Allergology International. 2007;56:249-255
DOI: 10.2332/allergolint.O-06-475

ORIGINAL ARTICLE

Analysis of Perimenstrual Asthma Based on Questionnaire Surveys in Japan

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ABSTRACT

Background: Perimenstrual asthma (PMA) has been documented in 30% to 40% of asthmatic women; the characteristics of PMA have also been well described. However, there have been few epidemiological investigations of PMA in practice. In this study, we analyzed PMA based on a questionnaire survey carried out in Japan and compared the results with those of studies reported previously.

Methods: For 8 weeks from September through October 2004, a questionnaire survey was administered to patients with bronchial asthma and their attending physicians. The questionnaire surveyed asthma control, asthma-related emergencies and satisfaction in daily life. The attending physicians were questioned about patient profiles and medications. All female patients who were menstruating during the survey period and who were known to have asthma exacerbation related to menstruation were allocated to the PMA group; those who were not were allocated to the non-PMA group.

Results: The rate of PMA in female patients who were menstruating during the survey period was 11.3% in this study. Characteristic features of the PMA group (n = 54) included more severe disease, worsened disease control and more aggressive patient management, including increased oral corticosteroid use compared with the non-PMA group. The rates of emergency episodes in the PMA group were higher than in the non-PMA group. There was a significant increase in aspirin intolerant asthma (AIA, 25.5%) in the PMA group compared with the non-PMA group (8.4%).

Conclusions: Attention should be paid to the lack of knowledge regarding PMA in patients with asthma in actual clinical settings. The low rate of PMA reported in this study may be due to the study method using self-reports of PMA by patients without sufficient knowledge, and may not be an accurate representation of the actual incidence of the disease. The clinical similarity of PMA to AIA in this study may also provide a new insight into the mechanism of PMA.

KEY WORDS

aspirin intolerant asthma, perimenstrual asthma, questionnaire survey

INTRODUCTION

It is well known that some female patients with asthma experience an exacerbation of asthma symptoms during the premenstrual or menstrual phase of their cycle. This has been described using the term menstrual or perimenstrual asthma (PMA). After Frank's first report on PMA in 1931,[1] many studies focused on the relationship between menstruation and asthmatic symptoms.[2,3] In the 1980s, the characterization of PMA was well established, including peak expiratory flow (PEF) abnormalities in addition to increases in asthmatic symptoms during the perimenstrual phase in PMA patients.[4] Recent studies have

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Received 13 October 2006. Accepted for publication 25 December 2006.

highlighted the causes of PMA, such as the role of hormones.[5,6]

Because bronchial asthma is one of the most common diseases, management of bronchial asthma, including medical interviews, can play an important role in actual clinical settings. During the medical interview, it is very important for the physician to note predictive factors of asthma exacerbation, such as menstruation. However, there is likely to be a discrepancy between studies of PMA and the perception of PMA by physicians in practice and the relationship between asthma exacerbation and menstruation may not receive adequate attention. Although around 30% to 40% of women with asthma report perimenstrual worsening of symptoms,[7-10] many physicians tend to think that the rate of PMA is much lower. This is because both female patients and their physicians have paid little attention to PMA.[11] It is clear that adequate information about PMA, including characteristic symptoms, hyperresponsiveness and respiratory dysfunction,[12-15] pathogenesis[5,6] and therapy,[12,16] are well documented. However, there are few studies that compare PMA patients with non-PMA patients using a questionnaire survey, include all patients with asthma, and are administered in an actual clinical setting. Hence, we designed a study of PMA in actual practice. The prevalence of the conception that PMA is not widely accepted in an actual clinical setting can improve the management of asthma.

A questionnaire survey was administered by the Niigata Asthma Treatment Study Group; the survey took problems regarding asthma management into consideration. The subjects in this survey were adult patients with bronchial asthma who visited medical institutions in Niigata Prefecture, starting in 1998. The attending physicians of these patients were included in the survey. Based on these surveys, we have reported the clinical characteristics of adult bronchial asthma patients,[17] the characteristics of elderly bronchial asthma[18] and near fatal asthma,[19] the relationship between smoking and gender in asthma patients[20] and changes in asthma management.[21,22] At the beginning of this survey (1998), there were no questions about the relationship between asthma symptoms and the menstrual phase: these questions were added in 2004 for the reasons mentioned above. In this paper, the analysis was based on the results obtained from surveys conducted from 2004 onwards in order to examine PMA in an actual clinical setting.

