbid axis I conditions to healthy control subjects and reported no difference in the pituitary volumes. In another study, MacMaster et al. (2006) reported that pituitary volumes were significantly smaller in pediatric patients with OCD as compared with healthy control subjects (11% smaller).

Selective serotonin reuptake inhibitors (SSRIs) are the first line choice of pharmacological treatment of OCD. To date, several investigations were done on the effetcs of psychotropic drugs and psychotherapeutic techniques on brain volumes in the patients with OCD. The effect of cognitive behavioral therapy (CBT) on the volumes of the orbito-frontal cortex (OFC) and thalamus regions in twelve patients with OCD and same number of healthy controls were examined and was found that thalamus volumes significantly decreased throughout the period for both sides and that the OFC volumes significantly increased throughout the period for only seft side (Atmaca et al., unpublished study). We also evaluated the neurochemical alterations of the hippocampus before and after the CBT treatment and determined that lower ratio of NAA/CHO in the patients with OCD compared to that of healthy control subjects at baseline statistically significantly increased after CBT treatment of sixteen sessions. On the other hand, our team also examined volumetric changes of the OFC and thalamus regions after twelve weeks of anti-obsessional treatment in the patients with OCD and found that thalamus volumes reduced statistically significantly throughout the treatment period while OFC volumes did not change statistically significantly throughout the treatment period. Limited number of studies were performed on brain volume changes in OCD patients before and after treatment (Hoexter et al. 2012, Huyser

et al. 2013, 2014). Jung et al. examined pituitary volume in drug-naïve and medicated male patients with OCD and reported that pituitary volumes were significantly smaller in drug-naïve patients compared to medicated patients and control subjects, without any difference between controls and medicated patients (Jung et al 2009). Given our previous literature and studies revealing probable LHPA axis abnormality in the patients with OCD, we hypothesized that our finding of reduced pituitary volumes in the patients with OCD would change after twelve weeks of treatment with anti-obsessional drugs.

SUBJECTS AND METHODS

Subjects and clinical evaluation

Sixteen patients with a DSM IV diagnosis of OCD, with the mean age ± standard deviation of 33.02±3.76 years old and same number of healthy control subjects comprised the study population. The patients of the present study were those of our previous unpublished study (Atmaca et al.). The mean duration of illness was 6.21±4.40 years. Prospective patients for the study who were recruited from inpatient and outpatient services at Firat University School of Medicine Department of Psychiatry were evaluated using the Structured Clinical Interview for DSM-IV, Patient-Edition (SCID-P) (First et al. 1997). Patients were eligible to be included in the present investigation if they had: 1) Diagnosis of OCD 2) 6) not having any contrendication for suffering from MRI investigation such as cardiac stent, 3) between 18 and 65 years old, 4) not having any current or history of comorbid psychiatric disorder apart from depression which is frequently comorbid with OCD, 5) no previous history of severe mental retardation, alcoholism and drug dependence or abuse in the last six months; 6) no previous head injury with loss of consciousness, and 7) no history of any kind of psychotropic medication including antidepressants, antipsychotics, stimulants, and mood stabilizers. As for the healthy control sample, as mentioned in our unpublished study (Atmaca et al.), they were taken from our data pool who had been taken from the hospital staff and had been invited to obtain their magnetic resonance imagings for the present study. On the other hand, inclusion criteria for healthy control subjects were followings: 1) no presence of current or history of DSM-IV axis I disorders, 2) no history of psychiatric disorders among their first-degree relatives, 3) no current major neurological or medical illness, 4) no history of alcohol or substance abuse, and no contrendication for suffering from MRI investigation. As in our previous studies, we performed the present study under the guidelines of the Helsinki Declaration. In addition, the patients and healthy control subjects provided informed consent to take part in the study. The University of Pittsburgh Biomedical Internal Review Board approved this research study. The Local Ethics Committeee of at Firat University School of Medicine approved to be done the present study.

Procedure

At baseline, the procedure for the study was told to the patients. For twelve weeks, the patients took selective serotonin reuptake inhibitors or clomipramine. As in indicated in our unpublished study (Atmaca et al, unpublished study), of the patients, two did not complete the study period. One experienced gastrointestinal complaints whereas the other one had sexual side effects. Consequently the study was maintained with fourteen patients. The patients were evaluated every four weeks to observe the efficacy of the treatment. If required, it was permitted the use of benzodiazepines, but no other treatment option was allowed. At the end of the study, the drugs used and their doses were as followings: paroxetine in four patients, with the dose of 60 mg per day for one patient, 40 mg per for three patients, sertraline, with the dose of 100 mg per day for two patients, clomipramine, with the dose of 225 mg per day for one patient, 150 mg per day for one patient, and 75 per day for one patient, fluoxetine, with the dose of 60 mg per day for one patient, and fluvoxamine, with the dose of 200 per day for one patient. The progress of the OCD was evaluated by using the Yale-Brown Obsession Compulsion Scale (Y-BOCS) (Goodman et al. 1989). Hamilton Depression Rating Scale (HDRS) was also used (Hamilton 1960). This scale was used for the patients at baseline and after twelve weeks, and for healhy controls just at the beginning of the investigation. On the other hand, magnetic resonance scanning for the patients with OCD were performed at baseline and at the end of the investigation while healthy contyrol subjects suffered from only one scanning at baseline.

