The symptomatology of climacteric syndrome: whether associated with the physical factors or psychological disorder in perimenopausal/postmenopausal patients with anxiety–depression disorder

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Received: 5 August 2011 / Accepted: 15 November 2011 / Published online: 29 November 2011
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Abstract

Purpose To explore whether the symptoms of climacteric syndrome associated with its physical factors or psychological disorder in perimenopausal/postmenopausal patients with anxiety–depression disorder.

Methods We recruited 78 climacteric patients with anxiety–depression disorder and 72 control participants in perimenopausal/postmenopausal without anxiety–depression disorder for this study. We measured symptoms using the Greene Climacteric Symptom Scale in all cases. We also collected demographic data and tested sexual hormone, blood pressure, bone density, cognitive, estrogen receptor-alpha (ERα) gene polymorphism as physiological factors, using HARS-14 and CHDS assessed psychological disorder degree.

Results C-MMSE scores as well as Estradiol and progesterone levels in the anxiety–depression disorder group were significantly lower compared to the control group ($P < 0.01$). In addition, the anxiety–depression disorder group had significantly higher Greene Climacteric Scale scores, as well as somatic symptoms compared to controls ($P < 0.01$). Moreover, the anxiety, depression and somatic symptoms of the Greene Climacteric Scale were positively correlated with HARS-14 and CHDS scores ($P < 0.001$) and negatively with estrogen level and C-MMSE scores ($P < 0.05$) in the anxiety–depression disorder group. Greene Climacteric Scale Symptoms were not significantly correlated with blood pressure, bone density or other factors ($P > 0.05$). There was no significant change in the allele frequency or the estrogen receptor-alpha gene polymorphisms, between the two groups ($P > 0.05$); however, the Pp genotype was negatively associated with C-MMSE scores ($r =$ appraises, $P = 0.033$).

Limitations The sample size was relatively small.

Conclusions The symptoms of somatic symptoms in patients with climacteric syndrome and anxiety–depression disorder are associated with the emotional disorder but not with a physical disease. The Pp ERx polymorphism Pvu II is associated with a cognitive decrease.

Keywords Climacteric · Anxiety–depression · Somatic symptoms · Cognitive · Physical disease

Introduction

Women in perimenopausal or postmenopausal, with the gradual degradation of ovarian function in the female hormone decreasing, can appear some physiological and psychological aspects of symptoms, main performance: hot, sweaty, tired, headache, dizziness, numb, sore limbs, attention poor, anxious and nervous, insomnia, mood swings, and sorrow depression, clinical called “menopause syndrome” or “climacteric syndrome” [1, 2]. Depression or anxiety or depression combined anxiety (anxiety–depression) is a common psychological disorder in menopausal women. In
SWAN 2010, 18% of elderly women had psychological disorders [3], and anxiety–depression in addition to have major depression, dropping interest, outside self-evaluation, anxiety, nervousness, tendency to get angry, and also may be associated with fatigue, insomnia, inattention, memory loss, pain and so on menopause syndrome-like symptoms. Two diseases have common some syndromes characteristic (especially somatic syndrome) easily confused in clinic, but also have difference risk for healthy. Although emotional disorders occur frequently in climacteric syndrome, climacteric syndrome (which severely compromises life and work is rare. In contrast, anxiety–depression disorder has serious risk for women [4]. On the other hand, decline in the health of patients (e.g., hypertension and osteoporosis) often accompanies mild cognitive dysfunctions [5, 18, 20]. Some patients are excessively concerned about their health and visit clinics frequently, which can lead to many misdiagnoses and waste medical resources [6, 7]. Do these patients have multisystem symptoms resulted from somatized anxiety–depression disorder or from truly organic diseases?

Reports on syndromes characteristic patients with anxiety–depression disorder in perimenopausal are limited. Are the multisystem symptoms of patients with anxiety–depression disorder in perimenopausal/postmenopausal as severe as their psychological ones? This question needs to be investigated further. Estrogen receptor (ER) polymorphisms are associated with many disorders including Alzheimer’s disease (AD), osteoporosis and coronary heart disease [8–11]; however, little is known about the association between ER polymorphisms and anxiety–depression comorbid with climacteric syndrome. In this study, we analyzed ER polymorphisms, sex hormone levels, psychological symptoms, cognitive function, blood pressure, bone density, menopausal transition (MT) stages and diseases course based on the Greene Climacteric Scale categories [12]. This study would be to recognize syndromes characteristic and provide the theoretical base for the early diagnosis of depression or anxiety in perimenopausal/postmenopausal.