METHODS

The questionnaire used in this study was administered in Niigata Prefecture, Japan, under the Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki. The institutions involved were 28 large hospitals (200 beds or more), 15 small hospitals (<200 beds) and 35 clinics (no beds). Three thousand six hundred and fifty questionnaires were prepared and 2,865 were answered (response rate: 78.5%). The contents of the questionnaire are shown in Table 1 (originally in Japanese). The questionnaire was carried out over 2 months from September to October 2004. Subjects were adult patients (aged 16 years and over) with bronchial asthma who regularly visited the participating institutes for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves. Therefore, the understanding of technical terms such as "attack" or "unconsciousness" in the questionnaire (Table 1) depended upon the individual patients.

For an evaluation of asthma control, patients were asked about their mean expiratory peak flow value (PEFV) and the incidence of asthma attacks during the 2 weeks prior to answering the questionnaire. During the year prior to the questionnaire, the patients were also asked about their asthma by choosing one of the following three answers: "few attacks," "seasonal attacks," and "frequent attacks." They were also asked about asthma-related work or school absences. The questionnaires asked about asthma-related symptoms in the 2 weeks prior to the questionnaire, including cough and sputum in the morning and at night, and sleep disturbances. The questionnaire also inquired about asthma-related emergencies, including ambulance use, emergency department visits and hospitalization, and life-threatening events such as unconsciousness during asthma attacks, attacks requiring respirator management, and asthma attacks induced by an anti-inflammatory agent (aspirin intolerant asthma, AIA). The subjects were required to answer "yes" or "no" to the following five questions: "Have you ever been hospitalized due to asthma?" "Have you ever been taken by ambulance or visited an emergency room due to an attack?" "Have you ever used a respirator due to an asthma attack?" "Have you ever been unconscious due to an asthma attack?" and "Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicines?" To evaluate problems in asthma management and treatment related to normal activity levels, the questionnaires asked patients about their satisfaction in daily life. The subjects answered by choosing 1 of 5 answers: "very satisfied," "fairly satisfied," "mediocre," "slightly dissatisfied, "and "dissatisfied."

In addition to the patients' completing the questionnaire, their physicians were asked to supply details of current treatment, primarily identifying control medication, the type of asthma (atopic or nonatopic) in accordance with the elevation of serum total IgE or detection of specific IgE for allergens, and the severity of asthma in accordance with the Japanese Society of Allergology guideline for the diagnosis and management of bronchial asthma. The definition of severity of asthma is essentially the same as that used by the

Table 1 Questionnaires administered to asthma patients in this study (the original was in Japanese.)

Age: years Gender: male/female
Question 1
When were you first given a diagnosis of bronchial asthma? Year: Month: Day:
Question 2
1) Choose your smoking status
(non-smoker, ex-smoker, current smoker)
2) To ex-smokers, please answer the following:
At what age did you start smoking? Your starting age:
At what age did you stop smoking? Your stopping age:
How many cigarettes did you smoke per day? Cigarettes/day (mean):
Is your smoking cessation related to your asthma? Yes or No:
3) To current smokers, please answer the following:
At what age did you start smoking? Your starting age:
How many cigarettes do you smoke per day? Cigarettes/day (mean):
Question 3
1) Do you use a peak-flow meter? (Yes, No)
2) What was the average value of your peak-flow meter during the last 2 weeks?
morning: night:
Question 4 Select one answer to each of the following questions:
1) How often did you have asthma attacks during the last 12 months?
(frequent attacks, seasonal attacks, few attacks)
2) How often did you have asthma attacks during the last 2 weeks?
(5–7/week, 3–4/week, 1–2/week, absent)
3) How severe were your asthma attacks during the last 2 weeks?
(impossible to move, impossible to lie down, possible to lie down, strider, dyspnea on exertion)
4) Have you ever been hospitalized due to asthma?
(yes, no)
5) Have you ever been taken by ambulance or visited an emergency room due to an attack?
(yes, no)
6) Have you ever been placed on a respirator due to an asthma attack?
(yes, no)
7) Have you ever been unconscious due to an asthma attack?
(yes, no)
8) Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicine?
9) Have you been absent from work or school due to an asthma attack?
(yes, no)
Question 5
How bad was your asthma during the last 2 weeks?
(very good, fairly good, mediocre, slightly bad, bad)
Question 6
Describe your symptoms during the last 2 weeks:
1) in the morning
(cough, sputum, chest tightness, stridor, dyspnea, no symptoms)
2) at night
(cough, sputum, chest tightness, stridor, dyspnea, no symptoms)
3) sleep disturbance
(sometimes cannot fall asleep due to dyspnea, cannot have a good sleep due to dyspnea, waking up in the night due to chest tightness, none)
Question 7
Do you feel satisfied with your daily life?
(very satisfied, fairly satisfied, mediocre, slightly dissatisfied, dissatisfied)
Question 8
Select one answer to each of the following questions if you are a woman.
1) Are you currently menstruating?
(yes, no)
2) Does your menstruation influence your asthma symptoms?
(always, sometimes, no)
Only answer the following questions if you answered 'always' or 'sometimes' in Question 8.2.
3) In what way does your menstruation influence your asthma symptoms?
(worsens symptoms, improves symptoms)
4) When are your asthma symptoms influenced?
(before menstruation, during menstruation, after menstruation)

