Structural Abnormality on Brain Magnetic Resonance Imaging in Late-onset Major Depressive Disorder

Hsiu-Fen Lin, Yu-Ting Kuo,[1] I-Chan Chiang,[1] Hui-Mei Chen,[2] and Cheng-Sheng Chen[3,4]
Departments of Neurology, [1]Medical Imaging, and [3]Psychiatry, Kaohsiung Medical University Chung-Ho Memorial Hospital, [2]Department of Occupational Therapy, College of Health Science, Kaohsiung Medical University, [4]Department of Psychiatry, Kaohsiung Municipal Hisao-Kang Hospital, Kaohsiung, Taiwan.

The purpose of this study was to examine the structural abnormalities of patients with late-onset major depressive disorder using brain magnetic resonance imaging (MRI) and to assess clinical correlates of these structural abnormalities. Thirty-seven elderly patients with DSM-IV major depressive disorder that first occurred after the age of 50 years, and 18 control subjects without depression were recruited. All participants underwent comprehensive psychiatric assessment and cerebral MRI. Brain ventricular and sulcal sizes and white matter hyperintensities were assessed visually. Relative to control subjects, patients with late-life major depressive disorder showed more severe brain atrophy ($p = 0.043$) and white matter hyperintensities ($p = 0.024$), especially in the periventricular area ($p = 0.012$). Over 60% of the patient group had significant brain MRI hyperintensities. White matter hyperintensity was correlated with later onset of depressive illness ($r = 0.49$, $p = 0.002$) among patients. Brain atrophy and white matter hyperintensities are prevalent in patients with late-onset major depressive disorders. These two abnormalities may represent different pathophysiologic processes of depressive disorders. White matter hyperintensities may be predisposing factors for late-onset major depressive disorder.

Key Words: aged, depressive disorder, MRI, brain atrophy, hyperintensities
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Late-life major depressive disorder is associated with greater risk of disability, morbidity, and mortality, has been identified as a major public health problem [1], and is heterogeneous in clinical presentation, etiology, and clinical outcome. For example, some late-life depressives present with the first depressive episode in late life, while others have had recurrent depression from a young age. There are different risk profiles between these two groups. Compared to early-onset late-life depressives, patients with late-onset major depressive disorder appear to have more comorbidity with vascular disease [2], more cognitive impairment [3,4], and a higher rate of dementia on follow-up [5]. Neurobiologic processes in the brain may play a crucial role in the occurrence of late-onset major depressive disorder.

The brain abnormalities of brain atrophy and white matter hyperintensities on magnetic resonance imaging (MRI) are common among patients with late-life depression [6–8] and are considered to represent relatively independent pathways to late-life major depression [9]. Smaller brain volume is seen in subjects with earlier age of depression onset, and recurrent or chronic depression may have a neurotoxic effect on brain tissue [10]. White matter hyperintensities are considered a predisposing factor for late-onset depression [11].

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Address correspondence and reprint requests to: Dr. Cheng-Sheng Chen, Department of Psychiatry, Chung-Ho Memorial Hospital, Kaohsiung Medical University, 100 Tzyou 1st Road, Kaohsiung 807, Taiwan.
E-mail: sheng@cc.kmu.edu.tw

We conducted this case–control study to investigate the brain structural abnormalities detected by MRI in patients with late-onset major depressive disorder, as compared to healthy elders. We also attempted to characterize clinical correlates of brain abnormalities among depressive elders, in order to provide some information on the relationship between anatomy and psychopathology. We hypothesized that brain atrophy and white matter hyperintensities would be more prominent in late-onset major depressive disorder. Older age at onset of major depression would be correlated with the severity of white matter hyperintensities, while brain atrophy would be greater in patients experiencing the first episode of major depressive disorder earlier in life.

Patients and Methods

Thirty-seven consecutive elders aged 60 years or more with late-onset major depressive disorder and who were seen at one teaching hospital psychiatric clinic were recruited, while 18 volunteer elderly subjects aged 60 years or more without any mental or neurologic disorders or history were used as controls. Each study participant underwent physical examination, routine biochemistry testing, and psychiatric interview by one psychiatrist using the Chinese version of the Geriatric Mental State Schedule [12], and diagnosis was made according to DSM-IV criteria [13]. Depression severity was measured using the 17-item Hamilton Rating Scale for Depression (HRSD) [14]. A questionnaire to ascertain any history of vascular diseases such as hypertension, diabetes mellitus, heart disease, and hyperlipidemia was also administered.

