Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 203–207

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Pituitary volume in patients with panic disorder

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ARTICLE INFO

Article history:
Received 1 September 2010
Received in revised form 3 November 2010
Accepted 3 November 2010
Available online 12 November 2010

Keywords:
Agoraphobia
HPA axis
Magnetic resonance imaging
Panic disorder
Pituitary gland volume

ABSTRACT

Panic patients have many functional deficiencies in the hypothalamic–pituitary–adrenal (HPA) axis. Previous studies have shown changed pituitary gland volume in some psychiatric disorders that have functional deficiencies in the HPA axis. However, to date no study has evaluated the pituitary gland volume in patients with panic disorder (PD). We investigated the pituitary gland volume in patients with PD (n = 27) and age- and sex-matched healthy controls (n = 27), using 1.5-T magnetic resonance imaging in this study. Analysis showed that patients with PD had significantly smaller pituitary volume compared to healthy subjects. Patients with agoraphobia especially had a significantly smaller pituitary volume than patients without agoraphobia. There was a significant relationship between the pituitary volume and both the severity of symptoms and the illness duration in the patient group. The results show that patients with PD have reduced pituitary volume, which may reflect the functional abnormalities seen in this disorder. These findings may help us better understand the pathology of PD.

1. Introduction

Panic disorder (PD) is an incapacitating and overwhelming condition characterized by the occurrence of unexpected and repeated panic attacks. Such panic attacks include intense, sudden and unexpected surge of extreme fear accompanied by major neurovegetative and psychological changes such as dyspnea, palpitations, tachycardia, sweating, tremor, nausea, depersonalization and fear of losing control which lasts for about 20 min. As a consequence of these attacks, a persistent concern about additional attacks and avoidance of places where an attack would be embarrassing may gradually develop. This extreme avoidance is known as agoraphobia, in which case the patient is afraid of leaving home unaccompanied, becoming incapacitated for most social functions (American Psychiatry Association, 1994). Around 2/3 of patients with PD also demonstrate agoraphobia (Del-Ben and Graeff, 2009).

Several brain structures that organize defensive reactions and represent the neural substrate of fear and anxiety have been implicated in the functional neuroanatomy of PD. Some authors have reported that some structural alterations in the periaqueductal gray matter and locus coeruleus, hippocampus and parahippocampal gyrus, anterior cingulate cortex, amygdala, hypothalamic paraventricular and lateral nucleus, brain stem structures, and the temporal and right frontal lobes are more frequently observed in panic patients than in controls (Al-Haddad et al., 2001; Engel et al., 2009; Gorman et al., 2000; Massana et al., 2003; Sobanski et al., 2010; Uchida et al., 2008). The amygdala and paraventricular nucleus especially play an important role in the pathophysiology of PD. According to Gorman et al. (2000), the hypothalamic paraventricular nucleus that activates the hypothalamic–pituitary–adrenal (HPA) axis is controlled by the amygdala, indicating that the HPA axis is a component of the panic pathway that starts from the amygdala.

The abnormalities of HPA that are specifically implicated in the pathophysiology of depression (Nemeroff et al., 1992; Sheline, 2000; Swaab et al., 2005) have also been reported in other psychiatric disorders (Bailly et al., 1994; Carroll et al., 1981; Krishnan et al., 1985; Lammers et al., 1995; Volsan and Berzewski, 1985; Walker et al., 2008), including anxiety disorders (Risbrough and Stein, 2006; Young et al., 2003). There is some evidence for abnormalities in the HPA system regulation in PD. For example, increased basal cortisol production, abnormal dexamethasone suppression test(DST) and blunted adrenocorticotropic hormone (ACTH) and cortisol responses to corticotropin-releasing hormone (CRH) infusion are reported in patients with PD, along with differences in the feedback sensitivity of the axis (Abelson et al., 2007). Furthermore, some studies have demonstrated that patients with PD also have numerous

Abbreviations: ACTH, adreno-corticotropic hormone; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; HPA, hypothalamic-pituitary-adrenal; HPT, hypothalamus-pituitary-thyroid; ICV, intracranial volume; OCD, obsessive-compulsive disorder; PAS, panic and agoraphobia scale; PD, panic disorder; RPV, relative pituitary volume; SCID- IV, structured clinical interview for the DSM-IV; STAI, state-trait anxiety inventory; TRH, thyrotropin releasing hormone; TSH, thyrotropin stimulating hormone.