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Among all female patients who were menstruating during the survey period, patients who reported asthma exacerbation related to menstruation were allocated to the PMA group and those who did not were allocated to the non-PMA group.

Table 2 Patient background

	non-PMA	PMA
age (mean +/− SD)	36.8 +/− 9.5	38.2 +/− 9.7
duration (year: mean +/− SD)	11.9 +/− 10.7	13.9 +/− 10.7
type: % (N: atopic/nonatopic)	84.6/15.4 (351/64)	87.5/12.5 (49/5)
severity: % (N: Step1/2/3/4)	34.3/34.8/28.8/2.8 (137/139/115/11)	22.2/25.9/42.6*/9.3* (12/14/23/5)
smoking status: % (N: Non/Ex/Cu)	57.1/24.3/18.2 (238/103/76)	74.5*/21.8/3.6* (41/12/2)
number of PEF user (%)	115 (36.6)	21 (37.5)

*: $p < 0.05$ *v.s.* non-PMA, PMA: perimenstrual asthma, Non: non-smoker, Ex: ex-smoker, Cu: current smoker, PEF: peak flow meter

Table 3 Drug/Medication

	non-PMA	PMA
ICS use/non-use (%use)	358/64 (84.4)	47/8 (83.9)
LTRA use/non-use (%use)	157/265 (37.0)	30/26 (53.6) *
OCS use/non-use (%use)	12/410 (2.8)	6/50 (10.7) *
OCS dose (mg/day: calculated as PSL)	5.9 +/− 3.6	9.3 +/− 5.5
LABA use/non-use (%use)	136/286 (32.1)	29/17 (51.8) ***
salmeterol use/non-use (%use)	79/343 (18.6)	15/41 (26.8)
OSRT use/non-use (%use)	190/232 (44.8)	39/17 (69.6) ***

*: $p < 0.05$, ***: $p < 0.001$ *v.s.* non-PMA, PMA: perimenstrual asthma, ICS: inhaled corticosteroid, LTRA: leukotriene receptor antagonist, OCS: oral corticosteroid, PSL: predonisolone, LABA: long acting beta2 agonist, OSRT: oral sustained-released theophylline

Table 4-a Incidence of asthma attacks, percentages of predicted peak flow values, asthma-related symptoms and sleep disturbances during the 2 weeks prior to answering the questionnaire

	non-PMA	PMA
asthma attacks present/absent (%)	100/273 (26.8/73.2)	26/29** (47.2/59.8)
PEFV (morning, mean +/− SD)	385.5 +/− 70.1	357.1 +/− 99.4
PEFV (night, mean +/− SD)	395.7 +/− 67.8	364.7 +/− 92.2
ARS in morning: present/absent (%)	211/213 (49.8/50.2)	36/20* (64.3/35.7)
ARS in night: present/absent (%)	173/251 (40.3/59.7)	28/28 (50.0/50.0)
sleep disturbance: present/absent (%)	91/333 (21.5/78.5)	17/39 (30.4/69.6)

