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Comparison of the symptoms of menopause and symptoms of thyroid disease in Japanese women aged 35–59 years

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ABSTRACT

Objective In this study, we surveyed thyroid function abnormalities and menopausal symptoms in young as well as in menopausal women.

Methods We conducted a random survey among outpatients at our facility from September 2008 to June 2011. The study included 853 women aged 35–59 years. We assessed the subjects according to the Simplified Menopause Index, menstrual status, thyroid hormone measurements (thyroid stimulating hormone, free thyroxine, free triiodothyronine), the presence of Hashimoto's disease antibodies (anti-thyroid peroxidase antibody or anti-thyroglobulin antibody), the presence of Grave's disease (anti-TSH receptor antibody), markers of thyroid tumor (high thyroglobulin), and thyroid ultrasonography studies. The data were analyzed by means of the statistical program JMP version 8.0.

Results 'Facial flushing', 'sweating', and 'thyroid tumor' were all positively related with age and menstrual status. 'Breathlessness and palpitations' were positively related to Grave's disease. Moreover, 'sweating', 'irritability', and 'stiff shoulders, low back pain, and joint pain' were related to thyroid tumors. 'Insomnia' decreased with age. Patients with Hashimoto's disease were very rare because they were usually treated at other hospitals that specialize in thyroid disease.

Conclusion The symptoms of thyroid function abnormalities were shown to be very similar to menopausal symptoms and were found to occur in younger women before the onset of menopause. This study shows the need to differentiate menopausal symptoms from those of thyroid diseases.

INTRODUCTION

The symptoms of hypothyroidism strongly resemble those of menopause[1]. A positive anti-thyroglobulin antibody (anti-TgAb) or anti-thyroid peroxidase antibody (anti-TPOAb) and diminished thyroid function indicate a diagnosis of Hashimoto's disease. Urgent therapeutic intervention is often required to treat hypothyroidism; hence, correct diagnosis is important. On the other hand, Grave's disease is diagnosed when the result of the anti-thyroid stimulating hormone (TSH) receptor antibody (TRAb) test is positive and thyroid function is increased. Because thyroid function abnormalities resemble the symptoms of menopause[1], they are difficult to differentiate from the symptoms associated with the decline in ovarian function. Moreover, menopause is generally thought to extend broadly from 45 to 55 years of age; however, not many studies have been conducted on the menopause-like symptoms that are seen at a younger age prior to the onset of menopause[2]. The authors decided to analyze women in a wide age group, from 35 years of age, when ovarian function starts to decline, to 59 years of age[2], which includes the postmenopausal period. The participants in this survey were divided into groups

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according to their menstrual status, as defined by the International Menopause Society[3], and each of the groups was analyzed in relation to menopausal symptoms, hypothyroidism, Hashimoto's disease antibodies, Grave's disease, and thyroid tumor.

MATERIALS AND METHODS

Subjects

We limited our patient population to random outpatients visiting our women's specialized department between September 2008 and June 2011 for the first time, and who were aged 35–59 years. Moreover, their chief complaints were recorded in accordance with the Simplified Menopause Index (SMI)[4]. The 853 subjects consented to a detailed interview and measurement of anti-TgAb, anti-TPOAb, TSH, free triiodothyronine (f-T3), free thyroxine (f-T4), and thyroglobulin at the time of the initial examination, and to the measurement of TRAb and thyroid ultrasonography as needed. Outpatients who were receiving care for thyroid abnormalities were excluded; however, we included patients who were previously under hormone replacement therapy (HRT) for menopause symptoms at other hospitals. Our women's health department does not include gynecology; hence, only three outpatients were treated by HRT.

Menstrual status

As reported by Utian[4], female hormone levels vary with menstrual stage; hence, they were not recorded. The subjects were classified into the following four groups according to their menstrual status, as defined by the International Menopause Society[3]:

- Premenopausal group: before menopause, and with regular menstrual cycles,
- Perimenopausal group: menopause in progress (irregular menses and no menstruation for at least 3 months but less than 1 year),
- Postmenopausal group: at least 1 year but less than 5 years since the last menstruation,
- Post-postmenopausal group: 5 years or more since the last menstruation.

