Increased prevalence of white matter hyperintensities in patients with panic disorder

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Abstract

The aim of the current study is to compare the prevalence, severity and location of cerebral white matter hyperintensities (WMH) between patients with panic disorder (PD) and healthy control subjects. Patients with PD (n = 24) and matched healthy control subjects (n = 24) were scanned using a 3.0 Tesla whole-body magnetic resonance scanner. Axial T2-weighted and fluid-attenuated inversion recovery images were acquired and evaluated for the prevalence, severity and location of WMH using the modified composite scale of Fazekas and Coffey and coded separately for deep and periventricular WMH. Logistic regression analyses were used to assess the association between WMH and the diagnosis of PD. A greater severity of total WMH was associated with a diagnosis of PD in a dose-dependent pattern (odds ratio [OR] = 8.8, P = 0.005 for mild WMH; OR = 27.7, P = 0.007 for moderate to severe WMH). Deep WMH, where most group differences originated, were predominantly located in the frontal region of the brain (n = 16 in PD, n = 1 in control). The current report is the first study to report an increased prevalence of WMH in patients with PD.

Key words

brain magnetic resonance imaging; panic disorder; white matter hyperintensities

Introduction

Panic disorder (PD) is characterised by recurrent unexpected panic attacks followed by persistent worry about additional attacks or about the consequences of the attacks (American Psychiatric Association, 2000). Lifetime prevalence of PD is estimated to be approximately 4% of the general population with more than 90% of patients with PD seeking treatment (Kessler, et al., 2006). Patients with PD have a substantially decreased quality of life over a long period of time (Markowitz, et al., 1989; Kessler, et al., 2006; Culpepper, 2004).

In an effort to identify the brain-based aetiology of this disabling disorder, brain imaging studies have been conducted. Most consistent findings include abnormal prefrontal function and altered temporal and limbic structures such as parahippocampus and amygdala (Pillay, et al., 2007; Maddock, et al., 2003; Bystritsky, et al., 2001; Ontiveros, et al., 1989; Massana, et al., 2003a, 2003b; Fontaine, et al., 1990). Previous studies conducted by our group have also reported decreased levels of temporal cerebral blood flow (CBF), decreased putaminal grey matter densities and lower gamma-aminobutyric acid (GABA) levels in the cingulate gyrus and basal ganglia of patients with PD relative to healthy control subjects (Lee,
et al., 2006; Yoo, et al., 2005; Ham, et al., 2007). We have also reported in a diffusion tensor imaging study that there is an alteration in white matter tract integrity in patients with PD (Han, et al., 2008).

White matter hyperintensities (WMH) are high signal strength area as distinct from surrounding normal white matter, detected on T2-weighted brain magnetic resonance (MR) images (Awad, et al., 1986). The size of WMH ranges from small dots to patchy or diffuse regions. In part, due to an increased accessibility of MR scanner, WMH are more commonly reported on routine brain MR scans and frequently designated as small vessel disease or unidentified bright object.

Although WMH were commonly regarded as incidental findings or benign senile changes of brain in the past, they have consistently been reported to have close associations with pathological conditions like cognitive impairment (Gouw, et al., 2006; Debette, et al., 2007) and with a number of psychiatric disorders including schizophrenia (Keshavan, et al., 1996), bipolar disorder (Ahn, et al., 2004), major depressive disorder (de Groot, et al., 2000; Iosifescu, et al., 2006; Lenze, et al., 1999), and drug dependence (Bae, et al., 2006; Lyoo, et al., 2004). These WMH found in patients with psychiatric disorders are generally hypothesized to represent deficits in white matter tracts. Structural and functional abnormalities of white matter tracts have been reported not only to be present in psychiatric disorders but also related to their clinical severity (Skelly, et al., 2008; Szeszko, et al., 2005).

Considering the high prevalence and association with clinical severity of WMH in various psychiatric disorders, it would be worthwhile to investigate the prevalence of WMH in patients with PD. WMH in PD, however, have not been reported to the best of our knowledge.

Based on previous studies on other psychiatric disorders, we hypothesized that there would be a greater prevalence of WMH in patients with PD relative to healthy control subjects. We also investigated the association between the prevalence or severity of WMH and clinical severity of PD. As an auxiliary hypothesis, we tested whether white matter lesions are located in frontotemporal regions in the brain, based on aforementioned studies showing the disrupted structures and functions in these brain regions (Maddock, et al., 2003; Fontaine, et al., 1990; Bystritsky, et al., 2001).