*: $p < 0.05$, **: $p < 0.01$ *v.s.* non-PMA, PMA: perimenstrual asthma, PEFV: peak flow value, ARS: asthma-related symptoms

Table 4-b Asthma attacks and asthma-related work absences during the 1-year period prior to answering the questionnaire

	non-PMA	PMA
seasonal/few/frequent/NA (%)	158/180/36/50 (37.3/42.5/8.5/11.8)	25/12**/12**/7 (44.6/21.4/21.4/12.5)
ARWA: present/absent (%)	73/326 (18.3/81.7)	12/41 (22.6/77.4)

**: $p < 0.01$ *v.s.* non-PMA, PMA: perimenstrual asthma, ARWA: asthma-related work or school absences

Table 5 Satifaction in daily life

	very satisfied, fairly satisfied, mediocre, slightly dissatisfied, dissatisfied (%)
non-PMA	78/221/86/29/6 (18.4/52.1/20.3/6.8/1.4)
PMA	7/26/14/8/0 (12.7/47.3/25.5/14.5/0.0)

PMA: perimenstrual asthma

The results are expressed as arithmetic means (±SD) for continuous variables. The differences between dichotomous variables were analyzed by chi-square test. The Kruskal-Wallis test was used to test for the equality of distributions of continuous variables. The pairwise year-to-year comparison was per-

Table 6 Hospitalization, ambulance use or ED visits, attacks with unconsciousness, respirator management and AIA attacks

	non-PMA	PMA
hospitalization: present/absent (%)	153/260 (37.0/63.0)	28/27* (50.9/49.1)
ambulance use or ED visits: present/absent (%)	174/242 (41.8/58.2)	36/18*** (67.9/32.1)
attacks with unconsciousness: present/absent (%)	15/392 (3.7/96.3)	9/46*** (16.4/83.6)
respirator management: present/absent (%)	20/382 (5.0/95.0)	4/49 (7.5/92.5)
AIA attacks: present/absent (%)	35/380 (8.4/91.6)	14/41*** (25.5/74.5)

*: $p < 0.05$, ***: $p < 0.001$ *v.s.* non-PMA, PMA: perimenstrual asthma, ED: emergency department, AIA: aspirin induced asthma

formed by chi-square test and Wilcoxon's rank sum test with Bonferroni's correction for the significance level. All statistical analyses were performed with the statistical software BMDP 3S (BMDP, Los Angeles, CA, USA) and Statxact (Cytel Software Co., Cambridge, MA, USA).

RESULTS

PATIENT BACKGROUND

Of the female patients who were menstruating during the study period, 56 were classified as being in the PMA group and 424 were classified as being in the non-PMA group. Of the PMA patients, 37 (66.1%) reported that menstruation sometimes influenced their asthmatic symptoms, and 19 (33.9%) reported that menstruation always influenced their asthma. Asthmatic symptoms worsened in 51 patients (91.1%) with PMA; there were no reports of improved symptoms during menstruation. Asthma symptoms were affected in 30 patients (53.6%) before, in 9 patients (16.1%) before/during and in 14 patients (25.0%) during menstruation. The backgrounds of patients in the PMA and non-PMA groups are summarized in Table 2. The proportion of patients with step 3 and 4 disease severity was significantly higher in the PMA group than in the non-PMA group. The proportion of non-smokers was also significantly higher in the PMA group than in the non-PMA group. There were no significant differences in age, disease duration, type of asthma, or in the number of PEF users between the groups.

DRUG/MEDICATION

In terms of medication (Table 3), there was a significantly higher usage of leukotriene receptor antagonists (LTRA), oral corticosteroids (OCS), long-acting beta2 agonists (LABA) and oral sustained-released theophylline (OSRT) among patients in the PMA group compared with the non-PMA group. A tendency towards higher usage of salmeterol in the PMA group was noted but was not significant.

