Clinical and Endocrinological Features of Statistical Clusters of Women with Climacteric Symptoms

TETSURO ABE, MASAKUNI SUZUKI, YUICHI WADA,
YOSHIHIRO YAMAYA and TAKEJIRO MORITSUKA*

*Department of Obstetrics and Gynecology, Tohoku
University School of Medicine, Sendai 980 and*

**Department of Obstetrics and Gynecology, Sendai National
Hospital, Sendai 983*

ABE, T., SUZUKI, M., WADA, Y., YAMAYA, Y. and MORITSUKA, T. *Clinical and Endocrinological Features of Statistical Clusters of Women with Climacteric Symptoms*. Tohoku J. exp. Med., 1985, **146** (1) 59-68 — Clinical and endocrinological features of women with climacteric symptoms, who were clustered by means of factor analysis and cluster analysis, were evaluated as to serum concentrations of estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone, and also as to mean ages as well as a rate of premenopausal women or that of postmenopausal women against all women in each one of the clusters. Comparison of these parameters among these clusters indicated, with statistical significance, that vasomotor symptoms, neurotic symptoms, and depressive state of the climacteric women are endocrinologically characterized by a depressed level of serum estrogen, relatively high level of serum estrogen, and an elevation of serum gonadotropin, particularly of luteinizing hormone, respectively. — climacteric symptoms; estrogen; gonadotropin; follicle-stimulating hormone; luteinizing hormone

The etiology of climacteric symptoms is still considered to lie in complicated chaos, although many studies have been carried out separately focusing on various aspects such as endocrinological factors, psychosomatic factors, etc. In order to develop a comprehensive approach to the etiology of climacteric symptoms, the authors have undertaken a series of studies of these symptoms; in our previous report (Abe et al. 1984), statistical factor analysis and cluster analysis were applied to data consisting of sets of 17 symptoms of climacteric women. Six distinct factors were extracted and the women were divided into 7 groups by hierarchical cluster analysis in terms of their factor scores. In the present study, the authors investigated clinical and endocrinological features of these clustered groups of women with climacteric symptoms in order to elucidate etiologies of the

Received May 14, 1984; accepted for publication December 11, 1984.

Reprint requests: Dr. Tetsuro Abe, Department of Obstetrics and Gynecology, Tohoku University School of Medicine, 1-1 Seiryomachi, Sendai 980, Japan.

symptoms and also to demonstrate the validity of the statistical method employed in the previous report.

MATERIAL AND METHODS

One hundred and ninety-four premenopausal and postmenopausal women with climacteric symptoms in the present study were the same subjects that had been already subjected to statistical analysis of their symptoms in the previous report (Abe et al. 1984). One hundred and eighteen premenopausal women were at 37 to 55 years of age (45.22 ± 5.60 , mean $\pm$ s.d.); about 60% of them had irregular menstrual cycles and others had regular ones. When these premenopausal women were divided into age classes by one year and correlation between rates of women with irregular menstrual cycles against all women with irregular and regular ones in each class and their ages were evaluated, no significant relationship was observed. Seventy six postmenopausal women were at 41 to 62 years of age and the length of postmenopausal period among them ranged from 1 to 10 years. These women had neither gynecologic nor other demonstrable unusual diseases. Among these subjects, 9 (4.6%) were nulligravid, 9 (4.6%) were multigravid and nulliparous, and 176 (90.7%) were multigravid and multiparous. They had not received any hormonal or other psychotropic medication during the preceding month.

These women were evaluated by rating the severities of 17 symptoms shown in Table 1, which was derived from those employed for the menopausal index of Kupperman and