Methods

Participants and sampling

Based on our study aim and requirements for statistical analyses, between 2007 and 2010, we recruited over 78 patients with anxiety and depression in perimenopausal and postmenopausal, as well as control participants with climacteric syndrome only. Concerning menopausal status we used the following definitions: perimenopausal women having irregular menses, less than 12 menses during the last 12 months and postmenopausal: no more menses in the last 12 months. All participants meet the Stages of Reproductive Aging Workshop (STRAW) criteria for peri/postmenopause, MT score of STRAW be −1 to +2 [2], combined with at least one symptom of climacteric syndrome. The age range of this sample was 40–60 years old. Exclusion criteria of All participants undergoing hormonal therapy, hormone therapy by implant in the preceding 6 months, endocrinopathies leading to menstrual irregularities, hepatopathies, thrombopathies, use of drugs which interfere in the menstrual cycle, anxiolytics and antidepressants (as their use indicates previous diagnosis of mood disorders), hysterectomy, oophorectomy, cancer or psychiatric disease or other severely organic diseases. This study was approved by the institutional review board of the Third Affiliated Hospital of Guangzhou Medical College (Guangzhou, China) and written informed consent was obtained from every participant.

We placed participants in the anxiety–depression group using the anxiety and depression diagnosis standard listed in ICD-10 [13]. The criteria include the following: (1) use of the Hamilton Anxiety Rating Scale-14 items (HARS-14) [14, 15] and the Chinese version of the 17-item Hamilton Depression Rating Scale (CHDS) [16], all patients HARS-14 scores ≥14 and or CHDS ≥17; (2) experience of major anxiety symptoms for at least 3 months or major depression symptoms for at least 2 weeks; and (3) decline in functioning at work and home. Using these standards, we recruited 78 patients with major anxiety and or depression symptoms as anxiety–depression group, of whom 58 had mixed anxiety and depression disease(MADD, ICD-10 code F41.2), 13 of whom had anxiety only (ICD-10 code F41.8) and 7 of whom had depression only (ICD-10 code F32.0).The average age of these patients was 52.14 ± 5.74 years. Although somatization disorder is a somatoform disorder that overlaps with a number of functional somatic syndromes and has high comorbidity with major depression and anxiety disorders [17]. The study anxiety–depression patients were not coincided with somatization or somatization form disorder diagnosis criterion (ICD-10 code F45.0, F45.1).

Procedure

We recorded patient demographic information including age, education, disease course and menopausal status. Education level was defined as time spent in school. Disease course was defined as the duration of their symptoms in years; a disease course of over 6 months was considered to be 1 year. Menopause was defined as the cessation of menses for over 12 months according to SRTAW [2]. The early postmenopausal cases was 26 (33.33%) and 28 (38.89%) in anxiety–depression group and control group. There were no difference between them (P < 0.01). We used the HARS-14 and CHDS to determine anxiety and depression levels [14–16].
We analyzed the characteristics of climacteric syndrome based on the Greene Climacteric Scale. In 2010, the validation and reliability of Greene Climacteric Scales (validation 0.68–0.76, reliability 0.83–0.87 in Chinese population) was reported by Zheng et al. in Hong Kong. The Greene Climacteric Scale measures a total of 21 symptoms (Table 1) [12, 18]. Each symptom is rated by the woman herself according to its current severity using a four-point rating scale: not-at-all symptoms (0); a little symptoms (1); quite a bit symptoms (2); extreme symptoms (3). The Greene Climacteric Scale scores include 21 items scores and an individual score within five symptom clusters: (1) anxiety symptoms (symptoms 1–6), (2) depression symptoms (symptoms 7–11), (3) somatic symptoms (symptoms 12–18), (4) vaso-motor symptoms (symptoms 19–20) and (5) sexual function (symptoms 21). The mean score for each symptom is calculated by the sum of all individual scores divided by the number of subjects. The mean score of each symptom clusters are the mean scores of the symptoms within that cluster.