Differences between Hashimoto's disease and hypothyroidism

If the patient was positive for anti-TgAb or anti-TPOAb, she was considered as Hashimoto's disease antibody-positive. However, both hypothyroidism and Hashimoto's disease antibody-positive are the only diagnosis of Hashimoto's disease[5,6]. Hypothyroidism was defined as a condition characterized by a low level of normal thyroid hormones.

Hypothyroidism was defined by: TSH >4.31 μIU/ml, f-T3 <2.1 pg/ml, or f-T4 <0.82 ng/dl.

Diagnosis of Grave's disease

A diagnosis of Grave's disease was made when thyroid function was increased and the patient was TRAb-positive[5,6].

Menopausal Symptom Scale

The SMI[4], which is the most commonly used menopause scale, was used for the indices of menopausal symptoms and was devised on the basis of the characteristics of Japanese women as listed below:

- My face flushes,
- I tend to sweat,
- My lower back and hands and feet tend to get cold,
- I become short of breath and experience palpitations,
- It's hard to fall asleep, and my sleep is shallow,
- I get angry easily, and I'm irritable,
- I brood over things and get depressed,
- I often experience headaches, dizziness, and nausea,
- I tire easily,
- I have stiff shoulders, low back pain, and pain in my hands and feet.

Diagnosis of thyroid tumors

Thyroid tumors were diagnosed by first measuring thyroglobulin; if the thyroglobulin level was high, a thyroid ultrasonography was performed. A definite diagnosis was made after analyzing the results of the diagnostic studies[7,8].

Statistical analysis

The survey results of all of the subjects were statistically analyzed by using the JMP version 8.0 software program.

RESULTS

Patient background

The mean age of the 853 subjects was 47.5 years. Outpatients who received care for thyroid disease were excluded; however, we included patients who were previously under HRT for menopause symptoms at other hospitals. Our department does not include gynecology; hence, only three outpatients were treated by HRT. The patient distribution according to age was as follows: 35–39 years, 108 subjects (12.7%); 40–44 years, 169 subjects (19.8%); 45–49 years, 226 subjects (26.5%); 50–54 years, 229 subjects (26.8%); 55–59 years,

Table 1 Number of women experiencing menopause symptoms by age group

Menopause symptoms	*n*	*Age* (years) 35–39	40–44	45–49	50–54	55–59	*p*
Facial flushing	128 (15.0%)	4.7%	6.3%	30.5%	43.8%	14.8%	<0.001
Sweating	119 (14.0%)	5.9%	10.0%	30.3%	41.2%	12.6%	0.0030
Feeling cold	71 (8.3%)	11.3%	18.3%	22.5%	28.2%	19.7%	0.6293
Breathlessness and palpitations	108 (12.7%)	12.0%	16.7%	29.7%	25.9%	15.7%	0.9079
Insomnia	94 (11.0%)	03.2%	12.8%	39.4%	25.5%	19.1%	0.0038
Irritability	74 (8.7%)	16.2%	25.6%	23.0%	31.1%	8.1%	0.0386
Depression	93 (10.9%)	11.8%	20.4%	29.0%	29.0%	9.8%	0.5415
Headaches, dizziness and nausea	186 (21.8%)	15.6%	20.4%	25.8%	24.2%	14.0%	0.6540
Tired easily	135 (15.8%)	13.3%	23.0%	26.0%	26.7%	11.0%	0.9565
Stiff shoulders and joint pain	116 (13.6%)	7.8%	18.1%	28.4%	36.2%	9.5%	0.5476

121 subjects (14.2%). The menopausal symptoms 'my face flushes' and 'sweating' were positively related to age ($p < 0.001$ and $p = 0.0030$, respectively), and they were most common around menopause, i.e. between 48 and 53 years. 'Insomnia' declined with age ($p < 0.0038$) (Table 1).

Menstrual status

The distribution of subjects according to their menstrual status was as follows: premenopausal group, 329 subjects (38.6%); perimenopausal group, 253 subjects (29.7%); postmenopausal group, 160 patients (18.7%); post-postmenopausal group, 111 patients (13.0%).

