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Study on Integrative Therapeutic Response and It's Relation to HPA Function in Depressive Patients with Different TCM Syndrome

Abstract

Background: As for depression, Traditional Chinese medicine (TCM) classified it as "Yu disease" and divided it into "excess disease" and "asthenic disease", which may have different function in HPA.

Methods: 30 cases were depression with TCM syndrome of deficiency of heart and spleen and other 30 cases were depression with TCM syndrome of stagnation of liver qi. The HAMD and HAMA were assessed and DST was completed at began of study. The all patients were observed for 4 weeks.

Results: 1. The both blood cortisol of patients with stagnation of liver qi at 8:00am and 4:00pm before dexamethasone were higher significantly than that of deficiency of heart and spleen. The relative change of blood cortisol in patients with stagnation of liver qi at 8:00am was higher significantly than that of deficiency of heart and spleen. The suppression ratio of patients with stagnation of liver qi was lower than that of deficiency of heart and spleen.

2. The HAMD and HAMA relative changes of patients with different syndrome are significantly different.

3. The blood cortisol level correlated with some symptom and it's change.

Conclusion: The lower the cortisol level after DST indicate better the response to antidepressant treatment, especially in the patients with TCM syndrome of stagnation of liver qi.The two syndrome of depression was different in some clinical symptom, response to treatment and HPA regulation function. It also suggests that the different therapeutic methods should be sued in the two groups.

Keywords

Depression; TCM syndrome; HPA; Cortisol; TCM

Research Article

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Background

Major Depressive Disorder (MDD) is one of the most common and debilitating mental disorders; however, its etiology remains unclear. It has been hypothesised that genetic, immune-inflammatory and psychosocial factors and the presence of MS-related structural brain alterations might be the potential causes of Depression [1]. Some possible pathophysiological mechanisms of depression include altered neurotransmission, Hypothalamic-Pituitary-Adrenal (HPA) abnormalities involved in chronic stress, inflammation, reduced neuroplasticity, and network dysfunction. Cytokines are pleiotropic molecules with important roles in inflammatory responses. Pro-inflammatory cytokines and neuroinflammation are important not only in inflammatory responses but also in neurogenesis and neuroprotection. Sustained stress and

the subsequent release of pro-inflammatory cytokines lead to chronic neuroinflammation, which contributes to depression [2]. All of these proposed mechanisms are integrally related and interact bidirectionally. In addition, psychological factors have been shown to have a direct effect on neurodevelopment, causing a biological predisposition to depression, while biological factors can lead to psychological pathology as well [3]. Among them, HPA function plays a certain role in the occurrence and development of depression. The link between the abnormalities of the HPA axis and depression has been one of the most consistently reported findings in psychiatry. The major depression with psychosis (PMD) patients had higher evening cortisol levels than did schizophrenic patients and heath controls [4]. It suggested that depression was accompanied by de-suppression [5]. Especially, antidepressant can improve this de-suppression of HPA [5, 6], which also predict the response of antidepressant [7]. Also it was found that there was relationship between abnormal HAP and clinical symptom, cognition [8]. Xiaochaihutang (XCHT) can alleviate perimenopausal depression-like behaviors, restore 5-HT and hormones in OVX-CUMS mice, which may be related to normalizing the functions of HPA/HPO axis and enhancing expression of ERβ and TPH2 in prefrontal cortex and hypothalamus [9]. However, the most direct result is to compare the difference of HPA function between patients with or without depression. Depressed older persons showed higher morning cortisol levels at awakening (T1) and a less dynamic awakening response compared to non-depressed older persons, which demonstrated a hypercortisolemic state and a diminished ability to respond to the stress of awakening among depressed older persons [10]. But it is possible that there are several different endophenotypes of depression with distinct pathophysiological mechanisms, it may be helpful to think of depression as one united syndrome, in which these mechanisms interact as nodes in a matrix. Depressive disorders are considered in the context of the RDoC paradigm, identifying the pathological mechanisms at every translational level, with a focus on how these mechanisms interact. Finally, future directions of research are identified [3]. At the same time, multiple studies have demonstrated a stronger association between the increased activation of HPA-axis and melancholic, or endogenous depression subtype. Some findings indicate that there is a difference in the activity of the HPA-axis between melancholic and atypical depressive subtypes. However, these are more likely explained by hypercortisolism in melancholia; and most often normal than decreased function in atypical depression. Further research should seek to distinguish a particular subtype of depression linked to HPA-axis abnormalities, based on symptom profile, with a focus on vegetative symptoms, neuroendocrine probes, and the history of adverse childhood events [10]. The study also show that HPA axis dysregulation is not an endophenotype of bipolar depression, but seems related to environmental risk factors, such as childhood trauma [11]. It may means that there were different HPA function between unipolar and bipolar depression. This suggests that different depression subtypes may have different neurobiological basis, such as P300, neuropeptide and neuroendocrine [12, 13].

