

Chronic Tension Type Headache, An Analog for Fibromyalgia and Depression Disorder?

Ping Qu¹, Jin-Xia Yu², Lan Xia¹ and Gui-Hai Chen^{3*}

¹Department of Neurology, the Second Affiliated Hospital of Anhui Medical University, Hefei 230601, China

²Official Hospital of The people's Government, Anhui Province, Hefei 230001, China

³Department of Neurology, The Affiliated Chaohu Hospital of Anhui Medical University, Chaohu 238000, China

Abstract

Background: Chronic tension type headache (CTTH) is the most prevalent headache and is associated with a high socio-economic impact. The exact pathogenesis of CTTH remains unclear. It has been shown CTTH has many similar clinic features with fibromyalgia (FM) and major depression disorder (MDD). Several studies have found some changes of hypothalamic-pituitary-adrenal (HPA) and hypothalamus-pituitary-thyroid (HPT) axes, sex hormones and pro-inflammatory cytokines in FM and MDD. We speculated CTTH has the same changes. Striving to provide new insights into the pathophysiology of CTTH, we designed this trial to address the common and specific aspects of these three disorders in their clinic features and pathophysiological mechanisms, especially from neuroendocrine system and inflammatory pathways.

Method: The patients with CTTH, FM and MDD were recruited, and the healthy subjects were selected as controls. The sleep quality, depressive mood and cognitive function of all subjects were evaluated. The serum levels of corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), cortisol, thyrotrophin releasing hormone (TRH), thyroid stimulating hormone (TSH), total triiodothyronine (TT3), total thyroxine (TT4), gonadotrophin releasing hormone (GnRH), interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) were detected to find the changes of neuroendocrine system and inflammatory pathways which are believed to be linked with these disorders.

Results: Compared with the controls, the HAMD-17 and PSQI scores were significantly higher ($P_s < 0.001$) and the MoCA-C score was significantly lower ($P = 0.029$) in the CTTH, FM and MDD patients. The patients with the CTTH, FM and MDD showed different degrees of damage in spatial and object memories compared to the controls ($P_s < 0.05$). The changes of the HPA and HPT axes, GnRH and pro-inflammatory cytokines in the CTTH, FM and MDD patients were similar. In addition, the serum levels of CRH, cortisol, GnRH, TRH, IL-1 β and TNF- α were significantly higher ($P < 0.001$) while TT3, TT4 were significantly lower ($P < 0.001$) in the CTTH, FM and MDD groups relative to the controls. The FM patients showed lower value in the pituitary level of HPA and HPT axis.

Conclusion: The patients with CTTH had similar patterns of memory damage and changes of the HPA and HPT axes, GnRH and pro-inflammatory cytokines with the FM and MDD patients.

Keywords: Chronic tension type headache; Fibromyalgia; Major depression disorder; Memory; HPA axis; HPT axis; GnRH, Interleukin-1 β ; Tumor necrosis factor- α

Introduction

Tension-type headache (TTH) is the most prevalent primary headache disorder worldwide [1]. Epidemiological studies reveal that 20–30% of the Asian population suffers from TTH and the global prevalence of TTH in the adult population is 42% [1]. As its chronic form, chronic tension type headache (CTTH) is characterized by daily (or almost daily) headaches that last several hours per day [2] and is a serious subtype, which is difficult to treat. Besides headache, some additional symptoms apply frequently such as emotional disturbance and sleep disturbance [3]. Patients with CTTH often complain of their poor memory but research about memory of CTTH is rarely.

The exact etiology and pathophysiological mechanism of CTTH remains unclear. It seems that central mechanisms such as central sensitization might predominate in CTTH [4,5]. The peripheral mechanism includes increased pericranial muscle tenderness and generalized pressure pain hypersensitivity [6] and genetic factors [7,8] also contribute to the pathophysiology of CTTH. But these can't explain why emotional disturbance and sleep disturbance co-morbidities are common in patients with CTTH [3,9].

Fibromyalgia (FM) is another chronic pain syndrome, which also involve in central sensitization mechanisms [10]. The major symptoms

of FM include multifocal pain, fatigue, sleep disorder, psychological distress and cognitive impairment [11-13]. Major depression disorder (MDD) is also a common condition in the neurologic clinics. Patients with MDD often see a doctor because of the physical symptoms just like headache, back pain, fatigue, insomnia, memory problems, etc. [14-16]. We can find that the patients suffered from the three diseases share many overlapping symptoms mentioned above and tend to live poor-quality life or even with disability because of chronic pain and other symptoms. Furthermore, the three disorders are more prevalent in women with a higher comorbidity [1,12]. It seems plausible that the three diseases may have a similar pathophysiology.

Studies have found that the dysfunction of regulation in

***Corresponding author:** Gui-Hai Chen, Department of Neurology, The Affiliated Chaohu Hospital of Anhui Medical University, Chaohu 238000, China, Tel: 86-0551-82324234; Fax: 86-0551-82324234; E-mail: chenguihai1@163.com

Received September 08, 2015; Accepted October 13, 2015; Published October 17, 2015

Citation: Qu P, Yu JX, Xia L, Chen GH (2015) Chronic Tension Type Headache, An Analog for Fibromyalgia and Depression Disorder? Biochem Pharmacol (Los Angel) 4: 190. doi:10.4173/2167-0501.1000190

Copyright: © 2015 Qu P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

hypothalamic-pituitary-adrenal (HPA) axis may play an important role in FM and MDD [17,18]. Results on the HPA axis function in FM are heterogeneous, with both hyperactivity and hypoactivity [18-20]. The changes of hypothalamus-pituitary-thyroid (HPT) axis and hypothalamus-pituitary-gonadal (HPG) axis also have been found in MDD [21, 22]. Pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) play important roles in mediating depression and are implicated in the etiologies of clinical depression disorders [23-25]. IL-1 and TNF- α can increase the pain behavior and cause neuropathic pain [26,27]. So we speculate about whether the cognitive function and the serum levels of the HPA-, HPT- and HPG-axis hormones, and inflammatory factors also change in the patients with like the patients with FM and MDD.

