近畿大学

東洋医学研究所 紀要

(2023年度)



Journal of Research Institute of Oriental Medicine

KINDAI UNIVERSITY 2023



巻頭言

2023年度 東洋医学研究所紀要発刊によせて

東洋医学研究所 所長·教授 武田 卓

東洋医学研究所は、近畿大学病院の開設と同時に大学直属の漢方専門研究所として発足 し、日本で最初の漢方の臨床・基礎を研究する研究所として、多くの実績をあげてまいり ました。私は、平成24年4月1日より、新所長・新教授として東北大学医学部先進漢方 治療医学講座より赴任いたしました。

漢方診療は、西洋医学だけでは改善しにくいような難治性疾患や西洋医学では病気として相手にされないような不定愁訴に対して有効な場合がしばしば認められます。また、最近ではがん治療に伴う様々な副作用対策にも漢方が用いられるようになってきました。このように、従来からの東洋医学だけではなく、西洋医学の確かな専門性を持ったうえでの漢方治療も必要です。そこで、私の専門性を生かした女性漢方外来、冷え症外来を開設しています。さらに、最近のフェムテックへの感心の高まりを背景に、月経前症候群・月経前不快気分障害への新規治療薬開発や、アプリを用いた認知行動療法開発といった、東洋医学の枠組みを超えた女性ヘルスケア領域全般を対象とした臨床研究も実施中です。

また、大阪大学医学部より、脳神経科学研究をリードする遠山正彌名誉教授を客員教授 にお迎えし、宮田信吾教授を中心とした基礎研究部門も同時にスタートしました。漢方薬 の作用メカニズムを最先端の分子生物学的手法によって科学的に解明します。現在、「抑 肝散」「加味逍遙散」という漢方薬を中心に、漢方薬の神経機能に対する効果についての 科学的解析を行っており、有効成分の同定、作用機序の解明から新規創薬への展開を目指 しています。

古代中国からの長い歴史をもつ漢方治療ですが、これからは 21 世紀の現代医療にマッ チした診療・研究、さらにはトランスレーショナルリサーチを展開していきたいと考えて おります。

近畿大学

東洋医学研究所紀要 (2023年度)

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Women's Health and Pandemic Crisis(Springer International Publishing Switzerland 2023 年 12 月)

原著論文

 The Japanese Version of the Daily Record of Severity of Problems for Premenstrual Symptoms: Reliability and Validity Among the General Japanese Population. <u>Takashi Takeda</u>, Kana Yoshimi, Sayaka Kai, Fumi Inoue

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4. Association Between Loneliness, Premenstrual Symptoms, and Other Factors During the COVID-19 Pandemic: A Cross-Sectional Study with Japanese High School Students.

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競争的資金等の研究課題(公的資金)

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 AMED 予防・健康づくりの社会実装に向けた研究開発基盤整備事業 月経前 症候群の二次予防・三次予防に関するエビデンスの収集と評価 2023 年 4 月 -2026年3月(分担)

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ORIGINAL RESEARCH

The Japanese Version of the Daily Record of Severity of Problems for Premenstrual Symptoms: Reliability and Validity Among the General Japanese Population

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Purpose: The validity and reliability of the Japanese version of the Daily Record of Severity of Problems (DRSP-J) have already been confirmed in a population with premenstrual symptoms. This study aimed to assess the validity and reliability of the DRSP-J in the general population.

Patients and Methods: We analyzed data from 113 Japanese women with regular menstrual cycles who applied to participate in an ongoing study. Participants were recruited regardless of the severity of premenstrual symptoms, and their menstrual cycles were monitored using the DRSP-J for two cycles. Reliability was examined using Cronbach's α , a measure of internal consistency, and test-retest reliability. Structural validity was assessed using a principal component analysis (PCA). The Hospital Anxiety and Depression Scale (HADS) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) were used to examine concurrent validity. The agreement between the clinical diagnoses based on the diagnostic criteria for premenstrual syndrome/premenstrual dysphoric disorder and that based on the DRSP-J score was examined using the kappa coefficient.

Results: Cronbach's α for DRSP-J total score was 0.96. The DRSP-J total score showed high test-retest reliability. The PCA showed a two-factor model describing "Mood" and "Behavior/Physical" symptoms. The DRSP-J total score was highly correlated with the HADS total and EQ-5D-5L scores. The classification of "moderate to severe premenstrual syndrome" and "premenstrual dysphoric disorder" by clinical methods and the criteria based on the DRSP-J were in good agreement (kappa values = 0.78).

Conclusion: The DRSP-J is a reliable and valid measure of premenstrual symptoms in the general Japanese population, including those with few or no symptoms.

Keywords: premenstrual syndrome, premenstrual dysphoric disorder, psychometric testing, premenstrual symptom

Introduction

Premenstrual symptoms are characterized by a wide range of mood, behavioral, and physical symptoms limited to the luteal Phase^{1,2} and affect the social, familial, and school lives of most women. Epidemiological studies have revealed that 80% to 90% of menstruating women exhibit premenstrual symptoms.³ Premenstrual syndrome (PMS) is a pathological state of premenstrual symptoms, and a severe form of PMS is diagnosed as premenstrual dysphoric disorder (PMDD), primarily owing to its severe psychiatric symptoms.⁴ Both the PMS diagnostic criteria of the American College of Obstetricians and Gynecologists (ACOG) and the PMDD diagnostic criteria of the American Psychiatric and Neurological Association require evaluation using a prospective symptom diary.⁵ Both PMS and PMDD are viewed as premenstrual disorders (PMDs), a series of consecutive disorders.⁶

The Daily Record of Severity of Problems (DRSP) was originally developed by Endicott to aid in the diagnosis of PMDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.⁷ The DRSP is a prospective daily charting tool used worldwide for the strict evaluation of PMDs.^{8–10} The DRSP score has been

used as the primary endpoint in clinical trials to evaluate the efficacy of serotonin reuptake inhibitors and drospirenonecontaining oral contraceptives, which are globally recognized as the standard treatments for PMDs.^{11–14} The DRSP was translated into Japanese after linguistic validation according to a general cross-cultural adaptation process for clinical trials, and a Japanese version of the DRSP (DRSP-J) was developed.^{15–17} The DRSP-J has been systematically evaluated for its reliability and validity among participants in clinical trials of treatment for PMDs.¹⁸

The psychometric characteristics of a survey instrument vary depending on the characteristics of the surveyed population. The reliability and validity of the original version of the DRSP were examined for both clinical trial participants and participants with a wide range of symptom severity, including those with few or no premenstrual symptoms.⁷ The DRSP-J was considered insufficient compared to the original DRSP, as only clinical trial participants had been examined. Therefore, examining the psychological characteristics of the DRSP-J among the general female population is necessary. This study aimed to assess the validity and reliability of the DRSP-J among the general population.

Materials and Methods

Ethics Approval and Informed Consent

This study was performed according to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Kindai University Ethics Committee (approval number: R02-081). All participants provided informed consent before participating in the study.

Settings and Participants

The study was conducted between December 2020 and October 2021. Of the 150 participants in another menstruationrelated study, 113 Japanese women with regular menstrual cycles who had completed the study were used in the analysis. Generally, for a questionnaire to be considered reliable and valid, the number of respondents should be 5 to 10 times the number of items (or more than 100 in this case);¹⁹ since the DRSP-J total score consists of 21 items, this number of respondents was considered sufficient. Participants were recruited through advertisements placed in local free newspapers, posters displayed in Kindai University Hospital, and our institute's website. Participants were recruited regardless of the severity of premenstrual symptoms, and their menstrual cycles were monitored using the DRSP-J for two cycles.

The eligibility criteria included: Age 20–45 years; regular menstrual cycles (25–38 days); no oral contraceptive pill use for four weeks before beginning the study; avoiding changes in regularly used foods, supplements, and medications as much as possible after beginning study; and providing written informed consent. No participants were withdrawn from the study after entry for violating these exclusion criteria.

The study participants completed the DRSP-J on the website daily from day 15 of the first menstrual cycle to day 10 of the third menstrual cycle. Hospital Anxiety and Depression Scale (HADS) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) were also recorded simultaneously between day -5 and -1 before menstruation in the first and second cycles. Participants were interviewed by telephone after completion of the DRSP-J and before the start of the next menstrual period. The study schedule is outlined in Figure 1, and the details of the interviews are presented in the following "Interview" section.



Figure I Time course of the study design.

Abbreviations: MI, menstruation of the first cycle; M2, menstruation of the second cycle; M3, menstruation of the third cycle; DRSP-J, Japanese version of the Daily Record of Severity of Problems; CD, cycle of the day; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HADS, Hospital anxiety and depression scale.

Japanese Version of the Daily Record of Severity of Problems (DRSP-J)

The DRSP-J consists of 21 items related to emotional and physical premenstrual symptoms (listed in the note of Table 1 and three items related to impairment of social and life activities due to these symptoms (whether the premenstrual symptoms experienced

	Factor I (Mood)	Factor 2 (Behavior/Physical)
la	1.01	-0.12
lb	0.97	-0.09
3a	0.94	-0.11
3b	0.93	-0.06
lc	0.93	-0.05
2	0.87	0.04
10a	0.71	0.22
7	0.69	0.26
4b	0.65	0.16
5	0.59	0.32
4a	0.56	0.18
6	0.46	0.42
llc	0.40	0.36
8b	-0.05	0.85
8a	0.07	0.78
9b	0.09	0.75
IIb	0.03	0.66
lla	-0.15	0.63
IId	0.04	0.60
ТОБ	0.33	0.59
9a	0.39	0.50
Eigenvalue	12.18	2.27
% of variance explained	51.91	40.27
Correlation between factors		
Factor I	1.00	
Factor 2	0.59	1.00

 Table I Factor Coefficients of the DRSP-J After Promax Rotation

 (N=113)

Notes: Values above 0.3 are expressed in bold. 1a, Depressed/sad/blue; 1b, Hopeless; 1c, Worthless/guilty; 2, Anxious/tense/on edge; 3a, Mood swings; 3b, Sensitive to rejection; 4a, Anger/irritability; 4b, Conflict/problems; 5, Less interest, 6, Difficulty concentrating; 7, Lethargic/tired/fatigued; 8a. Increased appetite, 8b, Crave specific foods; 9a, Sleep more; 9b, Trouble sleeping; 10a, Overwhelmed, cannot cope; 10b, Out of control; 11a, Breast tenderness; 11b, Breast swelling/"bloated;" 11c, Headache; 11d, Joint/muscle pain.

Abbreviation: DRSP-J, Japanese version of the Daily Record of Severity of Problems.

interfere with (a) work efficiency or productivity, or home responsibilities; (b) social activities; or (c) relationships with coworkers or family). The severity of each symptom is rated on a 6-point scale (1, not at all; 2, extremely mild; 3, mild; 4, moderate; 5, severe; 6, extremely severe). The total DRSP-J score was calculated by summing the 21 premenstrual symptoms (21 to 126 points). The DRSP-J negative mood score was obtained by summing scores on eight core premenstrual mood symptoms (depressed/sad/blue, hopeless, worthless/guilt, anxiety/tense/on edge, mood swings, sensitivity to rejection, anger/irritability, and conflict/problems) (8 to 48 points).²⁰ The luteal phase scores were obtained by averaging the ratings of -5 to -1 day cycles. Follicular phase scores were obtained by averaging the ratings of 6 to 10 day cycles. Participants who answered the questionnaire for at least 4 days during both the follicular and luteal phases were selected.

Hospital Anxiety and Depression Scale (HADS)

A 14-item brief tool was used to assess participants' risk for anxiety and depression.²¹ The Japanese version was used, which has been thoroughly reviewed for validity and reliability.²² Since anxiety and depression are central symptoms of premenstrual symptoms, this measure was used to assess concurrent validity. The HADS consists of two parts, each with seven items: HADS-A (anxiety) and HADS-D (depression). Each item is rated on a 4-point scale ranging from 0 to 3, with anxiety and depression rated according to the total score of HADS-A and HADS-D, respectively. The total of both scores was used for the overall evaluation (HADS-T) (0 to 42 points).

EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L measures five dimensions of health-related quality of life (HRQOL): Mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression.²³ Each is answered on a 5-point scale, and index values are calculated using an algorithm. The Japanese version was used, which has been thoroughly reviewed for validity and reliability.^{24,25} The EQ-5D-5L is a reliable and valid general measure of health status, applicable to a wide range of populations and settings, and has been used to assess HRQOL for many conditions, including depression and anxiety.²⁶ Thus, it was used to assess concurrent validity.

Interview

After completing the DRSP-J, participants were interviewed to examine whether the severity of their premenstrual symptoms fulfilled the ACOG criteria for "moderate to severe PMS" or DSM criteria for "PMDD."^{4,5} This decision involved a consensus of two expert obstetricians and gynecologists (T.T. and S.K.) with reference to the DRSP-J data for two menstrual cycles. The DRSP-J data showed daily symptom data and menstrual periods. The evaluator visually assessed the relationship between the intensity and increase/decrease of symptoms and the menstrual cycle. In addition to the above, the classification of "moderate to severe PMS" and "PMDD" was made based on the following criteria regarding DRSP-J scores.

Criteria for "moderate to severe PMS" include the following:¹⁵

- 1. A follicular phase score (days 6–10) daily average ≤ 3.0 for each symptom.
- 2. A luteal phase score (days -5 to -1 before menstruation) daily average ≥ 3.0 for three distinct items.
- 3. A luteal phase daily average improvement by at least 30% compared with the corresponding follicular phase daily average for three distinct items.
- 4. A score \geq 3 (mild) on functional impairment items for at least 1 day during the premenstrual phase.

"PMDD" criteria include the following:⁷

- 1. A follicular phase score (days 6–10) daily average ≤ 3.0 for each symptom.
- 2. A luteal phase (premenstrual days -5 to -1) score of ≥ 4.0 for more than 2 days on five distinct items.
- 3. A luteal phase daily average improvement of at least 43% compared with the corresponding follicular phase daily average for five distinct items.
- 4. A score of \geq 4 (moderate) on functional impairment items for at least 2 days during the premenstrual phase.

Both criteria must be met in two consecutive menstrual cycles.

The agreement between classification based on diagnostic criteria and mechanical classification using the DRSP-J score was examined based on kappa values.

Statistical Analysis

Means and standard deviations (SD) were calculated for the age, weight, and height of the participants. The distribution of the DRSP-J total and negative mood scores were shown using the median and interquartile range (IQR).

Cronbach's a coefficient was used to assess the internal consistency reliabilities of the DRSP-J.

Day-to-day test-retest reliability was assessed using intraclass correlation coefficients (ICC) and a two-way randomeffects model. Adjacent days within the follicular and luteal phase (mid-follicular phase day 9 vs day 10 in Cycle 3 and late luteal phase day -2 vs day -1 in Cycle 2) were selected. The reliability was evaluated with a 95% confidence interval (CI), with less than 0.5 rated as poor, 0.5 to 0.75 as moderate, 0.75 to 0.9 as good, and 0.9 or greater as excellent.²⁷

The factor structure of the DRSP-J was examined using principal component analysis (PCA) with promax rotation of the luteal phase scores. The eigenvalue > 1.0 and scree plot criteria were used to determine the number of factors to be extracted.

Correlations were analyzed using Spearman's rank correlation coefficients. Correlation coefficients were classified as low (< 0.3), moderate (0.3–0.6), and high (> 0.6).²⁸

Kappa values were categorized as poor (< 0.2), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), and very good (0.81–1.00).²⁹

For the Student's *t*-test, effect size was measured using *r*. *r* was calculated using the following formula $(r = \sqrt{\frac{t^2}{t^2+df}})$. The effect sizes were judged as small (0.10), medium (0.30), or large (0.50).³⁰

Except for ICC, statistical analyses were performed using JMP Pro 16.0.2 (SAS, Cary, NC, USA). The ICC was calculated using the Excel add-in software BellCurve for Excel 4.0.5 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Statistical significance was set at P < 0.05.

Results

The basic characteristics of the participants are presented in Table 2. Based on the median and IQR of the DRSP-J scores, it can be assumed that most had mild premenstrual symptoms.

Cronbach's α for the DRSP-J total score showed very good internal consistency of 0.96 in the luteal phase and 0.95 in the follicular phase (Table 3). The Cronbach's α for the DRSP-J negative mood score also exhibited good internal consistency in the luteal and follicular phases, as in the DRSP-J total score.