TABLE 1. *Questionnaire for evaluation of the climacteric symptoms*

Check appropriate boxes concerning symptoms you have had which have persisted for the past few days					
Symptom No.	Symptoms	Severe	Moderate	Slight	None
1	Hot flushes	☐	☐	☐	☐
2	Perspiration	☐	☐	☐	☐
3	Local sensation of cold	☐	☐	☐	☐
4	Shortness of breath	☐	☐	☐	☐
5	Numbness	☐	☐	☐	☐
6	Hypesthesia	☐	☐	☐	☐
7	Difficulty in falling asleep	☐	☐	☐	☐
8	Fitful sleep	☐	☐	☐	☐
9	Irritability	☐	☐	☐	☐
10	Nervousness	☐	☐	☐	☐
11	Melancholy	☐	☐	☐	☐
12	Vertigo, nausea	☐	☐	☐	☐
13	Weakness (fatigue)	☐	☐	☐	☐
14	Stiff shoulder, pain in joints, muscular pain	☐	☐	☐	☐
15	Headache	☐	☐	☐	☐
16	Palpitation	☐	☐	☐	☐
17	Tingling sensation	☐	☐	☐	☐

associates (Kupperman et al. 1959). This rating was based upon written reports by the women to the questionnaires shown in the Table 1 and interviewer's observation of the women, and was quantified by numerical figures; 0 for absent, 1 for slight, 2 for moderate, and 3 for severe, based on degrees of the severities of the symptoms. This numerical conversion of the severities of the symptoms and statistical analysis of their data modeled methodology which had been used in developing the Brief Psychiatric Rating Scale (Overall and Gorham 1962; Overall et al. 1964, 1967; Overall and Hollister 1967, 1968; Overall and Klett 1972).

In the statistical evaluation of the climacteric symptoms, since only subjective classification of their severity by the women might be a source of unreliability of the data, severity of the symptoms, evaluated basing upon written reports by the women to the questionnaires, was corrected by interviewer's observation of the women. In a previous report by the present authors (Abe et al. 1977), the menopausal indices of Kupperman and associates, which were also based on subjective findings by the women on their climacteric symptoms and corrected by interviewer's observation of the women in the same way as in the present study, were subjected to statistical analysis. This analysis yielded significant correlation between the indices and serum hormone levels, assuring reliability of this estimation of severity of the symptoms and indicating validity of the statistical analysis in the present study.

At the same time, sera of the women were obtained by drawing peripheral venous blood as follows; blood samples were taken between 1 and 3 p.m. and sera were separated and stored at -10°C until assay. Serum concentrations of estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone were determined by the method described in previous reports (Furuhashi et al. 1977; Abe et al. 1983).

As described in the previous report (Abe et al. 1984), numerical data regarding the severity of the symptoms was analyzed by factor analysis, yielding six distinct extracted factors, and the women were divided into 7 groups by hierarchical cluster analysis in terms of their factor scores (Table 2). However, 2 of the 7 groups, group 2 (heart failure-like symptoms group with insomnia) and group 3 (heart failure-like symptoms group with vasomotor-, sensory disturbance-, and autonomic nervous dysfunction-symptoms) were characterized by more than one representative factors, one of which, the heart failure-like symptoms factor, was common to both groups and was also most representative factor in each one of them. Therefore, in order to simplify the clustered groups as possible, these two groups were combined from clinical standpoints, and the original 7 groups of the previous work (Abe et al. 1984) were regrouped into 6 groups as follows (Table 2): Group 1, insomnia group with neurotic symptoms, remained unchanged; the original group 2 as well as group 3 were combined and reclassified as group 2 to be called heart failure-like symptoms group with insomnia, vasomotor-, sensory disturbance-, and autonomic nervous dysfunction-symptoms; the original group 4, the vasomotor-symptoms group, the original group 5, the neurotic symptoms group, the original group 6, the sensory disturbance-symptoms group, and the original group 7, the mild symptoms group, were reclassified as groups 3, 4, 5 and 6, respectively, without any alteration of their designations.

Among these six new groups of women, mean age, rate of premenopausal women or postmenopausal women against all women including premenopausal and postmenopausal women in each group, and serum concentrations of estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone were compared, in order to provide the etiology of climacteric symptoms with endocrinological basis and also to demonstrate the validity of statistical clustering of women with climacteric symptoms, being reported previously (Abe et al. 1984).