Methods

Subjects

The subjects come from Neurologic Clinic of the First Affiliated Hospital of Anhui Medical University. The patients met one of the following criteria, including International Classification of Headache Disorders, Second Edition for CTTH [2], the American College of Rheumatology criteria for FM (1990) [28], Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR) for MDD [29]. Meanwhile, the healthy subjects were recruited as the controls. Subjects with infective diseases and the diseases in endocrine system and immune system (such as thyroid diseases, rheumatoid arthritis) or any other psychiatric disorders, and those under such related medical treatment were excluded. The participants were informed in advance of the aims and procedures of the experiment. All participants signed informed consent before the study, which is qualified by the Clinical Trial Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

Baseline data collection

The baseline data, including age, sex, the years of education, medical history, were collected in all of the subjects.

Assessment of depressive mood, the quality of sleep and cognitive functions

40 CTTH, 26 FM and 50 MDD patients and 29 health controls completed Pittsburgh sleep quality index scale (PSQI), 17-term Hamilton's Depression Scale (HAMD-17), the Chinese version of the Montreal cognitive assessment scale (MoCA-C) and special memory test, respectively. In China, a PSQI score ≥ 7 has high diagnostic sensitivity and specificity in distinguishing patients with sleep problems from normal subjects. A HAMD-17 score ≥ 17 suggests moderate to severe depression. A MoCA-C score <26 is considered abnormal cognition.

We used a slightly improved version of the Nine Box Maze Test [30] to assess object reference memory (ORM), spatial reference memory (SRM), object working memory (OWM) and spatial working memory (SWM). Materials utilized in the test consisted of 10 daily objects, including a button, key, coin, battery, watch, pencil sharpener, nail clipper, shears, scotch tape and clothespin, 9 identical opaque containers of height 9 cm and diameter 8 cm, and 5 photographs arrays of the 10 objects. The 9 containers were equidistantly located along the border of a round table. The procedure consisted of an object familiarization phase, a training phase and a testing phase. During the object familiarization phase, the subject was shown as 10 objects, and

was instructed to name and remember them. In the training phase, the examiner put 2 objects from the object familiarization phase into 2 separate containers, told the subject to remember the objects and the containers, and instructed him/her to move around the table 2 cycles clockwise and anticlockwise successively. Then the examiner showed the photographs to the subject to recognize the objects and point out the containers hiding them. If the subject had a correct response, the test got into the next step. If not, he/she is required to continue to point out until a correct answer was given. The result in this period wasn't recorded. After the subject passing the training period, the examiner would ask him/her to memorize the 2 objects and their positions which wouldn't be changed until the whole test was over. In the testing phase, the examiner put another 2 objects from the object familiarization phase into another 2 containers and required the subject to remember them. The subject's movement and sequential recognition of the context were identical to the training phase. The errors were recorded as the OWM and SWM. Following another 3 identical trails, the subject was required to point out the first 2 unchanged objects and containers. The errors were recorded as the ORM and SRM, respectively.

Blood sample collection and hormones and cytokines tests

34 CTTH, 28 FM and 31 MDD patients and 30 health controls completed the serum test. The blood samples were collected in the morning over 60 min after waking up (between 07:30 AM and 08:00 AM) in a sitting position after resting and relaxing for 30 min without any strenuous exercise. After the blood was immediately centrifuged, the obtained sera were stored at -80°C until the hormones and cytokines were assayed. The enzyme-linked immunosorbent assay was used to detect the serum concentrations of hypothalamic releasing hormones, pituitary and target-gland hormones and pro-inflammatory cytokines, including corticotrophin-releasing hormone (CRH), thyrotrophin releasing hormone (TRH), gonadotrophin releasing hormone (GnRH), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), cortisol, total triiodothyronine (TT3), total thyroxine (TT4), IL-1 β and TNF- α . The whole process was completed following the manufacturer's instructions from the Kits purchased, with sensitivity $>84\%$ and specificity $>98\%$ respectively. All sample measurements were run in duplicate, and the averages were calculated for analysis. Intra and inter-assay coefficients of variation were less than 9% and 11%, respectively.

Statistical analysis

All statistical tests were carried out by the standard SPSS package, Version 13.0 for windows. The data were explored to reveal their feature of distribution before statistical tests were performed. Among the normally distributed data, the variables were expressed as means (standard deviation [SD]), and analysis of variance (ANOVA) with Fisher's least-significant difference test was chosen to make a pairwise comparison in the parameter test. Considering the influence factors of cognitive function, such as age, sex and educational degrees, we used multivariate analysis of variance to make a comparison of MoCA-C and memory performances. Among the abnormally distributed data, the variables were expressed as the 50th quartile (25th and 75th quartile) (P50 [P25, P75]), and the Kruskal-Wallis H test was put into use. For the SPSS didn't have the pairwise comparison program in Kruskal-Wallis H test, we make the pairwise comparison by manual computation. The level of statistical significance was set at a two-tailed P -value of 0.05.