As for depression, Traditional Chinese medicine(TCM)classified it as “Yu disease” and divided it into “excess disease” and “asthenic disease”, which have different syndrome types□In the excess symptoms, the typical representative type was stagnation of liver qi, in the asthenic disease, the typical representative type was deficiency of heart and spleen, which were different in many aspects of neurobiocology [13].The clinical manifestations of stagnation of liver qi were depression, more anxiety or irritability. The physical symptoms include swelling pain of two ribs. The tongue was purplish dark or had blood stasis, with yellow and greasy tongue coating. Their pulse was dazzled, and amenorrhea in women [14]. The clinical manifestations of deficiency of heart and spleen were depression, more pessimism and fatigue, insomnia, dreaminess and decreased movement. Physical symptoms include palpitation, poor appetite and abdominal distention. The tongue was fat and tender, with white and thin tongue coating. The pulse was weak. The most women had less or weak menstruation [15]. These indicated the different clinical traits of two TCM syndrome of depression maybe related to existed the difference on biology, such as neuroendocrinology. The reaction of HPA also related to combination of genetic variability and external factor. For example, some findings indicated that 5-HTTLPR genetic variability appears to influence the association between stress-related factors and late-life depression. Participants homozygous for the short allele appeared to have a cortisol-related neuroendocrine vulnerability to depression, while long allele homozygotes were more reactive to stressful events in terms of depression risk [16].

All above help us put out a question that different TCM syndrome of depression may had different HPA function status. This suggestion should be explained.

Methods

1. Study design: The trial was designed in two groups. One group was depression with TCM syndrome of stagnation of liver qi. The other group was depression with TCM syndrome of deficiency of heart and spleen. At base line of began of study, the HAMD and HAMA were assessed in all depressive patients. The DST was also completed at began of study. The all patients were observed for 4 weeks, during which the combination treatment of TCM and western medicine were carried out and symptoms change with HAMA and HAMD. The study schedule was to see figure1.

2. Sample: All samples were 100 patients with depression which meet the criteria of depression in ICD-10.The criteria of inpatients were tested:(1) The inpatients meet the ICD-10 diagnostic criteria for depression ; (2) the age of inpatients is greater than or equal to 18 years old, less than or equal to 60 years old; (3) The inpatients had not brain organic diseases and mental disorders caused by them; (4) The inpatients had not dependence on psychoactive substances and mental disorders caused by them; (5) The inpatients had not some diseases for the presence and taking of hormones; (6) The inpatients informed consent of taking combination therapy; (7) The guardian of patients informed consent of trials.(8)The inpatients meet diagnostic criteria for stagnation of liver qi or deficiency of heart and spleen.

3. The two study groups were randomly given SSRI and TCM decction after dividing group according diagnostic criteria of retardation depression or agitated depression.The TCM decoction was given according to TCM syndrome.The patients was received both therapy of SSRI and TCM decoction.

4. Main index: The first index was blood cortisol, suppression ratio and positive ratio of DST. The Second index were HAMD, HAMA and their changes. HAMD, HAMA were assessed by two psychiatrists with medium-degree or high-degree professional title at least. The pair two psychiatrists have better reliability in assessment of HAMD, HAMA.