Magnetic resonance imaging (MRI) procedure

All scannings were performed by using General Electric 1.5 Tesla signa Excite high speed scanner (Milwakuee, USA). It was used earplugs to reduce the noise of the machine. To obtain volumetric data, floowing scanning paramateres were used: Time of echo:15.6 ms, time of repetition=2000 ms, flip angle=200, field of view (FOV)=240 mm, bandwidth=20.8, slice thickness=2.4 mm, spacing of echo=15.6 ms, 8 echoes, resolution=0.9375×0.9375×1.328 mm. Workstation voxtool 4.2 program was used for volumetric analysis. Manual tracings were performed by a neuroradiologist who was blind to the patients' diagnosis. Tracings were done by assistance of standard neuroanatomical atlases (Yuh et al. 1994, Jackson & Duncan 1996). To define the boundaries of the pituitary gland, some guides were used. They were adapted from neuroimaging studies on the pituitary gland (Krishnan et al. 1991, Sassi et al. 1991) and followed by the study of MacMaster et al.'s (2006). The inferior boundary of the pituitary gland was sphenoid sinüs. The superior boundary of the pituiatry gland was accepted as the optic chiasm and infundibular recess of the third ventricle. Sample scanning of the pituitary gland is presented in Figure 1. All volumes are

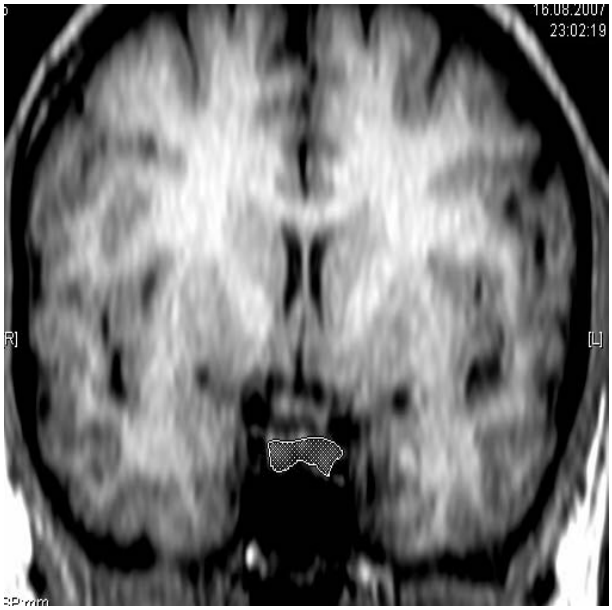

Figure 1. Manual tracing of pituitary gland

reported in cubic centimeters. Intra-rater reliability was evaluated by means of the intraclass correlation coefficient (ICC; absolute agreement) using ten scan images from a separate MRI database established specifically for this purpose. ICC values for the pituitary gland were all 0.90 or over, with a r value, indicating acceptable reliability.

Statistical analysis

The Statistical Package for the Social Sciences for Windows software, version 13.0 (SPSS, Chicago, IL) was used to do statistical analyses. In SPSS, Chi-square test was used to compare categorical variables between the patient and healthy control groups. Other group differences in demographic variables were compared by using independent t-test. At baseline, age, gender and total brain volume was taken as covariates to compare the volumes of the pituitary gland volumes between the patients and healthy control subjects, with the use of General Linear Model in the SPSS. On the other hand, to compare the pituitary gland volumes of the patients before and after anti-obsessional drugs, paired t test was used. In addition, Pearson's correlation test was used to determine the relationship between the pituitary gland volumes and symptom severity of OCD.

RESULTS

Sociodemographical data owning to the patients with OCD and healthy controls are summarized in Table 1. We did not find any statistically significant differences regarding these variables (independent sample t test, P>0.05 for age and educational status; chi-square test, P>0.05 for sex distribution and handedness ratio) but on the scores of the HDRS and Y-BOCS between the study groups (HDRS, mean score ± S.D=11.26±4.02 vs. 4.15±3.27 for the patients and controls respectively,

Table 1. Some characteristics and pituitary volumes of the two study groups

	OCD group (n=14)	Healthy controls (n=14)
Gender (F/M)		
Female	8	7
Male	6	7
Age	33.02±3.76	30.35±4.09
Handedness		
Right	12	13
Left	2	1
Y-BOCS score		
Pre-treatment	26.41±4.22	$6.83\pm3.2^{\alpha}$
Post-treatment	$10.12\pm4.72^{\alpha\alpha}$	-
Pituitary volumes (cm^3)		
Pre-treatment	0.51±0.22	$0.84\pm0.32^{\alpha}$
Post-treatment	$0.69\pm0.38^{\beta}$	-