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doi:10.1016/j.pnpbp.2010.11.005

abnormalities in the hypothalamus–pituitary–thyroid (HPT) axis (Roy-Byrne et al., 1986b; Tukel et al., 1999).

The pituitary gland plays a central role in HPA and HPT axis activity. The volume of the pituitary gland changes during life and these anatomic changes are believed to reflect the functional status of the gland (Takano et al., 1999). Previous studies have demonstrated that endocrine abnormalities in the HPA axis are associated with changes in pituitary morphology (Chakeres et al., 1989; Gonzalez et al., 1988). Several studies have shown variations (smaller or larger) in pituitary gland volume in patients with major depression (Krishnan et al., 1991, MacMaster and Kusumakar, 2004; MacMaster et al., 2006b), bipolar disorder (MacMaster et al., 2008; Sassi et al., 2001; Takahashi et al., 2009a) and psychosis (Pariante et al., 2004, 2005; Takahashi et al., 2009b). Meanwhile pituitary volume changes have been reported in anxiety disorders. MacMaster et al. (2006a) found reduced pituitary volume in pediatric drug-naïve obsessive–compulsive disorder (OCD) patients. Atmaca et al. (2009) also found statistically significant smaller pituitary volumes in OCD patients compared to those of healthy controls.

We therefore felt that there may be pituitary gland volume changes in PD, as in other disorders accompanied by functional irregularities of the HPA. We also thought that this change would be a reduction as in other anxiety disorders due to the similar pathophysiological processes. However, there is no study to date that has evaluated the pituitary volume in patients with PD. Therefore, the purpose of the present study was to examine potential reduction in pituitary volume in PD patients.

2. Methods

2.1. Participants

Twenty-seven outpatients with PD and 27 healthy comparison subjects participated in this study. The patient group was later reduced to 26 subjects when an anatomical abnormality was detected in the neuroimaging examination of one patient. There were 11 males and 15 females with a mean age of 35.08 (SD = 10.73) in the panic group and 12 males and 15 females with a mean age of 33.74 (SD = 9.11) in the control group. The Turkish version of the Structured Clinical Interview for the DSM-IV (SCID-IV) (Çorapçıoğlu et al., 1999) was used to diagnose PD with or without agoraphobia. The patients have been referred from the Psychiatry Outpatient Clinic of the Department of Psychiatry, Inonu Faculty of Medicine. All of the subjects were right handed. Severity of illness was evaluated by using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) and the Panic and Agoraphobia Scale (PAS) (Bandelow, 1995). Patients with comorbid psychiatric disorders were excluded from the study. Eight patients (30.8%) met the criteria for PD with agoraphobia. Eleven of the 26 patients were not receiving pharmacological treatment at the time of evaluation. Fifteen patients were taking a selective serotonin reuptake inhibitor (citalopram; n = 6, paroxetine; n = 5, sertraline; n = 4), combined with a benzodiazepine in four cases.

Normal volunteers whose age and sex matched each patient were recruited from the hospital staff. Control subjects who were evaluated by a senior psychiatrist had neither Axis I psychiatric disorders or first-degree relatives with a psychiatric disorder. No subject in either group had a history of head trauma, major medical and endocrine illness, history of any neurological disorder or lifetime history of alcohol or drug dependence.

This study was carried out according to the Helsinki Declaration guidelines and was approved by the Local Ethics Committee. All the participants signed written informed consent before they were included in the study.

2.2. Brain imaging procedures

All magnetic resonance imaging was performed at the Inonu University School of Medicine on a 1.5-T magnet (Gyroscan Intera Master, Philips). Comfortable head positioning was provided. The whole brain was scanned with a 3-D fast field echo (FFE) T1-weighted data set. T1-weighted images were obtained in the coronal plane with 1.5 mm contiguous sections. TR was 25 ms, TE was 4.6 ms, and the flip angle was 30°, with a 256 × 256 mm matrix used.

Anatomic measurements were obtained on an independent workstation. Intracranial volume (ICV) and the pituitary were measured by a single rater (M.D.; second author) blind to the subject's identity. Boundary definition and tracing of the pituitary were done using standard neuroanatomical atlases (Daniels et al., 1987; Talairach and Tournoux, 1988) with methods and definitions adapted from neuroimaging studies on the pituitary (MacMaster and Kusumakar, 2004; Sassi et al., 2001; Thomas and De Bellis, 2004) and following MacMaster et al. (2006a). The superior border of the structure was described as the optic chiasm and infundibular recess of the third ventricle, while the inferior border was the sphenoid sinus. The volume of the pituitary (in mm^3) was calculated by adding the volumes for all relevant slices (Fig. 1).