The Greene Climacteric Scale

| Groups | Anxiety–depression group (n = 78) | Control group (n = 72) |
|--------|---------------------------------|-----------------------|
| 1. Heart beating quickly or strong | 1.14 ± 0.78* | 0.56 ± 0.6 |
| 2. Feeling tense or nervous | 1.42 ± 0.86* | 0.63 ± 0.54 |
| 3. Difficulty in sleeping | 1.33 ± 0.81* | 0.58 ± 0.65 |
| 4. Excitable | 1.31 ± 0.86* | 0.37 ± 0.47 |
| 5. Attacks of panic | 0.74 ± 0.82* | 0.21 ± 0.35 |
| 6. Difficulty in concentrating | 1.11 ± 0.81* | 1.02 ± 0.62 |
| 7. Feeling tired or lacking in energy | 1.56 ± 0.83* | 0.38 ± 0.4 |
| 8. Loss of interest in most things | 1.05 ± 0.90* | 0.25 ± 0.32 |
| 9. Feeling unhappy or distressed | 1.20 ± 0.86* | 0.86 ± 0.51 |
| 10. Crying spells | 0.85 ± 0.90* | 0.18 ± 0.36 |
| 11. Irritability | 1.32 ± 0.93* | 0.47 ± 0.5 |
| 12. Feeling dizzy or faint | 1.42 ± 0.99* | 0.52 ± 0.38 |
| 13. Pressure or tightness in head or body | 1.23 ± 0.89* | 0.25 ± 0.31 |
| 14. Parts of body feel numb or tingling | 1.21 ± 0.85* | 0.52 ± 0.45 |
| 15. Headaches | 1.41 ± 0.91* | 0.98 ± 0.62 |
| 16. Muscle and joint pains | 1.27 ± 0.92* | 0.85 ± 0.49 |
| 17. Loss of feeling in hands or feet | 0.44 ± 0.70* | 0.24 ± 0.34 |
| 18. Breathing difficulties | 0.59 ± 0.76* | 0.18 ± 0.27 |
| 19. Hot flashes | 0.85 ± 0.88* | 1.29 ± 0.91 |
| 20. Sweating at night | 0.74 ± 0.77* | 1.06 ± 0.81 |
| 21. Loss of interest in sex | 0.85 ± 0.88 | 0.78 ± 0.61 |

Using a Chi-square test

*P < 0.01, b P < 0.05

Sexual hormone determination

We measured estradiol (E2), progesterone and testosterone levels using radioactive immunoassays. Peripheral vein blood was collected between 7:00 and 8:00 am. Blood from non-menopausal women were collected 3 days after their menstrual cycles. The variation of estradiol, progesterone and testosterone levels within anyone group was 5.6, 7.2 and 8.01%, respectively. The differences of estradiol, progesterone and testosterone levels between the groups were 6.5, 7.8 and 8.5%, respectively. The sensitivity of each ELISA assay was 0.01, 0.001 and 0.0001 pg/ml, respectively.

The analysis of polymorphisms in ERα genes, PvuII and XbaI primer design and synthesis

The sequence for the estrogen receptors is as follows: P1: 5′-CTGCCACCTATCTGTATTTTCTATTCTCC-3′;
and P2: 5′-TCTTTCTGCCACCCTGCGTCGATTAT CTGA-3′. In descending order, the DNA molecular weight (Mark Shenzhen, Yishengtang Biological Enterprises Ltd.) of these receptors are 2,000 bp/1,600 bp/1,200 bp/800 bp/600 bp/400 bp/200 bp.