**Materials and methods**

**Participants and clinical assessment**

Twenty-four PD patients with or without agoraphobia, as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) administered by an experienced psychiatrist, were recruited through the outpatient-based Panic Disorder Clinic and inpatient units at the Seoul National University Hospital, Seoul, South Korea. Twenty-four matched healthy control subjects were recruited through advertisements in local newspapers in Seoul, South Korea.

Exclusion criteria for study participants included (1) a current diagnosis or history of axis I psychiatric disorder other than PD, (2) axis II antisocial or borderline personality disorders, as identified by the Personality Disorder Questionnaire-4 (Hyler, et al., 1990), (3) current or past serious medical or neurological disorders, (4) contraindications to MR scanning including metal implants, pregnancy or claustrophobia and (5) any lifetime exposure to DSM-IV dependence- or abuse-related drugs except nicotine, caffeine, social drinking of alcohol or prescribed medication. Illicit drug use of cocaine, opiate, methamphetamine, phencyclidine or marijuana was also screened using urine toxicology at the time of scan.

Patients with PD were assessed for clinical severity of panic symptoms using the Panic Disorder Severity Scale (PDSS) (Shear and Maser, 1994). Comorbid depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) administered by a clinical psychologist and the Zung Self-Rating Anxiety Scale (Z-SAS) (Zung, 1971; Wang, 1978) completed by study participants. After complete description of the study, written informed consent approved by the Institutional Review Boards at the Seoul National University Hospital was obtained from all subjects prior to enrolment.

**Magnetic resonance imaging and WMH rating**

Brain magnetic resonance imaging (MRI) was performed using a 3.0 Tesla General Electric (GE) whole-body imaging system (VH/i, Wis., USA). In addition to the anatomical T1 MR imaging (Yoo, et al., 2005), axial T2-weighted images (echo time, TE = 118 ms; repetition time, TR = 3500 ms; 256 × 192 matrix; field of view, FOV = 22 cm; flip angle = 90°; three number of excitation, NEX; 5-mm-thick slices; 1.5 mm skip) and fluid-attenuated inversion recovery (FLAIR) axial images (TE = 145 ms; TR = 9900 ms; inversion time, TI = 2250 ms; 256 × 192 matrix; FOV = 22 cm; flip angle = 90°; 1 NEX; 5-mm-thick slices; 1.5 mm skip) were obtained to evaluate brain structural abnormalities including WMH. No gross structural abnormalities other than WMH were found in both groups of subjects.

A neuroradiologist, who was blind to clinical information including the reason for referral and diagnosis, reviewed T2 and FLAIR images on all MRI scans. These readings were used to determine the prevalence and location of WMH. The prevalence of WMH was assessed and coded separately for deep and periventricular WMH (Coffey, et al., 1990; Kertesz, et al., 1988). Insular WMH were included in the deep WMH ratings (Ahn, et al., 2004; Lyoo, et al., 2002).

The Fazekas classification (Fazekas, et al., 1987) defined foci of hyperintensity in the deep white matter as follows: grade 0 = absence, grade 1 = punctuate foci, grade 2 = beginning confluence of foci and grade 3 = large confluent area. Subjects with grade 1 WMH by the Fazekas classification...
were further classified based on a modified version of the Coffey classification (Coffey, et al., 1990): grade 1–1 = (number \( n \) of 1 or 2 and each with a diameter of less than 5 mm), grade 1–2 = (\( n \) less than 10 and the largest lesion having a diameter between 5 and 10 mm) and grade 1–3 = (\( n \) of 10 or more or at least one lesion with a diameter greater than 10 mm). There were no grade 2 and 3 deep white matter lesions observed on brain MR images for our study subjects. We therefore rated deep WMH into 2 grades (no WMH and grade 1 WMH).

Fazekas classification was used to assess periventricular white matter severities: grade 0 = absence, grade 1 = cap or pencil-thin lining, grade 2 = smooth halo and grade 3 = irregular periventricular WMH extending into the deep white matter. There were no grade 3 periventricular lesions observed on brain MR images in our study subjects. Laterality as well as the specific location in the cerebrum of WMH was also noted. Location was classified as follows: frontal, temporal, parietal, occipital and insular regions for deep WMH; frontal, temporal and occipital for periventricular WMH.