Result

Background data

The results are listed in Table 1. There were significant differences of HAMD-17 and PSQI scores among the four groups, while no significant differences of age, sex and years of education were indicated. Compared with the controls, all the MDD, CTTH and FM groups had significant higher HAMD-17 and PSQI scores ($P_s < 0.05$). The MDD patients had the highest HAMD-17 scores, reaching the severe criteria of this scale for moderate to severe major depression. The patients with CTTH and FM also met the standard of mild depression. The MDD patients had the highest score of PSQI, indicating the worst sleep quality, and the FM patients had the lowest PSQI scores.

Comparison of cognitive functions

Verified by pre-analysis, MoCA-C, OWM, SRM and SWM turned out to be within the condition of covariance analysis. Since ORM was not covariance-analysis-friendly, Kruskal-Wallis H test was applied instead. Multivariate analysis of variance showed the sex had no influence on the cognitive functions. The age and years of education significantly affected the MoCA-C scores, but appeared negative on the performance in the Nine Box Maze Test. Diseases had significant effects on all the cognitive tests. After adjusted the age and years educated, the results are shown in Table 2. The MoCA-C scores were significantly lower in all the patients ($t_{CTTH} = -1.651, P = 0.011$; $t_{FM} = -1.930, P = 0.007$; $t_{MDD} = -1.956, P = 0.002$) relative to the controls. In the Nine Box Maze, all the CTTH, FM and MDD groups had significant more error numbers of ORM ($t_{CTTH} = 2.794, P < 0.01$; $t_{FM} = 2.706, P < 0.01$; $t_{MDD} = 2.881, P < 0.005$), SRM ($t_{CTTH} = 2.095, P = 0.04$; $t_{FM} = 2.89, P = 0.006$; $t_{MDD} = 2.408, P = 0.018$), OWM ($t_{CTTH} = 2.192, P = 0.032$; $t_{FM} = 3.495, P = 0.001$; $t_{MDD} = 2.21, P = 0.03$) and SWM ($t_{CTTH} = 2.753, P = 0.008$; $t_{FM} = 3.605, P = 0.001$; $t_{MDD} = 4.251, P < 0.001$) compared with the controls. No differences shown between the CTTH, FM and MDD groups in the performances of MoCA-C and the Nine Box Maze.

Alterations in the hormones and pro-inflammatory cytokines

The hormonal and pro-inflammatory cytokines data are displayed in (Table 3), with the statistic values concluded from a whole comparison for the four groups. For the HPA axis, the serum level of CRH was significantly higher in the CTTH ($t = 5.716, P < 0.001$), FM ($t = 6.207, P < 0.001$) and MDD ($t = 5.563, P < 0.001$) groups relative to the control group, with no difference among the disease groups. The level of ACTH was higher in the CTTH ($t = 3.458, P < 0.001$) and MDD ($t = 2.963, P < 0.001$) patients than that in the FM patients. The cortisol was significantly higher in all the disease groups than the controls ($t_{CTTH} = 12.428, t_{MDD} = 23.684$ and $t_{FM} = 12.198, P_s < 0.001$). However, the CTTH ($t = 11.944, P < 0.001$), FM ($t = 10.961, P < 0.001$) groups had significantly lower level of cortisol compared with the MDD patients. For the HPT axis, the TRH was significantly different among groups ($F = 385.47, P < 0.001$). The three groups of patients showed relatively higher level of TRH ($P_s < 0.05$). Among the three groups of patients, the TRH level of CTTH was higher than that of the MDD ($P < 0.05$), which was in turn higher than that of FM ($P < 0.005$). The TSH level in CTTH was similar with MDD and controls but higher than FM ($P = 0.007$). The serum TT3 and TT4 were significantly lower in the CTTH ($t = 3.455, 12.700; P_s < 0.001$), FM ($t = 5.001, 5.194; P_s < 0.001$) and MDD ($t = 4.944, 12.900; P_s < 0.001$) groups compared with the control group. Among the three disease groups, there were no significant differences for the TT3, however, the CTTH ($t = 7.119, P < 0.001$) and MDD ($t = 7.435, P < 0.001$) patients had lower TT4 compared with the FM patients. For the HPG axis, the only hormone detected, GnRH, was significantly higher in the CTTH ($t = 16.511, P < 0.001$), FM ($t = 5.414, P < 0.001$) and MDD ($t = 21.265, P < 0.001$) groups than that in the control group. The level of GnRH in the CTTH patients was higher than the FM patients ($t = 10.632, P < 0.001$) but lower than the MDD patients ($t = 5.276, P < 0.001$). For the pro-inflammatory cytokines, the level of IL-1 β and TNF- α was significantly higher in the CTTH ($t_{IL-1\beta} = 11.874, P < 0.001$; $t_{TNF-\alpha} = 12.156, P < 0.001$), FM ($t_{IL-1\beta} = 15.033, P < 0.001$; $t_{TNF-\alpha} = 14.767, P < 0.001$) and

	CTTH	FM	MDD	Controls	Statistic	P-value
Age (y)	38.2 (13.3)	38.3 (13.0)	38.3 (12.8)	33.5 (11.5)	$F = 1.87$	$= 0.37$
Sex (male/female)	15/25	10/16	20/30	18/11	$\chi^2 = 5.17$	$= 0.16$
Education (y)	11.3 (2.3)	11.3 (2.8)	12.0 (3.1)	12.0 (3.2)	$F = 0.77$	$= 0.51$
HAMD-D (17)	15.0 (9.0,21.0) *#	13.5 (9.0,21.5) *#	20.0 (16.0,24.0) *	5.0 (2.0,7.0)	$H = 65.15$	< 0.001
PSQI	12 (6.5,15.0) *†	7 (4.0,12.0) *	14 (9.0,16.0) *†	3 (1.5,6.0)	$H = 50.5$	< 0.001

Abbreviations: CTTH: Chronic Tension Type Headache; FM: Fibromyalgia; MDD: Major Depression Disorder; HAMD-17: 17-term Hamilton's Depression Scale; PSQI: Pittsburgh Sleep Quality Index Scale.