The method for genotyping estrogen receptors uses three steps. (1) Whole genomic DNA was extracted using the fast extraction method. (2) A polymerase chain reaction (PCR) where the total reaction estrogen receptor volume was 50 μL and comprised 34.3 μL sterile deionized water, 5 μL 10× PCR buffer, 200 μmol/L dNTP 4 μL, 40 pmol primers, 100 ng DNA template and 1 U TaqDNA polymerase. Reaction conditions consisted of a denature step at 94°C for 3 min, followed by 35 cycles of 94°C for 30 s, 61°C for 40 s, 72°C for 90 s, and a final extension at 72°C for 5 min. The extension product size was 1.3 kb. (3) Finally, a restricted enzymatic reaction was performed using 6 U PvuII and 10 U XbaI for enzymatic digestion, followed by a 1.2 agarose gel with ethidium bromide electrophoresis for 40 min, which was then photographed.

Two professional psychologists tested patients’ neurological and psychological statuses. Prior to these tests, both psychologists were trained to adjust and unify their standards.

Statistical analysis

All data were recorded as mean ± standard deviation (x ± s). We used SPSS 17.0 software for all statistical analyses. (1) ANOVA and ANCOVA rank-sum tests (i.e., variance arrhythmias) analyzed the demographic and symptomatic differences between the anxiety–depression group and the control group. (2) Pearson’s correlation analyzed the relationships between symptoms, psychological scores and physiological status. (3) Chi-square tests analyzed the frequency of estrogen receptor-alpha polymorphisms. (4) Multifactorial logistic analyses analyzed the relationship between the ERα polymorphism and other symptoms such as sex hormone levels, psychological scores (HARS-14 and CHDS) and cognitive functions. A P value of less than 0.05 was considered significantly different.

Results

Differences in demographic information, HARS-14, CHDS, C-MMSE, Greene Climacteric Scale scores and sexual hormone levels between groups

As shown in Table 1, there were significant differences between the anxiety–depression group and the control group (P < 0.001) in all areas except difficulty in concentrating and sexual interest. The vasomotor symptoms scores as well as the facial redness and evening sweating scores for the anxiety–depression group were significantly lower (P < 0.05) compared to the control group; all other anxiety–depression group scores were higher than the control group (P < 0.01). As shown in Table 2, the Greene climacteric Scale scores of anxiety, depression and somatic symptoms were significantly higher in the anxiety–depression group (P < 0.001) compared to control group, although the vasomotor symptoms scores were significantly lower (P < 0.05). The HARS-14 and CHDS scores of the anxiety–depression group were significantly higher than the control group (P < 0.001) whereas the E2 and progesterone levels were significantly lower (P < 0.001). The HARS-14 and CHDS scores of the anxiety–depression group were significantly lower than the control group (P < 0.01). There were no significant differences in age, testosterone level, bone density, systolic and diastolic blood pressure between the two groups.

Correlation analysis between Greene Climacteric Scale symptoms with general condition, psychological score, bone density, average blood pressure in anxiety–depression disorder group

As shown in Table 3, Pearson’s correlational analyses, revealed positive correlations between Greene Climacteric Scale anxiety, depression and somatic symptoms scores with HARS-14 and CHDS scores (P < 0.001) as well as negative correlations between E2 and progesterone levels and C-MMSE scores (P < 0.05) within the anxiety–depression group. There was also a positive correlation between education years in the anxiety–depression group. There was an additional correlation between vasomotor symptoms and HARS-14 scores, whereas sexual factors were correlated with CHDS scores (P < 0.05). There was no significant correlation between Greene Climacteric Scale scores and blood pressure, bone density, menopause, disease course or other factors (P > 0.05).

Polymorphism analyses on the ERα gene

We used P, pX or x to indicate restriction enzymes. Lower-case letters indicated the digestion sites of the enzyme, whereas capital letters indicated the absence of restricted enzyme sites. The PvulI restriction enzyme distinguishes between three genotypes: PP (1.3 kb), Pp (1.3 kb + 850 bp + 450 bp) and pp (850 bp + 450 bp). The XbaI restriction enzyme distinguishes between three genotypes: XX (1.3 kb), Xx (1.3 kb + 910 bp + 390 bp), and xx (910 bp + 390 bp; Fig. 1)
Table 4 shows the allele frequency of the ERα Pvu II and Xba polymorphisms. The allele frequencies of the studied sample were consistent with the Hardy–Weinberg Genetic equations and representative populations. The genotype distribution in the anxiety–depression group was PP 17.95%, Pp 39.74%, pp 42.31%, XX 10.26%, Xx 32.50% and xx 57.69%. The allele frequency for P and X is 37.81 and 26.28%, respectively. Both groups have a majority of p and x gene sites. As shown in Table 4, there were no significant differences between the anxiety–depression and control groups in the genotypes of the ERα Pvu II or Xba I polymorphisms.

