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Treatment response and cognitive impairment in major depression: Association with C-reactive protein

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ABSTRACT

Levels of inflammatory markers have been found to be significantly associated with major depressive disorder (MDD) and cognitive impairment. The aim of this study was to investigate whether the level of C-reactive protein (CRP) is correlated with depressive mood and cognitive impairment in MDD patients. In 149 subjects with MDD, the 21-item Hamilton Rating Scale for Depression (HAM-D), Continuous Performance Test (CPT), Finger-Tapping Test (FTT), and Wisconsin Card-Sorting Test (WCST) were administered before and after antidepressant treatment. Besides, the level of CRP was measured. After 6 weeks of treatment, the total HAM-D scores decreased significantly. In addition, the subjects' performance in the masked CPT and the WCST with completed categories significantly improved ($p < 0.001$ and $p = 0.027$, respectively) after the reliable change indices were corrected for practice effects. The CRP levels had increased significantly after six weeks of treatment after adjustment for age and gender ($p < 0.001$). In addition, the CRP levels remained significantly high after six weeks of treatment in patients with a higher baseline level ($r = 0.657$, $p < 0.001$). Although the association between baseline CRP level and HAM-D score was not significant, the baseline CRP level was significantly correlated with treatment response at week 2 ($r = 0.327$, $p = 0.020$). The baseline CRP level was also negatively correlated with performance in the FTT before treatment ($r = -0.580$, $p = 0.006$). Moreover, the baseline CRP level was significantly correlated with performance in the FTT ($r = -0.501$, $p = 0.021$) and WCST with completed categories ($r = -0.521$, $p = 0.015$) at week 6. The cognitive function of patients with high baseline CRP levels might remain impaired even if their mood symptoms improve after antidepressant treatment. Whether adjunctive anti-inflammatory medication may help to preserve cognitive function merits further investigation.

1. Introduction

The interrelationship between inflammation and major depressive disorder (MDD) is well documented (Stewart et al., 2009). Inflammation might contribute to the comorbid conditions that occur in depressed patients (Bjerkeset et al., 2011; Pizzi et al., 2010). Epidemiological studies have demonstrated associations between MDD and elevated levels of inflammatory markers, including the C-reactive protein (CRP) level (Capuron et al., 2008; Danner et al., 2003; Howren et al., 2009; Liukkonen et al., 2006; Miller et al., 2009). Of these, some population studies have demonstrated associations between MDD and elevated levels of CRP (Kuo et al., 2005; Liukkonen et al., 2006). Vulnerable individuals with a high CRP level have also been shown to have a significantly increased probability of recurrence of depressive episodes (Halder et al., 2010; Liukkonen et al., 2006). However, an earlier meta-analysis did not support this result. The association between CRP and depressive disorder therefore remains indefinite.

In addition to depressive mood, a broad range of cognitive deficits have also been demonstrated in MDD patients, among which attention and executive deficits associated with frontal lobe dysfunction could be the most prominent (Fossati et al., 2002; Gruber et al., 2007; Paelecke-Habermann et al., 2005). Furthermore, in remitted MDD patients, cognitive impairments may last, and cause poorer general functioning (Baune et al., 2010; Paelecke-Habermann et al., 2005), which could lead to chronic psychosocial stress and thus cause subsequent chronic inflammation (Alley

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et al., 2006; Owen et al., 2003). It is of great importance to identify factors associated with lasting cognitive impairment, and there have been no conclusive reports of these factors.

Although the association between inflammation and MDD has been identified, the association between CRP and cognitive function in MDD patients remains indefinite (Howren et al., 2009; Wersching et al., 2010). Population-based studies have demonstrated an association between high levels of CRP and cognitive impairment (Laurin et al., 2009; Wersching et al., 2010). The role of CRP in cortical dementia, a condition highly correlated with geriatric depression, has been discussed (Duong et al., 1997; Iwamoto et al., 1994). Another population-based longitudinal study showed that chronic sub-clinical inflammation may have a detrimental effect on cognitive performance in those becoming depressed at 12-year follow-up (Gimeno et al., 2009). To further investigate the role of CRP in MDD patients, medication-free MDD patients were enrolled and then randomly assigned to be treated with fluoxetine or venlafaxine. The study aimed to investigate: (1) the correlations between baseline CRP level and depressive symptom severity and treatment response, (2) the correlation between baseline CRP and neuropsychological function, and (3) the correlation between baseline CRP and neuropsychological function after antidepressant treatment.