Expression: normal distribution variables (Mean [SD]); non-normal distribution variables (P50 [P25, P75]).

* $P < 0.05$, Denotes a significant difference compared to controls

$P < 0.05$, Denotes a significant difference compared to MDD

† $P < 0.05$, Denotes a significant difference compared to FM

Table 1: Demographic characteristic of subjects.

	CTTH	FM	MDD	Controls	Statistic	P-value
MoCA-C	25.63 (2.37) *	25.35 (2.15) *	25.32 (3.04) *	27.28 (2.58)	$F = 3.1$	0.029
ORM	2.38 (2.52) *	2.23 (2.12) *	1.94 (1.62) *	0.97 (1.78)	$H = 11.03$	0.012
SRM	3.48 (2.46) *	3.96 (2.24) *	3.68 (2.65) *	2.31 (2.00)	$F = 2.69$	0.049
OWM	2.98 (2.83) *	4.04 (3.04) *	2.92 (2.75) *	1.62 (2.04)	$F = 3.70$	0.013
SWM	7.58 (4.67) *	8.77 (4.89) *	9.06 (4.80) *	4.83 (3.12)	$F = 5.97$	0.001

Abbreviations: CTTH: Chronic Tension Type Headache; FM: Fibromyalgia; MDD: Major Depression Disorder; MoCA-C: Chinese-Beijing Version of Montreal Cognitive Assessment; SEM: Self-Evaluation Of Memory; ORM: Object Reference Memory; SRM: Spatial Reference Memory; OWM: Object Working Memory; SWM: Spatial Working Memory; ORcM: Object Recognition Memory

Expression: normal distribution variables (Mean [SD]); non-normal distribution variables (P50 [P25, P75]).

* $P < 0.05$, Denotes a significant difference compared to controls

Covariates appearing in the model are evaluated at the following values: age=37.3; educational degrees=11.7

Table 2: The performances of cognitive functions in the different groups.

	CTTH	FM	MDD	Controls	Statistic	P-value
CRH (ng/l)	100.3 (82.8, 137.1)*	107.4 (85.4, 153.1) *	101.3 (81.0, 126.7) *	69.5 (48.7, 76.7)	H=36.83	<0.001
ACTH (ng/l)	91.5 (87.3, 96.2) †	83.3 (79.5, 90.9)	91.2 (85.4, 93.5) †	87.3 (84.1, 91.6)	H=12.81	0.005
Cortisol (µg/l)	199.0 (181.7, 221.4) *#	208.3 (192.7, 213.9) *#	310.9 (298.2, 335.7) *	125.6 (118.5, 135.8)	H=102.62	<0.001
TRH (ng/l)	129.1 (5.0) *#	87.4 (6.7) †*#	98.4 (5.7) *	82.7 (6.8)	F=385.47	<0.001
TSH (mIU/l)	2.7 (0.4)	2.6 (0.3) #	2.8 (0.2)	2.7 (0.3)	F=2.76	0.045
TT3 (µg/l)	4.3 (4.0, 4.6) *	3.8 (2.7, 4.7) *	4.1 (3.6, 4.3) *	6.1 (5.8, 6.4)	H=26.41	<0.001
TT4 (µg/l)	199.5 (180.1, 229.1)*	236.6 (230.4,243.0) †*#	203.2 (182.1, 211.7) *	317.1 (281.3, 341.3)	H=80.56	<0.001
GnRH (ng/l)	26.9 (24.8, 28.2)* †#	20.2 (19.0, 20.9) *#	28.4 (27.8, 29.4) *	18.1 (17.5, 18.9)	H=100.81	<0.001
IL-1β (ng/l)	42.6 (38.4, 64.5) *#†	53.0 (44.4, 69.4) *#	79.5 (78.2, 81.9) *	26.8 (24.7, 28.5)	H=104.76	<0.001
TNF-α (ng/l)	49.1 (43.7, 78.5) *#	59.1 (50.4, 74.6) *#	91.2 (88.1, 92.3) *	33.1 (31.1, 34.7)	H=103.12	<0.001

Abbreviations: CTTH: Chronic Tension Type Headache; FM: Fibromyalgia; MDD: Major Depression Disorder; CRH: Corticotrophin-Releasing Hormone; ACTH: Adenocorticotrophic Hormone; TRH: Thyrotrophin- Releasing Hormone; TSH: Thyroid Stimulating Hormone; TT3: Total Triiodothyronine; TT4: Total Thyroxine; GnRH: Gonadotropin-Releasing Hormone; IL-1β: Interleukin-1β; TNF-α: Tumor Necrosis Factor-α

Expression: normal distribution variables (Mean [SD]); non-normal distribution variables (P50 [P25, P75]).

*P<0.05, Denotes a significant difference compared to controls

#P<0.05, Denotes a significant difference compared to MDD

†P<0.05, Denotes a significant difference compared to FM

‡P<0.05, Denotes a significant difference compared to CTTH

Table 3: Serum levels of hormones and cytokines in subjects.

MDD ($t_{IL-1\beta}=26.825, P<0.001$; $t_{TNF-\alpha}=25.433, P<0.001$) groups than that in the controls. The CTTH patients had the lower IL-1β and TNF-α than the MDD patients ($t_{IL-1\beta}=15.686, P<0.001$; $t_{TNF-\alpha}=13.969, P<0.001$). The level of IL-1β in CTTH was also lower than in the FM patients ($t=3.823, P<0.001$) but was no significant difference in TNF-α.