The test-retest reliability of the DRSP-J is presented in Table 4. The test-retest value of the DRSP-J total score in the luteal phase was "moderate" to "excellent" and that of the DRSP-J negative mood score was "moderate" to "good." In the follicular phase, the DRSP-J total score was "moderate" to "good" and the DRSP-J negative mood score was "moderate."

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Characteristic								
Age (years), mean (SD)	34.0 (7.6)							
Height (cm), mean (SD)	158.5 (5.3)							
Body weight (kg), mean (SD)	53.2 (7.8)							
DRSP-J total score (luteal phase, Cycle I), median (IQR)	32.4 (24.6–45.1)							
DRSP-J total score (luteal phase, Cycle 2), median (IQR)	30.2 (24.2–43.4)							

Table 2 Characteristics of Study Participants (N=113)

Abbreviations: SD, standard deviation; DRSP-J, Japanese version of the Daily Record of Severity of Problems; IQR, interquartile range.

	Luteal Phase Score (Cycle 2)	Follicular Phase Score (Cycle 3)
Total score	0.96	0.95
Negative mood score	0.95	0.96
Factor I: Mood	0.96	0.95
Factor 2: Behavior/Physical	0.88	0.87

Table 3 Internal Consistency (Cronbach's α) for the Summary Scores of the DRSP-J (N=113)

Abbreviation: DRSP-J, Japanese version of the Daily Record of Severity of Problems.

 Table 4
 Test-Retest
 Intraclass
 Correlation
 Coefficients
 of
 DRSP-J
 Total
 Scores
 and

 Negative
 Mood
 Score
 (N=113)*

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	Mid Follicular Phase Day 9 vs Day 10 (Cycle 3)	Late Luteal Phase Day –2 vs Day –I (Cycle 2)
Total score (95% CI)	0.69 (0.58–0.78)	0.84 (0.60–0.92)
Negative mood score (95% CI)	0.65 (0.53–0.74)	0.79 (0.71–0.85)

Note: *All *P* < 0.001.

Abbreviations: CI, confidence interval; DRSP-J, Japanese version of the Daily Record of Severity of Problems.

PCA was performed to explore the factor structure of the DRSP-J. Two factors were identified by the eigenvalue > 1.0 criterion and scree plot (Figure 2). Table 1 lists the factor coefficients of DRSP-J after promax rotation. The first factor (Factor 1) explained 51.91% of the data variance and the second factor (Factor 2) 40.27%. Factor 1 can be interpreted as a "mood" dimension and Factor 2 as a "behavior/physical" dimension. The Cronbach's α for Factors 1 and 2 are provided in Table 3. All data were higher than 0.80, indicating good internal consistency.

We then analyzed the consistency of the evaluation of premenstrual symptoms between the DRSP-J, HADS, and EQ-5D-5L (Table 5). The DRSP-J total score and negative mood score were highly positively correlated with the HADS total score in both Cycles 1 and 2. For the EQ-5D-5L, the DRSP-J total score and the negative mood score were found to have a high negative correlation.

Additionally, we examined the consistency between conventional clinical diagnosis based on the diagnostic criteria and severity classification based on the DRSP-J score (Table 6). The kappa scores indicated good agreement.



Figure 2 Scree plot for the DRSP-J. Abbreviation: DRSP-J, Japanese version of the Daily Record of Severity of Problems.

		c	ycle I					
	HADS		EQ-5D-5L	HADS			EQ-5D-5L	
	Α	D	Total		Α	D	Total	
Total score	0.587	0.547	0.627	-0.677	0.721	0.550	0.707	-0.659
Negative mood score	0.635	0.505	0.628	-0.719	0.741	0.476	0.671	-0.693

Table 5 Correlation of Luteal Phase DRSP-J Score with HADS and EQ-5D-5L (N=113)

Abbreviations: A, anxiety scores; D, depression scores; DRSP-J, Japanese version of the Daily Record of Severity of Problems; HADS, Hospital Anxiety and Depression Scale; EQ-5D-5L, EuroQol 5 dimensions 5-level.

Table 6 Consistency Between Conventional Clinical Judgement and Severity Classification

 by DRSP-J Score (N=113)

			DRSP-J	
		No or Mild PMS	Moderate to Severe PMS	PMDD
Clinical judgement	No or mild PMS	101	I	0
	Moderate to severe PMS	4	6	0
	PMDD	0	0	I

Notes: The relevant number of participants in each table cell is presented. Weighted kappa (95% confidence interval):0.78 (0.57-1.00), P < 0.001).

Abbreviations: DRSP-J, Japanese version of the Daily Record of Severity of Problems; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.

Table 7 Comparison of EQ-5D-5	Scores in the Luteal Phase b	y Severity of Premenstrual Symptoms
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Clinical Judgement	Cycle I	P (r)	Cycle 2	P (r)
No or mild PMS, mean (SD), N=102	0.843 (0.119)	0.009 ^a (0.245)	0.870 (0.122)	0.003 ^a (0.278)
Moderate to severe PMS + PMDD, mean (SD), N=I I	0.743 (0.117)		0.751 (0.127)	

Note: ^aStudent's t-test.

Abbreviations: EQ-5D-5L, EuroQol 5 dimensions 5-level; SD, standard deviation; PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder.

To the best of our knowledge, there are no previous EQ-5D-5L scoring studies on participants who kept prospective two-cycle diaries according to the diagnostic criteria for PMS and PMDD. Therefore, we compared the EQ-5D-5L scores in the luteal phase according to the severity of premenstrual symptoms. As only one patient had PMDD in this study, it was considered a PMD group along with a moderate-to-severe PMS group (Table 7). EQ-5D-5L scores were significantly lower in the PMD group for both Cycles 1 and 2.

Discussion

In a previous study, we examined the validity and reliability of the DRSP-J for assessing PMDs in clinical trial participants with premenstrual symptoms.¹⁶ This study was conducted on general participants with milder symptoms, and the results indicated adequate validity and reliability.

In the luteal and follicular phases, Cronbach's α of the total DRSP-J score showed high internal consistency, which has been similarly reported in clinical trial settings.¹⁶ This value was also similar to the original DRSP value in general participants reported previously.⁷

The test-retest reliability of the total luteal DRSP-J score in this study matched that reported in clinical trial settings.¹⁶ Conversely, the results of the follicular phase data were not as good as those of the luteal phase but were still rated "moderate to good" and are considered reliable enough. This indicates that DRSP-J is sufficiently reproducible for evaluating patients with few premenstrual symptoms.

Regarding PCA, as with the clinical trial participants, we were able to categorize the items into two factors: "Mood" and "Behavior/Physical." Most of the 21 items comprising the DRSP can be classified into these two categories; however, only 10b (out of control) and 11c (headache) differed from their original classifications. Focusing on the values of these two items, we can assume that both categories are likely related, as both "Mood" and "Behavior/Body" have values above 0.3. Among the DRSP, 1a through 4b, which comprise the negative mood score, are core symptoms that are considered particularly important. The fact that all of these items could be perfectly classified into the "Mood" category is satisfactory for the present study, which targeted the general population, the majority of whom have mild premenstrual symptoms.

The ACOG and DSM diagnostic criteria specify the diagnosis of PMS/PMDD based on a prospective two-cycle symptom diary. There was good consistency between these conventional diagnoses and those defined by the DRSP-J scores. This study was conducted on participants with premenstrual symptoms of various intensities; therefore, the results can be used for actual clinical diagnosis.

The EQ-5D-5L scores for the PMDs group in this study were 0.743 and 0.751 for Cycles 1 and 2, respectively. Considering that the standard value of the EQ-5D-5L for Japanese women aged 30–39 years is 0.944,³¹ the loss of quality-adjusted life years (QALYs) was 0.201 and 0.193 if luteal phase symptoms persisted throughout the menstrual cycle. Considering that these impairments disappeared during the follicular phase, the loss of QALYs due to PMDs would be less than half. An earlier study examining 66 patients with PMDD reported an EQ-5D-3L score 0.795 of the mean value for menstrual cycles.³² Therefore, they concluded that the loss of QALYs from PMDD was approximately 0.14 years. However, it should be noted that in this previous study, PMDD was not diagnosed using a diary of two menstrual cycles of prospective evaluation and was not strictly based on the DSM.

This study has some limitations. The first limitation was the relatively small number of participants (n = 113). These numbers are similar to those reported in previous studies targeting the general population. In the original English version, the number of participants was 27, and 126 in the Chinese version.^{7,10} Keeping daily records of DRSP is very cumbersome and challenging for participants with few premenstrual symptoms who lack the motivation to describe them. This may be the reason for the difficulty in collecting data from such participants. For exploratory factor analysis, a sample size of at least five times greater than the number of items is required, and the number of people in this study met this requirement. Second, the participants were not sampled from the general population but were participants in a clinical study, which may have overestimated the premenstrual symptoms. However, the purpose of this clinical study was not to study premenstrual symptoms themselves, and there was no advantage for participants to falsely report symptoms and presumably make a correct assessment. As this clinical study was conducted during the COVID-19 pandemic, it had the advantage of covering a wide range of ages in various regions throughout Japan owing to the online enrollment process. Third, there were a small number of cases of moderate to severe PMS and PMDD (ie, PMDs). Owing to the study design involving the general population, the number of PMDs was small (11). Therefore, the results of the QALYs provide limited information. To examine a large number of participants, it is necessary to use clinical trial data of participants treated for PMS/PMDD. Currently, we are collecting EQ-5D-5L data from ongoing clinical trials. The results of this study, which will be reported in the future, will provide more reliable information.

Conclusion

This study provides evidence for the validity and reliability of the DRSP-J as a measure of premenstrual symptoms in the general Japanese female population, including those with symptoms of varying intensity.

Data Sharing Statement

The data obtained in this study are available from the corresponding author upon request.

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Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of the data; took part in drafting the article and revising it critically for important intellectual content; agreed to submit it to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

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Gender Differences in Premenstrual Syndrome and Premenstrual Dysphoric Disorder Diagnosis and Treatment among Japanese Obstetricians and Gynecologists: A Cross-Sectional Study

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Premenstrual symptoms are characterized by unpleasant psychophysical symptoms that appear during the luteal phase before menstruation and interfere with a woman's quality of life. Premenstrual syndrome (PMS) is a pathological condition with premenstrual symptoms, of which premenstrual dysphoric disorder (PMDD) is a particularly severe psychological symptom. This study aimed to examine the gender differences in the diagnosis and treatment of PMS and PMDD among obstetricians and gynecologists (OB/ GYNs) in Japan. Data were obtained from the survey conducted by the Japanese Society of Obstetrics and Gynecology. We used data from 1,257 of the 1,265 OB/GYNs who are engaged in PMS/PMDD practice and reported their gender. Multivariate regression analysis adjusted for propensity scores was performed. Female OB/GYNs were more frequently engaged in treating patients with PMS/PMDD than males [odds ratio (OR) 1.74; 95% confidence interval (CI) 1.36-2.21]. With regard to the diagnostic methods, more female OB/GYNs selected the two-cycle symptom diary than males (OR 2.88; 95% CI 1.80-4.60). Regarding treatment, fewer female OB/GYNs selected selective serotonin reuptake inhibitors as their first-line drug (OR 0.39; 95% CI 0.17-0.89). Gender differences were found in the selection of PMS/ PMDD diagnosis and treatment methods among Japanese OB/GYNs.

Keywords: doctor-patient relationships; gender; oral contraceptive pills; prospective symptom diary; selective serotonin reuptake inhibitor Tohoku J. Exp. Med., 2023 October, **261** (2), 95-101. doi: 10.1620/tjem.2023.J059

Introduction

Premenstrual symptoms are characterized by unpleasant psychophysical symptoms that appear during the luteal phase before menstruation and interfere with a woman's quality of life (Yonkers and Simoni 2018; Takeda 2023). Premenstrual syndrome (PMS) is a pathological condition with premenstrual symptoms, of which, premenstrual dysphoric disorder (PMDD) is a particularly severe psychological symptom. The concept of premenstrual disorders (PMDs), which considers both conditions on a continuum, has recently been proposed (O'Brien et al. 2011).

The American College of Obstetricians and Gynecologists diagnostic criteria were used for PMS, and the Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria were used for PMDD (Hofmeister and Bodden 2016; American Psychiatric Association 2022). No specific biomarkers can be used for diagnosis; the only way to make a diagnosis is through subjective symptom assessment by patients. When symptoms are assessed retrospec-

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tively, there is an overestimation due to recall, and these diagnostic criteria require a prospective two-cycle diary (Rubinow and Roy-Byrne 1984; Henz et al. 2018). The Daily Record of Severity of Problems (DRSP) is a popular prospective symptom diary often used for research purposes such as clinical trials (Endicott et al. 2006; Green et al. 2017; Takeda et al. 2021). The DRSP requires 24 items to be recorded daily on a 6-point scale. However, maintaining a daily diary for prospective evaluation is burdensome for patients and is not widely used in actual clinical practice (Craner et al. 2014). Therefore, a gap exists between the diagnostic criteria and actual clinical practice.

Although selective serotonin reuptake inhibitors (SSRIs) and oral contraceptive pills (OCPs) are the standard pharmacotherapy (Green et al. 2017), Kampo (a traditional herbal medicine) therapy is widely used in Japan. According to the Japan Society of Obstetrics and Gynecology's (JSOG) treatment guidelines for PMS/ PMDD, treatment requires the prescription of OCPs, such as drospirenone-ethinylestradiol, Kampo medicines, and SSRIs, especially in the presence of psychiatric symptoms (Kawaguchi et al. 2019). Despite these recommendations, OCPs and SSRIs are not adequately prescribed for PMS/ PMDD in Japan and are not covered by national health insurance. Furthermore, both OCPs and SSRIs have a negative image in Japan (Ando et al. 2013; United Nations, Population Division 2022), making medication treatment difficult.

Under these circumstances, the Women's Health Care Academic Committee survey of the JSOG was conducted through a web survey in 2021, targeting physicians who are members of the society, to investigate the status and problems related to the diagnosis and treatment of PMS/PMDD (Yoshimi et al. 2023). The results revealed that only a few OB/GYNs that treat PMS/PMDD use prospective diaries or screening questionnaires for diagnosis, and that SSRIs are also used infrequently. The majority of this report involved descriptive statistics that were not examined in detail.

Regarding doctor-patient relationships, gender differences have been reported to affect the selection of medication and other aspects of treatment (Roter et al. 2002; Champagne-Langabeer and Hedges 2021). Female physicians have been reported to adhere more to guidelines (Kim et al. 2005; Baumhakel et al. 2009), and are more likely to be patient-centered in their practice (Krupat et al. 2000; Roter and Hall 2004). They spend more time treating patients directly to lower costs (Ganguli et al. 2020). For PMS/PMDD, since the patients were only women, there are two possible doctor-patient combinations: female/female and male/female. Previous studies have reported that more emotional and fewer analytical conversations occur in the female/female combination during medical treatment (Sandhu et al. 2009; Bertakis and Azari 2012). The female/ female combination has been reported to result in patientcentered conversations, raise patient satisfaction and trust, and even have a positive effect on cardiovascular risk treatment (Schmittdiel et al. 2009). Meanwhile, with respect to OB/GYNs, unlike primary care physicians, male physicians have been reported to engage in a talk that is more emotional with their patients (Roter et al. 1999, 2002). To the best of our knowledge, no study has investigated whether gender differences among physicians are related to the diagnosis and treatment of PMS/PMDD.

An earlier survey conducted by JSOG revealed several problems in the diagnosis and treatment of PMS/PMDD. The main problems were the very low use of prospective diaries and screening questionnaires for diagnosis and the infrequent use of SSRIs for treatment. To address these problems, factors that are not directly related to medical care, such as gender differences among physicians should be investigated. Therefore, this study aimed to reanalyze these problems in previous survey data and examine the impact of gender differences on the diagnosis and treatment of PMS/PMDD.

Materials and Methods

Ethics

In this study, we reanalyzed data from physicians who were members of the JSOG as part of a survey conducted by the Academic Committee on Women's Health Care, and all data generated or analyzed in this study were published in our previous report (Yoshimi et al. 2023). This study was conducted in accordance with the principles of the Declaration of Helsinki. The survey was anonymous and did not include personal information. Before completing the survey, all participants read a description of the study's purpose and agreed to participate by providing their online consent.