The correlation between ER gene polymorphisms and anxiety–depression symptoms

One-way factorial analyses indicated that the Pp and pp genotypes were correlated with anxiety, depression, and organic diseases, as well as CHDS, HARS-14 and C-MMSE scores. The xx genotype was correlated only with organic disease and vasomotor symptoms. When we introduced the ten factors above into a multifactorial logistic model, only the Pp genotype and C-MMSE scores were negatively correlated ($y = 4.51 \times 1.043 - 2.22$, $r = -0.108$, 95% CI 0.014 ± 0.883, $P = 0.033$).
Discussion

Our study shows that HARS-14, CHDS and Greene Climacteric Scale scores of anxiety, depression and somatic symptoms were significantly higher in perimenopausal/postmenopausal patients with anxiety–depression disorder compared to a control group, whereas E2 and Progesterone levels were significantly lower ($P < 0.01$). These findings indicate that, in addition to anxiety and depression disorders, somatic symptoms are characteristics of climacteric patients with anxiety–depression disorders. This finding is also consistent with a previous report using Greene Climacteric Scale results [25, 26]. Using a Pearson’s correlation analysis, we found that a decreased E2 level is correlated with anxiety, depression and somatic symptoms, which in turn might be correlated with the onset of anxiety–depression disorder. Previous work by other researchers corroborates this finding [27, 28]. Additionally, our study indicates that anxiety, depression and somatic symptoms are correlated with psychological scores but not with blood pressure, bone density, menopause or disease course. These findings indicate the following: (1) the Greene Climacteric Scale is valid for determining climacteric patients with anxiety and depression disorders; and (2) the somatic symptoms in climacteric patients with anxiety–depression disorders might be correlated with emotional disorders only [28, 29] and not with organic diseases, such as hypertension and osteoporosis.

The anxiety–depression group showed a significant decrease in vasomotor symptoms, which is positively correlated with the HARS-14 score. This result is inconsistent with our other findings. Based on the symptoms of patients with anxiety–depression disorder, our study shows that there is correlation between vasomotor symptoms and the occurrence of anxiety disorders. Patients with light anxiety may keep their symptoms hidden, whereas patients with severe anxiety may show vasomotor. However, patients with anxiety–depression disorder showed a significant decrease in vasomotor symptoms, indicating that these symptoms may be characteristic of climacteric syndrome. Seritan and others have shown that vasomotor symptoms in patients with climacteric syndrome are closely associated with psychological status [28, 30]. Although we sampled patients with climacteric syndrome and anxiety–depression disorder, our results are consistent with previous findings. A recent report has shown that the somatic symptoms in climacteric syndrome might be the accumulative effect of anxiety and facial redness, which is also consistent with our observations [29].

Our study found a correlation between education level and anxiety and depression symptoms, indicating that people with more education are more likely to be anxious during menopause. This finding is inconsistent with the study by Kakkar et al. [1]. We did not find a significant change in sexual interest in the anxiety–depression group compared to the control group; this finding is also not consistent with the SWAN report. Asian attitudes toward sex-related issues tend to be conservative, which could explain our results. There seems to be no change in the sexual interest of patients with anxiety and depression. Moreover, our study

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Table 4  The analysis of ERz Pvu II genotypes and allele frequencies

| Groups                      | PvuII restriction enzyme genotype (%) | Allele (%) | XbaI restriction enzyme genotype (%) | Allele (%) |
|-----------------------------|---------------------------------------|------------|--------------------------------------|------------|
|                             | PP                                    | P          | Xx                                   | X          |
| Anxiety–depression group ($n = 78$) | 14 (17.95)                              | 37.81 (10.26) | 11 (15.27)                           | 33.33 (26.28) |
|                             | 31 (39.74)                             | 62.19 (32.50) | 26 (36.11)                           | 66.67 (73.72) |
|                             | 33 (42.31)                             |            | 45 (57.69)                           |            |
|                             |                                        |            |                                      |            |
| Control group ($n = 72$)     | 15 (20.83)                             | 44.44 (17.95) | 11 (15.27)                           | 33.33 (26.28) |
|                             | 34 (47.22)                             | 55.56 (32.50) | 26 (36.11)                           | 66.67 (73.72) |
|                             | 23 (31.90)                             |            | 45 (57.69)                           |            |