TABLE 2. *Relationship between the original grouping of the women complaining of the climacteric symptoms in the previous report and the modified grouping in the present study*

Group No.	Original grouping			Modified grouping	
	Representative factors	Designation of groups	Group No.	Designation of groups	
1	Insomnia, neurotic symptoms	Insomnia group with neurotic symptoms	1	Insomnia group with neurotic symptoms	
2	Heart failure-like symptoms, insomnia	Heart failure-like symptoms group with insomnia	2	Heart failure-like symptoms group with insomnia, vasomotor-, sensory disturbance-, autonomic nervous dysfunction-symptoms	
3	Heart failure-like symptoms, vasomotor-symptoms, sensory disturbance-symptoms, autonomic nervous dysfunction-symptoms	Heart failure-like symptoms group with vasomotor-, sensory disturbance-, autonomic nervous dysfunction-symptoms			
4	Vasomotor-symptoms	Vasomotor-symptoms group	3	Vasomotor-symptoms group	
5	Neurotic symptoms	Neurotic symptoms group	4	Neurotic symptoms group	
6	Sensory disturbance-symptoms	Sensory disturbance-symptoms group	5	Sensory disturbance-symptoms group	
7	None	Mild symptoms group	6	Mild symptoms group

Fig. 1. Ages of climacteric women allocated to the 6 groups divided by statistical clustering. "Insomnia" indicates group 1; "Heart-failure-like", group 2; "Vasomotor", group 3; "Neurotic", group 4; "Sensory disturbance", group 5; and "Mild symptoms", group 6. As for the group numbers, see Table 2.

Fig. 2. Rates of premenopausal and postmenopausal women allocated to the 6 groups. For abbreviated designation of the groups, see Fig. 1.

RESULTS

Mean ages of the subjects

As shown in Fig. 1, mean age in years which was 42.9 ± 1.0 in group 1 was higher in group 4, group 6, group 5, and group 2 in the order, and attained a maximum of 48.1 ± 0.8 in group 3. When mean ages of these groups were compar-

Fig. 3. Serum concentrations of estradiol of the climacteric women allocated to the 6 groups. For abbreviated designation of the groups, see Fig. 1.

ed, there were statistically significant differences between groups 1 and 2 ($p < 0.05$), between groups 2 and 4 ($p < 0.05$), and between groups 1 and 3 ($p < 0.01$). This indicates that ages of women with neurotic symptoms are relatively low and those of women with vasomotor symptoms are relatively high.

Rate of premenopausal or postmenopausal women

A rate of premenopausal women and that of postmenopausal women against all women in each one of the groups divided by statistical clustering are shown in Fig. 2. Among the six groups, the rates of premenopausal women were lowest in group 3 and highest in group 4. On the contrary, the rates of postmenopausal women were highest in group 3 and lowest in group 4. Differences in the rates of premenopausal women were statistically significant ($p < 0.05$) between group 3 and group 4.

Serum concentrations of estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone.

Estradiol: As shown in Fig. 3, mean serum concentrations of estradiol among the six groups of subjects were maximum in group 1 and decreased in group 6, group 5, group 4 and group 2 in the order and attained a minimum in group 3. When the serum estradiol concentrations of these groups were compared, statistically significant differences were found between group 3 and group 1, 2, 4 as well as 6 with p less than 1%, 5%, 1% and 1%, respectively. When each of the six groups was subdivided into premenopausal subgroup and postmenopausal subgroup, and serum estradiol concentrations of these twelve subgroups were compared, the postmenopausal subgroup of group 3 showed the lowest concentration

Fig. 4. Serum concentrations of progesterone of the climacteric women allocated to the 6 groups. For abbreviated designation of the groups, see Fig. 1.

Fig. 5. Serum concentrations of follicle-stimulating hormone (FSH) of the climacteric women allocated to the 6 groups. For abbreviated designation of the groups, see Fig. 1.

(23.0 ± 4.5 pg/ml, ; $n=7$) among these subgroups and that of the premenopausal subgroup of the same group was next to lowest (29.0 ± 2.5 pg/ml, mean $\pm$ s.e. ; $n=6$). These results indicate that serum estradiol concentrations of women were depressed, not only in postmenopausal women but also in premenopausal women of group 3.