Discussion

The patients with CTTH had mood, sleep and memory damages

In the current study, the similar clinic dimensions were found among the patients with CTTH, FM and MDD, including the dimensions in the age, sex, mood, sleep and cognition. The patients who visited a clinic were at the midlife with about averaged 38 years old, and the number of women was more relative to the men. The patients with CTTH had dysfunction of mood and sleep like FM and MDD in line with previous studies [3]. The depression mood is more similar to FM and sleep quality is more similar to MDD in CTTH.

Studies have stated that impairment of multi-cognition domains in the FM and MDD patients, including complex attention function, working memory, long-term memory and executive functions [31-33]. But there were few researches about cognitive function in CTTH for reference. Only a study revealed that children with CTTH most likely to be less brilliant at verbal skills [34]. Our study focused on cognitive function in CTTH especially memory. We used MoCA-C, a widely accepted cognitive test to evaluate all the participants. The result showed that all the patients had the lower scores compared to the controls. But this test is limited in clinical application for it is influenced by age and educational degree. With modified age and educational degree, all the patients hit similar scores in MOCA-C.

In order to accomplish more objective and accurate evaluation of memory, we introduced Nine Box Maze Test for the first time to evaluate ORM, SRM, OWM and SWM of the participants with the three diseases. Nine Box Maze Test based on Abraham's design [35], involves aspects of declarative memory (including semantic and episodic memory), non-declarative memory (e.g., procedural memory), and short- and long-term memory [36]. We modified the protocol of the Nine Box Maze Test to obtain more accurate sensitive measurements of memory function. This test can be easily operated and doesn't need special software and professional trainer. Furthermore, it

is not influenced by age and education and is efficient to test slightly declined memory. Therefore, it is so far an optical means to detect the mild impairment of multiple memory system in the clinic settings. Our results indicated that patients with CTTH had declined object (working and reference) and spatial (working and reference) memories, which was remarkably consistent of FM and MDD. The results also enlarged the information of memory impairment in FM and MDD in the former reference [31-33].

The changes of hormones and pro-inflammatory cytokines in CTTH were similar to the other two illnesses

The results of the neuroendocrine hormones and pro-inflammatory cytokines pointed out a similar profile of changes in the three diseases. The obvious elevated level of CRH and cortisol reflecting a hyperactivity of function in the HPA axis in CTTH like the other two diseases. The level of ACTH in all the patients didn't have significant difference compared to the controls but the FM patients had the lower level of ACTH than the CTTH and MDD patients. This may be contributed to that the pituitary hormones are lags in response to the hypothalamus hormones or/and are acted by the over-feedback of target-gland hormones with more obvious in the FM patients. Contrasted to the HPA axis, the elevated TRH and decreased TT3 and TT4 in CTTH suggested a hypoactivity of function in the HPT axis, so were the FM and MDD. Similarly, the pituitary hormone TSH of HPT axis also had no difference between all the patients except FM patients had a lower level. The level of GnRH was increased in the patients with CTTH compared to the controls, suggesting the hypothalamus hormone of HPG axis was hypersecretion in CTTH. The same change was also found in FM and MDD, but the ascent range of GnRH was different, the MDD patients had the highest level and the FM patients had the lowest level relatively. The elevated levels of pro-inflammatory cytokines IL-1β and TNF-α in CTTH suggest an over-activation in the inflammatory pathway in accordance with the other two diseases and the inflammatory response was lower in the CTTH patients and higher in the MDD patients relatively. In brief, the patients with CTTH had a consistently changed profile in the HPA axis, HPT axis, GnRH and pro-inflammatory cytokines with the FM and MDD patients.

The possible mechanisms of CTTH

Everyone will encounter life stressors such as physical, emotional or sexual abuse in his or her life, which can emphatically cause a

condition known as stress sensitization. HPA axis is involved in stress sensitization circuits. HPA axis respond to acute stress is to boost the release of CRH, ACTH and cortisol. Under normal condition, increased serum cortisol levels induce an inhibition of the HPA axis to diminish the release of CRH and returning the HPA system to normal circumstance. Nevertheless, after prolonged stress, this negative feedback mechanism is disrupted. Individuals who have the susceptibility gene to stress appear to be more vulnerable to the effect of stress. HPA axis of these people is more active and the normal negative feedback is more likely to be damaged. As a result, the level of CRH often elevated. CRH plays an important role in prolonged clinical pain and affective disorders [37]. Increased CRH receptor in some brain regions like amygdale, hippocampal can contribute to pain and depressive mood in the absence of tissue pathology or disease state [38]. Early studies have found CRH can decrease the slow wave sleep and increase light sleep and awakenings in men [39]. The elevated CRH and cortisol have a significant impact on sleep quality and even leads to insomnia [40,41]. A recent study has showed that CRH is an independent risk factor for insomnia rather than cortisol [40] as it may be more influential on sleep than cortisol is. Additionally, the elevated level of cortisol can destroy memory [42]. So we could assume that the hyperactivity of the HPA axis plays a central role in the onset and development of CTTH and the hormones changes of the HPA axis are associated with the clinic symptoms of CTTH.

From our study, the function of HPT axis in CTTH was decreased. HPT axis can be influenced by stress and abnormal function of HPA axis. Stress is a modulator of HPT axis, but the response of HPT axis to stress is different. The levels of TSH and thyroid hormones depend on the type, length and severity of the stressors and the function of HPA axis. Severe stressors often cause a decrease in thyroid hormone levels [43]. Over-activated function of HPA axis can suppress the activity of HPT axis [44]. The decreased function of thyroid may associate with pain [45]; affect mental status such as leading to depression [46]. Thyroid hormones are also associated with cognitive function. Adults with elevated thyroid hormones performed better on tests of visuo-spatial/visuo-construction ability, psychomotor speed and language/verbal than the ones with lower level of thyroid hormones [47]. Patients with hypothyroidism often experience sleep disturbances [48].