The inclusion criteria were that subjects' current age was at least 60 years, there was a diagnosis of major depressive disorder, a current HRSD score of at least 15, and an age of at least 50 years at the onset of major depressive disorder. Cases with another DSM-IV Axis I diagnosis or a clinical history of major neurologic illness (such as stroke, Parkinson's disease, epilepsy, traumatic head injury) were excluded. Control subjects were recruited by advertisement and underwent the same assessment as the case group. They had no psychiatric diagnosis according to DSM-IV. The research protocol was approved by the institutional review board of Kaohsiung Medical University, and written informed consent was obtained from each participant.

MRI acquisition and rating

MRI scans were obtained on a 3-T scanner (Signa VH3, GE Medical Systems, Milwaukee, WI, USA). Spin-echo T1-weighted axial and sagittal images (TR 484, TE 8–9 msec; two signals acquired; matrix size 256 × 192; section thickness 7 mm; intersection gap 0 mm), fast spin-echo T2-weighted axial images (TR 4000, TE 98 msec; two signals acquired; matrix size 256 × 256; section thickness 7 mm; intersection gap 0 mm), and fluid-attenuated inversion recovery and diffusion-weighted axial images with single-shot echo-planar imaging (TR/TE 10,000/minimum; b = 0, 1,000; field of view 30; slice thickness 5 mm; intersection gap 1 mm) were obtained.

Brain MRI studies were rated by a radiologist blinded to clinical data. Brain atrophy on MRI was assessed according to the Cardiovascular Health Study (CHS) protocol [15,16], while Fazekas criteria were used to assess the severity of white matter hyperintensities [17]. Ischemic infarctions were defined as the presence of infarct-like lesions. Variables estimated in the CHS protocol were ventricular and sulcal size on a 10-point scale (0–9). Cerebral ventricular size was assessed on a scale of 0–9 with successively increasing ventricular size ranging from small and presumably normal (grade 1) to severe enlargement (grade 8). Grade 0 was considered smaller than grade 1, while grade 9 was worse than grade 8. The assessment for sulcal widening was similar. A composite grade of ventricular size and sulcal size was the indicator of brain atrophy. The Fazekas scale was used to measure hyperintensities in periventricular white matter (PWM) and deep white matter (DWM). PWM hyperintensities were graded as absent (grade 0), cap (grade 1), smooth halo (grade 2), or irregular and extending into DWM (grade 3); DWM hyperintensities were graded as absent (grade 0), punctate foci (grade 1), early-confluent (grade 2), or confluent (grade 3). A score of 2 or more in any area was counted as a significant white matter hyperintensity [11]. The intrarater reliability represented by intraclass correlation coefficient of MRI hyperintensities in two regions and brain atrophy rating ranged from 0.80 to 0.89.

Statistical analysis

Student's *t* test or Chi-squared analysis was used to compare demographic data between the patient and control groups. Bivariate correlations were calculated using Pearson's product-moment analysis. The alpha criterion for significance was 0.05 or less.

Results

There were no statistical differences in gender distribution, age, marital status, and education between the two groups (Table 1). The depressive elderly scored lower on the Mini Mental State Examination (MMSE) and were more likely to

have at least one vascular disease, but the difference was not statistically significant. The mean age at onset of the first episode of major depressive disorder was 63.7 ± 9.7 years, and mean HRSD score was 21.9 ± 6.6 in the patient group.

Table 2 compares brain structural abnormalities in terms of ventricular size, sulcal size, white matter hyperintensities, and infarction lesions. Patients had more severe total brain atrophy (10.88 ± 2.58) than controls (9.29 ± 2.49). White matter hyperintensities were also more severe in patients compared to controls. The hyperintensities were more prominent in the PWM (1.52 ± 0.80) than in the DWM (0.88 ± 0.74). Twenty-three patients (62.2%) had significant white matter hyperintensities. Brain infarct lesions were observed in four patients (10.8%) and one control subject (5.6%), but the difference was not significant ($\chi^2 = 0.49$, $p = 0.486$). Cerebral MRIs of a patient aged 77 years and a control subject aged 78 years are shown in Figure 1.

Total brain atrophy and white matter hyperintensities were selected for further analysis for clinical correlates. For patients, total HRSD and MMSE scores were not correlated with either total brain atrophy or white matter hyperintensities. Age at onset was not correlated with total brain atrophy ($r = 0.21$, $p = 0.218$) (Figure 2), but later onset was associated with more severe white matter hyperintensities ($r = 0.49$, $p = 0.002$) (Figure 3). Duration since onset of major depressive disorder was not correlated with total brain atrophy ($r = 0.07$, $p = 0.673$).