2.3. Data analyses

All statistical analyses were performed by using SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA). The statistical significance level was defined as $P<0.05$. Demographic and clinical variables were compared between the groups using the independent sample t-test. Statistical difference in the pituitary volume was analyzed using analysis of covariance (ANCOVA) and analysis of variance (ANOVA). In ANCOVA analyses, age and ICV were covariates while the diagnosis and gender were fixed factors. Post hoc Tukey analyses were performed to determine any significant main effects or interactions. Categorical variables were analyzed using the chi-square test. Pearson's correlation analysis was used to evaluate the interaction between the pituitary volume and clinical variables such as duration of illness or severity of illness.

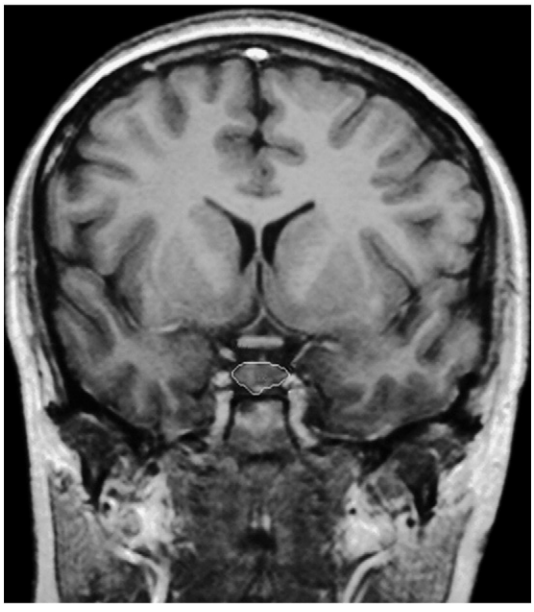

Fig. 1. The pituitary gland in the magnetic resonance coronal image used for the tracing.

Table 1
Demographic, clinical and volumetric characteristics of the subjects.

	Patients n = 26 Mean ± SD	Controls n = 27 Mean ± SD	Group comparisons t	p
Age (years)	35.1 ± 10.7	33.7 ± 9.1	0.489	0.627*
Gender (female/male)	15/11	15/12		0.548**
Agoraphobia(yes/no)	8/18			
Illness duration (years)	10.0 ± 8.5			
Age of onset (years)	25.1 ± 7.1			
PAS	31.3 ± 6.4			
STAI-T	62.5 ± 6.9	35.0 ± 5.4	16.197	0.000*
Pituitary volume (mm^3)	471.0 ± 96.1	625.0 ± 118.1	−5.198	0.000*
ICV (cm^3)	1563.8 ± 160.0	1612.9 ± 150.8	−1.150	0.255*
RPV	0.303 ± 0.063	0.388 ± 0.062	−4.956	0.000*

PAS: Panic Attacks and Agoraphobia Scale; STAI-T: State-Trait Anxiety Inventory Trait Score; ICV: intracranial volume RPV: relative pituitary volume (absolute volume/ICV) × 100).
* : t-test.
** : chi-square test.

3. Results

There was no significant group difference in regard to age (t = 0.489; df = 51; P = 0.627), gender composition (chi-square = 0.875; df = 1; P ≥ 0.05), and ICV (t = −1.150; df = 51; P = 0.255) between the control subjects and PD patients (Table 1).

The pituitary volume in PD patients was smaller than in healthy subjects (t = −5.198, df = 51, P = 0.000). After controlling the age and ICV, the ANCOVA of pituitary volume revealed significant effects of diagnosis (F = 26.88; df = 1; P = 0.000) and gender (F = 5.93; df = 1; P = 0.019). There was no significant difference in pituitary volume between female and male patients (p = 0.555) and female and male control subjects (p = 0.435) in post-hoc analyses but female patients had significantly smaller pituitary volumes than female controls (p = 0.001) and male patients had smaller pituitary volumes than male controls (P = 0.007) and female controls (P = 0.000). (Fig. 2).

Age (F = 1.25; df = 1; P = 0.269), ICV ((F = 3.13; df = 1; P = 0.083) and ICV-age effect sizes (F = 1.27; df = 1; P = 0.265) were not significant regarding the pituitary volume difference.

