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Longitudinal volume changes of the pituitary gland in patients with schizotypal disorder and first-episode schizophrenia

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ABSTRACT

An enlarged volume of the pituitary gland has been reported in the schizophrenia spectrum, possibly reflecting the hypothalamic–pituitary–adrenal (HPA) hyperactivity. However, it remains largely unknown whether the pituitary size longitudinally changes in the course of the spectrum disorders. In the present study, longitudinal magnetic resonance imaging (MRI) data were obtained from 18 patients with first-episode schizophrenia, 13 patients with schizotypal disorder, and 20 healthy controls. The pituitary volume was measured at baseline and follow-up (mean, 2.7 years) scans and was compared across groups. The pituitary volume was larger in the schizophrenia patients than controls at baseline, and both patient groups had significantly larger pituitary volume than controls at follow-up. In a longitudinal comparison, both schizophrenia (3.6%/year) and schizotypal (2.7%/year) patients showed significant pituitary enlargement compared with controls (−1.8%/year). In the schizophrenia patients, greater pituitary enlargement over time was associated with less improvement of delusions and higher scores for thought disorders at the follow-up. These findings suggest that the pituitary gland exhibits ongoing volume changes during the early course of the schizophrenia spectrum as a possible marker of state-related impairments.

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1. Introduction

Hypothalamic–pituitary–adrenal (HPA) axis hyperactivity is thought to reflect stress-related hormonal dysregulation and has been described in schizophrenia and related disorders (Phillips et al., 2006; Walker et al., 2008). Neuroendocrine studies in schizophrenia and schizotypal (personality) disorder (SPD), a prototypic disorder within the schizophrenia spectrum (Siever and Davis, 2004), have demonstrated that these disorders might share similar HPA axis dysfunctions, such as higher salivary cortisol level (Mittal et al., 2007; Walker et al., 2001) or blunted cortisol response to acute metabolic stress (Mitropoulou et al., 2004), as a potential indicator of common stress vulnerability. Furthermore, the association of HPA axis dysfunction with symptom severity (Goyal et al., 2004; Walder et al., 2000; Walker et al., 2001), medication (Cohrs et al., 2006; Scheepers et al., 2001), and illness stages (Phillips et al., 2006; Walker et al., 2008) in these disorders suggests that HPA activity reflects state-related impairments in the course of the schizophrenia spectrum.

The pituitary gland, an integral part of the HPA axis, may be one of the brain regions most affected by the hormonal stress response (Phillips et al., 2006). Recent magnetic resonance imaging (MRI) findings of increased pituitary volume in first-episode psychosis (Pariante et al., 2004, 2005), recent onset schizophrenia or schizotypal disorder (Takahashi et al., 2009), and individuals at high risk of developing psychosis (Garner et al., 2005) have been attributed to HPA hyperactivity in the early stages of these disorders, whereas normal (Tournikioti et al., 2007) or even decreased (Pariante et al., 2004) pituitary volume in chronically medicated schizophrenia patients could be explained by the notion that pituitary size is reduced over time as a result of prolonged HPA activation (Pariante et al., 2004; Sassi et al., 2001). However, the few longitudinal MRI studies of pituitary volume in psychotic disorders have yielded inconsistent findings from non-significant decrease (<2% over a 3-month period) (Nicolo et al., 2010) to 12% increase over 12 months (MacMaster et al., 2007b) during the first episode of illness. The effect of medication is also an important consideration for the pituitary

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CASH, Comprehensive Assessment of Symptoms and History; HPA axis, hypothalamic–pituitary–adrenal axis; ICV, intracranial volume; MMPI, Minnesota Multiphasic Personality Inventory; MRI, magnetic resonance imaging; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SPD, schizotypal personality disorder.

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findings (MacMaster et al., 2007b; Nicolo et al., 2010; Phillips et al., 2006), but a cross-sectional finding of decreased pituitary volume in antipsychotic-naïve schizophrenia patients with relatively recent onset (Upadhyaya et al., 2007) suggests that factors other than illness stages or medication, such as early treatment response (Garner et al., 2009), might also affect the pituitary volume. However, the precise effect of these clinical factors in schizophrenia remains unclear, especially for pituitary volume changes over time. In addition, no longitudinal MRI studies have examined the pituitary volume in schizotypal subjects, who have no overt and sustained psychosis but partly share stress vulnerability with full-blown schizophrenia (Siever and Davis, 2004).