Discussion

In this clinical study, brain structural abnormalities were more prominent in patients with late-onset major depressive disorder compared with healthy control subjects. The abnormalities reflected an excess of total brain atrophy and white matter hyperintensities, especially in periventricular regions. Over 60% of subjects with late-onset major depressive disorder had significant white matter hyperintensities. More severe white matter hyperintensities were associated with later onset of depressive illness.

Table 1. Univariate analysis for demographic and clinical features

	Controls (n = 18)	Late-onset MDD (n = 37)	t or χ^2	p
Gender (female)	12 (66.7%)	23 (62.2%)	0.01	0.948
Age (yr)	70.2 ± 4.7	72.2 ± 3.6	1.64	0.108
Education (yr)	5.9 ± 5.2	5.3 ± 4.6	0.45	0.658
Married	12 (66.7%)	17 (45.9%)	1.68	0.196
Presence of vascular related disease	12 (66.7%)	25 (67.6%)	0.16	0.693
MMSE	28.4 ± 1.4	27.6 ± 1.7	1.63	0.109
17-item HRSD	3.7 ± 3.3	21.9 ± 6.6	10.63	0.001
Age at onset (yr)	–	63.7 ± 9.7	–	–
Years since onset	–	8.5 (8.8)	–	–

MDD = major depressive disorder; MMSE= Mini Mental State Examination; HRSD = Hamilton Rating Scale for Depression.

Table 2. Magnetic resonance imaging ratings in patients with late-onset major depressive disorder (MDD) and controls

	Controls (n = 18)	Late-onset MDD (n = 37)	t or χ^2	p
CHS classification				
Total atrophy	9.29 ± 2.49	10.88 ± 2.58	2.08	0.043
Sulcal widening	4.94 ± 1.64	5.82 ± 1.51	1.89	0.065
Ventricular dilation	4.35 ± 1.62	5.06 ± 1.48	1.55	0.127
Fazekas classification				
Total	1.67 ± 1.14	2.57 ± 1.44	2.32	0.024
PWMH	0.88 ± 0.86	1.52 ± 0.80	2.60	0.012
DWMH	0.88 ± 0.70	0.88 ± 0.74	0.02	0.987
Brain infarct	1 (5.9%)	4 (12.1%)	0.49	0.486

CHS = Cardiovascular Health Study; PWMH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities.

