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The relationship between quality of life and clinical phenotype in patients with treatment resistant and non-treatment resistant depression

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Abstract. – OBJECTIVE: The purpose of this investigation is to determine the differences in quality of life (QOL) and clinical phenotype between patients with treatment resistant (TRD) and non-treatment resistant depression (NTRD).

PATIENTS AND METHODS: The severity, QOL, and cognitive function of 107 TRD and 173 NTRD patients were evaluated and calculated by the Hamilton Depression Scale-17 (HAMD-17), the 36-Item Short Form Health Survey (SF-36), and the P300 component of event-related potentials (ERP), respectively.

RESULTS: The scores of HAMD-17 showed no significant statistical differences between TRD (28.8±6.7) and NTRD patients (29.3±8.2). The scores of anxiety/somatization (t=4.535, p=0.002), core item (t=3.514, p=0.005) and sleep item (t=6.079, p=0.000) were statistically significantly higher in TRD patients than in NTRD patients. The scores of physiological function (75.46±20.1, 88.23±21.4), body pain (61.39±17.1, 77.19±21.2) and social functioning (40.27±20.6, 58.82±22.1) in SF-36 were statistically significantly lower in TRD patients than in NTRD patients. The P300 latency of ERP was statistically significantly longer in TRD patients than in NTRD patients. Each item in the quality of life was negatively related to the items in HAMD-17 in TRD patients, especially for anxiety/somatization, and sleep items. The QOL was negatively related to core item and retardation item in NTRD patients, and the QOL was negatively related to the P300 latency of ERP in both groups, p<0.05. The sleep disorder, anxiety/somatization and core items were more serious in TRD patients than in NTRD patients, when the severity of depression was not significantly different. The QOL was significantly lower in TRD patients than in NTRD patients, the anxiety/somatization and sleep disorder were the main symptomatic factors that caused decreased QOL in TRD patients.

CONCLUSIONS: The abilities of abstract generalization, thinking transfer, and performing a function, were significantly lower in TRD patients than in NTRD patients, which were important factors which caused decreased QOL in TRD patients.

Key Words:
Treatment resistant depression, Clinical phenotype, Quality of life.

Introduction

Treatment resistant depression (TRD) is the term used in clinical psychiatry to describe cases of major depressive disorder (MDD) that meet ICD-10 (International Classification of Diseases 10th Revision) Code for Depression and do not respond adequately to an appropriate course (≥ 6 weeks) of at least two antidepressant medications (sufficient dose)[1]. There are many published studies about the quality of life (QOL) in TRD patients that focus on the differences between before and after treatment, or compare the QOL with a normal control group. The QOL in TRD and non-treatment resistant depression (NTRD) patients, as well as the relationship with clinical phenotype, have not been adequately established. Therefore, the purpose of this investigation is to compare the QOL in TRD and NTRD patients, analyze the relationship with their clinical phenotypes, and further identify the symptom measurements that affected the QOL in TRD patients.

Patients and Methods

All inpatients diagnosed with a major depressive episode by the Mini-International Neuropsychiatric Interview (MINI) in Xuzhou People's

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Oriental Hospital (Xuzhou, Jiangsu, China) from June, 2013, to December, 2014, were potential study participants.

Inclusion criteria were: (1) Meeting the diagnosis criteria of major depressive episode in ICD-10; (2) a score of HAMD (Hamilton Depression Rating Scale)-17 ≥ 17; (3) no prior medication administration within two weeks before inclusion in the study, (4) no history of other mental disorders, head trauma and neurological diseases; and (5) no mental disorders due to psychoactive substances and non-addictive substances.

Exclusion criteria were: (1) patients with suicide attempts or self-inflicted injuries that required treatment or (2) patients with secondary depression due to organic disease or other mental illness. Patients who did not respond adequately to appropriate courses (the reduction of HAMD-17 < 50%) of at least two antidepressants were assigned to the TRD group, the rest of patients were assigned to the NTRD group. This study was approved by the Hospital Ethics Committee, and all patients signed the informed consent. TRD group included 107 patients (44 males and 63 females) with a mean age of 33.8±12.5 years. NTRD group included 173 patients (69 males and 104 females) with a mean age of 35.2±10.4 years.

Depression severity was evaluated by the HAMD-17 scale by two qualified psychiatrists (Kappa=0.81 for consistency monitoring). The 4th, 5th, and 6th items in HAMD scale were related to sleep disorders (i.e. difficulty falling asleep, middle-of-the-night insomnia, and early awakening). The 1st, 7th, 8th, and 14th items were retardation items, including depressive mood, work and interest, retardation, and sexual symptoms. The 1st, 2nd, 7th, 8th, 9th, and 10th items were Maier symptoms, including depressive mood, feelings of guilt, work and interest, retardation, excitement, and mental anxiety. The 10th, 11th, 12th, 13th, 15th, and 17th items were anxiety/somatization items, including mental anxiety, somatic anxiety, gastrointestinal symptoms, systemic symptoms, hypochondria, and insight. The 1st, 2nd, 3rd, 4th, and 7th items were core items, including depressive mood, feelings of guilt, suicide, difficulty falling asleep, work and interest. Health survey (SF-36) was used to evaluate the patient's QOL. SF-36 consisted of 8 subscales (i.e. physiological functions (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (SF), general mental health (MH)). The calculated score of each subscale = (actual score-lowest possible score) / (highest possible score-lowest possible score) ×100.