Total WMH were calculated by summing the grades of deep WMH and periventricular WMH. Three patients with PD had summed scores of greater than 3. However, because no control subjects had score of 3, the subjects with scores 2 or 3 of total WMH were put into one group to estimate the odds ratio (OR) for severe total WMH versus no lesions. The resulting three groups were denominated as no WMH group (\( n = 23 \), WMH in neither deep nor periventricular areas), mild WMH group (\( n = 16 \), grade 1 WMH in either deep or periventricular areas) and moderate to severe WMH group (\( n = 9 \), any grade 2 WMH or grade 1 WMH in both deep and periventricular areas).

Kappa values of intrarater reliability measures were 0.86 and 0.84 for severity of deep and periventricular WMH, respectively. Those for severity of deep and periventricular WMH were 0.79 and 0.78, respectively.

**Statistical analysis**

Group differences in continuous and categorical variables were computed by independent \( t \)-tests and chi-square tests, respectively.

To assess group differences in severity of deep or periventricular WMH between patients with PD and healthy control subjects, logistic regression analyses were performed with PD as a dependent variable after adjusting for age and sex composition.

To determine the clinical relevance of WMH in PD, associations between symptom severity (measured by PDSS and Z-SAS scores) and stratified severity of total WMH (no WMH/mild WMH/moderate to severe WMH) were evaluated by using multiple linear regression analyses controlling for HDRS scores, age and sex composition.

Statistical significance was defined at an alpha level of less than 0.05, two-tailed. Stata 7.0 for Windows was used for all computations.

**Results**

Detailed clinical and demographic information is presented in Table 1. There were no significant differences in age or sex composition between groups (Table 1). All patients with PD were under treatment with a combination of antidepressants and/or anxiolytics. Detailed information on medication is shown in Table 1. After adjusting age and sex composition, a greater severity of total WMH was associated with a diagnosis of PD (dose-dependent pattern; mild WMH, OR = 8.8, \( P = 0.005 \); moderate to severe WMH, OR = 27.7, \( P = 0.007 \)). A similar pattern was observed in the association between deep WMH and PD (grade 1 WMH, OR = 75.8, \( P = 0.001 \)).

<table>
<thead>
<tr>
<th>Table 1 Demographic and clinical characteristics of patients with panic disorder and healthy control subjects</th>
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<tbody>
<tr>
<td><strong>Panic disorder patients</strong> ((n = 24))</td>
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<td>---------------------------------</td>
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<tr>
<td><strong>Demographic variables</strong></td>
</tr>
<tr>
<td>Age (years) &amp; 32.3 (6.6)</td>
</tr>
<tr>
<td>Male &amp; 13 (54.2%)</td>
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<tr>
<td><strong>Clinical variables</strong></td>
</tr>
<tr>
<td>Duration of illness (years) &amp; 3.5 (2.0)</td>
</tr>
<tr>
<td>Duration of treatment (weeks) &amp; 11.2 (2.0)</td>
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<tr>
<td>PDSS scores &amp; 8.8 (5.6)</td>
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<tr>
<td>Z-SAS scoresa &amp; 42.1 (8.8)</td>
</tr>
<tr>
<td>HDRS scoresb &amp; 4.2 (5.1)</td>
</tr>
<tr>
<td><strong>Medication status</strong></td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Fluoxetine &amp; 10 (41.7%)</td>
</tr>
<tr>
<td>Paroxetine &amp; 7 (29.2%)</td>
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<tr>
<td>Mirtazapine &amp; 6 (25.0%)</td>
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<tr>
<td>Sertraline &amp; 1 (4.2%)</td>
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<tr>
<td>Bupropion &amp; 1 (4.2%)</td>
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<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Clonazepam only &amp; 15 (62.5%)</td>
</tr>
<tr>
<td>Alprazolam only &amp; 5 (20.8%)</td>
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<tr>
<td>Both &amp; 2 (8.3%)</td>
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<tr>
<td>None &amp; 2 (8.3%)</td>
</tr>
</tbody>
</table>

PDSS, Panic Disorder Severity Scale; Z-SAS, Zung Self-Rating Anxiety Scale; HDRS, 17-item Hamilton Depression Rating Scale.

Data are mean (SD) or number (%).

*There was one missing value for this variable.

*There were three missing values for this variable.