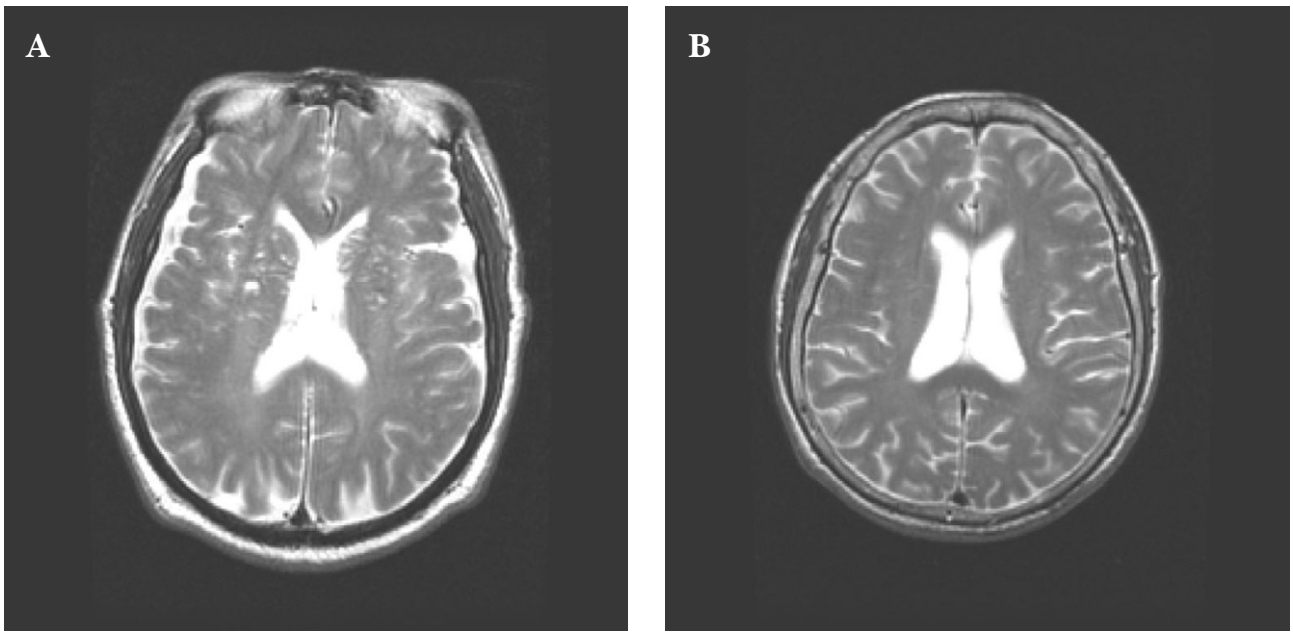

Figure 1. *Examples of T2-weighted magnetic resonance imaging of (A) a patient aged 77 years with prominent brain atrophy and white matter hyperintensities, and (B) a control subject aged 78 years.*

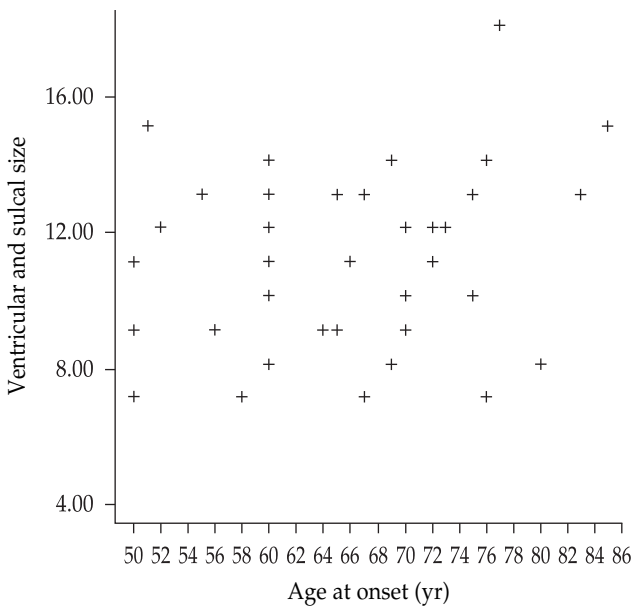

Figure 2. *Correlation between brain ventricular and sulcal size and age of depression onset among patients with late-onset major depressive disorder.*

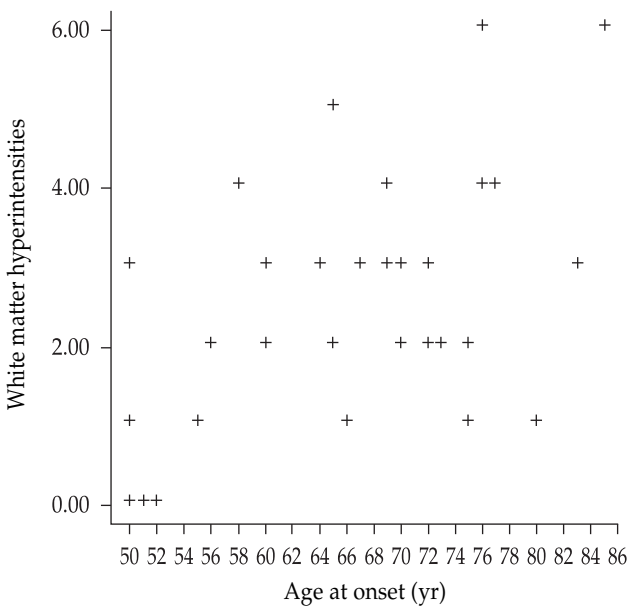

Figure 3. *Correlation between white matter hyperintensities and age of depression onset among patients with late-onset major depressive disorder.*

Our findings, which show the high frequency of white matter hyperintensities and brain atrophy in individuals with late-onset major depressive disorders, are consistent with previous studies [18–21]. Over 60% of the patient group had white matter hyperintensities, which is consistent with most but not all of the studies in the literature [18–22]. The brain structural abnormalities more prominently seen in depressed elders may be associated with both the trait of developing a mood disorder, the current state of depression, and brain changes that have occurred over time as a function of living with depression. It is a challenge to clarify which of these factors contribute to the brain structural abnormalities. We attempted to address this issue by examining the clinical correlates of brain structural

abnormalities, and found that white matter hyperintensity was associated with later age at onset of major depression. Since depressed patients with white matter hyperintensities had a limited duration of being in a depressed state and less exposure to psychiatric treatment, it is likely that white matter hyperintensity is more of a reflection of the etiologic factors that produce the depressive syndrome than an adverse consequence of being depressed.

