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Gender difference in vitamin A levels in first-episode drug-naïve depression patients: a case-control and 24-weeks follow-up study

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Depression is one of the major causes of disability in societies worldwide. However, only a few studies have been conducted to analyze the relationship between vitamin A levels and depression. This study aimed to explore the vitamin A levels in the plasma of first-episode drug-naïve depression patients. 48 healthy controls and 75 first-episode drug-naïve outpatients were recruited in our research and a total of 18 patients were followed for 24 weeks. There was no difference in plasma vitamin A levels among healthy controls and patients with depression. After 24 weeks antidepressant treatment, plasma vitamin A levels were decreased. Interestingly, this alteration of vitamin A was only found in female patients. Moreover, correlation analyses showed that plasma vitamin A levels were significantly associated with depressive symptomatic index only in female depression patients. We found that the levels of vitamin A were decreased in female patients with depression during antidepressant therapy. Further study of gender difference in vitamin A levels is needed to reveal the mechanism.

1. Introduction

Major depressive disorder (MDD), a highly complicated disease that affects the entire life of patient, such as mood, behavior, sleep, appetite, and other physical functions, ranks among the leading cause of the global burden (Whiteford et al. 2013; Post 1992). So far, the pathogenesis of the depression remains unclear. Research has suggested that supplements of nutrition, especially vitamin, contribute to a decreased risk of depression. A low intake of vitamin E, a fat-soluble antioxidant micronutrient, was related to altered mood and depression (Banikazemi et al. 2015) and serum vitamin E concentrations in plasmas of MDD patients were significantly lower than that of healthy controls (Maes et al. 2000). Another study demonstrated that deficiency in vitamin B derivatives was linked to symptoms of depression (Mikkelsen et al. 2017). Moreover, a potential negative correlation was found between vitamin D and depressive symptoms (Hoogendijk et al. 2008; Bertone-Johnson et al. 2011). However, little is known about the effects of vitamin A on depression.

Vitamin A (all-*trans*-retinol) is the parent compound of the retinoids, which is a family of natural and synthetic compounds (Lane and Bailey 2005). Vitamin A and retinoids can regulate the function of many important metabolic and physiologic activities (Chapman 2012). The importance of vitamin A for the central nervous system (CNS) was evident. Stoney et al. found that vitamin A is essential for neuroplasticity in the hippocampus (Stoney and McCaffery 2016). Recently, studies have shown that the lack of vitamin A can cause a significant reduction of long-term potentiation (LTP) in the hippocampus and a nearly entire loss of long-term depression (LTD) in the CA1 region (Misner et al. 2001). Moreover, previous studies demonstrated that vitamin A plays a role in the prevention and promotion of recovery from depression (LaChance and Ramsey 2018).

Recently, there were plenty of studies on gender difference in individuals with depression (Bijl et al. 2002; Cairney and Wade 2002). The prevalence rates of depression in females were approximately two-fold higher than that in male (Cyranowski et al. 2000; Guo et al. 2017). Moreover, depression appeared to cause more serious effects in female, manifested by a younger age of onset, more serious symptoms, poorer quality of life and lower social adjustment (Kornstein et al. 2000; Sekita et al. 2013). Interestingly, gender differences were also shown on the responsivity and tolerability of selective reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCA) (Kornstein et al. 2000; Sramek et al. 2016). However, gender differences in plasma vitamin A concentration between healthy people and depression patients and the change after antidepressants treatment are still unclear. To the best of our knowledge, this is the first study concerning gender differences in plasma vitamin A concentration in depressed population.

Our present study was aimed to investigate whether: (1) vitamin A concentration was different between patients with first-episode drug-naïve depression and healthy controls; (2) vitamin A concentration in depressed patients changed after antidepressants treatment; (3) vitamin A concentration in depressed patients showed gender difference; (4) vitamin A concentration had correlation with depressive symptoms.

2. Investigations and results

2.1. Sample characteristics and vitamin A plasma concentration (C_{VA}) in depression patients and healthy controls

In our study, 75 first-episode drug-naïve depressed outpatients and 48 healthy controls were included. Of the 75 patients with depression, 18 patients finished the follow-up study at 24 weeks. Table 1 demonstrates the demographic data, symptomatic index and vitamin A plasma concentration (C_{VA}) of healthy controls and patients. There were no significant differences between healthy controls and first-episode drug-naïve depression patients in gender ($X^2 = 1.181$,

Table 1: Comparison of demographic, clinical and C_{VA} between depression patients and healthy controls