One subject was taking both fluoxetine and mirtazapine.
but not between periventricular WMH and PD ($P = 0.19$) (Table 2).

Locations of deep WMH were as follows: frontal brain region ($n = 16$, PD; $n = 1$, control), temporal region ($n = 1$, PD; $n = 0$, control), parietal region ($n = 3$, PD; $n = 0$, control) and insula ($n = 1$, PD; $n = 0$, control). Numbers for the above WMH locations were not mutually exclusive. Deep WMH were either right lateralized ($n = 3$, PD; $n = 0$, control) no left-sided lesions for both groups or bilateral ($n = 13$, PD; $n = 1$, control).

Locations of periventricular WMH were as follows: frontal brain region ($n = 10$, PD; $n = 6$, control), temporal brain region ($n = 1$, PD; $n = 0$, control) and occipital brain region ($n = 3$, PD; $n = 0$, control). Lateralization of the periventricular WMH is as follows: right sided ($n = 1$, PD; $n = 0$, control), left sided ($n = 0$, PD; $n = 0$, control) and bilateral ($n = 10$, PD; $n = 6$, control).

To find out whether a greater prevalence of total WMH is correlated with symptom severity in PD, multiple linear regression analyses were performed with PDSS and Z-SAS scores as dependent variables and patient subgroup stratified according to severity of total WMH, as described in the Methods section, as a predictor variable. HDRS score, age and sex composition were included in the model as covariates. Significant association between clinical severity as measured by Z-SAS and severity of total WMH was noted ($b = 7.7$, $t = 2.65$, $df = 15$, $P = 0.018$). There was no significant association between the PDSS score and severity of total WMH ($b = -0.9$, $t = -0.47$, $df = 16$, $P = 0.64$).

**Table 2** Group differences in severity of WMH between patients with panic disorder and healthy control subjects, adjusted for age and sex composition

<table>
<thead>
<tr>
<th>Total WMH</th>
<th>Unadjusted</th>
<th>Adjusted</th>
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<tr>
<td></td>
<td>Panic disorder, $n$ (%)</td>
<td>Controls, $n$ (%)</td>
</tr>
<tr>
<td>No WMH</td>
<td>5 (20.8)</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Mild WMH</td>
<td>11 (45.9)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Moderate to severe WMH</td>
<td>8 (33.3)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Deep WMH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No WMH</td>
<td>8 (33.3)</td>
<td>23 (95.8)</td>
</tr>
<tr>
<td>Grade 1 WMH</td>
<td>16 (66.7)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Periventricular WMH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No WMH</td>
<td>13 (54.2)</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>≥Grade 1 WMH</td>
<td>11 (45.8)</td>
<td>6 (25.0)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; WMH, white matter hyperintensity.

*Odds ratios were adjusted for age and sex.

Discussion

The current study constitutes the first report of an increased prevalence of cerebral WMH in patients with PD relative to matched healthy control subjects, located predominantly in the frontal region of the brain. On the clinical side, the prevalence of WMH was associated with the level of anxiety symptoms.

These findings are in line with previous reports which have consistently shown increased prevalence of WMH and its association with clinical severity of psychiatric disorders. In patients with affective disorders, higher rates and severity of WMH were reported, especially in the elderly (Altshuler, et al., 1995; Aylward, et al., 1994; Coffey, et al., 1990; Iosifescu, et al., 2006; Lyoo, et al., 2002; O’Brien, et al., 1998; Sheline, et al., 2008). It has been suggested that disrupted emotional circuitry inclusive of the frontal brain regions may have resulted in mood dysregulation (O’Brien, et al., 1998; Sheline, et al., 2008). Patients with schizophrenia also had greater prevalence of WMH (Keshavan, et al., 1996; Sachdev and Brodaty, 1999).

Deep WMH, where most group differences originated, are known to have a more solid pathological basis than periventricular WMH (Ince and Fernando, 2002) even though controversy exists. Further, deep WMH have more frequently been associated with psychiatric disorders than periventricular WMH (Brown, et al., 1992; de Groot, et al., 2000; Krishnan, et al., 2006; Keshavan, et al., 1996).