Menopausal symptoms

The complaints of menopausal symptoms according to the SMI indices were 'facial flushing' in 128 patients (15.0%), 'sweating' in 119 patients (14.0%), 'feeling cold' in 71 patients (8.3%), 'breathlessness' in 108 patients (12.7%), 'insomnia' in 94 patients (11.0%), 'irritability' in 74 patients (8.7%), 'headaches and dizziness' in 186 patients (21.9%), 'tired easily' in 135 patients (15.9%), and 'stiff shoulders and joint pain' in 116 patients (13.6%) (Table 1). 'Facial flushing', 'sweating', and 'irritability' were positively and strongly related with perimenopause, but declined after menopause (Table 2).

Positive rate of Hashimoto's disease antibodies and clinical diagnosis

Hashimoto's disease antibody was positive in 282 patients (33.1%). In the patients who were Hashimoto's disease antibody-positive, a positive relationship was seen with 'tired easily' ($p = 0.0397$), and an inverse relationship was seen with 'irritability' ($p = 0.0333$) (Table 3). However, patients with a clinical diagnosis of Hashimoto's disease were very rare because they are usually treated at other hospitals specializing in thyroid disease; hence, their thyroid data were normal. The mean (average) values were as follows: TSH, 1.79 μIU/ml; f-T3, 2.48 pg/ml; f-T4, 1.13 ng/dl; TPOAb, 35.0 IU/ml; TgAb, 114 IU/ml. The median values were as follows: TSH, 1.39 μIU/ml; f-T3, 2.40 pg/ml; f-T4, 1.10 ng/dl; TPOAb, 7.0 IU/ml; TgAb, 11.0 IU/ml.

Table 2 Number of women experiencing menopause symptoms by menstrual status

Menopause symptoms	*Number of women with menopause symptom (%)*	*Menstrual status* *Pre*	*Peri*	*Post*	*Post-post*	*p*
Facial flushing	128 (15.0%)	14.8%	40.7%	32.0%	12.5%	<0.001
Sweating	119 (14.0%)	25.2%	37.8%	23.5%	13.5%	0.0107
Feeling cold	71 (8.3%)	28.2%	33.8%	28.2%	9.8%	0.0762
Breathlessness and palpitations	108 (12.7%)	37.0%	27.8%	19.4%	15.8%	0.8106
Insomnia	94 (11.0%)	29.8%	36.2%	22.3%	11.7%	0.2137
Irritability	74 (8.7%)	44.6%	37.8%	12.2%	5.4%	0.0445
Depression	93 (10.9%)	39.8%	35.5%	16.1%	8.6%	0.3649
Headaches, dizziness and nausea	186 (21.8%)	45.7%	25.8%	16.1%	12.4%	0.1525
Tired easily	135 (15.8%)	46.0%	25.9%	14.8%	13.3%	0.2265
Stiff shoulders and joint pain	116 (13.6%)	36.2%	32.8%	22.4%	8.6%	0.3110

Table 3 Menopause symptoms and Hashimoto's disease antibody

Menopause symptoms	*Number of women with menopause symptom (%)*	*Hashimoto's disease antibody*		*p*
		Positive (%)	*Negative (%)*	
Facial flushing	128 (15.0%)	30.5	69.5	0.2849
Sweating	119 (14.0%)	32.8	67.2	0.5167
Feeling cold	71 (8.3%)	33.8	66.2	0.6110
Breathlessness and palpitations	108 (12.7%)	37.0	63.0	0.8529
Insomnia	94 (11.0%)	39.4	60.6	0.9309
Irritability	74 (8.7%)	23.0	77.0	0.0333
Depression	93 (10.9%)	35.5	64.5	0.7418
Headaches, dizziness and nausea	186 (21.8%)	29.6	70.4	0.1453
Tired easily	135 (15.8%)	40.0	60.0	0.0397
Stiff shoulders and joint pain	116 (13.6%)	35.3	64.7	0.7497

Incidence rate of hypothyroidism

Hypothyroidism was observed in 118 patients (13.8%). An inverse relation with 'headaches, dizziness, and nausea' ($p = 0.0379$) was observed in the patients with hypothyroidism (Table 4).