Characteristics	Healthy controls (n=48)	Depression patients (n=75)	Depression follow-up (n=18)	*t*/X^2	*P*-Value[a]	*t*/X^2	*P*-Value[b]
Males/females	22/26	27/48	4/14	1.181	0.277	1.240	0.265
Age (years)	27.76±8.55	26.24±8.01	25.29±8.21	0.924	0.358	0.430	0.669
Education (years)	14.05±2.15	13.30±3.28	14.50±2.03	1.351	0.180	-1.780	0.083
Height (cm)	165.00±7.70	163.03±8.30	164.08±8.34	1.212	0.434	-0.381	0.704
Body weight (kg)	61.23±11.51	56.01±9.03	65.00±7.07	**2.554**	**0.012**	-1.390	0.170
BMI (kg/m^2)	22.37±3.13	21.02±2.62	21.45±1.99	2.339	0.229	-0.228	0.820
HAMD	-	29.73±7.03	9.56±5.85	-	-	**10.553**	**0.000**
HAMA	-	23.52±7.78	6.38±5.74	-	-	**8.239**	**0.000**
BDI	6.43±7.58	29.38±9.05	5.50±6.22	**-14.837**	**0.000**	**9.926**	**0.000**
C_{VA} (µmol/L)	3.51±1.44	3.23±1.31	1.98±0.95	1.122	0.264	**3.810**	**0.000**

[a]compared with healthy controls; [b]compared with depression patients at baseline

Table 2: Gender effects on demographic, clinical and C_{VA} profiles in healthy controls and depression patients

Characteristics	Healthy controls				Depression patients			
	Male (n=22)	Female (n=26)	t	*P*-Value	Male (n=27)	Female (n=48)	t/ X^2	*P*-Value
HAMD	-	-	-	**-**	31.14±7.27	28.95±6.87	1.175	0.244
HAMA	-	-	-	**-**	26.23±7.16	22.03±7.78	2.091	**0.041**
BDI	7.45±9.33	5.50±5.60	-	-	28.72±12.80	28.53±8.38	0.7073	0.942
Age (years)	29.30±9.16	26.36±7.90	1.115	0.271	24.88±6.05	26.55±8.98	-0.820	0.416
Education (years)	13.55±2.28	14.50±1.97	-1.448	0.155	13.68±2.77	13.14±3.46	0.616	0.541
Height (cm)	170.65±5.65	159.86±5.34	6.350	**0.000**	171.02±5.75	158.66±5.77	8.226	**0.000**
Body weight (kg)	66.80±9.68	56.17±10.84	3.339	**0.002**	62.29±8.86	52.64±7.19	4.701	**0.000**
BMI	22.93±3.07	21.85±3.17	1.116	0.271	21.82±3.04	21.16±2.63	0.595	0.554
C_{VA} (µmol/L)	4.63±1.23	2.56±0.77	7.076	**0.000**	3.87±1.33	2.84±1.11	3.345	**0.000**

P = 0.277), age (*t* = 0.924, *P* = 0.358), education (*t* = 1.351, *P* = 0.180), height (*t* = 1.212, *P* = 0.434), BMI (*t* = 2.339, *P* = 0.229) and C_{VA} (*t* = 1.122, *P* = 0.264), while body weight (*t* = 2.554, *P* = 0.012) was significantly different between healthy controls and depression patients. However, follow-up of depressed patients revealed a significant decrease in C_{VA} (*t* = 3.810, *P* = 0.000) compared with the baseline.

2.2. Gender differences in characteristics and C_{VA} in healthy controls and depression patients

Considering physical and psychological differences between males and females, gender differences in C_{VA} were taken into consideration for subgroup analysis. Except for lower height (*t* = 6.350, *P* = 0.000) and weight (*t* = 3.339, *P* = 0.002), decreased C_{VA} (*t* = 7.076, *P* = 0.000) was also found in female than male controls. We investigated whether there was a gender difference in C_{VA} in depression patients. Compared to male depression patients, female depression patients also have lower height (*t* = 8.226, *P* = 0.000), body weight (*t* = 4.701, *P* = 0.000), HAMA (*t* = 2.091, *P* = 0.041) and C_{VA} (*t* = 3.345, *P* = 0.000) (Table 2).

2.3. Changes in clinical and C_{VA} in patients with first-episode drug-naïve depression during 24-weeks follow-up

As shown in Table 3, paired *t* tests indicated that male and female depressed patients have different trends in C_{VA} after 24 weeks antidepressant treatment. Female depression follow-up showed significantly lower C_{VA} (*t* = 3.068, *P* = 0.003) than female depression patients. However, we did not find any statistically significant differences of C_{VA} between male depression patients and follow-up patients.