5. Treatment method: All patients receipted combination of TCM and western medicine, which was one drug of SSRI that be considered suitable to the patients. The patients in group of stagnation of liver qi were given Chai Hu Shu Gan San decoction [17]. The patients in group of deficiency of heart and spleen were given Gui Pi decoction [18]. Chaihushugansan decoction is composed of tangerine peel, Chaihu, Chuanxiong, Xiangfu, Fructus Aurantii, peony, and licorice. Guipitang decoction composed of Baizhu, Fushen, Huangqi, Longan Meat, and Sour Jujube Kernel.Add 500 ml water and fry for 30 minutes, take 100 ml juice and take it orally twice respectively.

6. Blood cortisol determination and DST Blood cortisol was measured by radioimmunoassay in laboratory of Zhejiang province Tongde hospital. At 11:00 p.m. of the day, 1 mg of dexamethasone was taken orally. Blood was drawn at 8:00 a.m. and 4:00 p.m. next day to check the cortisol again. In one case, the plasma cortisol concentration exceeded 5 ug / dl, which was defined as DST positive [19], but it was old way. The new positive way was that ratio of cortisol level after dexamethasone at 8:00 am/cortisol level before dexamethasone at 8:00 am was lager 50% [20], which was called suppression ratio that mean higher suppression ratio represented poor regulation of HPA.

7. Statistic methods: All data were processed by SPSS18.0 statistical software, and the measurement data between groups were tested by mean t test, $P < 0.05$ was statistically significant. And ANOVA were tested by mean F test, $P < 0.05$ was statistically significant. Correlation relationship were tested by correlation analysis(r).

8. This study was approved by the ethics committee of Tongde Hospital of Zhejiang Province.

Results

1. The information of all patients was listed in (Table 1).56 patients completed the study,which included 26 cases in TCM syndrome of stagnation of liver qi and 19 cases in TCM syndrome of deficiency of heart and spleen.

2. The cortisol level after and before dexamethasone and DST

The both blood cortisol of patients with stagnation of liver qi at 8:00am and 4:00pm before dexamethasone were higher significantly than that of deficiency of heart and spleen. But no difference after dexamethasone, see (Table 2). The relative change of blood cortisol in patients with stagnation of liver qi at 8:00 am was higher significantly than that of deficiency of heart and spleen, see (Table 2). The suppression ratio of patients with stagnation of liver qi was lower than that of deficiency of heart and spleen, see (Table 2). There was no difference in DST positive rate between two groups, also see (Table 2)

3. The HAMD, HAMA and their changes
The HAMD, HAMA of patients with stagnation of liver qi at base line were not different from than that of deficiency of heart and spleen, see (Table 3). But HAMD of patients with stagnation of liver qi was significantly different from that of deficiency of heart and spleen at fourth weekend, and HAMA of patients with stagnation of liver qi was significantly different from that of deficiency of heart and spleen at second weekend, see (Table 3).The HAMD relative changes of patients with stagnation of liver qi was significantly higher than that of deficiency of heart and spleen at fourth weekend, and the HAMA relative changes of patients with stagnation of liver qi was significantly higher than that of deficiency of heart and spleen at fourth weekend, also see (Table 3, 4).

4. The correlation between cortisol level, cortisol changes and mental symptoms, their changes. The both of 1st day 8am Blood cortisol level and 1st day 4pm Blood cortisol level positively correlated significantly with HAMD relative change at 4th weekend and negatively with HAMD at 4th weekend, HAMA at 2nd weekend, HAMA at 4th weekend. The suppression ratio negatively correlated significantly with HAMA relative change at 2nd weekend, HAMA relative change at 4th weekend. The both cortisol relative change at 4pm and 8am positively correlated significantly with HAMA relative change at 2nd weekend, at 4th weekend. see (Table 5).

	Retardation depression (deficiency of heart and spleen)	Agitated Depression (stagnation of liver qi)
Case	19	26
Gender	Male□4, Female□15	Male□5, Female: 21
Age (Years)	18 ~ 60(31.3±13.6)	18 ~ 60(32.5±14.8)
Duration (month)	1-1.5(0.81±0.21)	1-2(0.85±0.32)
Education (years)	6-14(9.4±3.8)	5-15(9.8±4.9)
Marriage	Unmarried:3□Married:10□Divorce:6	Unmarried:10□Married:16
Family History	Positive□15□Negative□4□	Positive□7□Negative□19
Drug	Sertrali:10 Escitalopram:5 Fluxetine:4	Sertraline□8 Escitalopram:10 Fluxetine:1 Paroxetine:7
TCM	Guipi decotion	Chaihushugansan decotion
TCM: Traditional Chinese Medicine; Guipi decotion: A TCM soup from decotion for treatment of retardation depression;Chaihushugansan decotion:A TCM soup from decotion for treatment of agitated Depression		

