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PINEAL GLAND VOLUME IN SCHIZOPHRENIA AND MOOD DISORDERS

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SUMMARY

Background: *The majority of patients with schizophrenia and mood disorders have disruptions in sleep and circadian rhythm. Melatonin, which is secreted by the human pineal gland, plays an important role in sleep and circadian rhythm. The aim of the present study was to evaluate and compare pineal gland volumes in patients with schizophrenia and mood disorders.*

Subjects and methods: *We retrospectively evaluated the pineal gland volumes of 80 cases, including 16 cases of unipolar depression, 17 cases of bipolar disorder, 17 cases of schizophrenia, and 30 controls. The total pineal gland volume of all cases was measured via magnetic resonance images, and the total mean pineal volume of each group was compared.*

Results: *The mean pineal volumes of patients with schizophrenia, bipolar disorder, unipolar depression, and the controls were 83.55±10.11 mm³, 93.62±11.00 mm³, 95.19±11.61 mm³ and 99.73±12.03 mm³, respectively. The mean pineal gland volume of the patients with schizophrenia was significantly smaller than those of the other groups.*

Conclusions*: Our data show that patients with schizophrenia have smaller pineal gland volumes, and this deviation in pineal gland morphology is not seen in those with mood disorders. We hypothesize that volumetric changes in the pineal gland of patients with schizophrenia may be involved in the pathophysiology of this illness.*

Key words: *pineal gland volume – MRI - bipolar disorder - unipolar depression - schizophrenia*

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INTRODUCTION

Circadian rhythm disturbances are commonly seen in patients with schizophrenia and mood disorders (Jagannath et al. 2013). These disturbances are risk factors for the onset of psychiatric disorders and are precursors of relapse that are associated with residual symptoms and treatment resistance (Jackson et al. 2003, Cho et al 2008, Nierenberg et al. 1999). For many years an association between pineal gland metabolism, circadian rhythm and mental illness has been suggested (Watterberg 1985). The pineal gland is a small, pinecone-like neuroendocrine organ that influences circadian rhythm and sleep by the secretion of melatonin in a circadian manner (Acer et al. 2011). Melatonin rhythm is generated by an endogenous circadian master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, and is secreted according to the 24 hour cycle of light and darkness (Tan et al. 2003). Abnormalities in pineal function, altered secretion of melatonin, and altered diurnal or nocturnal peaks have been detected in patients with unipolar depression (UD), bipolar depression (BD) and schizophrenia (Brown et al. 1985, Khaleghipour et al. 2012, Rubin et al. 1992, Srinivasan et al. 2006, Whalley et al. 1991, Vigano et al. 2001, Rao et al. 1994).

It is important to determine circadian rhythm disruptions in the study of potential prevention, causes, mechanisms, maintaining factors, and treatment of psychiatric illnesses. To our knowledge, there have been few studies investigating the association between pineal volume and psychiatric disorders. These studies, which have conflicting results, utilized radiological modalities such as brain computerized tomography (CT) and magnetic resonance imaging (MRI). Sarrazin et al. (2011) and Rajarethinam et al. (1995) found no volumetric difference in total pineal volume between patients with BD and schizophrenia and controls. In contrast, Bersani et al. (2002) reported that pineal volume was reduced in male schizophrenic patients, and recently Bumb et al. (2014) found reduced pineal volume in patients with primary insomnia compared to healthy controls.

In the present study, we aimed to evaluate and compare pineal gland volumes in patients with schizophrenia and mood disorders, such as unipolar depression and bipolar disorder.

SUBJECTS AND METHODS

Subjects

We retrospectively evaluated 231 psychiatric outpatients who underwent cranial MRI for various reasons (such as headache and ruling out any organic pathology in outpatients that first admitted to our hospital) according to our electronic hospital information database between 2013 January and 2014 January. These patient had been consulted by neurology and no neuropathology had been detected. Patients with alcohol abuse, recent skull trauma or surgery, pineal tumor or cyst, any endocrinological disease and inadequate electronic hospital records were excluded. After excluding patients based on these criteria, 50 patients were included in this study. Each patient was diagnosed according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition). Sixteen patients were diagnosed with UD, 17 with BD and 17 with schizophrenia. All UD patients were taking antidepressant medication such as SSRI (essitalopram, sertraline, citalopram), most of the BD patients were taking valproate and adjunctive antipsychotics (olanzapine,risperidone, aripiprazole) and only two of them were receiving lithium treatment, and all patients with schizophrenia were taking antipsychotics (risperidone, amisulpiride, flupentixole).