Participants

In the original study, a survey request email was sent to all JSOG members (16,732), and a web-based survey was conducted using Google Forms between the end of September and November 2021. A total of 1,312 respondents completed the questionnaire, of whom 1,265 were engaged in PMS/PMDD treatment (Fig. 1). Among them, we used data from those who answered that they were female or male (1,257). The characteristics of 47 respondents who were not engaged in PMS/PMDD treatment were shown in Supplementary Table S1.

Questionnaire

The details of the survey items have been described in a previous report (Yoshimi et al. 2023). Among them, this study utilized results from the following items. The first item of investigation concerned the basic attributes: their gender (male, female, or I don't want to answer), years of experience as a physician, specialist qualification, place of work (university hospital, general hospital, clinic, or other), and frequency of engagement in PMS/PMDD treatment [rarely (a few per year), occasionally (a few per month), daily (several per week)]. The second item of investigation



Fig. 1. Flow diagram of study participants. Among those engaged in the treatment of PMS/PMDD, those who reported their gender as female or male were analyzed. JSOG, Japanese Society of Obstetrics and

Gynecology; PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder. concerned diagnostic methods: using a screening questionnaire [such as the Premenstrual Symptoms Screening Tool (Steiner et al. 2003), PMDD scale (Miyaoka et al. 2011), and Premenstrual Symptoms Questionnaire (Takeda et al. 2006, 2020)] and keeping a two-cycle symptom diary. The third item of investigation concerned pharmacotherapy: first-line drugs [OCPs, SSRI/SNRI (luteal phase only and continuous administration), and Kampo medicines], and first-line OCPs [norethisterone-ethinylestradiol 20/35 μg, cyclic dosing (LUNABELL[®] tablets LD/ULD or FREWELL[®] Combination TAB. LD/ULD MOCHIDA), drospirenone-ethinylestradiol, cyclic dosing (YAZ[®] combi-

nation tablets), drospirenone-ethinylestradiol, extended dosing (Yaz Flex[®] combination tablets)]. Regarding first-line drugs, data pertaining to OCPs and SSRIs were extracted as they are considered standard treatments worldwide, and Kampo medicines-related data were extracted as they are the second most common first-line choice in Japan. As first-line drugs for OCP, these drugs were extracted from the original study because of their high selectivity.

Statistical analysis

Proportions were calculated for the categorical variables. The baseline characteristics were compared between the female and male groups using the Wilcoxon signed-rank test and Pearson's chi-square test, as appropriate.

We used a propensity score to adjust for baseline differences. In the analysis of gender differences in OB/GYNs who frequently engaged in PMS/PMDD practice, a propensity score was calculated using logistic regression based on the number of years since obtaining medical licenses and the OB/GYN specialty status. In the analysis of diagnosis and drug therapy selection, propensity scores were calculated using logistic regression based on the number of years since obtaining medical licenses, OB/GYN specialty status, and working hospitals. Multivariate logistic regression analysis adjusted for propensity scores was used to examine gender differences in the frequency of practice engagement and diagnostic and treatment methods. The odds ratio for female OB/GYNs to males was calculated.

Statistical analyses were performed using JMP 16.0.0 (SAS, Cary, NC, USA). Statistical significance was set at p < 0.05.

Results

The overall basic characteristics and gender-related differences are presented in Table 1. The post-licensure years for medical practitioners were significantly lower among female OB/GYNs than among male OB/GYNs. The percentage of OB/GYN specialists was higher among males than females. Gender differences were observed in the types of medical institutions in which they worked. Patients with PMS/PMDD were more frequently treated by female OB/GYNs than male OB/GYNs.

Next, we examined gender differences in OB/GYNs who were frequently treated PMS/PMDD (Table 2). In the entire analysis, the odds were found to be predominantly higher for female OB/GYNs than for males. As gender differences were also observed in the form of practice, analyses stratified by pattern were conducted. When analyzed separately by place of work, the analysis demonstrated that female OB/GYNs treated PMS/PMDD significantly more frequently than male OB/GYNs did, except among hospitalists.

Gender differences in the diagnostic methods were similarly examined using screening questionnaires and twocycle symptom diaries (Table 3). There were no gender differences in the use of screening tools. However, female OB/GYNs used two-cycle symptom diaries significantly more than male OB/GYNs did.

In addition, gender differences in treatment selection were examined (Table 4). Regarding first-line drugs, there were no differences in the use of OCPs and Kampo medicines. In contrast, significantly fewer female OB/GYNs prescribed SSRIs than their male counterparts. Regarding first-line OCPs, we examined the drospirenone and norethisterone formulations, which are the most frequently prescribed in Japan. There were no gender differences in the use of drospirenone-ethinylestradiol (extended dosing), drospirenone-ethinylestradiol (cyclic dosing), and norethisterone-ethinylestradiol 20/35 μ g (cyclic dosing).

Discussion

The data demonstrated that the post-licensure period among female OB/GYNs was significantly shorter than it was among their male counterparts. This finding is consistent with the annual increase in the proportion of female doctors in Japan (Ministry of Health, Labour and Welfare 2020). Notably, this phenomenon has been observed not

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Table 1. Characteristics of study participants (n = 1,257).

	Total (n = 1,257)	Female $(n = 638)$	Male (n = 619)	р
Post-licensure period (years) for medical practitioners, number (%)				< 0.001*.a
period < 10 years	116 (9.2)	83 (13.0)	33 (5.3)	
$10 \le \text{period} < 20 \text{ years}$	321 (25.5)	211 (33.1)	110 (17.8)	
$20 \le \text{period} < 30 \text{ years}$	373 (29.7)	214 (33.5)	159 (25.7)	
$30 \le \text{period} < 40 \text{ years}$	307 (24.4)	101 (15.8)	206 (33.3)	
$40 \le \text{period} < 50 \text{ years}$	127 (10.1)	23 (3.6)	104 (16.8)	
50 years \leq period	13 (1.0)	6 (0.9)	7 (1.1)	
OB/GYN specialist, number (%)	1,203 (95.7)	601 (94.2)	602 (97.2)	0.008* ^{,b}
Working hospital, number (%)				< 0.001* ^{,b}
University hospital	271 (21.6)	119 (18.7)	152 (24.6)	
General hospital	520 (41.4)	305 (47.8)	215 (34.7)	
Clinic	404 (32.1)	170 (26.7)	234 (37.8)	
Others	62 (4.9)	44 (6.9)	18 (2.9)	
Engaged in PMS/PMDD treatment, number (%)				$< 0.001^{*,a}$
Rarely (a few per year)	228 (18.1)	99 (15.5)	129 (20.8)	
Occasionally (a few per month)	487 (38.7)	234 (36.7)	253 (40.9)	
Daily (several per week)	542 (43.1)	305 (47.8)	237 (38.3)	

*p < 0.05; "Wilcoxon signed-rank test, "Pearson's chi-square test."

OB/GYN, obstetrics and gynecology; PMS/PMDD, premenstrual syndrome and premenstrual dysphoric disorder.

only in Japan but also in the U.S. and Canada (Buys 2014; Georgakopoulos et al. 2022). Under these circumstances, the examination of factors not directly related to medicine, such as gender differences in physicians, may provide a reference for future measures.

During the period between becoming a physician and acquiring a medical specialty, the focus of clinical practice is on inpatient units; PMS/PMDD care mostly involves outpatient care. Among those that are not engaged in PMS/ PMDD practice in this survey, the highest percentage (34.0%) had been licensed as a physician for less than 10 years (Supplementary Table S1). In this study, gender differences were observed in physician history and medical specialty status, which required adjustment for these factors in the analysis. After making these adjustments, female OB/GYNs more frequently treated PMS/PMDD than their male counterparts. Stratified analysis by practice type revealed gender differences, except among hospitalists. As for general practitioners, patients were free to choose their preferred clinic, and patients who visit a clinic for PMS/ PMDD may choose a clinic based on doctor's gender. In university hospitals, the practice is specialized, and more female OB/GYNs may be interested in specializing in PMS/ PMDD care. A survey pertaining to patient consultations for PMS/PMDD would provide some insight into the reasons for these findings.

The problem with the diagnostic method is that a prospective two-cycle evaluation is required, in line with the diagnostic criteria and guidelines (Hofmeister and Bodden 2016; Green et al. 2017; American Psychiatric Association 2022). However, because of the complexity of the evaluation, it is not often used in actual practice. The discrepancy between actual clinical practice and diagnostic criteria is not a problem exclusive to Japan-it was 11.5% in a previous U.S. study and 8.4% in the study from where we extracted data for this study (Craner et al. 2014; Yoshimi et al. 2023). Screening questionnaires are infrequently used in Japan (10.3%), similar to the prospective two-cycle evaluation; however, no gender differences have been observed. Using a prospective questionnaire was found to be more complicated than using a screening questionnaire for both the examining physician and the patient. In addition, female OB/GYNs are presumed to be more patient-centered while using the prospective evaluation questionnaire. This is consistent with findings in previous studies in which female physicians were more patient-centered and practiced with a higher degree of empathy (Schmittdiel et al. 2009; Gleichgerrcht and Decety 2013; Chaitoff et al. 2017). This practice trend is advantageous for the treatment of PMS/ PMDD, and future studies on gender differences in the effectiveness of treatment are warranted.

Regarding first-line treatment selection, no gender differences were found for the most commonly used medications, such as OCPs and Kampo medicines. In contrast, fewer female OB/GYNs selected SSRIs than their male counterparts. SSRIs are highly recommended for the treatment of PMDs because of their reliable evidence-based medicine (EBM) efficacy (Marjoribanks et al. 2013;

	OR (95% CI)	р
Total $(n = 1,257)$	1.74 (1.36-2.21)	< 0.001*
University physician $(n = 271)$	2.34 (1.20-4.59)	0.013*
General hospitalist ($n = 520$)	1.44 (0.96-2.17)	0.076
General practitioner $(n = 404)$	2.13 (1.31-3.45)	0.002*
Others $(n = 62)$	9.11 (1.8-70.40)	0.005*

Table 2. Gender differences of physicians who frequently treat premenstrual syndrome and premenstrual dysphoric disorder (PMS/PMDD) by place of work.

*p < 0.05; adjusted for years since obtaining a medical license, OB/GYN specialty status. The OR for female OB/GYNs to males was calculated.

OR, odds ratio; CI, confidence interval; OB/GYN, obstetrics and gynecology.

Т	al	bl	e 3	3.	D	iagnostic	method	l se	lection	and	gend	ler (lif	ference	es.

	OR (95% CI)	р
Screening questionnaire ($n = 128$)	0.99 (0.66-1.47)	0.953
Two-cycle symptom diary $(n = 107)$	2.88 (1.80-4.60)	< 0.001*

*p < 0.05; adjusted for years since obtaining a medical license, OB/GYN specialty status, and working hospital. The OR for female OB/GYNs to males was calculated.

OR, odds ratio; CI, confidence interval; OB/GYN, obstetrics and gynecology.

	OR (95% CI)	р
First-line drugs		
OCPs (n = 966)	0.90 (0.67-1.20)	0.474
SSRIs $(n = 32)$	0.39 (0.17-0.89)	0.025*
Kampo medicines $(n = 243)$	1.19 (0.87-1.62)	0.267
First-line OCPs		
DRSP+EE (E) ($n = 535$)	1.20 (0.94-1.54)	0.139
DRSP+EE (C) (n = 291)	0.99 (0.74-1.32)	0.959
DRSP+EE (C) or DRSP+EE (E) $(n = 826)$	1.22 (0.94-1.57)	0.135
NET+EE (C) (n = 297)	0.87 (0.66-1.16)	0.350

Table 4. Gender differences in treatment choice.

*p < 0.05; adjusted for years since obtaining a medical license, OB/GYN specialty status, and working hospital. The OR for female OB/GYNs to males was calculated.

OR, odds ratio; CI, confidence interval; OCPs, oral contraceptives; SSRIs, selective serotonin reuptake inhibitors; DRSP+EE (E), drospirenone-ethinylestradiol (extended dosing); DRSP+EE (C), drospirenone-ethinylestradiol (cyclic dosing); NET+EE (C), norethisterone-ethinylestradiol 20/35 µg (cyclic dosing).

Hofmeister and Bodden 2016; Ismaili et al. 2016; Green et al. 2017). However, the limited selection of SSRIs in Japan seems to be the most significant problem in the treatment of PMDs. Previous studies revealed that female physicians tend to follow guidelines more strictly than male physicians (Kim et al. 2005; Baumhakel et al. 2009). When applied to the present results, this was true in the case of diagnosis, but unexpectedly, untrue in the case of treatment. In Japan, there is a strong stigma surrounding psychiatric disorders, which has presumably led to SSRIs and antidepressants being viewed negatively (Ando et al. 2013; Zhang et al. 2019). Female OB/GYNs are likely not choosing SSRIs because of their patients' negative intentions toward these drugs.

To the best of our knowledge, this study is the first to

examine gender differences among OB/GYNs in the diagnosis and treatment of PMS/PMDD. However, it has some limitations. First, the study from which we obtained the data had a poor response rate of 7.8% and, therefore, may have predominantly included practitioners who are focused on PMS/PMDD treatment. To understand the actual medical practice, it would be beneficial to conduct a study examining the patient's perspective, as data from clinicians alone would be incomplete. Second, this study was limited to OB/GYNs, a specialty that has many female physicians; more male physicians are known to be psychiatrists. We have already conducted a similar survey of psychiatrists, and these data can be used to examine gender differences among practitioners. Third, the original data were collected only in Japan. In Japan, PMS/PMDD treatment is mainly provided by OB/GYNs, and psychiatrists and general family physicians appear to have little or no involvement. The situation in Japan seems unique, given that in Europe and the U.S., general family physicians are responsible for a significant portion of PMS/PMDD care (Craner et al. 2014; Hofmeister and Bodden 2016; Green et al. 2017). Notably, past reports indicate a different patient-physician relationship for OB/GYNs than for general family physicians (Roter et al. 2002). It would be interesting to conduct a survey in the U.S. and Europe and compare it with this study's findings. Finally, caution must be exercised when interpreting these results as these may be affected by gender stereotypes in the medical community (Mast and Kadji 2018). However, regardless of the cause, it is important to recognize that there are differences in diagnosis and treatment due to gender differences among physicians.

This study revealed gender differences among OB/ GYNs in the diagnosis and treatment of PMS and PMDD. Patients should be treated based on EBM. Therefore, we believe that the results of this study will be useful in improving PMS/PMDD treatment in Japan.

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Conflict of Interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE



Current status and problems in the diagnosis and treatment of premenstrual syndrome and premenstrual dysphoric disorder from the perspective of obstetricians and gynecologists in Japan

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Abstract

Aim: To investigate the current status and problems in the diagnosis and treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) from the perspective of obstetricians and gynecologists (OB/GYNs) in Japan, the Japanese Society of Obstetrics and Gynecology (JSOG) conducted a national-wide survey.

Methods: An email survey was sent to all JSOG members (16 732) and a webbased survey was conducted using a Google form between September and November 2021. The current status and problems in PMS/PMDD diagnosis and treatment were surveyed in this cross-sectional study.

Results: In total, 1312 respondents (7.8% of all JSOG members) completed the questionnaire. In terms of diagnoses and treatment, OB/GYN was preferred over psychiatrist for PMS (91.4% vs. 45%); however, no differences were noted for PMDD (76.1% vs. 73.7%). A total of 1267 (96.6%) respondents engaged in routine PMS/PMDD treatment. Regarding the general diagnosis procedure, 84.4% respondents answered "only a vague medical interview," 8.4% kept a two-cycle symptom diary, and 10.3% used a screening questionnaire. The most commonly used medication was oral contraceptive pills (OCPs) (98.1%), followed by the Kampo, traditional Japanese herbal medicines, Kamishoyosan (73.6%). Concerning first-line drugs for treatment, OCPs were the most common (76.8%), followed by Kampo medicine (19.5%); selective serotonin reuptake inhibitors (SSRIs) were less frequently used (2.6%). Regarding first-line drugs among OCPs, 65.1% respondents reported drospirenone-ethinylestradriol use.

Conclusions: This study indicates that only a few OB/GYNs practicing PMS/PMDD in Japan use a prospective diary, which is an essential diagnostic criterion for PMS/PMDD. Regarding treatment, SSRIs were used less frequently.