Table 1. General information of two group with depression

	retardation depression □deficiency of heart and spleen□(n=19)	agitated depression □ stagnation of liver qi□(n=26)
8am, First day□μg/dl□	14.12±8.41a	28.07±10.95a
4pm, First day□μg/dl□	12.08±8.35a	22.67±11.25a
8am, Second day□μg/dl□	3.36±5.86	3.01±4.83
4am, Second day□μg/dl□	1.96±0.21	2.11±0.33
Relative change at 8am	0.76±0.28b	0.90±0.15b

Relative change at 4am	0.80±0.12	0.82±0.22
suppression ratio	0.24±0.28a	0.10±0.15a
DST positive ratio	4/15#	1/25#
a P<0.01,b P<0.05		

Table 2. The blood cortisol and their changes in two groups

	retardation depression□deficiency of heart and spleen□ (n=19)	agitated depression □ stagnation of liver qi□(n=26)
HAMD at base line	33.68±7.12	35.00±6.19
HAMD at first weekend	30.89±7.03	32.15±5.62
HAMD at second weekend	24.53±7.41	21.69±6.04
HAMD at forth weekend	21.26±6.98a	9.54±3.60a
HAMD relative change at first week-end	0.08±0.11	0.07±0.13
HAMD relative change at second weekend	0.27±0.19	0.37±0.17
HAMD relative change at forth weekend	0.37±0.17a	0.72±0.12a
a P<0.01		

Table 3. The HAMD and their changes in two groups

	retardation depression□deficiency of heart and spleen□ (n=19)	agitated depression □ stagnation of liver qi□(n=26)
HAMD at base line	23.58±8.15	19.12±8.69
HAMD at first weekend	22.74±8.69	17.96±7.58
HAMD at second weekend	19.89±6.74a	12.00±4.67a
HAMD at forth weekend	16.53±6.28	2.47±0.48
HAMD relative change at first week-end	0.04±0.13	0.05±0.10
HAMD relative change at second weekend	0.15±0.12a	0.35±0.18a
HAMD relative change at forth weekend	0.29±0.15	0.17±0.03
a P<0.01		

Table 4. The HAMA and their changes in two groups

	1st day 8am Blood cortisol	1st day 4pm Blood cortisol	2nd day 8am Blood cortisol	2nd day 4pm Blood cortisol	suppression ratio	Cortisol relative change at 4pm	Cortisol relative change at 8am
HAMD at base line	0.113	0.151	0.107	0.111	0.006	0.005	-0.006
HAMD at1st WK	0.150	0.197	0.009	0.012	-0.097	0.129	0.097
HAMD at 2nd WK	-0.089	-0.029	-0.096	-0.087	0.095	-0.078	-0.095
HAMD at 4thWK	-0.395*	-0.302*	-0.012	-0.022	0.238	-0.171	-0.238
HAMD relative change at1st WK	-0.066	-0.061	0.151	0.203	0.149	-0.067	-0.149
HAMD relative change at 2ndWK	0.165	0.121	0.158	0.170	-0.129	0.203	0.129

HAMD relative change at 4thWK	0.432**	0.349*	0.045	0.065	-0.25	0.164	0.250
HAMA at base line	-0.271	-0.239	-0.134	-0.155	-0.012	-0.048	-0.012
HAMA at 1s t WK	-0.279	-0.226	-0.089	-0.066	0.016	-0.011	-0.016
HAMA at 2nd WK	-0.428**	-0.345*	-0.003	-0.010	0.198	-0.146	-0.198
HAMA at 4thWK	-0.436**	-0.345*	0.023	0.019	0.229	-0.233	-0.229
HAMA relative change at1st WK	0.016	-0.039	-0.121	-0.123	-0.069	0.109	0.069
HAMA relative change at 2ndWK	0.265	0.169	-0.229	-0.226	-0.336*	0.356*	0.366*
HAMA relative change at4th WK	0.218	0.215	-0.210	-0.211	-0.310*	0.330*	0.310*
WK= weekend, **P<0.01, *P<0.05							