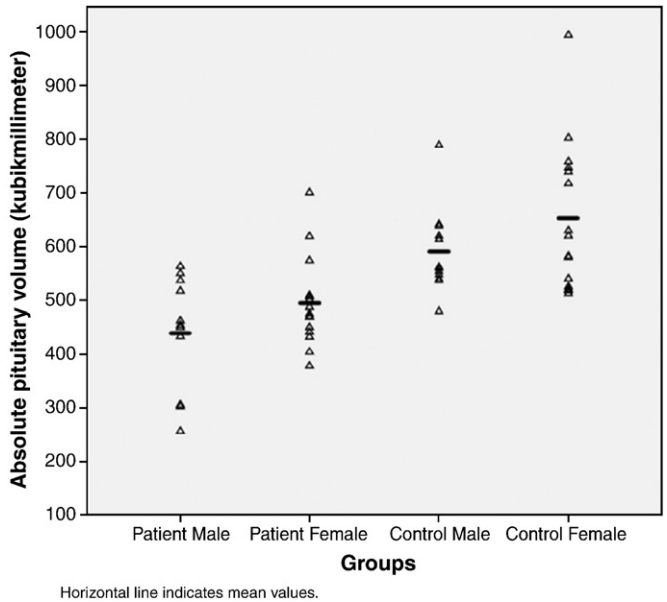

Fig. 2. Absolute volume of the pituitary gland in patients with panic disorder and healthy controls.

A significant negative correlation was found between pituitary volumes and PAS (r = −0.552, P = 0.003) and STAI values(r = −0.454, P = 0.001) in the patient groups.

Additionally, a significant negative correlation was found between pituitary volumes and duration of illness (r = −0.597, P = 0.001). The patients with PD were divided into three subgroups on the basis of duration of illness. There was a significant difference in pituitary volume between the patients who had been ill for less than 5 years (n = 10, 528.70 ± 84.1) and those who had been ill for more than 15 years (n = 5, 388.40 ± 80.6) (p = 0.015). ANOVA post hoc Tukey analysis revealed that the patients who had been ill for less than 5 years and healthy subjects had no significant difference in pituitary volume (P = 0.07). Using ICV as covariates showed that pituitary volumes were significantly smaller in the patients who had been ill for more than 15 years compared to control subjects (F = 15.251, df = 1, P = 0.001). Although pituitary volumes in the patients who had been ill 5–15 years (n = 11, 456.0 ± 84.53) were significantly smaller than the control subjects (P = 0.000), there was no significant difference with the patients who had been ill for less than 5 years (P = 0.383).

On the other hand, although there is no significant difference in the mean duration of illness between patients with(12.8 year) and those without (8.7 year) agoraphobia (P = 0.249), patients with agoraphobia (378.25 ± 80.69) had significantly smaller pituitary volume than patients without agoraphobia (512.17 ± 71.18) (t = −4.254, df = 24, P = 0.000).

4. Discussion

The results of the present study showed that patients with PD had significantly smaller pituitary volume than age- and sex-matched healthy subjects. In addition, the reduced pituitary volume was found to be negatively correlated with the severity of symptoms and duration of illness. To the best of our knowledge, the current study is the first work in patients with PD reporting pituitary gland volume changes.

The HPA axis is the primary biological system mediating the stress response; it has been associated with psychological, physical and social functioning (Abelson et al., 2007; Graeff and Del-Ben, 2008). In response to a threatening stimulus, CRH is released from the paraventricular nucleus and acts on receptors in the anterior pituitary to elicit the production and release of ACTH, which in turn systemically activates the production and release of glucocorticoids from the adrenal cortex. However, the functionality of stress response system is disrupted, causing several physical and mental diseases when the HPA axis disturbance continues for a long time, (Abelson and Curtis, 1996; Schreiber et al., 1996). Abnormalities of HPA axis have been considered in the development of PD as the axis is responsible for the autonomic response to a threatening stimulus, (Hobbs and Shekhar, 2003; Martin et al., 2009).