The control group included 30 subjects who underwent a brain MRI for suspect consequences of a recent skull trauma. They had negative results based on MRI, had no DSM-IV Axis I disorders, had no current medical problems, neurologic histories, and did not use psychoactive medication. Approval for this study was obtained from the Local Ethics Committee of the hospital where this study was undertaken (Table 1).

MRI procedure

All MRI studies were performed using the same 1.5 T system (Siemens Magnetom Avanto, Erlangen, Germany). The study protocol included sagittal T1-MPRAGE (TR/TE 1900/3.4, isotropic voxel size 1 mm), axial FLAIR (TR/TE/TI 8500/89/115, slice thickness/5 mm), axial T2*-FLASH (TR/TE 814/26, sl 3 mm), axial triple echo T2-TSE (TR/TE/ TE/TE 3000/98/65/11, sl 3 mm), trueFISP (TR/TE 6.9/3.5, isotropic voxel size 0.8 mm), and T1-MPRAGE (see above) after the administration of 0.2 mmol/kg Gd-DTPA (Magnevist, Bayer-Schering, Germany).

The linear measurements of the pineal gland were obtained automatically for each patient using the appropriate measurement software for previously acquired T1 weighted MRI images. We used FLAIR and T1-weighted images because they provided better contrast resolution for the gland than did the T2-weighted sequences. The neuroradiological measurements were performed by expert research radiologists who were kept blind to other protocol data, the diagnosis, and the identity of the patients. The quadrigeminal cisterna, the superior colliculus and the posterior part of the third ventricle were used as guides for the selection of the axial cuts. The pineal boundary was identified exactly on the sagittal sections taken in addition to the coronal and axial views. The maximum width (W) and height (H) of the pineal gland were measured on the medial coronal images and the length (L) was measured on the axial images. The volume (V) was calculated according to the following formula: V=1/2xHxLxW (Sumida et al. 1996) (Figure 1).

Table 1. Demographic and clinical characteristics of the participants

	Healthy Control	Unipolar Depression	Bipolar Disorder	Schizophrenia
N	30	16	17	17
Age (years)	41.1±13.3	39.4±13.9	30±10.2	36.6±12.7
Sex	16M/14F	8M/8F	11M/6F	11M/6F
Onset (age in years)		35.3±15.5	25.06±10.8	29.00±12.02
Duration of illness (years)		4.1±4.2	4.3±4.09	7.8±6.2
Duration of medication (years)		3.1±2.8	4.7±4.2	7.1±6.5

Values are means ± SD; F: Female; M: Male

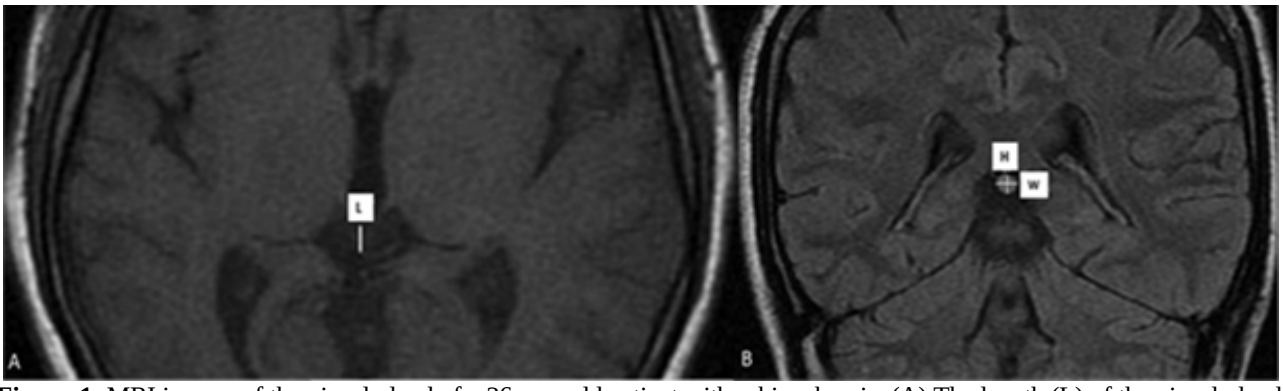

Figure 1. MRI images of the pineal gland of a 26 year old patient with schizophrenia. (A) The length (L) of the pineal gland on T1-weighted axial image, (B) The height (H) and width (W) of the pineal gland on FLAIR sequence coronal image

Table 2. Mean pineal gland volume in the control group and in the patient groups

	Healthy Control	Unipolar Depression	Bipolar Disorder	Schizophrenia
N	30	16	17	17
Mean volume in mm^3 ± SD	99.7±12.03	95.1±11.2	93.7±11.4	83.5±10.1[a]