Table 5. The relationship between blood cortisol,their changes and symptoms

Discussion

1. Abnormal HPA axis function in depression

Our study also found that in all cases ,5 cases appeared DST positive, indicating that some patients with depression did have the phenomenon of HPA axis inhibition, which can indicate that hyperactivity of the HPA axis may lead to depression. Some of the results in the study of neuroendocrine, inflammatory factors and other changes in rats induced by chronic paradoxical sleep deprivation showed that the levels of CRH, ACTH and CORT in serum of depressed rats were significantly increased (P<0.05) as signals of highly activated HPA axis [21]. The effects of Agarwood Essential Oil on the ACTH and CORT concentrations of bound stress-induced depressed mice were shown. the addition of Agarwood Essential Oil significantly reduced the levels of ACTH and CORT in the serum of mice, thus improving the hyperactivity of the HPA axis [22].

The regulation of HPA also was presented as suppression ratio and relative change of cortisol. The suppression ratio is used to represent the regulation function of the HPA axis, the more the suppression ratio is Higher, the worse the adjustment function. This result found that there is a relationship between the suppression ratio and the effective rate of anxiety. The Pearson correlation coefficient of the Hamilton Anxiety Scale (HAMA) and the suppression ratio is -0.336 (P<0.05), and the Hamilton Anxiety Scale (HAMA) The Pearson correlation coefficient between the four weeks and the inhibition rate was -0.310 (P<0.05), but it was not found to be related to the effective rate of depression. These conclusions are different from the results of other scholars. This shows that the depression is getting better at the same time, the improvement of anxiety symptoms is more closely related to the HPA axis, which also shows that the degree of adjustment of the HPA axis function may to some extent predict the anxiety improvement level of patients with depression. Some research also found that Hair cortisol sharply increased with stressor onset, decreased as internship continued, and rose again at year's end. Depressive symptoms rose significantly during internship, but were not predicted by cortisol levels [23]. In the paper summarized by Caroline Normann, genetic variation in four HPA-axis genes may influence the effects of CM in depression [24], This also indirectly explains the relationship between HPA and depression.

2. Differences of clinical manifestations and HPA function between two TCM subgroup

The depression was defined as "depression disease" by TCM (Yubing, Chinese phonetic alphabet, TCM term), which conclude two opposite subgroup of liver stagnation qi stagnation syndrome, heart and spleen deficiency syndrome. This study found HAMD, HAMA were significantly higher than those of liver depression and qi stagnation group (P <0.01). Conclusion There are HAMD□HMMA differences between the two syndromes in different clinical stages. Although there are few studies comparing the differences between liver stagnation and qi stagnation and deficiency of heart and spleen, in Chen, et al. The expression of Oatp2a1 and Oatp2b1 in liver cancer and gastric cancer tissues was lower than that in liver cancer mice. The expression of Oatp2a1 in liver cancer and colon cancer tissues was higher (P <0.05). The side shows that there are differences in depression between liver and spleen [25].

This study used multi-temporal evaluation and relative symptom changes to reflect the efficacy of different time points. We found that Hamilton Depression scale (HAMD) was measured after the fourth week, Hamilton anxiety scale after the second week, Hamilton Depression scale (HAMD) after the fourth week relative change rate, Hamilton anxiety scale (HAMA) after the second week relative change rate, liver stagnation depression and spleen deficiency depression in clinical efficacy (P <0.01). During the study of acupuncture and moxibustion on depression, the results showed that the two most common syndromes of depression syndrome were liver stagnation and qi stagnation and deficiency of heart and spleen, and there was significant difference in therapeutic effect (P <0.01) [26].

This study also found the difference on the regulation between two TCM group. There is a difference in the cortisol level before treatment between the liver stagnation and qi stagnation group and the heart and spleen deficiency group (P<0.01), and the relative change of 8am before and after treatment (P<0.05) and the inhibition rate of the two groups are different (P<0.01). This indirectly indicates that there are differences in HPA between different TCM syndrome types. These difference in HPA regulation between two group maybe beneficial for classification of TCM syndrome of depression. In fact, there are many differences

among different TCM syndrome types of depression, concluding neurotransmitter, EEG, neuroendocrinology [13].