KEYWORDS

diagnostic criteria, oral contraceptive pills, premenstrual dysphoric disorder, premenstrual syndrome, selective serotonin reuptake inhibitors

INTRODUCTION

Premenstrual symptoms are characterized by emotional, behavioral, and physical symptoms that occur during the late luteal phase of the menstrual cycle and terminate after menstruation onset.¹ Epidemiological surveys have estimated that the frequency of premenstrual symptoms is relatively high (80%–90%).² Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) is classified in gynecology and psychiatry, respectively, as a

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pathological condition of premenstrual symptoms.³ The prevalence of PMS in menstruating women is 20%–30%.¹ Further, 1.2%–6.4% women of reproductive age exhibit severe psychotic premenstrual symptoms that interfere with daily life as PMDD.¹ Premenstrual disorders (PMDs) include both PMS and PMDD. The International Society for Premenstrual Disorders has proposed to group both PMS and PMDD together as a continuum within the framework of PMDs.⁴

Since the definition of the disease concept has not been well established, there is a problem in Japan regarding which department should see the patient. For example, it is unclear whether obstetricians and gynecologists (OB/GYNs) should see the patient if the symptoms are mainly physical or psychiatrists should see the patient if the symptoms are mainly psychological. There are no biochemical disease markers; therefore, the diagnosis must rely on subjective symptoms. Because symptoms are confined to the premenstrual period, patients tend to overestimate their symptoms.^{5,6} To prevent this, the cyclicity of symptoms (symptom-free periods during the follicular phase) and reproducibility (presence of symptoms in most menstrual cycles) need to be checked for accuracy. Therefore, the diagnostic criteria for PMS according to the American College of Obstetricians and Gynecologists (ACOG) and PMDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 require a prospective two-cycle diary.^{7,8} As a prospective symptom diary, the Daily Record of Severity of Problems is a questionnaire comprising 24 symptoms answered in six stages and is often used for research purposes such as clinical trials worldwide.^{9,10} Prospective evaluation is helpful for accurate evaluation, but it is burdensome for patients. Therefore, it is questionable whether this is practiced in daily clinical practice. A survey of gynecologists and family physicians in the United States (US) in 2012 found that only 11.5% routinely performed a prospective two-cycle menstrual cycle assessment,¹¹ showing that there is a gap between research and actual clinical practice.

To compensate for the inconvenience of a forwardlooking daily chart, the use of screening tools for PMS/PMDD is helpful for an efficient examination. In a survey of family physicians and gynecologists in the US, 23.0% physicians used screening tools. Among them, the Premenstrual Symptoms Screening Tool (PSST) is commonly used globally.¹² The PSST is a self-rated retrospective questionnaire that is completed during clinical consultation with the patient. The PMDD scale in Japanese is essentially the Japanese version of PSST.¹³ In contrast, the Premenstrual Symptoms Questionairre (PSQ) is a screening tool developed in Japan independently of the PSST.¹⁴ The PSQ has been confirmed to be as effective as the PMDD scale.¹⁵

Standard pharmacological treatments for PMS/PMDD include the use of selective serotonin reuptake inhibitors (SSRIs) and oral contraceptive pills (OCPs). The treatment

guidelines of the Japanese Society of Obstetrics and Gynecology (JSOG) state that treatment should include counseling, lifestyle guidance, exercise therapy, prescription of OCPs such as drospirenone-ethinylestradriol, and administration of diuretics and Kampo medicines (traditional Japanese herbal medicines).¹⁶ If psychiatric symptoms are predominant, the patient should be treated with SSRIs. Despite these recommendations, OCPs and SSRIs are not indicated and not insured for PMS/PMDD in Japan. In addition to health care issues, there are several problems with both drugs. OCP use and awareness are low in Japan; approximately 5% women of reproductive age take OCPs, of which 0.9% take OCPs purely for contraceptive purposes.¹⁷ In Japan, there is a strong negative image of mental illness, and it is assumed that due to this, there is also a strong negative image of SSRIs, antidepressants.^{18,19} Moreover, it is difficult to administer SSRIs to minors as it increases the risk of suicide attempts in patients aged ≤24 years, according to its package insert.^{20,21}

Various issues are assumed to exist in PMS/PMDD diagnosis and treatment in Japan, but the actual status of these issues is unclear. Therefore, we surveyed the current status of PMS/PMDD diagnosis and treatment and the associated problems among JSOG members.

METHODS

Ethics

This study was conducted as a Women's Health Care Academic Committee survey of the JSOG, targeting physicians who are members of the society. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The survey was anonymous and did not include any personal information. Before completing the survey, all participants read the description of the study's purpose and agreed to participate in the study by providing online consent.

Participants

An email survey was sent to all JSOG members (16 732 people) and a web-based survey was conducted using a Google form between the end of September and the end of November in 2021. The questionnaire was completed by 1312 respondents, and those who engaged in routine PMS/PMDD treatment provided answers to questions about their routine PMS/PMDD diagnosis and treatment (Figure 1).

Questionnaire

We asked questions on the number of years they have been licensed as a doctor, their sex, their specialty **FIGURE 1** Flow diagram of study participants. Those treating PMS/PMDD were asked about diagnosis and treatment. JSOG, Japanese Society of Obstetrics and Gynecology; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.



(OB/GYN, psychiatry, internal medicine, or others), their specialist qualification, and their type of work (university hospital, general hospital or clinic). These questionnaires allowed us to have multiple answers. In addition, we surveyed the knowledge about the disease name, diagnosis, treatment, and practice; which department (OB/GYN, psychiatry, internal medicine, others) should diagnose and treat PMS and PMDD; and frequency of engagement. Those engaged in PMS/PMDD practice only were asked about the generic diagnosis procedure for PMS/PMDD (only vague interviews such as pre-menstrual physical and mental health problems, interview based on the ACOG or DSM-5 diagnostic criteria, keeping a one- or two-cycle symptom diary, using screening questionnaire [such as the PSST, PMDD scale, and PSQ], measurement of basal body temperature, and other free entry fields), which pharmacotherapies were most commonly used to treat PMS/PMDD (OCPs, hormone replacement therapy [HRT], levonorgestrel intra uterine system [LNG-IUS], GnRH-analogue [antagonist or agonist], dienogest, SSRI/SNRI [only luteal phase dosing and continuous administration], other antidepressants, anti-anxiety agents, sleep-inducing drugs, atypical [typical] antipsychotics, Kampo medicine [Tokisvakuvakusan, Kamishoyosan, Keishibukuryogan, Yokukansan, or others], chasteberry, vitamin B6, and other drugs and supplements), which non-pharmacotherapies were frequently used (lifestyle guidance, cognitive behavioral therapy, symptom diary observation method, counseling, acupuncture and moxibustion, exercise [including yoga, pilates, meditation and mindfulness], or others), which first-line drugs were used (OCPs, SSRI/SNRI [luteal phase only and continuous administration], and Kampo medicines), and which first-line OCPs were used (norethisterone-ethinylestradiol 20/35 µg, cyclic dosing [LUNABELL® tablets LD/ULD

FREWELL[®] or Combination Table LD/ULD MOCHIDA], drospirenone-ethinylestradiol, cyclic dosing [YAZ[®] combination tablets], drospirenone-ethinylestradiol, extended dosing [Yaz Flex[®] combination tablets], levonorgestrel-ethinylestradiol, cyclic dosing [Jemina® tablets], levonorgestrel- ethinylestradiol, extended dosing [Jemina® tablets], desogestrel-ethinylestradiol, cyclic dosing [MARVELON[®] 21, 28 Tablets or Favoir[®] tablets], levonorgestrel-ethinylestradiol, triphasic cyclic dosing [Triquilar® tablets 21/28, ANGE® 21,28 TABLETS or Labellefille[®] tablets], norethisterone-ethinylestradiol, cyclic dosing [Synphase T[®] 28 Tablets] or not used OCPs. SNRIs such as venlafaxine have also proven therapeutic efficacy for PMDD).^{22,23} In the American Academy of Family Physicians' guidelines for the treatment of PMS/PMDD, it is referred to as the second drug after SSRIs.²⁴ Therefore, in this survey, they were listed together as SSRI/ SNRI as therapeutic agents. Multiple answers were allowed for the question on which department should diagnose and treat PMS and PMDD and those on treatment and diagnosis.

Statistical analysis

Statistical analysis was performed using JMP 16.0.0 (SAS, Cary). Statistical significance was set at p < 0.05. Data on the proportion of those using a prospective twocycle diary or using a screening tool in their diagnosis were compared to the 2012 US data.¹¹ We used hypothesis testing for the difference in the population proportions and the χ^2 test. The effect size was measured using Cramer's V calculated with BellCurve for Excel (Social Survey Research Information Co., Ltd.). The effect sizes

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TABLE 1 Characteristics of study participants (n = 1312).

	n (%)
Post-licensure period (years) for medical pr	actitioners
<10	132 (10.1)
≥10 and <20	333 (25.4)
≥20 and <30	387 (29.5)
≥30 and <40	318 (24.2)
≥40 and <50	128 (9.8)
≥50	14 (1.1)
Gender	
Male	646 (49.2)
Female	658 (50.2)
No answer	8 (0.6)
Physician type	
OB/GYN	1307 (99.6)
Psychiatry	10 (0.8)
Internal medicine	29 (2.2)
Others	20 (1.5)
Specialist qualification	
OB/GYN specialist	1244 (94.8)
Psychiatry specialist	2 (0.2)
Internal medicine specialist	6 (0.5)
Another specialist	61 (4.6)
Nothing	64 (4.9)
Working hospital	
University hospital	298 (22.7)
General hospital	539 (41.1)
Clinic	409 (31.2)
Others	66 (5.0)

Abbreviations: OB/GYN, obstetrics and gynecology; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.

of 0.10, 0.30, and 0.50 were judged as small, medium, and large, respectively.²⁵

RESULTS

The questionnaire was completed by 1312 respondents (7.8% of all JSOG members [16 732]) (Figure 1). The background characteristics of the participants are described in Table 1. The sex ratio was 50:50, and most respondents (99.6%) specialized in OB/GYN. Among them, 94.8% had OB/GYN specialist qualifications—63% worked in university and general hospital facilities and 31% worked in clinics.

Table 2 shows the degree of involvement and awareness regarding PMS/PMDD care. A total of 1191 (90.8%) respondents were "knowledgeable and involved in diagnosis and treatment." In terms of diagnoses and treatment, OB/GYN was preferred over psychiatry for PMS (91.4% vs. 45%); however, no differences were **TABLE 2** Knowledgeable about and engagement in PMS/PMDD (n = 1312).

	n (%)
Knowledgeable about PMS/PMDD, diagnosis a	and treatment
No	15 (1.1)
Knowledge of name only	31 (2.4)
Knowledge of diagnosis and treatment only	75 (5.7)
Practice on diagnosis and treatment	1191 (90.8)
Departments that diagnose and treat PMS (mult	tiple answers allowed)
Gynecology	1199 (91.4)
Psychiatry	459 (35.0)
Internal medicine	79 (6.0)
Either	145 (11.1)
Departments that diagnose and treat PMDD (m allowed)	ultiple answers
Gynecology	998 (76.1)
Psychiatry	967 (73.7)
Internal medicine	970 (73.9)
Either	155 (11.8)
Engaged in PMS/PMDD treatment	
No	45 (3.4)
Rarely (a few per year)	229 (17.5)
Occasionally (a few per month)	491 (37.4)
Daily (several per week)	547 (41.7)

Abbreviations: PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.

noted for PMDD (76.1% vs. 73.7%). In total, 1267 (96.6%) participants were currently engaged in routine PMS/PMDD treatment; however, 45 (3.4%) participants were not engaged (Figure 1).

The results regarding the diagnosis and treatment of PMS/PMDD are shown in Table 3. Regarding the generic diagnostic procedures, 84.4% answered "only a vague medical interview," and a few respondents reported assessment with a symptom diary (7.1% for one cycle and 8.4% for two cycles). Only 8.4% respondents kept a two-cycle symptom diary, as indicated by the ACOG and DSM diagnostic criteria, which is not significantly different compared to the US data (11.5%) (p = 0.328, Cramer's V = 0.027, χ^2 test). Only 10.3% answered they used a screening questionnaire, significantly less than that in the US data (23.0%) (p < 0.001, Cramer's V = 0.100, χ^2 test).¹¹

OCPs (98.1%) were the most commonly used drug for generic therapeutic medication, followed by Kampo medicine (*Kamishoyosan* [73.6%], *Tokisyakuyakusan* [53.3%], and *Yokukansan* [51.5%]). For SSRIs, continuous dosing and luteal phase administration were reported by 39.2% and 16.9% respondents, respectively.

Lifestyle guidance (75.0%) was the most common non-pharmacological treatment, followed by counseling (27.2%), exercise guidance (16.3%), and the symptom diary observation method (14.8%).

TABLE 3	Diagnosis and treatment	for PMS/PMDD (a	n = 1267)
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	n (%)
Generic diagnosis procedure for PMS/PMDD (multiple allowed)	answers
Interview only vague pre-menstrual health problems	1069 (84.4)
Interview based on ACOG's diagnostic criteria	237 (18.7)
Interview based DSM-5	89 (7.0)
Rating for one cycle	90 (7.1)
Rating for two cycles	107 (8.4)
Screening measure/questionnaire (e.g., PSST or PSQ)	131 (10.3)
Measurement of basal body temperature	178 (14.0)
Others	14 (1.1)
Generic therapeutic medication for PMS/PMDD (multip allowed)	ole answers
OCPs	1243 (98.1)
HRT	241 (19.0)
LNG-IUS	170 (13.4)
GnRH-analogue	64 (5.1)
SSRI/SNRI (continuous dosing)	497 (39.2)
SSRI/SNRI (luteal phase dosing)	214 (16.9)
Other antidepressants	74 (5.8)
Anti-anxiety agent	360 (28.4)
Sleep inducing drug	252 (19.9)
Atypical (typical) antipsychotics	11 (0.9)
Kampo medicine, Tokisyakuyakusan	675 (53.3)
Kampo medicine, Kamishoyosan	933 (73.6)
Kampo medicine, Keishibukuryogan	463 (36.5)
Kampo medicine, Yokukansan	653 (51.5)
Kampo medicine, others	324 (25.6)
Chasteberry	18 (1.4)
Vitamin B6	34 (2.7)
Other drugs and supplements	64 (5.1)
Generic non-pharmacological treatment for PMS/PMDI answers allowed)) (multiple
Lifestyle Guidance	950 (75.0)
Cognitive-behavioral therapy	179 (14.1)
Symptom Diary Observation Method	188 (14.8)
Counseling	344 (27.2)
Exercise	206 (16.3)
Acupuncture and moxibustion	17 (1.3)
Others	10 (0.8)
Nothing	44 (3.5)
First-line medication	
OCPs	973 (76.8)
SSRI (luteal phase dosing)	21 (1.7)
SSRI (continuous dosing)	12 (0.9)
Kampo medicine	247 (19.5)
Depends on the case	15 (1.2)
First-line medication of OCPs for PMS/PMDD	
Norethisterone-ethinylestradiol 20/35 µg (cyclic dosing)	311 (23.7)

(Continues)

TABLE 3 (Continued)

	n (%)
Drospirenone-ethinylestradiol (cyclic dosing)	298 (22.7)
Drospirenone-ethinylestradiol (extended dosing)	556 (42.4)
Levonorgestrel-ethinylestradiol (cyclic dosing)	27 (2.1)
Levonorgestrel-ethinylestradiol (extended dosing)	62 (4.7)
Desogestrel-ethinylestradiol (cyclic dosing)	23 (1.8)
Levonorgestrel-ethinylestradiol triphasic (cyclic dosing)	14 (1.1)
Norethisterone-ethinylestradiol (extended dosing)	0 (0)
Not use	17 (1.3)
Not specialist in OB/GYN	4(0.3)

Abbreviations: ACOG, the American College of Obstetricians and Gynecologists; DSM-5, the Diagnostic and Statistical Manual of Mental Disorders-5; GnRHanalogue, gonadotropin-releasing hormone agonists and antagonists; HRT, hormone replacement therapy; LNG-IUS, levonorgestrel intrauterine system; OCPs, oral contraceptives; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; PSQ, The Premenstrual Symptoms Questionnaire; PSST, the Premenstrual Symptoms Screening Tool; SNRI, serotonin noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Regarding the first-line drugs for PMS/PMDD treatment, OCPs were the most commonly prescribed (76.8%), followed by Kampo medicine (19.5%); SSRIs were less frequently prescribed (2.6%; 0.9% for continuous administration and 1.7% for luteal phase administration).