Epidemiological studies have shown that CTTH is more prevalence in women [1] which suggest sex hormones maybe involved in CTTH. Lower estradiol and higher progesterone levels in women with MDD have been observed in many studies [21,22] By reason of the complex effects of age and gender, we examined only GnRH in the HPG axis. Our results showed an increased level of GnRH in the CTTH patients. One case is indispensable here in the paper about a woman treated with a GnRH analogue for endometriosis who developed typical clinical features of FM [49]. Using GnRH-agonist to women, a significant phase effect was unveiled for depression symptoms during in vitro fertilization-embryo transfer cycles [50]. These suggested that GnRH is associated with pain and depression which are the main symptoms of CTTH.

Over-activation of inflammatory pathways has been found in the patients with CTTH [51], FM [52] and MDD [53], and further was supported by the current researches. Pro-inflammatory cytokines affects the secretion of CRH, ACTH and glucocorticoids through the regulation of HPA axis activity in the brain [54] and may markedly affect neurotransmission within regulatory brain circuits for emotion [55]. The elevated levels of pro-inflammatory cytokines such as IL-1 and TNF- α have been shown to be a significant contributor of the

sleep disturbances [56], and are also associated with the cognitive impairment [57].

Regarding the recent study, we could infer the possible mechanism underlying the CTTH. The people who had the susceptibility gene to stress under the stressors may be liable to lead the dysfunction of HPA axis, then the changes of HPT axis, HPG axis and inflammatory pathways appeared subsequently. Elevated level of CRH, cortisol, GnRH, pro-inflammatory cytokines and decreased function of thyroid all contributed to the clinic symptoms like pain, depression mood, cognitive impairment and sleep disorders.

Hint of treatment

In the past, there are few good-quality trials of preventive treatment of CTTH. The best evidence exists for amitriptyline 75 mg daily [58]. Mirtazipine and venlafaxine have also been shown to be effective in prevent CTTH [59,60]. But another study suggested that selective serotonin reuptake inhibitors (SSRIs) and venlafaxine for the prevention of chronic tension-type headache is not supported by evidence [61].

From our study, we infer that restore the function of HPA axis maybe a useful method to cure the CTTH. Researchers have found that treatment with tricyclic antidepressants increases glucocorticoid receptor (GR) binding affinity and GR mRNA expression in rat hypothalamic and hippocampal neurons, suggesting that antidepressants may enhance glucocorticoid sensitivity and function, specifically in the brain, and thereby may restore GR-mediated feedback inhibition on HPA axis then the function of HPA can restore to normal extent [62]. SSRI and tricyclic antidepressants increase nuclear translocation of GR and also facilitate GR-mediated gene transcription [63]. The serotonin-norepinephrine reuptake inhibitors (SNRI) like duloxetine can up-regulate the expression of GR responsive genes then modulate the activity of HPA axis [64]. Studies have shown that antidepressant treatment, mainly selective serotonin reuptake inhibitors, was also associated with decreases in inflammatory markers [65]. Antidepressants have been proved be effective on MDD not only act on monoamine neurotransmitter, impact on HPA axis maybe another important role. In fact, evidence from treatment studies has revealed that tricyclic antidepressants (TCAs), duloxetine has been shown to be efficacious in treating FM [66,67]. So we thought SSRI and SNRI are still the worthwhile treatment for CTTH. Thyroxin and GnRH-antagonist may be useful in CTTH either, this need further research to confirm.

Deficiencies

Certainly, the pathophysiological mechanisms of the three diseases are far more beyond these. Because of the limitations, we only explored the endocrine and inflammatory factors in the three diseases. It was a pity that because of the design defect, we could not complete an analysis to explore the effect of the serum levels of hormones and cytokines on the depression, sleep quality and cognitive function. Another deficiency was the small sample size, which resulted in that we could not separate sex to study the sex hormones comprehensively.

Conclusion

The patients with CTTH had similar patterns of memory damage and changes of the HPA and HPT axes, GnRH and pro-inflammatory cytokines with the FM and MDD patients.

Acknowledgments

This work was financially supported by The Annual Research Plan of Anhui Province (1301043041).