The P300 of ERP was measured by an Evoked Potential Instrument (040C004, Oxford, UK). The potential was recorded by International standard 10/20 system electrode coordination. Three electrodes were placed; one in the central zone of calvarium; a second in left earlobe (was set as the reference electrode) and the third in the inside of the left wrist which was grounded. All tests were performed in a soundproof room. The resistance between the electrode and the scalp was < 5000 Ω and the resistance between the electrodes was < 2000 Ω. The disc electrode (silver chloride) was 8 mm in diameter. The auditory oddball task was used with acoustic stimulation (80 dB) through an earphone. Two types of acoustic stimulation were selected: a non-target stimulus (NT), 1000 Hz, regular low-frequency pure tone, probability 80%; and a target stimulus (T), 2000 Hz, random high-frequency pure tone, probability 20%. T and NT were randomly alternate; the ratio of T/NT was 0.2/0.8. The total number of stimulations was 100. The evaluation was performed within 500 ms after acoustic stimulation. Evoked Potential Instrument could differentiate and exclude EEG artifact as well as resist noise. The test was performed by a uniform guide and fixed operator and the P3 latency and amplitude were recorded.

Statistical Analysis

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were represented by mean ± SD, inter-group data was analyzed by independent samples *t*-test, and the correlation analysis was performed by Spearman correlation analysis. Categorical data were analyzed by the Chi-square test. $p<0.05$ was considered statistically significant.

Results

The differences in sex and age between TRD group and NTRD group were not significant ($\chi^2=1.65$, $p=0.89$; $t=0.97$, $p=0.07$). Other patient characteristics including education (10.3±5.8, 11.1±6.2), years of illness (39.8±10.6 months, 41.4±11.1 months) and family history ($\chi^2=2.01$, $p=0.65$), were comparable between TRD group and NTRD group.

The score of each item in HAMD in TRD patients and NTRD patients are shown in Table I.

Table I. The difference in HAMD and the score of each item (mean±SD) in TRD patients and NTRD patients.

Group	n	Total HAMD score	Core item	Retardation item	Sleep	Anxiety/ somatization	Maier
TRD	103	28.8±6.7	13.7±5.6	8.9±3.6	5.5±2.1	10.2±4.8	9.3±8.4
NTRD	173	29.3±8.2	10.2±6.2	12.5±3.9	3.1±1.9	6.1±2.4	12.4±6.7
t		1.657	3.514	4.314	6.079	4.535	2.293
p		0.064	0.005*	0.003*	0.000*	0.002*	0.045*

Table II. QOL and P300 (mean±SD) in TRD patients and NTRD patients.

Group	n	PF	RP	BP	GH	VT	SF	RE
TRD	103	75.46±20.1	38.62±11.3	61.39±17.1	38.56±14.6	46.78±19.5	40.27±20.6	25.3±13.4
NTRD	173	88.23±21.4	45.77±14.5	77.19±21.2	40.35±16.7	52.66±21.3	58.82±22.1	28.3±14.6
t		3.292	2.713	4.437	1.021	1.152	5.082	1.458
p		0.013*	0.056	0.007*	0.783	0.665	0.006*	0.441

Note: *indicated $p<0.05$.

The severity of depression was not significantly different between the TRD and NTRD patients; however, the scores of core item, sleep item, anxiety/somatization were statistically ($p<0.05$) significantly higher than retardation item and Maier item between groups.

The QOL and P300 in TRD patients and in NTRD patients are shown in Table II. The scores of PF, BP, and SF were significantly lower in TRD patients than in NTRD patients; the P300 latency was significantly longer in TRD patients than in NTRD patients.

The relationship between QOL and clinical phenotype in TRD patients and in NTRD patients are shown in Tables III and IV. Correlation analysis of each item in the HAMD scale between TRD patients and NTRD patients was performed; the quality of life was negatively related to anxiety/somatization item in TRD patients. The severity of depression was not significantly different between groups, and the QOL was negatively related to core item and retardation item in NTRD patients. The QOL was negatively related to the P300 latency of ERP in both groups, $p<0.05$.

Discussion

Previous studies on the QOL in TRD patients found that the scores of HAMD scale in TRD patients were always higher than those in NTRD patients. This study focused on "refractory" rather than "severe" with respect to TRD, thus included the patients without significant difference in the severity of depression. This study found that the score of each item in HAMD scale was significantly different between TRD patients and NTRD patients. The scores of core item, anxiety/

Table III. The relationship between clinical phenotype and P300 and QOL in NTRD patients.