Regarding first-line drugs among OCPs preparations in PMS/PMDD treatment, drospirenone-ethinylestradriol (65.1%; 22.7% for cyclic dosing and 42.4% for extended dosing) was the first choice.

DISCUSSION

This study aimed to show the current status of diagnosis and treatment for PMS/PMDD in Japanese OB/GYNs. In the Ministry of Economy, Trade and Industry, the issue of labor losses due to women's health issues costs approximately 490 billion yen per year.²⁶ In particular, menstrual symptoms in mature women are an important issue. To address these problems, OB/GYNs are expected to play a significant role. Despite the fact that the majority of OB/GYNs who responded to this survey indicated that they were knowledgeable about PMS/PMDD and are engaged in their practice, their treatment and diagnostic options include several problems from an evidence-based medicine (EBM) perspective.

Regarding which department is responsible for treating PMS and PMDD, 91% think that OB/GYNs should treat PMS and 76% think that OB/GYNs should treat PMDD. Considering that JSOG guidelines recommend a psychiatry referral when psychiatric symptoms are strong, this value for PMDD was unexpectedly high. This result suggests that survey respondents are likely to be biased toward OB/GYNs who are dedicated to treating PMS/PMDD.

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In response to the question on how to diagnose, only 8.4% respondents performed a two-cycle prospective menstrual cycle assessment according to the ACOG guidelines or DSM-V as a diagnosis method. This result is similar to the 2012 US study data (11.5%).¹¹ Diarizing with prospective assessment such as DRSP is essential for research purposes, but the diagnostic method of symptom diarizing is inconsistent with clinical practice.9 Most participants (84.4%) were diagnosed based on a vague medical history taking of PMS/PMDD, whereas 18.7% and 7.0% were interviewed based on the ACOG and DSM-5 diagnostic criteria, respectively. Therefore, the accuracy of the PMS/PMDD diagnosis is questionable, and education for OB/GYNs regarding PMS/PMDD diagnosis is needed. Although the screening methods such as the PSST and PSQ do not allow for a rigorous diagnosis because they are not a prospective evaluation, they may prove useful as they can evaluate the severity of premenstrual symptoms at the first visit according to the DSM PMDD criteria. In the future, it will be necessary to establish clinically accurate and simple diagnostic methods and disease markers that can quantitatively measure the disease severity.

Although 98% of OB/GYNs choose to treat with OCPs, acceptance is poor in the general population due to fears of OCPs' side effects.²⁷ Regarding drospirenone-containing OCPs, literature on their therapeutic efficacy for PMDD exists.^{28–30} With regard to PMS, solid evidence of efficacy is lacking, but Japanese and UK guidelines recommend dosing these drugs for PMS.^{10,16} Therefore, it is correct that 65.1% of Japanese OB/GYNs choose this drug. In other words, the remaining 34.9% make treatment choices that are not based on the guidelines.^{10,16}

Additionally, there are limitations in addressing PMDD with OCPs alone, and the use of SSRIs is necessary. SSRIs are considered the first line of treatment.^{10,31} However, relatively few OB/GYNs in this study opted for SSRIs for treatment (persistent 39.2%; luteal phase: 16.9%). Despite the recommendation in the JSOG guide-lines, OB/GYNs in Japan seem to be unfamiliar with the use of SSRIs. Education for OB/GYNs on the use of SSRIs and collaboration with psychiatrists is considered necessary.

One notable treatment aspect is the high selection of Japanese herbal medicine (Kampo) use. Although Kampo are traditional drugs in Japan, the drugs used can be industrial products similar to Western medicines, and high quality is assured. Kampo is also used universally in non-obstetrics and gynecology departments and is well accepted by patients.^{32,33} Due to the poor acceptance of OCPs and SSRIs among the general population in Japan, Kampo preparations are probably the preferred choice. Of these, *Kamishoyosan* is the most frequently selected, used by 73.6% OB/GYNs for treatment. In a study using a mouse menopausal depression model, *Kamishoyosan* showed anti-stress effects mediated by serotonin signaling.³⁴ It may be effective in PMS/PMDD

considering that serotonin abnormalities are an etiologic factor of PMS/PMDD. Future studies with double-blind comparative trials are needed to verify its efficacy in PMS/PMDD.

It should be emphasized that this is the first study on PMS/PMDD diagnosis and treatment in Japan, but it also has some limitations. First, there may be a bias as only 7.8% of all JOGR members responded to this survey. The reasons for only some participants answering the survey may vary according to their clinical practice and interest in PMS/PMDD. The fact that 96.6% participants engaged in PMS/PMDD treatment is a very high percentage judging from the experience in the field of obstetric and gynecological treatment in Japan. It can be inferred that the respondents to this survey should be taken as data from those who are actively involved in PMS/PMDD treatment. Second, concerning the study population, we excluded other types of health professionals who might be involved in PMS/PMDD assessment, such as psychiatrists and family physicians. We plan to investigate psychiatry as a subset in the future as well. Further, as we only looked at Japan, it is important to conduct future surveys of clinical practice for PMS/PMDD in other countries to evaluate whether there are any reports of better practices in other regions. Finally, regarding the assessment method, this study only used self-reported data. There are no data to verify the frequency with which doctors in this study encountered women with PMDD or what assessment method they used. Doctors might have under- or over-reported this information. As the study relied on retrospective reports of typical practice, doctors' recollections might have been biased in their reporting of this information. Therefore, the ability to locate physicians' practices in a prospective method could increase the accuracy of their responses about PMS/PMDD diagnosis and treatment.

This study found that most OB/GYNs practicing PMS/PMDD in Japan do not regularly use a prospective monitoring method according to the diagnostic criteria for PMS/PMDD. In addition, the effectiveness of treatment based on vague medical interviews, without even using screening tools, was strongly suspected. Regarding treatment, some drug choices were not based on EBM, and the need to educate OB/GYNs about PMS/PMDD was considered necessary, including addressing the low selection of SSRIs for use.

AUTHOR CONTRIBUTIONS

Conception and design: All authors. Acquisition of data: All authors. Analysis and Interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Kana Yoshimi and Takashi Takeda. Administrative technical or material support: Kana Yoshimi, Fumi Inoue, and Takashi Takeda. Supervision: Tamami Odai, Nahoko Shirato, Zen Watanabe, Tempei Otsubo, Masakazu Terauchi, and Takashi Takeda.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL RESEARCH

Association Between Loneliness, Premenstrual Symptoms, and Other Factors During the COVID-19 Pandemic: A Cross-Sectional Study with Japanese High School Students

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Purpose: Adolescence is a period of transition from childhood to adulthood where people are vulnerable to stress. The COVID-19 pandemic continues to cause sustained stress in the population. Since the COVID-19 pandemic, social isolation and loneliness have increased. Loneliness is associated with increased stress, psychological distress, and a higher risk of mental illnesses, such as depression. This study examined the association between loneliness, premenstrual symptoms, and other factors in the era of the COVID-19 pandemic among adolescent females in Japan.

Patients and Methods: A school-based cross-sectional survey of 1450 adolescent female students in Japan was conducted in mid-December of 2021. Specifically, paper-based questionnaires were distributed in class, and the responses were collected. The Premenstrual Symptoms Questionnaire (PSQ), 6-item Kessler Psychological Distress Scale, 3-item Revised UCLA Loneliness Scale (R-UCLA), and Fear of COVID-19 Scale were used as measurement tools. The prevalence of loneliness was defined as a total R-UCLA score ≥ 6 .

Results: The prevalence of loneliness was 29.0%. The prevalence of serious psychological distress was also high (8.2%), especially in the lonely group (16.0%). Multivariable regression analysis identified the following factors associated with loneliness: second year (odds ratio [OR] 1.53; 95% confidence interval [CI] 1.09–2.14), longer internet use (OR, 1.11; 95% CI, 1.02–1.20), total PSQ score (OR 1.08; 95% CI 1.06–1.11), and psychological distress (OR 1.05; 95% CI 1.01–1.08).

Conclusion: Adolescent females in Japan showed a high prevalence of loneliness. School year (2nd year), longer periods of internet use, premenstrual symptom severity, and psychological distress were independently associated with loneliness. For clinicians and school health professionals, special concern should be given to the psychological health of adolescent females during the COVID-19 pandemic. **Keywords:** adolescent female, digital media, mental health, psychological distress, stress

Introduction

The outbreak of the coronavirus disease 2019 (COVID-19) has resulted in a global pandemic, and although conditions are better now than in the early days, it still has a significant impact on the physical and mental health of people worldwide.¹ Adolescence is the transition period from childhood to adulthood, where people are particularly vulnerable to stress. During the COVID-19 pandemic, adolescents are under great stress due to sudden school breaks, distance from society, domestic violence, and reduced family income.² Adolescent high school students are reportedly at high risk for psychological distress, depression, anxiety, loneliness, and trauma symptoms.³

Loneliness is an individual's subjective feeling of isolation and is recognized as an important health issue that is closely related to cardiovascular diseases and mental illnesses such as depression and anxiety.^{4,5} Loneliness in adolescence has also been reported as a risk factor for positive mental health.⁶ According to data from 37 Organization for Economic Co-operation and Development member countries, prior to the COVID-19 pandemic,

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loneliness in adolescence was not only an important issue but had also been reported to be increasing worldwide since 2012.⁷ In particular, girls have reported more severe degrees of loneliness than boys. Although the precise cause is unknown, the spread of the internet, particularly smartphones, has been speculated to be a major factor in the weakening of human relationships.⁷ Since the COVID-19 pandemic, social distancing has been recognized as a way to prevent infection; however, this has reduced social interaction and increased social isolation and loneliness. A meta-analysis of 80 studies and a prospective longitudinal study on loneliness in adolescents during the COVID-19 pandemic showed that loneliness was associated with subsequent anxiety and depression.^{8,9} In these studies, girls were found to be more strongly affected than boys.

Unlike men, women have menstrual cycles and exhibit psychosomatic symptoms caused by hormonal fluctuations. Premenstrual symptoms are typical of these symptoms; specifically, they consist of a variety of mood, behavioral, and physical symptoms specific to the late luteal period.^{10,11} Premenstrual disorders (PMDs) consist of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) (a severe form of PMS with predominantly mental symptoms).¹² These are the pathological conditions associated with premenstrual symptoms. Not only do PMDs significantly impair women's quality of life, but a meta-analysis has shown a significant correlation with increased suicidal ideation with respect to PMDD.¹³ Our study of Japanese high school students revealed that PMDs are relatively common.¹⁴ The exact pathogenesis of PMDs is unknown, but stress has been suggested to be one of the triggers.^{15–17} The Great East Japan Earthquake that occurred in March 2011 caused extensive destruction, including tsunami damage, in the Tohoku region. In our previous study, we observed an exacerbation of premenstrual symptoms before and after the earthquake, as well as a correlation between earthquake-induced posttraumatic stress symptoms and the severity of premenstrual symptoms.¹⁸ Another study of Japanese high school students in 2020 found an association between COVID-19-induced posttraumatic stress symptoms and the severity of premenstrual symptoms.¹⁹

A systematic review and meta-analysis of studies of the general population showed increased psychological distress during the COVID-19 pandemic.²⁰ The association between severe psychological distress (SPD) and loneliness was shown in a previous report on psychological distress among Japanese pregnant women conducted in June 2021.²¹ Stressful living, coupled with vulnerability to stress, causes psychological distress and elevates the risk of psychiatric disorders, including depression and anxiety; however, its association with PMDs is unclear. Moreover, the relationship between loneliness and PMDs has not yet been investigated. Adolescent females, who are as vulnerable to stress as pregnant women, may also be more susceptible to psychological distress. During the COVID-19 pandemic as well, adolescent females can be assumed to be vulnerable to stress, and therefore, to experience high levels of psychological distress. Loneliness is enhanced by infection prevention measures. The association between psychological distress and loneliness, as well as loneliness and depression, suggests a possible relationship between loneliness and premenstrual symptoms, which is a disorder analogous to depression. Thus, a correlation between loneliness, psychological distress, and premenstrual symptoms can be postulated. Therefore, investigating the relationship between feelings of loneliness, premenstrual symptoms and psychological distress among high school students is necessary. This study aimed to (1) determine the level of loneliness among high school students during the COVID-19 pandemic, (2) test for whether loneliness is positively correlated with premenstrual symptoms, and (3) investigate associations between other related sociodemographic and psychological parameters, namely, school year, menstrual pain severity, age of menarche, internet use time, sleep time, psychological distress, and the fear of COVID-19.

Materials and Methods

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Kindai University approved the trial protocol (approval number: R03-174, approval date: October 14, 2021). The participating students provided informed consent before answering the survey.

Settings and Participants

We conducted a school-based survey of a sample of 1450 female Japanese students at two public high schools in Sendai, the largest city in the Tohoku region, from December 13 to 17, 2021. At this time, the fifth wave of COVID-19 infections had ended, and the number of infected patients began to increase rapidly toward the sixth wave. In Japan, schools were closed from March to May 2020, in the early stages of the pandemic; otherwise, only mild lockdowns were implemented. At the time of the survey, classes were conducted face-to-face, and no online classes were offered.

No personal information was collected in this survey. The ethics committee approved a waiver of parental informed consent because the students' intention to participate could be confirmed. The decision to not obtain parental informed consent was in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by Japan's Ministry of Education, Culture, Sports, Science and Technology and Japan's Ministry of Health, Labour and Welfare. The data were anonymized and contained no personally identifiable information about the participants. The survey was filled out, sealed in an envelope, and collected during the class. In all, 1175 students responded, and 275 students refused to participate. Out of the 1175 students, 987 had regular menstrual cycles (25 to 38 days) (Figure 1). As PMDs appear only during ovulatory cycles, those with normal menstrual cycles were selected. Furthermore, 907 students who completed all items of the Premenstrual Symptoms Questionnaire (PSQ), the 3-item Revised UCLA Loneliness Scale (R-UCLA), the 6-item Kessler Psychological Distress Scale (K6), the Fear of COVID-19 Scale (FCV-19S), and the Numerical Rating Scale (NRS) were selected. The inclusion criteria were having a menstrual cycle of 25 to 38 days and responding to all items of the PSQ, R-UCLA, K6, FCV-19S, and NRS. All those who did not meet the inclusion criteria were excluded.

Questionnaire

Premenstrual Symptoms Questionnaire

The PSQ was used to evaluate premenstrual symptoms.^{14,22} This questionnaire was developed in Japan and currently exists only in Japanese. The reliability and validity of the PSQ were fully evaluated.²³ The PSQ begins by asking,



Figure I Flow chart of the study.

"Within the past three months, have you had any of the following premenstrual symptoms that begin in the week before menstruation and stop a few days after menstruation begins?" The questions on premenstrual symptoms comprised 11 items listed in the DSM PMDD diagnostic criteria. Furthermore, the PSQ asks whether the premenstrual symptoms experienced interfere with (a) Work performance and productivity and family responsibilities, (b) Social activities, or (c) Relationships with coworkers and family members. The severity of premenstrual symptoms and their interference with social activities were rated on a four-point scale (1 = not at all, 2 = mild, 3 = moderate, or 4 = severe). The total PSQ score was calculated as the sum of all 14 items. Therefore, the total PSQ score ranged from 14 to 56. In this study, Cronbach's alpha coefficient of the PSQ was 0.935.

The 3-Item Revised UCLA Loneliness Scale

The Japanese version of the 3-item Revised UCLA Loneliness Scale (R-UCLA) was used to assess loneliness.²⁴ The reliability and validity of this scale have been well established.²⁴ The R-UCLA consists of three items, which are rated on a four-point scale (1 = not at all, 2 = almost never, 3 = sometimes, or 4 = always). The total R-UCLA score ranged from 3 to 12. In this study, the Cronbach's alpha coefficient of the 3-item R-UCLA was 0.875. We classified students with a total R-UCLA score ≥ 6 as having loneliness, according to the criteria described previously.²⁵

The 6-Item Kessler Psychological Distress Scale

The Japanese version of the 6-item Kessler Psychological Distress Scale (K6) was used to assess psychological distress.²⁶ The original version was made in English, and the Japanese version, which has been checked for validity and reliability, was used in this study.²⁷ The K6 consists of six items scored on a five-point scale (0 = not at all, 1 = a little, 2 = yes, 3 = almost, or 4 = all). The total K6 score ranged from 0 to 24. The Cronbach's alpha coefficient of the K6 was 0.921 in this study. SPD was defined by a total K6 score ≥ 13 .²⁸ Some past studies in Japan have used a cutoff point of 10 points, and this criterion was also adopted.^{21,29}

Fear of COVID-19 Scale

The Japanese version of the Fear of COVID-19 Scale (FCV-19S) was used to assess the fear of COVID-19.³⁰ The original version was made in English, and the Japanese version, which has been checked for validity and reliability, was used in this study.³¹ The FCV-19S consists of seven items, which are scored on a five-point scale (1 = strongly disagree, 2 = disagree, 3 = undecided, 4 = agree, or 5 = strongly agree). The total FCV-19S score ranges from 7 to 35. In this study, the Cronbach's alpha coefficient for the FCV-19S was 0.817.