Progesterone: Serum concentrations of progesterone in the six groups are illustrated in Fig. 4. While the level was apparently lowest in group 3 as was the case with serum estradiol concentration, there was no significant difference

Fig. 6. Serum concentrations of luteinizing hormone (LH) of the climacteric women allocated to the 6 groups. For abbreviated designation of the groups, see Fig. 1.

between any two of the six groups.

Follicle-stimulating hormone (FSH): Serum concentrations of follicle-stimulating hormone in the six groups are shown in Fig. 5 indicating, in contrast to concentrations of estradiol, a minimum in group 1 and an increase in groups 4, 6, 3, 2 and 5, in the order. Statistically significant differences were found between groups 1 and 2 and between groups 1 and 5.

Luteinizing hormone (LH): The serum concentration of luteinizing hormone was lowest in group 1 but increased in groups 3, 6, 4, 5 and 2 in the order (Fig. 6), as was the case with follicle-stimulating hormone. When these serum concentrations of the two groups were compared, there were statistically significant differences as shown in Fig. 6.

COMMENTS

Based on their results of estrogen therapy used in cases of climacteric symptoms, Utian (1972) and Campbell (1976) concluded that vasomotor symptoms such as hot flashes were likely to be related to estrogen deficiency. Exact etiology of these symptoms, however, still remains unknown. Following the clinical observations, Abe et al. (1977) reported that, when severities of climacteric symptoms represented by the menopausal index of Kupperman and associates (1959) were compared with serum hormone levels, they were correlated with serum levels of luteinizing hormone and were inversely correlated with those of estradiol, at least in the lowest age class of premenopausal women. Moreover, Abe et al. (1979) and Chakravarti et al. (1979) observed a close correlation of vasomotor symptoms with low plasma estradiol concentrations.

In the present study, clinical and endocrinological features of women

classified in the group 3 (vasomotor-symptoms group) were found to lie in 1) high mean age, 2) low rate of premenopausal women against all women of this group, and 3) low serum level of estradiol. On the other hand, in this group, a representative factor, definition of which had been described in the previous report (Abe et al. 1984), was vasomotor-symptoms. Thus, when compared with other groups, women of group 3, complaining exclusively of vasomotor symptoms, were in relatively higher age, in predominantly postmenopausal state, and also upon low serum level of estradiol. Therefore, the hypothesis that the vasomotor symptoms are intimately correlated with depressed serum estradiol level was supported clinically and endocrinologically by the present study.

In this connection, it is also interesting to point out that group 2 (the heart failure-like symptoms group with insomnia, vasomotor-, sensory disturbance-, autonomic nervous dysfunction-symptoms) demonstrated a relatively low level of serum estradiol. These data may further support the hypothesis that the vasomotor symptoms are correlated with depressed serum estradiol level.

The second characteristic of the hormone profile of the statistically clustered groups is relatively higher levels of serum estradiol in group 1 (the insomnia group with neurotic symptoms) and group 4 (the neurotic symptoms group) than in group 3 (the vasomotor-symptoms group). These results coincide with relatively lower mean ages and higher rates of premenopausal women against all women in each one of group 1 and group 4 than those in group 3. Therefore, it is suggested that a neurotic symptoms factor in group 1 and group 4 is related to a high level of serum estrogen, supporting results obtained by Schiff et al. (1979) who reported that estrogen administration to hypogonadal women altered their psychological state.

The third characteristic of the statistical grouping of the climacteric women is an elevation of serum levels of gonadotropin in group 2 (the heart failure-like symptoms group with insomnia, vasomotor-, sensory disturbance-, autonomic nervous dysfunction-symptoms) and group 5 (the sensory disturbance-symptoms group). Peters et al. (1982) have reported that secondary amenorrhoea patients with mental symptoms such as depressive moods, anxiety, etc. showed a high basal LH level and high LH response to GnRH. During the course of the present study, the women in groups 2 and 5 were diagnosed most frequently as neurotic or depressed. Thus, an elevation of gonadotropins, particularly of LH, in these groups may be related to mental symptoms of the women.