This longitudinal MRI study investigated the pituitary volume changes over time in patients with first-episode schizophrenia and schizotypal disorder compared with those in healthy equivalents. On the basis of the potential role of the pituitary volume as an indicator of HPA dysfunction in the schizophrenia spectrum (Takahashi et al., 2009), which could reflect state influences of the disorders (Garner et al., 2009; Phillips et al., 2006; Walker et al., 2008), we predicted that both schizophrenia and schizotypal patients would show progressive pituitary enlargement. We also explored the relationship between the pituitary volume changes over time and several clinical factors (e.g., antipsychotic medication and early treatment response) in these disorders.

2. Methods

2.1. Participants

Eighteen first-episode schizophrenia patients who fulfilled the ICD-10 research criteria (World Health Organization, 1993) were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. In accordance with the literature (Hirayasu et al., 2000; Kasai et al., 2003; Schooler et al., 2005; Takahashi et al., 2009; Yap et al., 2001), first-episode patients were defined as patients experiencing their first episode of schizophrenia whose illness onset was within 1 year of baseline scanning ($N=14$) or those undergoing their first psychiatric hospitalization ($N=4$). The diagnosis of schizophrenia was confirmed at the follow-up scan for all cases.

Schizotypal disorder patients ($N=13$) who met the ICD-10 research criteria (World Health Organization, 1993) were recruited from among patients who visited the clinics of the Department of Neuropsychiatry of Toyama University Hospital. This patient group had exhibited at least four of the schizotypal features (inappropriate affect, odd behavior, social withdrawal, magical thinking, suspiciousness, ruminations without inner resistance, unusual perceptual experiences, stereotyped thinking, and occasional transient quasi-psychotic episodes) over a period of at least 2 years, accompanied by distress or associated problems in their lives and required clinical care including low-dose antipsychotics. Their characteristics have been described previously (Kawasaki et al., 2004; Suzuki et al., 2005; Takahashi et al., 2006). All available clinical information and data obtained from a detailed review of the patients' clinical records and structured interviews for Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by a consensus reached by at least two psychiatrists using these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria for SPD on Axis II, two subjects had previously experienced transient quasi-psychotic episodes fulfilling a DSM Axis I diagnosis of brief psychotic disorder (American Psychiatric Association, 1994). The mental condition of each subject was regularly assessed by experienced psychiatrists to check for the emergence of full-blown psychotic symptoms, and none of the 13 patients has developed overt schizophrenia to date (mean clinical follow-up period after baseline scanning = 5.1 years, SD = 2.1).

The control subjects consisted of 20 healthy volunteers recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g., a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (2 items) histories of illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives. All controls were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by experienced psychologists to obtain a relatively homogeneous control group without eccentric profiles on the MMPI and were excluded if they had an abnormal profile, namely, any T-score on the validity or clinical scales exceeding 70.

The clinical symptoms of the schizophrenia and schizotypal patients were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). At the baseline, 12 schizophrenia and 6 schizotypal patients were treated with atypical antipsychotics, and 6 schizophrenia and 7 schizotypal patients were receiving typical antipsychotics. The patients were also receiving benzodiazepines (15 schizophrenia and 8 schizotypal patients), anticholinergics (14 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 6 schizotypal patients), and/or mood stabilizers [lithium carbonate (1 schizotypal patient), sodium valproate (1 schizophrenia patient), or carbamazepine (2 schizotypal patients)]. At the follow-up scan, 11 schizophrenia and 10 schizotypal patients were on atypical antipsychotics, and 7 schizophrenia and 3 schizotypal patients were on typical antipsychotics. Some patients were also receiving benzodiazepines (13 schizophrenia and 10 schizotypal patients), anticholinergics (15 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 4 schizotypal patients), and/or mood stabilizers [sodium valproate (1 schizophrenia and 1 schizotypal patients), carbamazepine (1 schizophrenia and 2 schizotypal patients), or a combination of lithium and carbamazepine (1 schizophrenia and 1 schizotypal patients)]. During the follow-up period between scans, 9 patients (4 schizophrenia and 5 schizotypal patients) were predominantly treated with typical antipsychotics, 18 patients (11 schizophrenia and 7 schizotypal patients) were treated mostly with atypical antipsychotics (although 2 patients received typical antipsychotics for <1 month), and 4 (3 schizophrenia and 1 schizotypal patients) received substantial amounts of both typical and atypical antipsychotics.

All subjects were right-handed and physically healthy, and none of the participants were pregnant or taking exogenous estrogens at the time of the study. None had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease (e.g., primary hypothyroidism). All participants were also screened for gross brain abnormalities (e.g., pituitary or hypothalamic tumor) by neuroradiologists. However, hormonal levels as well as menstrual cycle in females were not assessed at scanning. Of the 51 participants in this study, 48 subjects (17 schizophrenia, 12 schizotypal, and 19 control subjects) were included in our previous cross-sectional study of pituitary volume (Takahashi et al., 2009). This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

The subjects were scanned twice on a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-

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