T2-weighted hyperintensities are associated with reduced regional cerebral vascular flow in the cerebral cortex [23,24]. Given that increased hyperintensity severity correlates strongly with cerebrovascular risk factors [17,25], vascular mechanisms or vascular pathology have been considered as a factor that causes a subgroup of late-life major depressive disorder, and a subtype of vascular depression has been proposed [11,26]. Pathologic ischemic changes associated with white matter hyperintensities have also been suggested [27–29]. The ischemic change may interrupt the frontostriatal pathway that regulates mood and produce depressive symptoms [30]. The fact that hyperintensities damage the structure of brain tissue was also supported by a recent diffusion tensor imaging study [31]. Thus, our findings support the vascular depression hypothesis, which suggests that vascular pathology is a predisposing factor for late-life depression [26].

It is possible that the causes of brain atrophy in depressed elders include an active neurodegenerative process or the effects of chronic disease on brain structure [9,32]. However, our results did not find a correlation between brain atrophy and any clinical features, including duration of illness. Depressed patients with brain atrophy, especially in the hippocampus, are reportedly more likely to develop dementia [33]. We attempted to assess the relationship between cognitive function and severity of brain atrophy in depressed patients by calculating the correlation coefficients. However, the relationship was negative. This negative association may be because we confined patients to those with an MMSE score of more than 24, in order to exclude patients with prominent cognitive impairment. Requiring high MMSE scores for study inclusion decreased the likelihood of observing significant associations between MMSE scores and brain atrophy. Hence, even though the correlations between MMSE score and brain atrophy did not reach significance, it is possible that depressed patients with more severe brain atrophy are at greater risk of developing cognitive decline or Alzheimer's disease on follow-up. Further prospective studies are needed to address this possibility.

One limitation of this study was the small sample size, which may lead to a greater type I statistical error. In addition, enlarged ventricular and sulcal size does not always reflect atrophic pathogenesis. More precise MRI volumetry would be an alternative and better method to define brain atrophy. Moreover, a cross-sectional design may limit the cause–effect inference. Although we tried to determine the cause–effect issue by calculating the association of brain abnormalities and clinical correlates, further prospective investigations with a larger sample size using MRI volumetry are needed to replicate the findings of this study.

In conclusion, this study found a relatively high rate of brain abnormalities, including white matter hyperintensities and brain atrophy, in patients with late-onset major depressive disorder relative to control subjects. White matter hyperintensities may be a predisposing factor for late-onset major depressive disorder.

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晚發型重度憂鬱症腦部磁振攝影掃描之異常

林秀芬[1] 郭禹廷[2] 蔣宜璋[2] 陳惠媚[3] 陳正生[4,5]

高雄醫學大學附設中和紀念醫院 [1]神經科 [2]醫學影像科 [4]精神科

[3]高雄醫學大學 健康科學院 職能治療學系

[5]高雄市立小港醫院 精神科

本研究目的為以磁振攝影掃描比較晚發型重度憂鬱症患者的腦部結構異常，並評估這些結構異常與臨床變項的相關性。研究對象為 37 位診斷為晚發型重度憂鬱症與 18 位對照組的老人。所有研究參與者接受完整的精神科評估、腦部磁振攝影檢查。比較對照組，晚發型重度憂鬱症的老人有較嚴重的腦部萎縮 ($p = 0.043$) 及白質高密度顯影的異常 ($p = 0.024$)，尤其位在腦室週邊的白質 ($p = 0.012$)。超過 60% 的病人有顯著的白質高密度顯影異常。這些白質高密度顯影的異常與發病年齡有正相關 ($r = 0.49$，$p = 0.002$)。腦部萎縮與白質高密度顯影的異常在晚發型老年憂鬱症是普遍的。這兩種影像學上的異常可能代表憂鬱症不同的疾病機轉。高密度顯影的異常可能為晚發型重度憂鬱症的潛存因子 (predisposing factors)。

關鍵詞：老年，憂鬱症，磁振掃描攝影，腦部萎縮，高密度顯影

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通訊作者：陳正生醫師

高雄醫學大學附設中和紀念醫院精神科

高雄市三民區自由一路 100 號