[a] p=0.001 compared to healthy controls

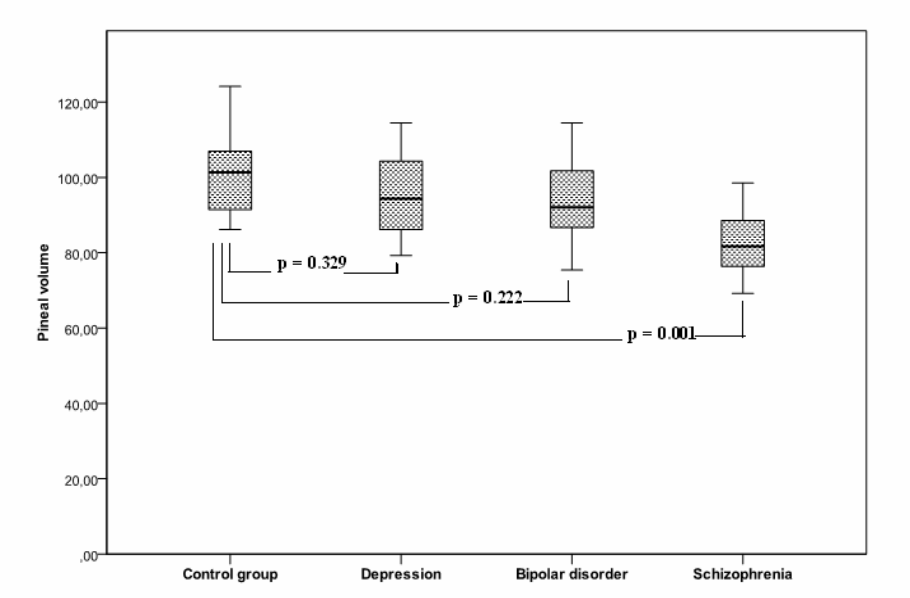

Figure 2. Pineal volume comparison with age- and sex-matched control group

Statistical analysis

The Statistical Package for Social Sciences (SPSS for Windows, version 17.0, SPSS, Chicago, IL, USA) was used for statistical analysis. Student's t-test was used to compare the mean age of the patients. Chi-square analyses were used to assess the gender distribution. Kruskal Wallis and U Mann-Whitney tests were used to compare more than two groups that did not meet the normal distribution. ANOVA and post hoc tests were used to compare groups that met the normal distribution. The Pearson's coefficient was used to investigate correlations between pineal gland volume and age, age at illness onset, duration of illness, and treatment duration. A value of $p<0.05$ was considered statistically significant. Post-hoc power analysis were conducted using pineal gland values as primary outcome and power was calculated as 98.5%.

RESULTS

Demographic data for the patients and controls are presented in Table 1. The differences between the ages and gender compositions of the patient and control groups were not significant ($p>0.05$). The mean total pineal volume was 99.73±12.03 mm^3 in the controls, 95.19±11.61 mm^3 in the UD patients, 93.62±11.00 mm^3 in the BD patients and 83.5±10.11 mm^3 in the patients with schizophrenia (Table 2).

Only the mean pineal gland volume of the patients with schizophrenia was significantly smaller than that of the controls (p=0.001) (Figure 2).

In addition, when patient groups were compared with each other, the pineal gland volume of the patients with schizophrenia was significantly smaller than those of the depressive and bipolar patients (p=0.005 and p=0.018, respectively). Although pineal gland volume in the BD group was smaller than that of the UD group, it was not statistically significant (p=0.721). In patients with schizophrenia, the relationships between pineal gland volume and onset age of the disease (r=-0.243, p=0.403), duration of the disease (r=-0.335, p=0.242) and duration of treatment (r=-0.238, p=0.412) were not statistically significant. In addition, the average pineal gland volume of women was smaller than that of men in schizophrenia group, but it was not statistically significant (77.9±7.4 mm^3 vs. 86.4±10.4 mm^3, respectively, p=0.128).

DISCUSSION

The most important result of our study was that the patients with schizophrenia had significantly smaller pineal gland volumes than did patients with mood disorders, such as unipolar depression and bipolar disorder. Literature suggests that disrupted circadian rhythm and the melatonergic system, which are associated with the pineal gland, may be involved in the pathophysiology of mood disorders and schizophrenia (Jagannath et al. 2013, De Berardis et al. 2013). Rajarethinam et al. (1995) reported that there were no volumetric differences in the pineal gland between patients with schizophrenia and controls. However, in that study, there was no information regarding medica-

tions, onset of illness age, duration of medication and pineal cysts, which are all parameters that may affect results (Sun et al. 2009). Results similar to those of our study were reported by Bersani et al. (2002) who found reduced pineal volume in male patients with schizophrenia.