Other information collected on each participant included age, school grade level, body weight, height, age at menarche, days of menstrual cycle, internet usage, and sleeping time. Regarding the menstrual cycle, a cycle of 25–38 days was defined as a regular menstrual cycle. Body mass index (BMI; kg/m²) was calculated by dividing weight in kilograms by height in meters squared.

Statistical Analysis

Cronbach's α coefficient was calculated to assess the reliability of each scale (PSQ, K6, 3-item R-UCLA, and FCV-19S). Means and standard deviations were calculated for continuous variables, and proportions were calculated for categorical variables.

Since 2008, we have conducted an annual survey on menstruation using this school cohort. Therefore, the prevalence of irregular menstruation in this school cohort was compared with data from 2019 and 2020.^{19,23} The Cochran-Armitage trend test was performed for this comparison.

Correlations between the four psychological questionnaires (PSQ total score, K6 total score, total R-UCLA score, and total FCV-19S score) were examined by performing a Pearson's correlation coefficient test.

Multivariable logistic regression analysis was performed to determine the factors significantly associated with loneliness. The school year was divided into two groups (2nd year and 1st plus 3rd year). The model included school year, BMI, age at menarche, menstrual pain intensity, internet usage, sleep time, PSQ total score, K6 total score, and total FCV-19S score. Statistical analyses were performed using JMP Pro 16.0.0 (SAS, Cary, NC, USA). Statistical significance was set at p < 0.05.

Results

As indicated by the flow of participants, a relatively high percentage of students (177, 15.1%) had irregular menstruation (Figure 1). Therefore, we compared the percentage of those with irregular menstruation with those with regular menstruation since the survey was conducted in 2019 before the pandemic. The percentage of menstrual irregularities has increased significantly since 2019 (Figure 2).

The participant characteristics are shown in Table 1. There were 644 participants in the non-lonely group (71.0%) and 263 in the lonely group (29.0%). The proportion of lonely and non-lonely groups differed by school year. Age ranges for each school year were as follows: first year (median 16, interquartile range [IQR] 15–16), second year (median 17, IQR 16–17), and third year (median 18, IQR 17–18). Results indicated that students showed higher rates of loneliness in the second than in the third year. The age at menarche was younger, and the internet use time was longer in the lonely than in the non-lonely group (mean (standard deviation): 12.0 (1.3) vs 12.3 (1.3); 3.29 (2.12) vs 2.65 (1.81), respectively). The lonely group had higher total PSQ, R-UCLA, and K6 scores than the non-lonely group. The percentage of those scoring \geq 13 and \geq 10 on the K6 cut-off was higher in the lonely than in the non-lonely group.

Furthermore, the correlations between the four psychological questionnaires used in this study were examined (Figure 3). There was a moderate correlation between the PSQ total score and K6 score and a mild correlation between the R-UCLA and PSQ total scores, as well as the K6 score.

Multivariable logistic regression analysis was performed to identify the factors significantly associated with loneliness (Table 2). These associated factors were more pronounced in the second year of school, with longer duration of internet use, higher total PSQ score, and higher K6 total score.

Discussion

Our results revealed a 29.0% prevalence of loneliness among female Japanese high school students. The results of a webbased survey of the general Japanese adult population from April to December 2020 that used the same scale as the current study showed that approximately 40% of the participants were in the loneliness group. However, a simple comparison cannot be made because the participants and the time of the survey are different, and the percentage of the loneliness group seems to be slightly lower in the present results. Nonetheless, at the time of the survey, face-to-face classes were being conducted in schools, and such a high rate of loneliness would be difficult to predict under mild social restrictions. Therefore, it should be noted that a significant percentage of adolescent females feel lonely.

Another important aspect of the present results is that the percentage of SPD (score of ≥ 13 on the K6) was remarkably high (8.2%) and even higher in the lonely group (16.0%). During the COVID-19 pandemic, Japan, unlike many



Figure 2 Comparison of menstrual irregularity among 2019, 2020, and 2021 groups. Each bar represents data in 2019, 2020, and 2021.

Characteristic		Non-Lonely n=644	Lonely n=263
Age (years), mean (SD)	16.7 (1.0)	16.7 (1.0)	16.6 (1.0)
School year, number (%)			
First year	325 (35.8)	234 (72.0)	91 (28.0)
Second year	271 (29.9)	176 (64.9)	95 (35.1)
Third year	310 (34.2)	233 (75.2)	77 (24.8)
Missing	I (0.I)		
BMI (kg/m²), mean (SD)	20.3 (2.2)	20.2 (2.0)	20.5 (2.6)
Missing, number (%)	23 (2.5)		
Age at menarche (years), mean (SD)	12.2 (1.4)	12.3 (1.3)	12.0 (1.3)
Missing, number (%)	7 (0.8)		
Menstrual pain intensity, mean (SD)	4.7 (2.6)	4.6 (2.6)	4.9 (2.6)
Internet using time (hr), mean (SD)	2.84 (1.92)	2.65 (1.81)	3.29 (2.12)
Missing, number (%)	10 (1.1)		
Sleeping time (hr), mean (SD)	6.05 (0.97)	6.05 (0.94)	6.07 (1.04)
Missing, number (%)	6 (0.7)		
PSQ total, mean (SD)	25.3 (9.2)	23.3 (8.0)	30.3 (10.0)
R-UCLA, mean (SD)	4.4 (1.7)	3.5 (0.8)	6.6 (1.1)
K6, mean (SD)	4.1 (5.3)	3.1 (4.6)	6.4 (6.1)
13≥, number (%)	74 (8.2)	32 (5.0)	42 (16.0)
10≥, number (%)	140 (15.4)	60 (9.3)	80 (30.4)
FCV-19S, mean (SD)	14.9 (5.0)	14.7 (0.2)	15.3 (0.3)

Table I Characteristics of Study Participants

Notes: Age ranges for each school year were as follows: first year (median 16, IQR 15–16), second year (median 17, IQR 16–17), and third year (median 18, IQR 17–18).

Abbreviations: SD, standard deviation; BMI, body mass index; PSQ, Premenstrual symptoms questionnaire; R-UCLA, 3-item Revised UCLA Loneliness Scale; K6, 6-item Kessler Psychological Distress Scale; FCV-19S, Fear of COVID-19 Scale; IQR, interquartile range.

American and European countries, did not impose a tight lockdown but rather a series of loose lockdowns. Except during the school closure period in the early stages of the pandemic, online classes were rarely conducted. Despite the far milder degree of lockdown, the suicide rate among young Japanese women increased sharply in 2020.³² A cohort study revealed that psychological distress is a major risk factor for suicide.³³ This data confirms that even 21 months after the start of the pandemic, Japanese adolescent females experienced great psychological distress. Stress leads to a range of irregular menstruation issues from ovarian dysfunction to hypothalamic action. The persistent increase in menstrual irregularities in 2020 and 2021 compared with 2019 before the pandemic may also be an indication of persistent stress.

Our results showed that for students in their 2nd school year, menstrual pain, internet usage, the severity of premenstrual symptoms, and psychological distress were independently associated with loneliness. Additionally, comparisons between school years showed that second-year students were more likely to be in the lonely group than third-year students. School education in Japan consists of six years of elementary school, three years of junior high school, and three years of high school. The transition from junior high to high school involves significant changes in the environment, with a large turnover of members of the same class. The second-year students at the time of this study were just entering their first year of high school and encountered a great deal of confusion, including lockdown in the early stages of the pandemic. At the beginning of high school, even though it was a critical time for building friendships, the lack of face-to-face classes and the suspension of club activities due to the pandemic caused a deficiency in personal relationships. Confusion at the start of high school may have created loneliness, which persisted unresolved in the second year. Repeated mild lockdowns are characteristic of the COVID-19 measures in Japan. A longitudinal study in Japan showed that in younger age groups (18–29 years), such repeated mild lockdowns have cumulative negative effects with respect to social isolation and loneliness.³⁴ Therefore, careful monitoring of the progress of this particular school year may be necessary in the future.



Figure 3 Correlations between the psychological questionnaires. In the heat map, red indicates a positive correlation and blue indicates a negative correlation. As indicated by the *r*-value bars, the darker the color, the higher the value of the correlation coefficient. Abbreviations: PSQ, Premenstrual Symptoms Questionnaire; K6, 6-item Kessler Psychological Distress Scale; R-UCLA, 3-item Revised UCLA Loneliness Scale; FCV-19S,

Fear of COVID-19 Scale.

With the widespread use of smartphones, adolescent relationships appear to have shifted to shallow online relationships.^{35,36} While digital media has many advantages, they also make relationships shallow and lead to loneliness.³⁷ The present results indicate that longer internet use is associated with loneliness, which is consistent with previous data. Although digital media is touted as an alternative to face-to-face relationships for the prevention of COVID-19 infections, it is important to note that internet use is independently associated with loneliness, even in this pandemic environment.

No studies have reported on the relationship between loneliness and premenstrual symptoms. The exact pathophysiology of PMDs remains unclear; however, the effectiveness of selective serotonin reuptake inhibitors (SSRIs) as

Characteristic	OR	95% CI
School year, 2nd year	1.53	1.09–2.14
BMI (kg/m ²)	1.03	0.96-1.11
Age at menarche	0.92	0.81-1.04
Menstrual pain intensity	0.92	0.86–0.99
Internet using time (hrs)	1.11	1.02-1.20
Sleep time (hrs)	1.08	0.92-1.28
PSQ total score	1.08	1.06-1.11
K6 total score	1.05	1.01-1.08
FCV-19S total score	1.00	0.97–1.04

Table 2 Factors Associated with Loneliness

Note: $R^2 = 0.130$.

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; PSQ, Premenstrual symptoms questionnaire; K6, 6-item Kessler Psychological Distress Scale; FCV-19S, Fear of COVID-19 Scale. therapeutic agents is reportedly related to the brain transmitter serotonin.¹¹ Experiments using rat models of social isolation have reported that the serotonin 1A receptor agonist buspirone and the SSRI fluoxetine improve behavioral abnormalities caused by isolation.³⁸ From this, isolation and loneliness can be inferred to be associated with serotonin. In terms of pathophysiology, there may be similarities between PMDs and loneliness.

In our study, we found an association between loneliness and psychological distress. In addition to psychological distress being an obvious risk factor for suicide,³³ loneliness during the COVID-19 pandemic has also been reported to be a risk for suicide.³⁹ Given that adolescent girls are vulnerable, our findings regarding a high prevalence of loneliness and SPD in Japan warrant attention.

Multivariable analysis showed that menstrual pain was negatively correlated with loneliness, which seems to be a paradoxical result. The exacerbation of loneliness from restricted social activities due to severe menstrual pain is expected. Previous studies have reported that interpersonal disturbances from menstrual pain are due to negative emotions from menstrual pain, not the pain itself.⁴⁰ In the present study, this may have been because the results were corrected for psychological distress.

Our study had several limitations. First, because of the cross-sectional design, determining a causal relationship between loneliness and associated factors was not possible. Second, we collected data using a self-reported survey in a class. The survey did not include data on students who were absent from school, and since these students may have been absent because of depression, the survey may have underestimated their loneliness and psychological distress. In this regard, a report on Japanese adolescents used structural equation modeling to show that loneliness influences feelings of school refusal.⁴¹ Finally, this study was conducted only in Japan, which limits its generalizability to other countries. The increase in loneliness since 2012 has been reported to be a global problem, but the increase is only mild in Confucian countries, such as Japan, South Korea, and Hong Kong.⁷ In other English-speaking countries, loneliness is considered a more serious problem, and in countries where strict lockdown due to COVID-19 has been implemented, the impact of loneliness from social isolation is likely to be greater than that in Japan. However, since the questionnaires used in this survey (K6, R-UCLA, FCV-19S) were adapted from those used worldwide and translated into Japanese for validity and reliability, these results may be applicable to adolescent females in Japan as well as in other countries.

Conclusion

This study demonstrated an association between loneliness, premenstrual symptoms, and other psychological factors among Japanese adolescent females during the COVID-19 pandemic. For clinicians and school health professionals, special attention should be given to the psychological health of adolescent females during the COVID-19 pandemic. In addition, special attention should be paid to the progress of these particularly vulnerable populations.

Data Sharing Statement

The data obtained in this study are available from the corresponding author upon request.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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原著論文

1. Miyata S.* and Wake H.

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和文総説

1. 集中治療と漢方薬、急性病態における意識障害・認知機能障害と漢方薬

宮田信吾

ICU & CCU, Japanese Journal of Intensive Care Medicine, 48(3): 137-143, 2024.

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<u>宮田信吾</u>

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招待公演・シンポジウム

第76回日本自律神経学会総会 2023.10.28-29 埼玉会館
 基礎と臨床の対話3 代替医療におけるトランスレーショナルリサーチ

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漢方薬の作用機序解明からみたトランスレーショナルリサーチ

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Novel signal transduction mechanisms involved in oligodendrocyte differentiation and psychiatric disorders

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*石野雄吾、清水尚子、遠山正彌、<mark>宮田信吾</mark>

Regulations of oligodendrocyte differentiation and myelination by protein-arginine methyltransferases

学会発表

1. 第 21 回 ORIGIN 神経科学懇話会 2023.08.22-23 千里ライフサイエンスセンター

*石野雄吾、清水尚子、遠山正彌、宮田信吾

アルギニンメチル化酵素 CARM1 によるオリゴデンドロサイト分化制御

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 *清水尚子、石野雄吾、遠山正彌、<u>宮田信吾</u> 生後発達期のオリゴデンドロサイト産生における DBZ の機能解析
 Functional analysis of DBZ in oligodendrocyte generation during early postnatal development
- 3. 第42回産婦人科漢方研究会 学術集会 2023.09.03 鹿児島城山ホテル
 *清水尚子、石野雄吾、小山佳久、武田卓、島田昌一、遠山正彌、宮田信吾
 更年期障害の精神神経症状を改善する加味逍遥散の作用機序解明

競争的資金等の研究課題(公的資金)

 うつ病発症機構におけるタンパクメチル化酵素によるリン酸化シグナル制 御の重要性
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宫田信吾(代表研究者), 遠山正彌, 清水尚子, 石野雄吾

 2. 慢性ストレスによる髄鞘構造異常・機能変化の分子機構解明 公益財団法人大阪難病研究財団 2023 年度 第 29 回医学研究助成 石野雄吾,清水尚子,宮田信吾(分担研究者)

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- 5. 第 130 回日本解剖学会・第 102 回日本生理学会・第 98 回日本薬理学会 合同 大会 (APPW2025)、プログラム委員
- 6. Frontiers in Cellular Neuroscience, Research Topic Editor,

"Oligodendrocytes: From Their Development to Function and Dysfunction"

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Editorial: Oligodendrocytes: from their development to function and dysfunction

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KEYWORDS

oligodendrocytes, brain disease, neurodegeneration, oligodendrocyte progenitor cells, myelin, remyelination

Editorial on the Research Topic Oligodendrocytes: from their development to function and dysfunction

Human central nervous system (CNS) myelination occurs before 20 years old and continues throughout our lives (Herbert and Monk, 2017). CNS myelination and remyelination by oligodendrocytes (OLs) is important for obtaining rapid conduction of action potentials and appropriate neuronal communications to support higher brain functions (Masson and Nait-Oumesmar, 2023). OLs and oligodendrocyte precursor cells (OPCs) exist in the corpus callosum, and OPCs have the ability to cell-divide and differentiate into OLs. Previous studies have examined various signal pathways of OL development, CNS myelination, and remyelination *in vivo* and *in vitro* analysis systems (Taylor and Monje, 2023). During CNS myelination and remyelination, OLs generate a multitude of processes and new myelin sheaths by wrapping suitable axons. However, the extent of involvement of various signal cascades and/or molecules in these developing OL lineage cells, CNS myelination, and remyelination remains to be fully elucidated. Thus, this Research Topic is looking to address key aspects of the function and dysfunction of OLs, promote the discussion around this Research Topic, and facilitate knowledge dissemination.