Incidence rate of Grave's disease

Grave's disease was diagnosed in 23 patients (2.7%). A positive relation with 'breathlessness and palpitations' ($p = 0.0187$) was observed in the Grave's disease patients (Table 5). Moreover, there was a positive relation between having Grave's disease and having a 'thyroid tumor' ($p = 0.0032$).

Incidence rate of thyroid tumors

Thyroid tumors were observed in 96 patients (11.3%). Thyroid tumours were positively related with age ($p = 0.0001$) and menstrual status ($p = 0.0027$). Specifically, they tended to be more common in women aged 47–53 years, less than 3 years either before or after menopause. In addition, having a thyroid tumor was positively related to the menopausal symptom 'sweating' ($p = 0.0323$) and inversely related to 'irritability' ($p = 0.0225$) and 'stiff shoulders, low back pain, and pain in my hands and feet' ($p = 0.0137$) (Table 6).

DISCUSSION

Based on the results of our study, patients with thyroid diseases, including hypothyroidism, showed symptoms similar to menopausal symptoms; hence, no significant differences were observed between the menopausal and premenopausal groups. In other words, menopausal symptoms may also occur in younger women. The results of this study showed a positive relationship between the symptoms 'facial flushing' and 'sweating' and the menstrual cycle; however, there was no significant difference with thyroid disease, and it can be concluded that these symptoms are indices of symptoms of the menopausal women. Lazarus[8] reported that patients with Hashimoto's disease or hypothyroidism tended to complain of the symptoms 'tired easily', 'depression', 'joint pain', and 'feeling cold'. In contrast, Godfrey[9] reported that the symptoms 'sweating' and 'irritability' are generally more common

Table 4 Menopause symptoms and hypothyroidism

Menopause symptoms	*Number of women with menopause symptom (%)*	*Hypothyroidism*		*p*
		Positive (%)	*Negative (%)*	
Facial flushing	128 (15.0%)	11.0	89.0	0.1879
Sweating	119 (14.0%)	14.3	85.7	0.4856
Feeling cold	71 (8.3%)	19.7	80.3	0.9482
Breathlessness and palpitations	108 (12.7%)	13.0	87.0	0.4584
Insomnia	94 (11.0%)	19.1	80.9	0.9547
Irritability	74 (8.7%)	9.5	90.5	0.9115
Depression	93 (10.9%)	12.9	87.1	0.4657
Headaches, dizziness and nausea	186 (21.8%)	9.7	90.3	0.0379
Tired easily	135 (15.8%)	12.6	87.4	0.3826
Stiff shoulders and joint pain	116 (13.6%)	12.1	87.9	0.3349

Table 5 Menopause symptoms and Grave's disease

Menopause symptoms	*Number of women with menopause symptom (%)*	*Grave's disease*		*p*
		Positive (%)	*Negative (%)*	
Facial flushing	128 (15.0%)	2.3	97.7	0.6959
Sweating	119 (14.0%)	1.7	98.3	0.8544
Feeling cold	71 (8.3%)	4.2	95.8	0.8834
Breathlessness and palpitations	108 (12.7%)	6.5	93.5	0.0187
Insomnia	94 (11.0%)	2.1	97.9	0.7416
Irritability	74 (8.7%))	0.0	100.0	0.1205
Depression	93 (10.9%)	2.2	97.8	0.5329
Headaches, dizziness and nausea	186 (21.8%)	3.2	96.8	0.3856
Tired easily	135 (15.8%)	3.7	96.3	0.8587
Stiff shoulders and joint pain	116 (13.6%)	3.5	96.5	0.8077