3. Relationship between HPA axis and efficacy of antidepressant and its prediction

The correlation analysis in this study shows that, the patient with a good HPA axis, The Pearson correlation coefficient of 8 am on the first day with Hamilton Depression Scale (HAMD) was -0.395(P<0.01), The Pearson correlation coefficient of blood cortisol 4 pm after the fourth week of Hamilton Depression scale (HAMD) was -0302(P<0.05). The Pearson correlation coefficient between 8 am on the first day and the fourth week of Hamilton Depression Scale (HAMD) was 0.432(P<0.01), The Pearson correlation coefficient between blood cortisol and the relative rate of Hamilton Depression Scale (HAMD) was 0.349(P<0.05). The Pearson correlation coefficient of blood cortisol was -0.428 am (P<0.01), The Pearson correlation coefficient of blood cortisol after the second week of Hamilton Anxiety Scale (HAMA) was -0.345(P<0.05). The Pearson correlation coefficient of 8 am on the first day with Hamilton anxiety scale (HAMA) was -0.436(P<0.01), The Pearson correlation coefficient between blood cortisol and Hamilton Anxiety Scale (HAMA) was -0.345(P<0.05). Which suggests a relationship between plasma cortisol levels and symptomatology. In Fatima M Kabia's study that in particular lower evening cortisol levels may predict poorer course in MDD. So This finding may proved clinical implications that a lower cortisol awakening response is a predictor of a worse prognosis of depression [27]. Alexander Fiksdal et al. found that symptoms of anxiety and depression among individuals without a psychiatric diagnosis are associated with blunted and exaggerated cortisol responses to and recovery from stress. Such patterns could indicate increased risk for unhealthy HPA axis dysregulation, allostatic load, and disease [28].

Limitation

First, the number of cases in the study is too less; second, the intervention drugs are not uniform; third, the HPA axis function is affected by external and internal factors, and the resulting may be uncertain.

First, the number of cases in the study is too small. The all sample only are 45 cases, who is a lack of representativeness. Second, the intervention drugs are not uniform, which conclude both SSRI and Chinese herb. Third, the HPA axis function is affected by external and internal factors, and the resulting may be uncertain.

Declarations

1. Ethics approval and consent to participate

1.1 Ethic certificate of Zhejiang Province Tongde Hospital Ethics Committee (V1.0/20170120)

1.2 Consent Form (V1.0/20170120: V1.0)

Title: study on the difference between depressive patients with stagnation of liver qi and deficiency of heart and spleen.

All participants agree to publish their data.

2. Consent for publication

All authors agree to publish our paper and no conflict in any interests.

3. Availability of data and material

The current study data are not publicly available, but are available from the corresponding author on need.

4. Competing interests

There were not any financial and non-financial competing interests. All authors do not have any conflicts in all benefits.

5. Funding

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6. Author's contribution

Our authors have different contributions to this article.Dr JWD participated in trial and the writing of the article, JHY, GZH participated in the trial, Prof.SFL participated in the design and statistical processing, and participated in the design , statistical processing and the final revision of the article.

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8. Abbreviations

HPA: hypothalamic–pituitary–adrenal; TCM: Traditional Chinese Medicine; MDD: Major Depressive Disorder; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; PMD: Psychotic major depression; XCHT: Xiaochaihutang; HPO: Hypothalamic Pituitary-ovarianas; RDoC: Research Domain Criteria; DST: Dexamethasone Suppression Test; CRH: Corticotropin Releasing Hormone; ACTH: Adrenocorticotropic Hormone; CORT: Corticosterone; CM: Childhood Maltreatment; EEG: Electroencephalo-graph; MDD: Major Depressive Disorde; 5 HTTLPR: 5 hydroxytryptamine transporter gene linked polymorphic region; ERβ:estrogen receptor beta; TPH2:Tryptophan hydroxylase 2; OVX ovariectomies; CUMS: chronic unpredictable mild stressed

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