The co-editor, Wake's lab members Yoshida et al., report that the different properties of Ca^{2+} responses of OLs are induced activity-dependent glutamate and adenosine triphosphate (ATP) release from neurons or astrocytes. Further, these activity-dependent responses were lost in the Alzheimer's disease (AD) mice model, but a higher frequency of ATP release induced Ca^{2+} responses due to neurodegeneration. Hong et al. perform a systematic analysis of multiple brain regions and cerebrospinal fluid (CSF), and socially isolating dog groups during the juvenile stage led to a small number of differentially expressed genes in multiple brain regions except the prefrontal cortex (PFC). Maruyama et al. apply global lipidomic analyses to identify circulating lipids that mediate amyotrophic lateral sclerosis (ALS) pathogenesis. They identified a decrease in circulating free fatty acids, including oleic acid (OA) and linoleic acid (LA), and OA and LA inhibited excitotoxic oligodendrocyte cell death via the cell surface receptor FFAR1 (free fatty acid receptor1) in ALS model mice. Zhao et al. find that the OPC differentiation and OL morphology were significantly different between the brain and spinal cord, and inhibition of endoplasmic reticulum (ER) stress could effectively attenuate OPC death.

Han et al. discuss recent findings suggesting an unexpected role of oligodendroglia, the cells that received far less attention than neurons and other glial cells. They also reviewed the possibility that OL lineage cells might be one of the most vulnerable cell types responding to the changing microenvironment in the brain during neurodegenerative diseases. Delfino et al. report that only platelet-derived growth factor receptor alpha (PDGFRa) positive oligodendrocyte lineage cells are ciliated and reveal heterogeneity in the frequency of cilium presence on OPCs, depending on primary culture conditions and cerebral regions of mice. Further, they show the plasticity of oligodendroglia primary cilium length in response to different drugs. Mei et al. indicate the important molecular and genetic evidence that inositol 1,4,5-trisphosphate receptor type 2 (Itpr2) is dramatically upregulated in differentiating OLs and regulates OL differentiation and myelin development through an extracellular signal-regulated kinase (ERK)-dependent mechanism. Valihrach et al. review the current understanding of OL heterogeneity in health and disease based on single-cell and single-nucleus transcriptomic technologies. They provide our OL research community with a unified overview of key transcriptomic studies dealing with OL heterogeneity in the mammalian CNS and consensus marker genes of selected OL populations. Chacon-De-La-Rocha et al. report that there is a premature decrease in OPC density at 9 months in AD model mice and that at 14 months, OPC displayed a shrunken and fibrous morphology, indicative of morphological dystrophy. They also indicate that changes in OPCs are potential factors in the progression of AD pathology. This Research Topic highlights the important themes of unraveling the mechanisms behind oligodendrocytes' formation and function, which may lead to a better understanding of their dysfunction and role in CNS pathologies.

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特 集中治療と漢方薬

急性病態における意識障害・認知機能障害と漢方薬

宮田 信吾*1

要約

抑肝散が高齢者認知症の周辺症状(BPSD)抑制に有効であるとの2005年の研究報告を契機に高齢者認知症などの精神神経領域での臨床および基礎研究が活発に行われてきた。この流れのなかで、これまで漢方薬が効果を示すとは考えにくかった救急医療領域、外科領域においても抑肝散の高齢者や術後せん妄への発症予防効果などに関する臨床研究が継続的に実施されている。抑肝散によるBPSDやせん妄の改善効果は、患者の生活の質の向上だけではなく医療関係者やご家族の負担軽減とも大きく関連することから、科学的根拠に基づいた的確な抑肝散処方の確立は救急医療領域、外科領域においても重要な課題の1つであるとの認識が確立されつつある。そこで本稿では、これまでの抑肝散の基礎研究成果とともに高齢者や術後せん妄などの意識障害・認知機能障害の症状改善への抑肝散の可能性について紹介したい。

🔍 はじめに

抑肝散は主に小児の夜泣きや疳症に処方されて いたように、興奮やイライラ、筋肉の緊張などを 鎮める働きを持つ漢方薬である。抑肝散は2000 年代に入るまで基礎研究はほとんどなされていな かったものの、2005年にようやく認知症の周辺 症状 Behavioral and Psychological Symptoms of Dementia (BPSD) 治療への有効性に関する報告 がなされた ^{L2}。また同年に米国食品医薬品局 (FDA) は、BPSD 治療のための抗精神病薬投与 を死亡率の高さから控えるべきとの勧告を出し た。これらの研究成果や勧告をきっかけとして抑 肝散の作用機序に関する基礎研究および臨床研究 が急激に進展し、われわれのグループの研究成果 も含め18年間で250報を越えるまでに発展して いる。また、せん妄と抑肝散に関する研究成果は 2010年に、国内の高齢者外傷性脳損傷患者での 臨床研究成果³⁾として報告されたのを契機に現 在まで18報の報告があり、そのほとんどが国内 の研究機関および病院の成果である。これらの抑 肝散をはじめとする漢方薬の作用機序の解明は, 科学的根拠に基づいた治療 EBM (Evidence-based medicine)による漢方治療の発展には不可欠であ る。また、抑肝散による BPSD やせん妄の改善 効果は、患者の生活の質の向上だけではなく医師 や看護師などの医療関係者やご家族の負担軽減と も大きく関連し、科学的根拠に基づいた的確な抑 肝散処方の確立は高齢者医療とともに救急医療領 域、外科領域においても重要な課題の1つである との認識が確立されつつある。本稿では、われわ れが得た知見や共同研究機関などで得られた知見 を中心に、これまでの抑肝散に関する基礎研究の 知見とともに高齢者や術後せん妄などの意識障 害・認知機能障害の症状改善への抑肝散の可能性 について紹介する。

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ユ. 抑肝散による認知機能障害改善効果 の検討

つい先日ようやく米国 FDA よりフル承認を得 たアルツハイマー型認知症の治療薬(一般名:レ カネマブ)は、AB凝集体除去による症状進行の 抑制という画期的な治療薬としての可能性を秘め ているものの、抗体医薬であることから高額な治 療費や2週間に1回の点滴投与が必須であり,脳 浮腫や脳出血などの重篤な副作用の存在が示唆さ れるなどいまだ有用性に不明点が多いのが現状で ある¹⁾。また、これまではコリンエステラーゼ阻 害薬や NMDA 受容体阻害薬などがアルツハイ マー型認知症の治療薬として開発され処方されて きたが、効果的な結果を得ているとは言いがたい。 一方, 認知症に伴う BPSD 治療に対して漢方薬 の抑肝散の有効性に関する報告が2005年以降増 加するに従い、認知症中核症状にも抑肝散が有効 性を示すのではないかという可能性が示されるな か、著者らのグループも認知症中核症状への抑肝 散の有効性の検討を行い、その作用機序を報告し ている5)。著者らは抑肝散の構成生薬のなかで神 経細胞死を抑制する成分はセンキュウであること を同定した。さらに、センキュウに含まれるフェ ルラ酸に神経細胞死抑制効果があることや家族性 アルツハイマー型認知症の原因遺伝子の1つプレ セニリン1の変異体(deltaE9)発現神経細胞に おいて、抑肝散およびセンキュウが小胞体ストレ ス応答経路を介して細胞死を抑制する分子機序に ついて見出した⁵⁾。

また著者らの検討以外にも、APP-Tgマウスな どのさまざまな認知症モデル動物への抑肝散投与 により、それらの記憶障害や学習障害の改善効果 を見出した報告がなされており^{6~99}、その作用機 序としては、脳内の興奮性神経伝達物質であるグ ルタミン酸過剰伝達抑制効果によるとの報 告^{10,11)}や脳内グリア細胞の1つであるアストロ サイトにおけるグルタミン酸トランスポーター機 能の活性化作用^{12,13)}、グルタミン酸や Aβ誘発 性の神経細胞死抑制効果などの関与の可能性が示 咬されている。さらに、含有成分としての化合物 の同定もある程度進んでおり、チョウトウコウ由 来のアルカロイド成分(ガイソシジンメチルエー テル、ヒルスチン、ヒルステイン、リンコフィリ ンなど)やカンゾウ由来の成分(グリチルリチン 酸,リクイリチン,イソリクイリチゲニンなど) などの可能性が示唆されている ^{14~16)}。

□. 抑肝散による抗ストレス効果の検討

認知症に伴う BPSD 治療に対して抑肝散が 効果を示すことはこれまで複数報告されてい る^{1.2.17.18)}。さらにこの BPSD の治療にはリス ペリドンなどの非定型抗精神病薬だけでなく、抗 うつ薬も効果があることがこれまでに知られてい る。これらの事実は、抗うつ薬と類似した成分が 抑肝散のなかにも含有されている可能性を示して おり、抑肝散の構成成分のなかにうつ病態である 不安や気分の落ち込みなどの症状にも有効な成分 が含まれている可能性が十分に考えられた。ま た、うつ病モデルとして用いられる各種ストレス 暴露動物は不安や攻撃性などさまざまなストレス 症状を呈する。これらのストレス暴露に対する生 体反応系として視床下部 - 下垂体 - 副腎軸 (Hypothalamic-Pituitary-Adrenal axis: HPA axis) が 知られており、通常はこの HPA axis は負の フィードバック機能により過剰な刺激が持続しな い。しかし、うつ病をはじめとする一部のストレ ス性の精神疾患の発症には、慢性的な繰り返しの ストレス暴露により、HPA axis が過剰に反応し 続け、負のフィードバックシステムが機能不全に 至ることが大きく関連すると考えられている。

そこで著者らは、マウスへのストレス暴露後の HPA axis 応答に対する抑肝散の効果の有無につ いて検討を行った。その結果、抑肝散投与により 血中コルチコステロン (グルココルチコイド) 値 が非ストレス群と同程度にまで低下し、GR mRNA 発現量は有意な変化を示さなかったが GR タンパク量は視床下部の室傍核(paraventricular nucleus: PVN) 神経細胞および脳梁オリゴデン ドロサイトにおいて有意に増加した 19.20)。また. タンパク発現量を転写後に調節する機構として non-coding RNA の1つである microRNA (miR) に注目した^{21.22)}。miR-18 および miR-124a は GR mRNA の 3' UTR(3' 非翻訳領域)に結合するこ とにより、GR タンパク質の翻訳レベルを抑制す る²³⁾。抑肝散投与により,ストレス負荷マウス の視床下部では miR-18, 脳梁オリゴデンドロサ イトでは miR-124a の発現が低下した。すなわち. 抑肝散は特定の miRNA 発現を低下させ GR 翻訳 抑制を解除し、その結果 GR タンパク量を正常量 に増加させることで HPA axis を正常化するとい う新たな抗ストレス効果の分子機序を明らかにし た^{19,20)}。

二. 抑肝散による興奮抑制作用および抗 不安作用の検討

隔離飼育動物や認知症モデル動物で観察される 興奮による攻撃性や社会攻撃性が抑肝散投与によ り改善することや、老齢動物や認知症モデル動物 で観察される不安様行動も抑肝散投与により改善 することなど、興奮抑制効果および抗不安効果の 検討もすでに多数報告されている^{1,2,6,7,8,24,25)}。

これらの興奮抑制効果および抗不安効果は、セ ロトニン1A (5-HT1A) 受容体作動薬と類似す ること. さらには 5-HT1A 受容体拮抗薬 (WAY-100635)により阻害されることなどから、抑肝散 は5-HT1A 受容体のアゴニストとして作用する ことで有効性を示す可能性が示唆されてい る^{26~28)}。また、抑肝散およびチョウトウコウの アルカロイド成分・ガイソシジンメチルエーテル (GM) に 5-HT1A 受容体に対するパーシャルア ゴニスト作用が見出された^{23,29)}。GM は他のセ ロトニン受容体 5-HT2A, 2C, 7 受容体への作用 や非定型抗精神病薬アリビプラゾールに類似した 作用としてドパミン D2 受容体へのパーシャルア ゴニスト作用も報告された^{30.31)}。さらに、抑肝 散を経口投与すると30~60分後に血中だけでな く血液脳関門 (Blood Brain Barrier: BBB) を透 過し、脳内でもGMが観察され、前頭前野、前 辺縁皮質および眼窩前頭皮質を含む前頭皮質領域 に強い局在を示すことが明らかになったことから GM が抑肝散の活性成分候補の1つとして考えら れている 32~31)。

抑肝散の興奮抑制作用のもう1つの機序とし て、脳内での興奮性神経伝達物質グルタミン酸の 過剰伝達の抑制作用などが示唆されている^{10~14)}。 この作用は、抑肝散に含まれるグリチルリチン酸 (配糖体)が腸内細菌により代謝されたグリチル レチン酸(GA)によるとの報告があり、GA は 海馬を中心に前頭前野、線条体、側座核、視床な どに局在することが示されている^{34,35)}。

Q. Ⅳ. 抑肝散によるせん妄予防効果の 可能性

「精神疾患の診断・統計マニュアル」第5版 (DSM-5)によると、せん妄とは「身体疾患や中 毒によって惹起される急性で変動する意識障害・ 認知機能障害」と定義されており、具体的には、 落ち着きがない,目線が泳ぐなどの注意障害.時 間や場所が分からない見当識障害、睡眠覚醒リズ ム障害、感情障害など、多彩な症状が短期間のう ちに出現し、とくに夕方から夜間にかけて増悪す る³⁶⁾。せん妄の診断には、急性および持続性の 区別や、低活動型、過活動型、混合型の分類など も必要となる。せん妄の発症要因としては、直接 的要因として脳血管障害,頭部外傷,脳腫瘍など の頭部疾患や外傷、敗血症、DIC、心筋梗塞、心 不全,悪性腫瘍といった全身症状,抗コリン薬や ベンゾジアゼピン系抗不安薬投与などが知られて いる。それ以外の誘発促進要因としては、うつ状 態、不安感などの精神的要因、身体拘束、疼痛な どの身体的要因、入院などの環境変化や睡眠障害 が、準備要因としては高齢、認知機能障害、アル コール多飲などがある。さらにせん妄の回復後の 認知機能障害に関する近年の報告のメタ解析か ら、せん妄を発症した患者では長期的な認知機能 の低下を示すことが見出され、高齢者の認知機能 維持においてもせん妄発症予防の重要性が再認識 されている 37)。

ICUや CCU 管理下および外科病棟における術 後せん妄は、幻覚、妄想、昼夜逆転、徘徊、易怒、 暴言などのさまざまな症状であり、術後回復が遷 延するのみではなく看護などの負担が著しく増大 するなど問題が多い。さらに、ICU で治療を受 けている新型コロナウイルス感染症患者における せん妄発症危険因子の調査から、高齢、ICU 滞在、 高血圧、人工呼吸器の補助、および神経筋遮断薬 の使用が ICU 管理の新型コロナウイルス感染症 患者せん妄の誘発促進要因であることが報告され る³³⁾ など、せん妄発症予防は病院全体の問題と して認識していかなくてはならない大きな問題で ある。

一般的なせん妄の治療薬である抗精神病薬は, 容量依存的に過鎮静となることが知られており, 術後経過において重要な経口摂取や早期離床が困 難になる。さらに過鎮静を起こさない容量での抗



図1 抑肝散の構成生薬

精神病薬投与はせん妄のコントロールが不十分に なることが多く、薬剤管理が困難であることが多 い。上述してきた抑肝散は、セロトニン受容体 5-HT1A 受容体のアゴニスト作用, ドパミン D2 受容体へのパーシャルアゴニスト作用、そして興 奮性神経伝達物質グルタミン酸の過剰伝達の抑制 作用により認知症 BPSD に対して有効である。 また,術後患者や ICU 入室患者,高齢患者で多 発するせん妄の多くの症状は BPSD と類似であ り、過鎮静を起こさない抑肝散のせん妄予防効果 に関する検討が国内で多く実施された。術後せん 妄に抑肝散の投与が有効であるとの報告が複数あ るものの、ランダム化比較試験(RCT)では、 抑肝散を術前から4日以上投与した群とプラセボ 群で有意な術後せん妄の発症予防効果はないとい う報告³⁹⁾もあり、研究途上でいまだはっきりと した結論には至っていないが、せん妄症状が軽い 思者で抑肝散が有効性を示す傾向にある。いずれ にしても、せん妄による異常行動を起こさないよ うにする対策は必須であり、抗精神病薬やメラト ニン受容体作動薬などの睡眠薬との併用療法な ど、ICUやCCUでのせん妄発症予防に対しての 抑肝散の有効性に関して今後の研究発展に期待し たい。