References

1. Stovner Lj, Hagen K, Jensen R, Katsarava Z, Lipton R, et al. (2007) The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia* 27: 193-210.
2. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 24 (Suppl 1): 9-160.
3. Caspersen N, Hirsvang JR, Kroell L, Jadidi F, Baad-Hansen L, et al. (2013) Is There a Relation between Tension-Type Headache, Temporomandibular Disorders and Sleep? *Pain Res Treat* 2013: 845684.
4. Bendtsen L (2000) Central sensitization in tension-type headache—possible pathophysiological mechanisms. *Cephalalgia* 20: 486-508.
5. Fernández-de-Las-Peñas C (2009) What do we know about chronic tension-type headache? *Discov Med* 8: 232-236.
6. Schmidt-Hansen PT, Svensson P, Bendtsen L, Graven-Nielsen T, Bach FW (2007) Increased muscle pain sensitivity in patients with tension-type headache. *Pain* 129: 113-121.
7. Russell MB (2007) Genetics of tension-type headache. *J Headache Pain* 8: 71-76.
8. Park JW, Kim JS, Lee HK, Kim YI, Lee KS (2004) Serotonin transporter polymorphism and harm avoidance personality in chronic tension-type headache. *Headache* 44: 1005-1009.
9. Battistutta S, Aliverti R, Montico M, Zin R, Carrozzi M (2009) Chronic tension-type headache in adolescents. Clinical and psychological characteristics analyzed through self- and parent-report questionnaires. *J Pediatr Psychol* 34: 697-706.
10. Yunus MB (2007) Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum* 36: 339-356.
11. Roizenblatt S, Neto NS, Tufik S (2011) Sleep disorders and fibromyalgia. *Curr Pain Headache Rep* 15: 347-357.
12. Dick BD, Verrier MJ, Harker KT, Rashid S (2008) Disruption of cognitive function in fibromyalgia syndrome. *Pain* 139: 610-616.
13. Bair MJ, Robinson RL, Katon W, Kroenke K (2003) Depression and pain comorbidity: A literature review. *Arch Intern Med* 163: 2433-2445.
14. Spiegelhalder K, Regen W, Nanovska S, Baglioni C, Riemann D (2013) Comorbid sleep disorders in neuropsychiatric disorders across the life cycle. *Curr Psychiatry Rep* 15: 364.
15. Lee RS, Hermens DF, Porter MA, Redoblado-Hodge MA (2012) A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *J Affect Disord* 140: 113-124.
16. Humphreys D, Schlesinger L, Lopez M, Araya AV (2006) Interleukin-6 production and deregulation of the hypothalamic-pituitary-adrenal axis in patients with major depressive disorders. *Endocrine* 30: 371-376.
17. Wingenfeld K, Nutzinger D, Kauth J, Hellhammer DH, Lautenbacher S (2010) Salivary cortisol release and hypothalamic pituitary adrenal axis feedback sensitivity in fibromyalgia is associated with depression but not with pain. *J Pain* 11: 1195-1202.
18. Haddad JJ, Saadé NE, Safieh-Garabedian B (2002) Cytokines and neuro-immune-endocrine interactions: A role for the hypothalamic-pituitary-adrenal revolving axis. *J Neuroimmunol* 133: 1-19.
19. Catley D, Kaell AT, Kirschbaum C, Stone AA (2000) A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. *Arthritis Care Res* 13: 51-61.
20. Gur A, Cevik R, Sarac AJ, Colpan L, Em S (2004) Hypothalamic-pituitary-gonadal axis and cortisol in young women with primary fibromyalgia: the potential roles of depression, fatigue, and sleep disturbance in the occurrence of hypocortisolism. *Ann Rheum Dis* 63: 1504-1506.
21. Holsen LM, Lee JH, Spaeth SB, Ogden LA, Klibanski A, et al. (2012) Brain hypoactivation, autonomic nervous system dysregulation, and gonadal hormones in depression: A preliminary study. *Neurosci Lett* 514: 57-61.
22. Holsen LM, Spaeth SB, Lee JH, Ogden LA, Klibanski A, et al. (2011) Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. *J Affect Disord* 131: 379-387.
23. Hayley S (2011) Toward an anti-inflammatory strategy for depression. *Front Behav Neurosci* 5: 19.
24. Hayley S, Poulter MO, Merali Z, Anisman H (2005) The pathogenesis of clinical depression: Stressor- and cytokine-induced alterations of neuroplasticity. *Neuroscience* 135: 659-678.
25. Munhoz CD, Garcia-Bueno B, Madrigal JL, Lepsch LB, Scavone C, et al. (2008) Stress-induced neuroinflammation: Mechanisms and new pharmacological targets. *Braz J Med Biol Res* 41: 1037-1046.
26. Sim YB, Park SH, Kang YJ, Jung JS, Ryu OH, et al. (2013) Interleukin-1 β (IL-1 β) increases pain behavior and the blood glucose level: Possible involvement of glucocorticoid system. *Cytokine* 64: 351-356.
27. Wu Z, Wang S, Wu I (2015) Activation of TLR-4 to produce tumour necrosis factor- α in neuropathic pain caused by paclitaxel. *Eur J Pain* 19: 889-898.
28. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, et al. (1990) The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 33: 160-172.
29. Association AP (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th edition, test review (DSM-IV-TR). Washington, DC: American Psychiatric Press. 599- 604.
30. Pentland LM, Anderson VA, Dye S, Wood SJ (2003) The Nine Box Maze Test: A measure of spatial memory development in children. *Brain Cogn* 52: 144-154.
31. Glass JM (2006) Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: New trends and future directions. *Curr Rheumatol Rep* 8: 425-429.
32. Leavitt F, Katz RS (2006) Distraction as a key determinant of impaired memory in patients with fibromyalgia. *J Rheumatol* 33: 127-132.
33. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallagher LA, et al. (2013) Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depress Anxiety* 30: 515-527.
34. Parisi P, Verrotti A, Paolino MC, Urbano A, Bernabucci M, et al. (2010) Headache and cognitive profile in children: a cross-sectional controlled study. *J Headache Pain* 11: 45-51.
35. Abrahams S, Pickering A, Polkey CE, Morris RG (1997) Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. *Neuropsychologia* 35: 11-24.
36. Paul CM, Magda G, Abel S (2009) Spatial memory: Theoretical basis and comparative review on experimental methods in rodents. *Behav Brain Res* 203: 151-164.
37. Ji G, Fu Y, Adwanikar H, Neugebauer V (2013) Non-pain-related CRF1 activation in the amygdala facilitates synaptic transmission and pain responses. *Mol Pain* 9: 2.
38. Paez-Pereda M, Hausch F, Holsboer F (2011) Corticotropin releasing factor receptor antagonists for major depressive disorder. *Expert Opin Investig Drugs* 20: 519-535.
39. Fukudo S, Nomura T, Hongo M (1998) Impact of corticotropin-releasing hormone on gastrointestinal motility and adrenocorticotrophic hormone in normal controls and patients with irritable bowel syndrome. *Gut* 42: 845-849.
40. Xia L, Chen GH, Li ZH, Jiang S, Shen J, et al. (2013) Alterations in hypothalamus-pituitary-adrenal/thyroid axes and gonadotropin-releasing hormone in the patients with primary insomnia: A clinical research. *PLoS One* 9: e71065.
41. Rodenbeck A, Huether G, Ruther E, Hajak G (2002) Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neurosci Lett* 324: 159-163.
42. Ackermann S, Hartmann F, Papassotiropoulos A, de Quervain DJ, Rasch B (2013) Associations between basal cortisol levels and memory retrieval in healthy young individuals. *J Cogn Neurosci* 25: 1896-1907.