2.4. Relationships between C_{VA} and clinical characteristics in depression

C_{VA} has a significant positive association with HAMD score (*t* = 0.343, *P* = 0.002), HAMA score (*t* = 0.270, *P* = 0.017) in depressed patients. The results of the male and female depressed

Table 3: Changes in clinical and C_{VA} in patients with first-episode drug-naïve depression during 24-weeks follow-up

Characteristics	Male depression patients (n=27)	Male depression follow-up (n=4)	t	*P*-Value	Female depression patients (n=48)	Female depression follow-up (n=14)	t	*P*-Value
HAMD	31.14±7.27	8.50±2.52	6.076	**0.000**	28.95±6.87	9.92±6.67	8.477	**0.037**
HAMA	26.23±7.16	3.25±1.50	6.288	**0.000**	22.03±7.78	7.42±6.29	5.935	**0.000**
BDI	30.86±10.13	2.75±3.10	5.420	**0.000**	28.52±8.38	6.42±6.81	8.295	**0.000**
C_{VA} (µmol/L)	3.92±1.36	2.48±0.85	2.042	0.050	2.85±1.11	1.84±0.95	3.068	**0.003**

Table 4: Partial correlation analysis between symptomatic index and C_{VA} profiles in the depression group

	HAMD	HAMA	BDI
Total C_{VA}	**0.343 (0.002)**	**0.270 (0.017)**	0.134 (0.148)
Male C_{VA}	0.247 (0.224)	0.157 (0.444)	0.350 (0.080)
Female C_{VA}	**0.365 (0.008)**	0.250 (0.074)	**0.339 (0.016)**

patients were also analyzed in subgroup to find whether gender differences in C_{VA} were associated with symptomatic index. As shown in Table 4, for female depressed patients, partial correlation analysis showed significantly positive associations between C_{VA} and both the BDI score (t = 0.339, P = 0.016) and HAMD score (t = 0.365, P = 0.008). While, for male depressed patients, no significant correlation was found between the C_{VA} and scores of scales.

3. Discussion

This is the first case-control study to compare plasma vitamin A concentration between first-episode drug-naïve depressed patients and healthy controls. In addition, no previous study has demonstrated gender differences on vitamin A and antidepressant-induced change of vitamin A in depressed patients yet. The major findings of our present study were as follows : (1) female subjects exhibited decreased C_{VA} compared with male subjects both in controls and depressed patients; (2) after 24 week's antidepressants treatment, C_{VA} in depressed patients was lower than the baseline; (3) after 24 week's antidepressants treatment, the C_{VA} was significantly decreased in female patients rather than male patients; (4) a significant positive correlations between HAMD, BDI and C_{VA} was only exists in female depression patients.

Vitamin A is essential for the growth and development, and the function of brain, especially the hippocampus for cognition, learning and memory (Stoney and McCaffery 2016). A cross-sectional analysis in 2791 participants over 20 years demonstrated positive associations among vitamin A concentration and depression (Huang et al. 2018). In another case-control study on male depression patients, the reduction in vitamin A can lead to increased risk of depression (Al-Fartusie et al. 2019). Moreover, isotretinoin, which is a naturally occurring retinoid that results from the metabolism of vitamin A, was also considered to improve anxiety, mood alteration, and depression (O'Reilly et al. 2008; Hahm et al. 2009; Kaymak et al. 2009). However, no association between depressive symptoms and vitamin A of prenatal supplement was found in pregnant teenagers (Singh et al. 2017). Our study included depression patients at the age of 18-35 and healthy controls with matched age and gender, and found no differences in plasma vitamin A among depression patients and healthy controls. Early in the 20th century, various studies indicated a gender difference in the physiologic dynamics of vitamin A (Hoffmann et al. 1950). Previous studies suggested that the average value of plasma vitamin A is higher in males than that in females (Abels et al. 1941; Murrill et al. 1941). Lindblad et al. (1998) also found lower levels of vitamin A in women, pregnant or non-pregnant, than in adult men, but a gender difference was not shown in infants. However, gender-specific differences between vitamin A and depression were not found in depression patients (Huang et al. 2018). Nevertheless, another cross-sectional study in 1634 elderly Japanese individuals investigated the association between vitamin A deficiencies and depressive symptoms in female participants, while in males, no significant association was found (Nguyen et al. 2017). Similarly, our results demonstrated that female subjects exhibited lower C_{VA} levels compared with male subjects both in controls and patients.

So far, few studies have been focused on the relationship between antidepressants and vitamin A. In chronic mild stress induced depression rats, the levels of vitamin A in cortex brain and medulla showed no significant change after venlafaxine administration (Eren et al. 2007). However, fluoxetine was found to dose-dependently increase the levels of retinoic acid, an active metabolite of vitamin A, by inhibiting CYP450 isozymes, notably CYP2C19 (Jeppesen et al. 1996; Hellmann-Regen et al. 2015), which were expressed in neuronal tissue and known as contributors to endogenous retinoic acid breakdown (McSorley and Daly 2000; Uhlen et al. 2010; Hellmann-Regen et al. 2012). However, to the best of our knowledge, interactions between antidepressants and vitamin A have not been investigated in depression patients. We found for the first time that after 24 week's treatment with antidepressants, female depression patients showed significantly decreased C_{VA} than the baseline, but this phenomenon was not found in male depressed patients.