α - p<0.001, between groups; αα - p<0.001, within OCD group for Y-BOCS changes; β - p<0.05, within OCD group for pituitary volume changes

P<0.001; Y-BOCS, mean score ± S.D=26.41±4.22 vs. 6.83±2.46 for the patients and controls respectively, P<0.001). Y-BOCS scores significantly decreased from the level of 26.41±5.22 to 10.12±4.72 (P<0.001). Likewise, HDRS scores significantly decreased from 11.26±4.02 to 6.31±3.55 (P<0.001).

Pituitary gland volumes were found to be statistically significantly smaller in the patients with OCD compared those of healthy control subjects at the beginning of the study (0.51±0.22 cm3 for the patients with OCD vs. 0.84±0.32 cm3 for healthy control subjects; P<0.001, with independent sample t test).

To examine the effects of antiobsessional drugs on the volumes of pituitary gland, it was compared baseline volumes of the patients with post-treatment ones, by using paired t test. Consequently, we found that pituitary volumes significantly increased throughout twelve weeks of treatment (P<0.05). The mean volume of the pituitary gland changed from 0.51±0.22 cm3 to 0.69±0.38 cm3. No statistically significant correlation was found between the change in pituitary gland volume change and any variable (P>0.05).

DISCUSSION

This study revealed that anti-obsessional drugs might affect the volumes of the pituitary gland in the patients with OCD. The mean volume of the patients increased from 0.51±0.22 cm3 to 0.69±0.38 cm3, with a statistically significance. To the best of our knowledge, no previous investigation has prospectively examined the effects of anti-obsessional drugs on pituitary volumes in these group of patients. For this reason, the findings of the present study should be accepted as preliminary. Limited number of studies were performed on brain volume changes in OCD patients before and after treatment (Hoexter et al. 2012; Huyser et al. 2013,

2014). First of all, we should emphasize the statistically significant difference of pituitary gland volumes between patients with OCD and healthy controls. This is also supported by our previous study (Atmaca et al. 2009) and Mcmaster et al. (2006). However, in a most recent study with larger sample, Narayanaswamy et al. (2015) compared 50 patients with obsessive-compulsive disorder without any comorbid axis I conditions to healthy control subjects and reported no difference in the pituitary volumes. These results might attenuate our present results and previous supporting findings. The effects of psychotropic drugs on pituitary volumes were previously examined in the patients with schizophrenia (MacMaster et al. 2007). In that study, the authors found pituitary volumes to increase twelve percent during twelve months of treatment. In the present study, we detected an increase in pituitary volumes much more over this ratio. We do not know the exact reason for volumetric changes of the pituitary gland in the patients with OCD under treatment. We can do some speculations. First of all, this increse may be related to the fact that antidepressants may directly affect pituitary gland volumes. Jung et al. (2009) examined pituitary volume in drug-naïve and medicated male patients with OCD and reported that pituitary volumes were significantly smaller in drug-naïve patients compared to medicated patients and control subjects, without any difference between controls and medicated patients, revealing that the increased pituitary volume in medicated patients might reflect the effect of drugs on the pituitary. Secondly, the improvements in the severity of OCD itself may lead to increase the gland volumes which were found to be statistically significant reduced at baseline compared to those of healthy control subjects. However, changes in pituitary volumes were not corelated with those in Y-BOCS scores. So, this does not support our speculation emphasizing the effects of improvement. In this context, to clarify this contoversy, it is required to study the effects of other treatment modalities such as cognitive behavioral therapy in these group of the patients to exclude the confounding effects of psychotropic drugs.

The present study has some limitations. Small sample size is an important limitation factor although it is very difiicult to maintain such studies in which the effects of a variety of drugs on brain volumes were evaluated. Especially, when cinsidering that there was no correlation between Y-BOCS score changes and gland volumes, the sample size becomes more important. On the other hand, we did not measure the hormone values released by pituitary gland. The fact that comorbid depression in patients was allowed is another point that should be evaluated as a limitation given reports that changes of pituitary size were connected to depression (Kessing et al. 2010). It would be important to mention the possibility that comorbid conditions like depression might affect results of the present. It would be important to mention the possibility that comorbid conditions like depression might affect results, and that those effects could not necessarily be clearly seen without using a larger sample. As mentioned in presenting scanning parameters, 0.9375×0.9375×1.328 mm matrix with the thickness of 2.4 mm should be emphasized as another limitation factor which could have affected the results.

CONCLUSION

Consequently, this study provided an evidence of the effect of anti-obsessional treatment on the volumes of pituitary gland in OCD patients. Novel studies with larger sample are required.

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Conflict of interest: None to declare.

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