Using a Chi-square analysis, we found no significant differences between the two groups in the six genes ($\chi^2 = 0.66–1.65, P > 0.05$)
indicated that sexual behavior is negatively correlated with depression scores, which is consistent with previous findings [3, 31].

The transcription factor of ER is located in the cytosol and nucleus and includes two isoforms: ERα and ERβ. Human ERα is located on the 6q24–27 gene [8] and includes eight exons and seven introns, at a total length of 140 kb. In the first ERα gene intron, we found a T to C mutation at 0.4 kb upstream of the second exon, and an A to G mutation 50 bp downstream of the locus, resulting in the restriction sites for PvuII and XbaI, respectively, thus creating a restriction site polymorphism [8, 9]. Previous studies have shown that the ERα gene polymorphism is correlated with hot flashes and vaginal dryness but not with emotional disorders in patients with climacteric syndrome [32].

Our study indicates that the allele distribution of anxiety–depression genotypes is PP17.95%, Pp39.74%, pp42.31%, XX10.26%, Xx32.50% and xx57.69%. The allele distribution frequency for the P and X alleles is 37.81% and 26.28%, respectively. The majority of alleles are p and x. Statistical analysis revealed no significant differences in the genotypes of the ERα PvuII and XbaI genes. Moreover, there was no correlation between the ERα allele and anxiety or depression symptoms. This finding is consistent with Malacara [32]. Based on a multifactorial logistic analysis, there is a negative relationship between the PP genotype in the ERα gene and the C-MMSE score in the anxiety–depression group ($r = -0.108, P = 0.033$).

Brandi et al. [8] showed that the PPXX genotype of ERα were more frequent in patients with Alzheimer’s disease (AD), compared to a control group [8]. Estrogen level decrease is correlated to AD. Estrogen protects neurons. Estrogen therapy has positive effects on anxiety–depression disorder, cognitive malfunction and AD in patients with climacteric syndrome [33]. Depression related to aging may be a symptom of early-onset AD [8]. The SWAN report found that 18% of older women have emotional disorders and that depression was significantly correlated with impaired cognitive function [5]; however, there was no such correlation between emotional symptoms and cognitive malfunction in patients with climacteric syndrome [34]. In our study, we showed that anxiety, depression and somatic symptoms were negatively correlated with C-MMSE scores in the anxiety–depression group; however, there was no such correlation in the control group. Thus, these findings are consistent with SWAN report which suggest cognitive decline correlation with anxiety and or depression, but not climacteric syndrome. There is a negative correlation between the Pp genotype in the ERα gene and C-MMSE scores, which is inconsistent with Olsen’s report. In Olsen’s study, the XbaI genotype XX was negatively correlated with impaired cognitive function in postmenopausal [35]. Recently, Kim et al. [36] reported similar results. The inconsistent results may be relation to the difference of samples. Is there a correlation between impaired cognitive function of emotion disorder and the occurrence of mild cognitive impairment (e.g., MCI or early-onset AD)? Are the ERα polymorphism and decreased estrogen levels common or different mechanisms in patients with climacteric syndrome as well as anxiety–depression disorders and patients with AD? These questions need to be further investigated in perimenopausal/postmenopausal patients with anxiety–depression disorders.

Conclusion

The somatic symptoms in patients with climacteric syndrome are correlated with emotional disorders but not with organic diseases. There was no correlation between the ERα allele polymorphism and anxiety or depression symptoms, whereas the Pp genotype of the ERα Pvu II gene may be related to impaired cognitive function in patients with anxiety or depression symptoms.

Acknowledgments This work was supported by the Natural Science Foundation of Guangdong Province, in China (06022385).

Conflict of interest The authors declare that they have no conflict of interest.

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