References

- 1) Abe, T., Furuhashi, N., Yamaya, Y., Wada, Y., Hoshiai, A. & Suzuki, M. (1977) Correlation between climacteric symptoms and serum levels of estradiol, progesterone, follicle-stimulating hormone, and luteinizing hormone. *Amer. J. Obstet. Gynecol.*, **129**, 65-67.
- 2) Abe, T., Furuhashi, N., Wada, Y., Suzuki, M., Miura, Y., Sakuma, K., Adachi, M. & Moritsuka, T. (1979) Endocrine aspects of the climacteric syndrome. In: *Interna-*

- tional Congress Series No. 512, Gynecology and Obstetrics, Proceedings of the IX World Congress of Gynecology and Obstetrics, Tokyo, October 25-31, 1979*, edited by S. Sakamoto, S. Tojo & T. Nakayama, Excerpta Medica, Amsterdam-Oxford-Princeton, pp. 104-107.
- 3) Abe, T., Yamaya, Y., Wada, Y. & Suzuki, M. (1983) Pituitary-ovarian relationships in women approaching the menopause. *Maturitas*, **5**, 31-37.
 - 4) Abe, T., Suzuki, M., Moritsuka, T. & Botan, Y. (1984) Statistical factor analysis and cluster analysis in the etiology of climacteric symptoms. *Tohoku J. exp. Med.*, **143**, 481-489.
 - 5) Campbell, S. (1976) Double blind psychometric studies on the effects of natural estrogens on postmenopausal women. In: *The Management of the Menopause and Post-Menopausal Years*, edited by S. Campbell, MTP Press, Lancaster, pp. 149-158.
 - 6) Chakravarti, S., Collins, W.P. Thom. M.H. & Studd, J.W.W. (1979) Relation between plasma hormone profile, symptom, and response to oestrogen treatment in women approaching the menopause. *Brit. med. J.*, **1**, 983-985.
 - 7) Furuhashi, N., Suzuki, M., Abe, T., Yamaya, Y. & Takahashi, K. (1977) Changes of hypophysio-ovarian endocrinological function by ageing in women. *Tohoku J. exp. Med.*, **121**, 231-238.
 - 8) Kupperman, H.S., Watchler, B.B. & Blatt, M.H.G. (1959) Contemporary therapy of the menopausal syndrome. *J. Amer. med. Ass.*, **171**, 1627-1637.
 - 9) Overall, J.E. & Gorham, D.R. (1962) The brief psychiatric rating scale. *Psychol. Rep.*, **10**, 799-812.
 - 10) Overall, J.E. & Klett, C.J. (1972) Part two factor analysis and related methodology. In: *Applied Multivariate Analysis*, edited by J.E. Overall, Mc Graw-Hill Book Co., New York, pp. 89-242.
 - 11) Overall, J.E. & Hollister, L.E. (1967) Major psychiatric disorders: A four dimensional model. *Arch. gen. Psychiatry.*, **16**, 146-151.
 - 12) Overall, J.E. & Hollister, L.E. (1968) Controlling for extrinsic variability associated with differences in background characteristics. Proceedings of the VI International Congress of the C.I.N.P., Excerpta Medica International Congress Series, No. 180.
 - 13) Overall, J.E., Kan, M. & Hollister, L.E. (1964) Computer procedures for classification of psychiatric patients. *J. Amer. med. Ass.*, **186**, 583-588.
 - 14) Overall, J.E., Hollister, L.E. & Dalal, S.N. (1967) Psychiatric drug research: Sample size requirements for one vs. two rates. *Arch. gen. Psychiatry*, **16**, 152-161.
 - 15) Peters, F., Richter, D. & Breckwoldt, M. (1982) Interactions between psychosomatic conflicts and gonadotropin secretion. *Acta obstet. gynecol. scand.*, **61**, 439-443.
 - 16) Schiff, I., Regestein, Q., Tulchinsky, D. & Ryan, K. (1979) Effect of estrogens on sleep and psychological state of hypogonadal women. *J. Amer. med. Ass.*, **242**, 2405-2407.
 - 17) Utian, W.H. (1972) The true clinical features of postmenopause and oophorectomy, and their response to oestrogen therapy. *S. Afr. med. J.*, **46**, 732-737.
-