Several limitations of our present study need to be mentioned. First, a small sample size of depression follow-up, particularly after categorizing into two gender groups, is included for difficulties in recruitment of first-episode and drug-naïve depression patients. Moreover, dietary factors were ignored, which have an effect on plasma vitamin A concentration. Finally, among healthy controls, psychiatric disorders were excluded by an unstructured psychiatric assessment, because of lacking specific instrument to rule out diagnoses.

In conclusion, the present case-control study indicated that gender differences in plasma vitamin A concentration exist in depressed patients. Female depression patients show significantly decreased C_{VA} after therapy. Furthermore, vitamin A concentration had positive correlations with depressive symptom in female patients.

4. Experimental

4.1. Participants

The present 24-weeks case-controlled research was approved by the ethics committee of Second Xiangya Hospital (NCT03295708) and carried out in the Mental Health Institute of the Second Xiangya Hospital at the Central South University, China.

The patients were 18-35 years old. All the participants were diagnosed with first episode of depression by two experienced psychiatrists according to criteria set out in the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition- Text Revision (DSM-IV-TR). The patients able to provide informed consent were enrolled in the study. Depression severity was assessed using 24-item Hamilton depression scale (HAMD) score, and the inclusion criteria was set at ≥21. Pregnant or lactating patients as well as those with high suicide risk, other serious physical diseases or comorbidities, serious nervous system diseases, in accordance with diagnostic standards of other mental illness, who need to take benzodiazepine every day, who currently need to be treated by electroconvulsive therapy or have received electroconvulsive therapy in the past 6 months were excluded from the study.

48 healthy controls and 75 first-episode drug-naïve depression outpatients were qualified and asked to participate in the study, and a total of 18 patients were followed for 24 weeks.

4.2. General and clinical assessment

The general and clinical characteristics of gender, age, education, height, body weight and Body Mass Index (BMI) were recorded for each subject. The patients were mainly assessed for plasma concentration of vitamin A (CVA) at baseline and week 24. The patients were also assessed with Hamilton depression scale (HAMD) and Beck depression inventory (BDI) at baseline and week 24.

4.3. Assessment of plasma vitamin A

Prior to analysis, samples were thawed at room temperature. Then, plasma (250 µL) was mixed with 1000 µL 50:50 (vol/vol) acetonitrile:methanol. After 2 min of vortexing, the mixture was centrifuged at 15000 x g for 8 min at 4 °C. The supernatant (900 µL) was transferred into an Eppendorf tube and lyophilized. Then, the residue was dissolved with 100 µL of 80% acetonitrile solution and 2 µL sample solution was analyzed.

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis was carried out on an Agilent 1290 ultra performance liquid Chromatography (Agilent, Santa Clara, CA, USA) connected to an Agilent 6545B time-of-flight mass spectrometry (Agilent, Santa Clara, CA, USA) equipped with an ESI source. The separation was performed using a C18 column (50×2.1 mm, 1.8 µm; Agilent, Santa Clara, CA, USA). The LC conditions were defined to have a good resolution of vitamin A in the whole analysis. Two mobile phases were used for elution, including distilled water with 0.1% formic acid (phase A) and acetonitrile with 0.1% formic acid (phase B). A linear gradient elution of 50-85% phase B was applied from 0-7 min, and increased to 100% B at 10 min, then held for 4 min. At last, the gradient was back to 50% B at 14.01 min and held for 3 min to stabilize the system. The column temperature was set at 30 °C, and the flow rate was set at 0.4 ml/min. Sample glass vials were maintained at 4 °C.

The ion source was operated in the ESI-positive ionization mode. The absolute values for electrospray ionization potential and collision-induced dissociation potential were 3500 V and 140 V, respectively. The flow rate of drying gas (N_2) pressure was 7 L/min. Nebulizer pressure was 45 psi, Sheath gas temperature was 350 °C and sheath gas flow was 12 L/min. The scan range was from 50 to 1000 m/z and data was acquired by Mass Hunter B.08 software (Agilent, Santa Clara, USA). Quantification was performed in the extraction ion mode using m/z of 269.2269 (vitamin A) and 274.2583 (d5-vitamin A, used as internal standard).

4.4. Statistical analysis

Statistical analysis was performed with the Statistical Program for the Social Science (SPSS), version 18.0 for windows. Demographic data, symptomatic index and C_{VA} profiles were compared by *t*-test (continuous variables) or $\chi 2$ tests (categorical variables) where appropriate. Partial correlation analysis was used to analyze correlation between symptomatic index and C_{VA} profiles in the depression group. A P-value < 0.05 indicated statistical significance for all analyses.

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