🔍 おわりに

漢方薬の1つである抑肝散は、蒼朮(ソウジュ ツ)、茯苓(ブクリョウ)、川芎(センキュウ)、 釣藤鈎(チョウトウコウ)、当帰(トウキ)、柴胡 (サイコ)、甘草(カンゾウ)の7つの構成生薬で 構成されている多成分合剤である(図1)。臨床 現場においてこれまでに高齢者認知症 BPSD を はじめ幅広い疾患や症状に応用されてきており、 これらの臨床効果を支持・裏付けるエビデンス、 薬効の作用機序、構成生薬の活性成分および薬物 動態などの基礎研究により科学的解明が進んでい る漢方薬の1つである(図2)^{40~43)}。ICU管理さ れた患者は、輸液・輸血状態であることや、体内 水分布の異常、循環血液量変化などで正常ではな い状態であり、晴れやかな気分であるとは考えに くい。この点から考えるととくに軽度の場合を想 定して、抑肝散の作用機序でICUやCCU患者の 病態の一部にでも貢献できる可能性を秘めてい る。現在も国内を中心に抑肝散の作用機序の解明 が進んでおり、ICUやCCUにおいても今後のさ らなる抑肝散の臨床適用の拡大が期待される。

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図2 科学的解明が進んでいる抑肝散の効果

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Abstract

Cognitive Dysfunction/Consciousness Disorders and Japanese Herbal Medicines in Acute Pathologies

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Yokukansan (YKS), a traditional Japanese medicine, has been administered to patients who show symptoms such as nervousness, short-tempered behavior, irritability, sleeplessness, and shaking of the limbs. Recently, several clinical reports have shown that YKS is effective against the Behavioral and Psychological Symptoms of Dementia (BPSD), such as aggression, anxiety, and depression in patients with Alzheimer's disease and other forms of dementia, and improves the daily living of patients. Furthermore, several clinical research indicated that YKS may have some effects in preventing the onset of postoperative delirium, where it was difficult to imagine that herbal medicine would be effective in emergency medicine and surgery. The effects of YKS on improving BPSD and delirium are significantly related to not only improving the quality of life of patients and their families but also reducing the burden on medical personnel. In this review, I would like to introduce several results of basic research on YKS and its potential for improving symptoms of consciousness disorders and cognitive dysfunction such as postoperative delirium.

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みにれびゅう

脳の発生および構造から見たアルギニン残基のメチル化制御

宮田 信吾

1. はじめに

遺伝暗号に従い翻訳されたタンパク質は、さまざまな翻 訳後修飾を受けて機能的多様性を獲得する.このタンパク 質の翻訳後修飾に関しては全世界的に主にリン酸化および 脱リン酸化を中心とした研究が行われ,他の翻訳後修飾の 解析は遅れをとっていた感が大きい.1967年になりアル ギニンにメチル基が含まれることが報告されたものの、そ の生理学的意義に関しての解析では、その後の進展があま りみられない状況が続いていた¹⁾.このようにメチル化を 受けたタンパク質が脳内に豊富に存在するとの報告のみで あったが、1997年にPC12細胞でのNGF依存的神経突起伸 展にタンパク質のメチル化が必要であることが生化学的に 示され、著者らが注目するきっかけとなった²⁾.

タンパク質の翻訳後修飾の一つとしてのアルギニン残基 のメチル化修飾は、当時から主にがん領域での検討を中心 にその機能解析が進んでいたものの、神経系領域において はまだ十分な検討が行われていなかった³⁾.しかし著者ら が注目してから20年以上が経過する間に、神経系領域で の研究は目覚ましい進展を遂げた⁴⁾.

タンパク質のアルギニン残基のメチル化制御は、細胞内 情報伝達においてのみでなく転写調節やmRNAスプライ シング,DNA修復など非常に幅広い細胞活動において重 要な役割を持っていることが以前から報告されている.ま た、アルギニン残基のメチル化異常ががんなどの疾患の発 症や悪性度に関与することや炎症を含む免疫応答異常など とも関連していることなども報告されており、個体発生か ら病態生理というさまざまな状況下での脳内タンパク質の アルギニン残基のメチル化制御機能の重要性が本格的に解

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DOI: 10.14952/SEIKAGAKU.2024.960086 © 2024 公益社団法人日本生化学会 明され始めている³⁻⁵⁾.

近年,著者らは脳神経系においてその機能解析の十分に 進んでいない領域であるグリア細胞の一つのオリゴデンド ロサイトの脳内発生におけるタンパク質アルギニン残基の メチル化制御の重要性に関する新たな知見を得ることがで きた(図1)⁶⁾.本稿では、ヒストンメチル化に関連する総 説は他家に譲り、これまでの脳内タンパク質アルギニン残 基のメチル化修飾の役割に関する我々のいくつかの知見と ともに今後の展望について概説する.

タンパク質アルギニンメチルトランスフェラーゼ

タンパク質のアルギニン残基メチル化は、タンパク質 アルギニンメチルトランスフェラーゼ(protein arginine *N*methyltransferases: PRMTs)が触媒することがすでに知ら れている³⁻⁵⁾. PRMTsの活性中心ドメイン構造は進化上高 度に保存されており、その機能の重要性が容易に想定され る.哺乳類においてPRMTsはこれまでに11個のサブタイ プが同定されており、メチル基供与体である*S*-アデノシ ルメチオニン(AdoMet, SAM)からのメチル基転移様式に より3種に分類されている. さらに例外があるもののサブ タイプにより RGG, RGR, AGRやRXRといったある程度 の特異性を持った標的配列が存在している(図2).

3. PRMT1

PRMTsファミリー中でPRMT1は細胞内の最も主要なサ ブタイプであり、ファミリー中の存在比率が8割以上を占 めるとの報告もある.酵母におけるアルギニンメチル化酵 素Hmt1/Rmt1のホモログであり、インターフェロン受容体 (IFNAR)と相互作用する因子として同定されるとともに 初期応答遺伝子TIS1/BTG1やTIS2/BTG2と相互作用する 因子としても見いだされた.そこで、著者らは神経突起伸 展におけるPRMT1とその基質の一つとして同定された初 期応答遺伝子BTG2の役割について検討した.その結果、 PRMT1は主に核内に局在し、アルギニン残基のメチル化 によるBTG2タンパク質の核内発現量の確保が神経突起伸 展に必要であることを見いだした⁷⁾.

PRMT1はホモ二量体を形成することでその酵素活性を示し、RNA代謝やゲノム安定性などに関与する. さらに

Regulation of protein Arginine methylation during brain development

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図1 オリゴデンドロサイトの増殖・分化・髄鞘化へのタンパク質アルギニン残基メチル化酵素 CARM1の関与 CARM1の発現が強い胎生期のオリゴデンドロサイト前駆細胞(OPC)の増殖レベル維持だけでなく、生後に進行 するオリゴデンドロサイトの分化から髄鞘形成に至る過程にも CARM1の発現が必要である.詳細は文献6を参照 のこと.

PRMT1自体として七つのアイソフォームが選択的スプラ イシングによって生成される.それらはN末端配列特異的 な基質選択性を持ち,核内だけでなく細胞質に局在するア イソフォームも存在することが知られている.PRMT1の ノックアウト(KO)マウスは胎生初期に致死であること が報告されており,個体発生におけるPRMT1による全身 の器官・組織でのアルギニンメチル化はその生存に必須で あることは間違いない.さらに,この数年でPRMT1の脳 特異的なコンディショナルKO(cKO)マウスの検討結果 も複数報告され,髄鞘形成不全により生後2週間前後しか 生存できないことや,その原因として炎症抑制機能の低下 が関与している可能性が見いだされており,今後のさらな る研究の展開に期待が持たれる⁸⁾.

4. PRMT3

PRMT3はPRMT1のホモロジー検索により見いだされ, PRMTsサブファミリーの中で唯一そのN末端にZnフィン ガードメインを有することが報告されているのみであっ た.そこで,著者らはまずPRMT3の脳内局在および細胞 内局在の検討から実施した.その結果,PRMT3は神経細 胞の細胞体および樹状突起に局在すること,成体マウスの 脳内においては大脳辺縁系や運動神経核,小脳,海馬神経 などでその発現が観察されること,PRMT1の脳内発現が 生後約1週で低下していくにもかかわらず, PRMT3は胎 生後期から脳内での発現が増加し, 生後1週から4週にか けてその高発現が維持されることを見いだした⁹⁾. ほぼ同 時期に, PRMT3はリボソームタンパク質をメチル化する との報告がなされたことから, 成体脳におけるPRMT3の 細胞質や樹状突起での機能に興味が持たれた. そこで, 細 胞体および樹状突起にPRMT3が高発現している海馬神経 細胞におけるシナプス形成機構へのPRMT3の関与につい て検討したところ, リボソームタンパク質rpS2がPRMT3 によるメチル化により安定化するとともに, シナプスの spine形成に重要な役割をするαCaMKII発現量が維持され るというメカニズムを明らかにすることができた¹⁰⁾.

5. CARM1

4番目のPRMTsサブファミリーであるPRMT4はp160 ステロイド受容体コアクチベーターGRIPをbaitとする Yeast Two-Hybrid法により同定されたことから,現在では coactivator-associated arginine methyltransferase 1 (CARM1) として認知されている. CARM1はその局在が核内である ことから転写コアクチベーターとして直接転写因子をメ チル化し転写活性化するだけでなく,PRMTsサブファミ リーであるPRMT5のメチル化にも関与している. CARM1 の活性化はCBP/p300アセチルトランスフェラーゼなどで



図2 タンパク質アルギニン残基メチル化機構

アルギニン残基はまず各PRMTsによりモノメチル化される (MMA). PRMTsはアルギニン側鎖 δ -グアニジノ基の ω-窒素原子に一つのメチル基転移を触媒する. その後, PRMT7以外のPRMTsによりもう一つのメチル基が付加さ れジメチル化される. ジメチル化の経路は2種類ある. Type IのPRMTsサブタイプにより, モノメチル化されたのと 同一の ω -窒素原子に二つ目のメチル基が付加する (ADMA). また, Type IIのPRMTsサブタイプでは, モノメチル化 されていないもう一つの ω -窒素原子に二つ目のメチル基が付加する (SMDA). 詳細は文献3~5を参照のこと.

調節され, CARM1の発現量は, miR-15, miR-181c, miR-223 等のmicroRNAsによって制御されていることがすでに報 告されている. またCARM1のKOマウスは胎生後期ある いは出生後すぐ致死になることから、個体発生において CARM1の機能が重要であることが容易に想定できた. そ こで、著者らは脳の発生時期に制御されなければならない 機能の一つである神経細胞の増殖や分化機構へのCARM1 の役割について検討を実施した. その結果, RNA結合タ ンパク質HuDがCARM1と相互作用し、特定のアルギニン 残基がメチル化される事実を見いだすとともに、メチル化 HuDによりp21cip1/waf1 mRNAの安定性が低下し、神経細 胞の増殖状態が維持されるという分子メカニズムを明らか にした¹¹⁾. さらに, 最近著者らは脳発達過程における脳 梁オリゴデンドロサイト前駆細胞にCARM1が高発現して 増殖レベルを調整する可能性だけでなく、CARM1発現抑 制により成熟オリゴデンドロサイトへの分化抑制および髄 鞘形成阻害が生じる事実も見いだし、オリゴデンドロサイ

ト前駆細胞の増殖分化から髄鞘形成までの成熟化機構への CARM1の積極的な関与について明らかにした(図1)⁶⁾.

6. **PRMT8**

PRMT8はデータベース検索により活性中心の配列が PRMT1と顕著な相同性(80%以上)を示した因子として 同定され、そのN末端はPRMT1よりかなり長い配列を有 している.その後、PRMT8は細胞膜にも局在することや、 そのN末端にミリストイル化配列を持つことが見いださ れた.さらにPRMT8は他のPRMTsファミリーとは異な り、中枢神経系のみの発現を示していた.当時はPRMT8 を特異的に認識する良い抗体がなく、著者らが抗体作製 を試みながら、まずはPRMT8 mRNAの脳内局在をin situ hybridization法により検討した.著者らは、マウス胎仔の whole mount切片および成体脳切片から、PRMT8 mRNAは 脳および脊髄のみの発現であること、さらにはグリア細胞 にはPRMT8 mRNAの発現がみられず神経細胞のみの発現 であることを明らかにした¹²⁾. その後. PRMT8を特異的 に認識する抗体が完成し、生後28日をピークにPRMT8タ ンパク質が発現増加することや海馬や扁桃体の神経細胞で 発現が強いことを見いだすことができた. しかし, 著者ら が作製したPRMT8抗体は神経細胞内のPRMT8の局在がほ ぼ核内で観察される結果となり、これまでに報告されてい るPRMT8の細胞膜局在とは異なる結果となった. そこで 著者らは次にこの原因追究のためPRMT8のN末端の翻訳 開始コドンの検討を行った¹³⁾. その結果,翻訳開始メチ オニンの可能性として3か所が見いだされ、1stメチオニン の配列で強制発現すると確かに細胞質だけでなく細胞膜に も局在を示した. さらに2ndメチオニンの配列で強制発現 すると細胞質のみの局在を示し、 ミリストイル化配列がな くなる3rdメチオニンの配列で強制発現すると主に核内の 局在を示すことを明らかにした. そして脳抽出サンプル中 のPRMT8の分子量と一致したのが3rdメチオニンの配列 で翻訳開始したPRMT8であったことから、脳内では何ら かの制御機構によりミリストイル化配列がない少し短い PRMT8の発現が神経細胞PRMT8としてdominantである可 能性を見いだした¹³⁾.最近になり他家から,PRMT8はタ ンパク質メチル化機能だけではなく神経細胞膜のホスファ チジルコリンの加水分解酵素であるホスホリパーゼ活性も 有するとの報告や、シナプスのspine 成熟化機構において、 RNA結合タンパク質であるG3PB1と翻訳開始因子eIF4E との相互作用レベルをPRMT8によるG3PB1のタンパク質 メチル化が制御していることが見いだされるなど、中枢神 経系における今後のPRMT8研究の推進に大きな期待を抱 いている14,15).

7. おわりに

本稿で紹介した著者らのPRMT1, PRMT3, CARM1, PRMT8に関するさまざまな研究により,胎生期および生 後発達から脳の成熟後にまでタンパク質のアルギニン残基 のメチル化がPRMTsの各サブタイプにより適切に制御を 受けることで,神経細胞やオリゴデンドロサイトの発達・ 成熟に多彩で重要な役割を果たすことが明らかになって きた.脳内PRMTsの機能に関しては,ここでは紹介しき れない数多くの内容の研究成果がすでに見いだされている が,サブタイプが11個もあることからも,脳神経系にお いてまだまだ未知のPRMTsの機能が豊富に存在すると考 えられる.さらに脱メチル化にまでその視野を広げるとさ まざまな神経系の疾患発症機序へのタンパク質のアルギニ ン残基のメチル化の重要性が明らかになる可能性を大いに 秘めている^{4,5)}.

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■研究テーマと抱負 神経科学研究の中 ではニッチな領域であると思われる、タンパクメチル化、オリ ゴデンドロサイトそして漢方という全くまとまりの感じられな い研究テーマ達にドッグファイトで挑戦中(スタッフの先生方 に超感謝).

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 *宮田信吾、清水尚子、<u>石野雄吾</u>、遠山正彌 Novel signal transduction mechanisms involved in oligodendrocyte differentiation and psychiatric disorders
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______ 生後発達期のオリゴデンドロサイト産生における DBZ の機能解析

Functional analysis of DBZ in oligodendrocyte generation during early postnatal development

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 2. 慢性ストレスによる髄鞘構造異常・機能変化の分子機構解明 公益財団法人大阪難病研究財団 2023 年度 第 29 回医学研究助成 石野雄吾(代表研究者), 清水尚子, 宮田信吾 2023 年度 (2023.04-2024.03) 東洋医学研究所 清水 尚子 業績一覧

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