43. Kilburn-Watt E, Banati RB, Keay KA (2010) Altered thyroid hormones and behavioural change in a sub-population of rats following chronic constriction injury. *J Neuroendocrinol* 22: 960-970.
44. Rasgon NL, Kenna HA, Wong ML, Whybrow PC, Bauer M (2007) Hypothalamic-pituitary-end organ function in women with bipolar depression. *Psychoneuroendocrinology* 32: 279-286.
45. Hagen K, Bjørro T, Zwart JA, Svebak S, Bovim G, et al. (2005) Do high TSH values protect against chronic musculoskeletal complaints? The Nord-Trøndelag Health Study (HUNT). *Pain* 113: 416-421.
46. Hage MP, Azar ST (2012) The Link between Thyroid Function and Depression. *J Thyroid Res* 2012: 590648.
47. Beydoun MA, Beydoun HA, Kitner-Triolo MH, Kaufman JS, Evans MK, et al. (2013) Thyroid hormones are associated with cognitive function: moderation by sex, race, and depressive symptoms. *J Clin Endocrinol Metab* 98: 3470-3481.
48. Steiger A (2007) Neurochemical regulation of sleep. *J Psychiatr Res* 41: 537-552.
49. Toussiro E, Wendling D (2001) Fibromyalgia developed after administration of gonadotrophin-releasing hormone analogue. *Clin Rheumatol* 20: 150-152.
50. Bloch M, Azem F, Aharonov I, Ben Avi I, Yagil Y, et al. (2011) GnRH-agonist induced depressive and anxiety symptoms during in vitro fertilization-embryo transfer cycles. *Fertil Steril* 95: 307-309.
51. Garrison RL, Breeding PC (2003) A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. *Med Hypotheses* 61: 182-189.
52. Koşer A, Koşer E, Memişoğlu R, Domaş FM, Yılmaz H (2010) Interleukin-6 levels in tension headache patients. *Clin J Pain* 26: 690-693.
53. Simon NM, McNamara K, Chow CW, Maser RS, Papakostas GI, et al. (2008) A detailed examination of cytokine abnormalities in Major Depressive Disorder. *Eur Neuropsychopharmacol* 18: 230-233.
54. Goshen I, Yirmiya R (2009) Interleukin-1 (IL-1): A central regulator of stress responses. *Front Neuroendocrinol* 30: 30-45.
55. Arnsten AF (2009) Stress signaling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci* 10: 410-422.
56. Ranjbaran Z, Keefer L, Stepanski E, Farhadi A, Keshavarzian A (2007) The relevance of sleep abnormalities to chronic inflammatory conditions. *Inflamm Res* 56: 51-57.
57. Briones TL, Woods J (2014) Dysregulation in myelination mediated by persistent neuroinflammation: Possible mechanisms in chemotherapy-related cognitive impairment. *Brain Behav Immun* 35: 23-32.
58. Bendtsen L, Jensen R, Olesen J (1996) A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. *J Neurol Neurosurg Psychiatry* 61: 285-290.
59. Bendtsen L, Jensen R (2004) Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. *Neurology* 62: 1706-1711.
60. Zisis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, et al. (2007) A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. *Cephalalgia* 27: 315-324.
61. Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, et al. (2015) Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of tension-type headache in adults. *Cochrane Database Syst Rev* May 1: CD011681.
62. Okugawa G, Omori K, Suzukawa J, Fujiseki Y, Kinoshita T, et al. (1999) Long-term treatment with antidepressants increases glucocorticoid receptor binding and gene expression in cultured rat hippocampal neurones. *J Neuroendocrinol* 11: 887-895.
63. Anacker C, Zunszain PA, Cattaneo A, Carvalho LA, Garabedian MJ, et al. (2011) Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. *Mol Psychiatry* 16: 738-750.
64. Guidotti G, Calabrese F, Anacker C, Racagni G, Pariante CM, et al. (2013) Glucocorticoid receptor and FKBP5 expression is altered following exposure to chronic stress: modulation by antidepressant treatment. *Neuropsychopharmacology* 38: 616-627.
65. Hamer M, Batty GD, Marmot MG, Singh-Manoux A, Kivimäki M (2011) Antidepressant medication use and C-reactive protein: Results from two population-based studies. *Brain Behav Immun* 25: 168-173.
66. Smith HS, Barkin RL (2011) Fibromyalgia syndrome: A discussion of the syndrome and pharmacotherapy. *Dis Mon* 57: 248-285.
67. Chappell AS, Littlejohn G, Kajdasz DK, Scheinberg M, D'Souza DN, et al. (2009) A 1-year safety and efficacy study of duloxetine in patients with fibromyalgia. *Clin J Pain* 25: 365-375.