In our study, the mean illness and treatment durations were longer in the schizophrenia group than in the others, but this difference was not statistically significant. In the study by Bersani et al. (2002) the mean durations of illness and treatment of schizophrenic patients were shorter than those of the patients with schizophrenia in our study. However, they obtained results similar to those from our study, which indicated that patients with schizophrenia had smaller pineal volumes. This indicates that the durations of illness and treatment do not significantly affect pineal volumes. Therefore, we considered that the reduction in pineal gland volume might be a result of delays in the neurodevelopmental process in patients with schizophrenia, as the neurodevelopmental and/or neurodegenerative hypothesis in schizophrenia is well known (Gupta & Kulhara 2010). The developmental period of some brain areas, such as the pineal gland, may be delayed early in life, and neurodegeneration may affect the molecular structure of pineal gland, causing its size to decrease. It is clear that any calcific process is a degenerative process. Results of CT studies revealed a significant association between pineal calcification and early onset and prefrontal cortical atrophy in schizophrenia (Sandyk & Kay 1991, Sandyk 1992) Therefore, we hypothesize that calcification may cause neurodegeneration, which affects the gland volume. In addition, hormonal and genetic factors or a hypofunctional pineal gland may be involved in this structural change as well.

The second most important result of our study was that there was no significant difference in volume of the pineal glands between BD and UD groups. To our knowledge, our study is the first to evaluate the association between UD and pineal gland volume. But there has been one study conducted by Sarrazzin et al. (2011) that investigated the association between the volumetric size of the pineal gland in BD patients and controls, and the results of that study were similar to ours. They concluded that pineal dysfunction was not related with its structure, but may be related to the functional properties of the gland. It is unclear why there are no pineal volume differences in mood disorders. One possibility is that pineal morphology have no effect on melatonin levels. In addition, the acetylserotonin O-methyltransferase (ASMT) is a key enzyme of the melatonin biosynthesis and variations in the melatonin biosynthesis pathway have recently been reported to be associated with psychiatric disorders such as BD and depression (Etain et al. 2012, Galecki et al. 2010, Kripke et al. 2011, Soria et al. 2010). This enzymatic process might be related to impaired functional property of the gland.

The possible molecular mechanisms by which psychotropic drugs effect pineal gland structure and melatonin secretion in psychiatric diseases (schizophrenia, UD, BD) are not fully elucidated. All of our patients were taking medication such as antidepressants (UD), valproate, lithium (BD) and antipsychotics (schizophrenic and BD). Monteleone et al. (1997) found that chronic treatment with antipsychotic drugs did not alter the secretory pattern of melatonin. Mann et al. (2006) reported that melatonin secretion was not significantly changed in schizophrenia after treatment with olanzapine. In contrast, Hallam et al. (2005a, 2005b) reported that both valproate and lithium significantly reduced the sensitivity of melatonin to light, but they had no effect on overall melatonin secretion or dim light melatonin onset. Miller et al. (2001) reported that antidepressants increase melatonin levels, although the mechanism was unclear. Benzodiazepines have been found to reduce nocturnal melatonin secretion (Hajak et al. 1996, McIntyre et al. 1993). In UD and BD patients pineal gland volumes might be affected with complex mechanisms from antidepressants or lithium and valproate that changes the melatonin levels. Previous studies suggest that pineal gland volume (quantified in MRI) is linked to melatonin blood levels (Liebrich et al. 2014, Nolte et al. 2009). In our study we did not determine the melatonin levels. However it is not clear if treatment with these drugs affect melatonin levels and thus pineal size and we could not find any investigation describing the effects of psychotropic medications on pineal volume. In addition, in our study there were no correlation with treatment duration and pineal gland volumes that can support the idea that psychotropics may change the gland sizes. So the effects of various drugs on pineal gland should be further clarified.

Our study has some important limitations. First, the sample size was relatively small. Second, there was no second blinded investigator involved to perform the manual tracing. Third, pineal calcifications were not taken into account. The degree of pineal calcification may vary across the patient groups, and may have affected our results and interpretation. Unfortunately, this study was retrospective, and MRI is not an appropriate method for studying the calcifications. Fourth, melatonin levels were not monitored. It would be useful to monitor plasma melatonin levels to determine their variations throughout the course of the illnesses.

CONCLUSIONS

Although the effects of medication and other mediating factors on gland volume should be further clarified, the results of this study showed that patients with schizophrenia have a significantly decreased pineal gland volume, compared to healthy individuals, that is not seen in patients with mood disorders. The volumetric deviations in the pineal gland in patients with schizophrenia may be involved in the pathophysiology of the illness.

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Conflict of interest: None to declare.

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