in Grave's disease, and that 'headaches, dizziness, and nausea' and 'palpitations and breathlessness' are unrelated to the thyroid gland. Regarding the probability of having a thyroid tumor, Godfrey[9] reported that tumors tend to be associated with Hashimoto's disease and Grave's disease; however, they are known to be discovered as incidental findings in patients without those diseases[1,5,6]. In addition, an inverse relation with 'headaches, dizziness, and nausea' was observed in hypothyroidism, a finding that was consistent with the reports by Lazarus[8] and Godfrey[9]. Thus, there appears to be a strong possibility that the symptom 'feeling cold' will serve as a clinical index for differentiating between hypothyroidism in menopausal women and menopausal syndrome. However, a positive relation with 'breathlessness and palpitations' was observed in Grave's disease patients. These results are consistent with the report by Surks and colleagues[7]; however, they are contrary to the results of Godfrey[9]. The difference has been attributed to the difference in age composition between the two reports, and Grave's disease is thought to peak at a younger age than menopause[1]. In thyroid tumors, the symptoms 'facial flushing' and 'sweating' were more common less than 3 years before and after menopause. These findings are consistent with the reports by Surks and colleagues[7] and Godfrey[9], and being able to limit the peak age during menopause to less than 3 years before and after menopause can be said to be an important point. However, many clinics in Japan specialize in the treatment of thyroid abnormalities and symptoms of menopause. Thus, there appears to be a strong possibility that the number of Hashimoto's disease antibody-positive patients coming to our clinic may show a higher rate of occurrence than the normal 1 in 10–20 rate for ordinary Japanese women[5,6]. In addition, 'headaches, dizziness, and nausea' was positively correlated with 'facial flushing' and 'sweating', and 'feeling cold' was positively related with 'stiff shoulders, low back pain, and joint pain', but was inversely correlated with 'headaches, dizziness, and nausea'. These results are consistent with the report by Mishra and Kuh[10] that hypothyroidism patients tend to complain of 'feeling cold', 'tired easily', 'stiff shoulders, low back pain, and joint pain'; however, there are few complaints of the symptoms 'headaches, dizziness, and nausea', 'facial flushing', or 'sweating'. In fact, we believe that there was a strong possibility that they are clinical indices of Japanese women that differentiate women with hypothyroidism from menopausal women. In Grave's disease patients, there was a positive correlation with 'breathlessness and palpitations' and 'thyroid tumor', whereas there were inverse relations with 'tired easily' and 'depression'. In addition, thyroid tumors were positively related with 'irritability' and 'sweating'. In other words, it was inferred that there is no 'depression', but there is a strong possibility

Table 6 Menopause symptoms and thyroid tumor

Menopause symptoms	*Number of women with menopause symptom (%)*	*Thyroid tumor*		*p*
		Positive (%)	*Negative (%)*	
Facial flushing	128 (15.0%)	14.8	85.2	0.1093
Sweating	119 (14.0%)	16.8	83.2	0.0323
Feeling cold	71 (8.3%)	12.7	87.3	0.4050
Breathlessness and palpitations	108 (12.7%)	13.0	87.0	0.3216
Insomnia	94 (11.0%)	9.6	90.4	0.7586
Irritability	74 (8.7%))	4.1	95.9	0.0225
Depression	93 (10.9%)	12.9	87.1	0.3484
Headaches, dizziness and nausea	186 (21.8%)	11.3	88.7	0.5376
Tired easily	135 (15.8%)	9.6	90.4	0.7852
Stiff shoulders and joint pain	116 (13.6%)	5.2	94.8	0.0137

of finding thyroid tumors or Grave's disease in women who complain of 'sweating'. This result is in agreement with those of reports by McConnell[11] and Lazarus[8]. However, 'depression' was positively related with 'insomnia', 'irritability', and 'tired easily', and it was found to have an impact both psychologically and physically. As reported by Kuh and colleagues[12] and Elavsky and colleagues[13], 'depression' is very important in terms of the prognosis for the quality of life of women who are approaching menopause[14–17], and it is important to differentiate it from thyroid disease and depression[18–20]. Nevertheless, in this study, excluding patients treated for thyroid disease, there was bias from the standpoint of sampling[19–21]. Furthermore, most outpatients were not treated by HRT; hence, symptoms of the general population of menopausal women might be different from those observed in our study[10,22].

CONCLUSION

It was concluded that menopausal symptoms and thyroid function abnormalities appeared in younger women before menopause and not just in menopausal women[23]. Because the symptoms caused by decreased ovarian function and the symptoms caused by thyroid function abnormalities are similar to those of women reaching menopause, differential diagnosis in clinical practice is very important in terms of increasing the quality of life of women nearing menopause.

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