2. Methods and materials

2.1. Subjects

One-hundred and forty-nine consecutive outpatients with MDD, all of whom fulfilled the *DSM-IV* criteria and had been interviewed using the Chinese version of the Mini International Neuropsychiatric Interview (MINI), were enrolled from the outpatient clinic at National Cheng Kung University Hospital (Table 1). The institutional review board of the hospital had approved the study proposal and all patients had signed informed consent forms prior to the start of the study. Patients meeting the following criteria were excluded: (1) monoamine oxidase inhibitor or antidepressant treatment within two weeks prior to entering the study; (2) a *DSM-IV* diagnosis of substance abuse within the past three months; (3) an organic mental disease, mental retardation or dementia; (4) a serious surgical condition or physical illness; and (5) patients who were pregnant or breastfeeding.

The 112 patients (97.4%) finally included in this study had never received antidepressant treatment prior to enrollment. Patients were randomly assigned to either the fluoxetine or the venlafaxine treatment group. The random sequence was generated by use of a random number table and was kept by an independent assistant who allocated the intervention to the consecutive sample. No stratification was used. The initial dose of fluoxetine was 20 mg once daily, which could be increased by 20 mg in divided doses to a maximal daily dose of 80 mg. The initial dose of venlafaxine was 37.5 mg once daily for 4 days titrated to 75 mg once daily, which could be increased by 75 mg in divided doses to a maximal daily dose of 225 mg. Lorazepam was the only concomitant drug allowed for both groups, to a maximal daily dose of 6 mg.

All MDD patients were evaluated at the start of the study then after 2, 4, and 6 weeks using the 21-item Hamilton Rating Scale for Depression (HAM-D), which was administered by senior psychiatrists. The same rater administered the scale at admission and in the subsequent weeks for each patient. Treatment response was defined as the percentage reduction in HAM-D score, and responders were defined as those with a minimum of a 50% decrease after treatment.

2.2. Neuropsychological assessment

2.2.1. Continuous Performance Test (CPT)

The CPT is a psychological test for humans that primarily measures attention (Chen et al., 1998; Hsieh et al., 2005). The critical stimulus may be defined either as a particular single stimulus out of the available set (X task: subjects were asked to respond to number "9") or a particular sequence of two stimuli out of the available set (AX task: subjects were asked to respond whenever the number "9" was preceded by the number "1"). Only the AX task was used in the present study. Each test session began with 2 min of practice (repeated if the subjects required it) to ensure that they knew how to press the button correctly. During the test, numbers from 0 to 9 were randomly presented for 50 ms each, at a rate of one per second. A total of 331 trials, 34 (10%) of which were target stimuli, were presented over 5 min in each session. Each subject undertook two sessions, including the non-masked task and the 25% masked task. During the masked session, a pattern of snow was used to toggle background and foreground so that the image was visually distorted. The masked CPT is more sensitive for the detection of cognitive deficits. In this study, subject responses were recorded automatically on a diskette using the CPT machine (Sunrise Systems, version 2.20, Pembroke, MA, USA) (Smid et al., 2006). The rater monitored each subject's performance through the computer monitor.

2.2.2. Finger-Tapping Test (FTT)

The FTT consists of tapping with the index finger on a computer mouse as many times as possible within 10 s. The test was repeated three consecutive times and performed randomly across subjects, and the order was kept constant in each subject at each

Table 1
The demographic characteristics of the patients.

	All	Fluoxetine	Venlafaxine	*p* values[a]
Male/female	42/107	20/53	22/54	0.753
Age (years)	38.8 ± 12.4	39.7 ± 12.4	38.0 ± 12.5	0.399
Smokers (*n*, %)	24 (16.1)	12 (16.4)	12 (15.7)	0.976
Average daily dose (mg)	–	21.5 ± 5.0	79.1 ± 36.7	–
Initial HAM-D score	23.9 ± 6.2	23.3 ± 5.1	24.7 ± 6.7	0.167
Baseline CRP level (ng/mL)	315.1 ± 176.8[b]	345.2 ± 184.5	272.4 ± 153.7	0.291
After 6 weeks of antidepressant treatment				
HAM-D score	9.2 ± 8.4	8.9 ± 8.3	9.3 ± 8.5	0.877
Change in HAM-D (%)	55.5 ± 32.4	54.2 ± 34.8	56.6 ± 28.4	0.758
Responders (%)	43.2	45.0	41.7	0.669
CRP level (ng/mL)	769.4 ± 144.7[b]	672.2 ± 158.5	935.9 ± 286.6	0.473

HAM-D: 21-item Hamilton Rating Scale for depression, CRP: C-reactive protein.
[a] Comparison of fluoxetine and venlafaxine subgroups.
[b] $p < 0.001$, comparison of CRP level before and after treatment.