Many such axis abnormalities have been described in patients with PD (Abelson et al., 2007; Schreiber et al., 1996) such as elevation of the basal cortisol level (Goldstein et al., 1987), abnormal DST (Coryell and Noyes, 1988; Coryell et al., 1989; Westberg et al., 1991) and blunted ACTH response to the CRH challenge test (Holsboer et al., 1987; Roy-Byrne et al., 1986a). Furthermore, some studies have demonstrated that patients with PD also have numerous abnormalities in the HPT axis, such as reduced thyrotropin stimulating hormone (TSH) and prolactin responses to thyrotropin releasing hormone (TRH) (Roy-Byrne et al., 1986b; Tukel et al., 1999).

Anatomic changes in the pituitary gland are believed to reflect the functional status of the gland (Takano et al., 1999). Previous studies have shown that functional abnormalities in the HPA axis are associated with changes in the morphology of the pituitary gland (Chakeres et al., 1989; Gonzalez et al., 1988). The reduced pituitary volume in panic patients we found in this study may therefore be related to the functional abnormalities that have been shown in the

HPA and HPT axes in this disorder. Some recent studies have shown the HPA axis to be relatively hyporesponsive to emotional stress in some panic patients (Garcia-Leal et al., 2005, 2010; Petrowski et al., 2010). The pituitary small size in our study may be a morphological feature supporting this inadequate hormonal response.

Previous studies have found pituitary volume changes in a variety of psychiatric conditions (Atmaca et al., 2009; Garner et al., 2005; Pariante et al., 2004, 2005; Pariante, 2008). Pariante et al. (2004) found that subjects with a first episode of psychosis had larger pituitary volumes than the control groups while those with established schizophrenia had smaller pituitary volumes than the controls. Garner et al. (2005) reported that baseline pituitary volumes of the non-prodromal subjects under ultra-high risk for developing psychosis were smaller than both prodromal subjects and healthy controls. Smaller pituitary volumes have also been reported in anxiety disorders. MacMaster et al. (2006a) found reduced pituitary volume in pediatric drug-naïve OCD patients (11% smaller compared to control subjects). Atmaca et al. (2009) also found statistically significant smaller pituitary volumes in patients with OCD compared to those of healthy controls. Given these associations, it is reasonable to expect similar pituitary volume alterations in patients with PD but no study to date has evaluated the pituitary volumes in these patients. Our findings are also consistent with other previous studies showing reduced pituitary volumes in patients with obsessive–compulsive spectrum disorders, which are classified as an anxiety disorder (Atmaca et al., 2009, 2010; Doraiswamy et al., 1991; Jung et al., 2009; MacMaster et al., 2006a). Finally, it is possible that common pathological mechanisms associated with stress response mechanisms lead to shrinkage of the pituitary gland.

There was a significant negative correlation between pituitary volumes and clinical variables related with anxiety severity (PAS, STAI) in our PD patients. There was also a significant relationship between pituitary volume and duration of illness. Increasing illness duration correlated with smaller pituitary volume. There was no statistically significant difference in pituitary volume between patients with PD for less than 5 years and the controls. However, the volume depletion was much more pronounced when the duration of disease was longer than 15 years, indicating that the pituitary gland had become smaller over time. It is possible that chronic activation of the HPA axis reduces pituitary volume. We can speculate that this decrease in pituitary volume might be related to the potential degenerative and progressive process of PD.

The other important finding of this study is that panic patients with agoraphobia have smaller pituitary gland than those without agoraphobia. This result suggests that anticipatory anxiety is more effective on pituitary volume reduction than panic attacks. Cortisol elevation in patients with PD was only observed during the anticipation of panic attacks (Coplan et al., 1998), not during the attacks themselves (Woods et al., 1987). While panic attacks are brief, anticipatory anxiety is long-lasting. Patients with PD frequently exhibit widespread catastrophic thinking (Hibbert, 1984). Defence mechanisms become bankrupt and depression develops if the stress system is constantly stimulated. Patients with agoraphobia have been shown to be under increased risk for the development of major depression (Klerman, 1990).

Our study involved several methodological limitations. First, the small sample may limit the generalization of our findings, and replication of the results using larger samples is necessary. Second, we were unable to determine whether reduced pituitary volume had any functional consequences in patients with PD because we did not measure pituitary hormones.

5. Conclusion

The present study has demonstrated that patients with PD have a reduced pituitary gland volume compared with healthy comparison subjects. The pituitary volume showed a negative correlation with the severity of symptoms and the duration of illness. In addition, patients with agoraphobia had smaller pituitary glands compared to those without agoraphobia. In conclusion, these results may help us better understand the pathophysiology of PD.

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