Our observation that WMH were predominantly located in the frontal region of the brain can efficiently be explained from the perspective of the previous studies. The fear circuitry model from animal studies indicates that dysfunction in the prefrontal brain region may play an important role in the pathophysiology of anxiety disorders (Charney, 2003; Sotres-Bayon, et al., 2006). Human neuroimaging studies also imply that there would be subtle deficits in the frontal brain region in patients with anxiety disorders (Berkowitz, et al., 2007; Cannistraro and Rauch, 2003; Gorman, et al., 2000; Milad, et al., 2005). Indirect evidence also suggests that higher cortical function might
be impaired in patients with PD (Galderisi, et al., 2008; Gorman, et al., 2000).

Underlying pathophysiology of increased prevalence and severity of WMH in patients with PD cannot be inferred from the current study. However, in the intriguing report of Woods, et al. (1988), patients with PD experiencing anxiety attacks had blunting or decreased CBF reflecting cerebral vasoconstriction, while lactate infusions generally increase the CBF in healthy volunteers (Woods, et al., 1988). Decreased blood flow and vasoconstriction may have affected the prevalence and severity of WMH (Mantyla, et al., 1999). Similarly, migraine, which is thought to be caused by cerebral vasoconstriction, is associated with increased prevalence of white matter lesions (Kruit, et al., 2004; De Benedittis, et al., 1995; Gladstone and Dodick, 2005; Swartz and Kern, 2004).

Perturbed serotonergic and noradrenergic systems and their miscommunication may explain the exaggerated cerebral vasoconstrictive response (Coplan and Lydiard, 1998; Gorman, et al., 2000). To our interest, this presumptive hypothesis may provide coherent explanations for symptoms of PD. The high coprevalence of hypertension and PD, both of which are known to show abnormal hemodynamic response and increased norepinephrine release, may potentially stem from dysfunctional noradrenergic system and impaired serotonergic system (Davies, et al., 2007; Faravelli, et al., 1997; Wilkinson, et al., 1998). Sudden physical symptoms mimicking those of the heart disease such as palpitation, sweating, flushes and chest pain during panic attacks which are closely associated with sympathetic dysregulation is also well explained in view of this “common aetiology hypothesis” between hypertension and PD (Davies, et al., 2007; Westenberg and Liebowitz, 2004). However, because this study does not provide data regarding the relationship between PD, hypertension and serotonergic/noradrenergic system, this point is only raised as an effort to understand the underpinnings of the current findings.

The association between clinical severity of anxiety symptoms with severity of WMH may provide clinical implication of WMH in patients with PD. However, caution is required in interpreting the results, because PDSS and Z-SAS scores were relatively low possibly owing to the treatment before evaluation, and Z-SAS scores are less specific to panic symptoms.

There are limitations of the present study that should be mentioned. Even though subjects who report serious medical or neurological disorders were excluded from the study participation, information regarding medical comorbidity was primarily obtained by self-reports and less serious medical conditions were not thoroughly investigated. Factors that have been reported to contribute to pathogenesis of WMH include cardiovascular diseases of cardiac failure, coronary heart disease or atrial fibrillation (Jeerakathil, et al., 2004). Risk factors for these cardiovascular diseases such as smoking, hypertension or diabetes have been known to be associated with increased prevalence or severity of WMH (Dufouil, et al., 2001; Novak, et al., 2006). Patients with neurologic disorders including migraine and multiple sclerosis also are at increased risk for cerebral WMH (Kruit, et al., 2004; Lyoo, et al., 1996). Consequently, smoking status, comorbid hypertension or diabetes may have potentially confounded our findings.

Relatively small sample size limits the generalizability of the findings. Prior exposure to benzodiazepines and antidepressants may have confounded our findings. Studies examining the association between antidepressant treatment and the prevalence or severity of WMH mainly focus on the effects of WMH on treatment response (Hickie, et al., 1995; Iosifescu, et al., 2006; Moore, et al., 2001; O’Brien, et al., 1998; Yanai, et al., 1998). A longitudinal study conducted in patients with major depressive disorder suggests that effective treatment with antidepressants may slow the rate of progression of cerebral WMH (Taylor, et al., 2003). Because the current study is a cross-sectional observation of the patients who have already taken psychotropic medications, the medication effects on WMH could not be determined and should be taken into account in interpreting the results.

Also, being a cross-sectional study, the causality of the findings cannot be determined. A longitudinal follow-up study is recommended to assess potential causality and to better understand the role of cerebral WMH in patients with PD.

In conclusion, we first report an increased prevalence of WHM in patients with PD relative to healthy control subjects. Further studies that explore the underlying pathophysiology of WMH in PD are needed.

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