TSD	Sleep	Retardation	Maier	Anxiety/somatization	Core item	P300 latency	P300 amplitude
PF	-0.13	-0.17	-0.36*	-0.21	-0.46*	-0.34*	0.24*
RP	-0.21	-0.41*	-0.21	-0.19	-0.51*	-0.22	0.17
BP	-0.19	-0.22	-0.24	-0.15	-0.39*	-0.53*	0.09
GH	-0.16	-0.39*	-0.11	-0.22	-0.24	-0.48*	0.33*
VT	-0.10	-0.12	-0.13	-0.37*	-0.42*	-0.37*	0.31*
SF	-0.21	-0.44*	-0.38*	-0.21	-0.50*	-0.18	0.13
RE	-0.28*	-0.23	-0.41*	-0.26	-0.14	-0.57*	0.15
MH	-0.15	-0.38*	-0.22	-0.20	-0.43*	-0.3*	0.28*

Note: *indicated $p<0.05$.

Table IV. The relationship between clinical phenotype and P300 and QOL in TRD patients..

TSD	Sleep	Retardation	Maier	Anxiety/ somatization	Core item	P300 latency	P300 amplitude
PF	-0.35*	-0.06	-0.16	-0.43*	-0.29*	-0.21	0.14
RP	-0.27	-0.13	-0.18	-0.48	-0.31*	-0.36*	0.19
BP	-0.44*	-0.20	-0.19	-0.51*	-0.14	-0.15	0.23
GH	-0.22	-0.18	-0.22	-0.58*	-0.21	-0.4*	0.10
VT	-0.36*	-0.13	-0.12	-0.44*	-0.19	-0.24	0.28*
SF	-0.39*	-0.17	-0.14	-0.35*	-0.26	-0.38*	0.33*
RE	-0.42*	-0.11	-0.24	-0.49*	-0.14	-0.55*	0.22
MH	-0.14	-0.23	-0.27	-0.62*	-0.26	-0.48*	0.14

Note: *indicated $p<0.05$.

somatization item and the severity of sleep item were higher in TRD patients than in NTRD patients. Even though the severity of the depression was not significantly different. Previous researches found that anxiety may affect the efficacy of anti-depressive agents and lead to slow efficacy and incomplete remission of symptoms in patients with depression, indicating concomitant anxiety may be a possible reason for refractory depression. This study also found that the score of sleep item was higher in TRD patients than in NTRD patients; sleep disorder may accelerate the passive state of patients with depression and affect the recovery of patients. Therefore, besides anxiety/somatization, the problems with long-term poor sleep may be a risk factor for progression into refractory depression.

Many studies had confirmed that the QOL was worse in patients with depression than the normal population. This work found that the QOL was significantly worse in TRD patients than in NTRD patients, predominantly in PF, BP, and SF. Zeng et al[8] reported that only BP and PF were significantly different between patients with recurrent brief depression and patients with primary depression, this may cause TRD, and this study confirmed this concept. Angermeyer et al[9] reported that the QOL in TRD patients was significantly lower, especially for extensive and persistent impairment in SF, and TRD was much more serious than diabetes and hypertension. SF was the capacity of performing social tasks and a central characteristic of QOL, which may be decreased when SF was impaired[10]. The P300 latency was the time required for recognition and the preliminary process of stimulus; it could reflect the abilities of abstract generalization, thinking transfer, and performing a function. For NTRD patients, only the coding, classification and the speed of recognition of external sensory and perceptual information were impaired, however, for TRD patients, not only the speed of process was impaired, but the degree of activation of the cerebral cortex was decreased, and the depth of process was impaired[11]. This investigation demonstrated that the P300 latency was longer in TRD patients than in NTRD patients, indicating that the abilities of abstract generalization, thinking transfer and performing function were significantly weaker in TRD patients than in NTRD patients, and this could impair the QOL in TRD patients to some degrees. This study also found that the QOL in both groups was negatively related to P300 latency, indicating that the impairment of recognition function may affect the QOL of patients.

This paper included patients that had no significant difference in depression severity, correlation analysis between the score of each item and each item of QOL was then performed. The results showed that the clinical phenotype that affected QOL was different among TRD patients and NTRD patients. The QOL of NTRD patients was predominantly related to core item and retardation item, which were the core symptom clusters in patients with depression, whereas the QOL of TRD patients was predominantly related to anxiety/somatization and sleep item. Davidson et al[12] reported that the deduction of anxiety item in TRD patients was positively related to the improvement of the QOL. This findings were consistent with the present study.

Conclusions

Therefore, the core symptoms, the anxiety/somatization and sleep of TRD patients should be always considered in the clinical practice. Thus,

the QOL and hospitalization compliance could be improved, and the suffering could be alleviated. This work was a randomized and controlled study. Further investigation will expand the sample size, include other clinical measurements of patients with depression, and explore the relevant factors that affect the QOL of patients.

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Conflict of interest

The authors declare no conflicts of interest.

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