ASTHMA CONTROL AND SYMPTOMS

There were no significant differences between the two groups in asthma control and symptoms during the 2 weeks prior to answering the survey, except that there was a higher rate of asthma attacks among patients in the PMA group compared with the non-PMA group (Table 4-a). During the 1-year period prior to answering the survey, the proportion of respondents who reported 'frequent' asthma attacks was significantly higher in the PMA group than in the non-PMA group, despite no significant differences in asthma-related work or school absences (Table 4-b).

SATISFACTION IN DAILY LIFE AND ASTHMA-RELATED EMERGENCY EPISODES

There was no significant difference in satisfaction in daily life between the two groups (Table 5). The results regarding asthma-related emergency episodes are summarized in Table 6. Higher rates of hospitalization, ambulance or emergency department visits were reported by patients in the PMA group compared with those in the non-PMA group. The rates of asthma attacks with unconsciousness and AIA episodes were also significantly higher in the PMA group than in the non-PMA group.

DISCUSSION

In this study, we reported on the characteristics of PMA based on responses to a questionnaire survey. The first problem when proposing a study of PMA is defining what PMA is. In spite of many studies on PMA, no standard definition of PMA has been established. In many of these studies, exacerbation of asthmatic symptoms in association with menstruation was used as the definition of PMA,[2,4,7-10,23,24] although decreases in forced expiratory flow (FEV1) or in PEF, scoring of symptoms and frequency of rescue medication for attacks were sometimes used instead. Note that the definition of PMA used in this report was retrospective self-reports of exacerbation of asthma symptoms based on responses to the questionnaire.

Regarding the rate of PMA, there was an interesting discrepancy between previous studies and our results. In western countries, the rate of PMA in menstruating female patients has been reported to be 30–40%. However, the PMA rate found in this study was only 11.3%. It is well known that some patients with PMA cannot recognize exacerbations of their asthmatic symptoms or decreases in respiratory function.[4,10] Chandler *et al.* showed that only 5 patients with PMA recognized the exacerbation of their asthmatic symptoms by themselves, even though de-

creases in FEV1 of more than 20% were associated with menstruation in all 20 patients.[12] This may be the reason for the low rate of PMA found in our study. In fact, a previous study in Europe, which similarly used self-reports of exacerbated symptoms in response to a questionnaire to define PMA, showed only an 8.2% PMA rate,[11] suggesting that the observed differences in the incidence of PMA are not due to race but to study design. However, both physicians and female asthma patients should pay attention to the current lack of patient knowledge relating to PMA because predictive factors of asthma exacerbation, such as menstruation, are, in practice, very important in the management of female patients with asthma.

Because our questionnaire survey only addressed limited clinical features of asthma, it is impossible to compare these results with the clinical characteristics of PMA that were discussed previously, namely, the associations with duration and cycle of menstruation, use of contraceptives and PMA-specified symptoms. However, there were some obvious clinical features of PMA in this study. Regarding the severity of asthma, including the frequency of asthma attacks and symptoms (shown in Tables 2, 4), patients in the PMA group suffered more severe asthma than patients in the non-PMA group, similar to results from previous studies.[8,9,16,24-26] Therefore, more aggressive patient management, including increased oral corticosteroid use, was used with patients in the PMA group than in the non-PMA group (Table 3). The rates of emergency episodes in the PMA group, including hospitalization, ambulance or emergency department visits, were higher than in the non-PMA group. These were also similar to those reported in previous studies.[27-31]

Among the clinical features of PMA outlined in this report, it is very interesting to note that there was a significantly greater proportion of AIA (25.5%) among patients in the PMA group compared with the non-PMA group (8.4%). This may indicate a significant association between PMA and AIA. Moreover, the characteristics of AIA reported previously are very similar to those of PMA.[19,32,33] LTRA have been reported to be effective in asthma control in both PMA[25] and AIA.[34,35] The use of nonsteroidal anti-inflammatory drugs in PMA might not cause this relation, because Forbes *et al*. reported that there was no association between the use of nonsteroidal anti-inflammatory drugs and PMA.[11] These results may indicate that a shared dysfunction of leukotriene and prostaglandin metabolism may be involved in PMA and AIA. Although there is no established cause of PMA, this similarity may contribute to the elucidation of the mechanism of PMA and may present a new strategy not only for PMA but also for AIA.

In summary, using a questionnaire survey conducted in Japan, we compared the clinical features of PMA with those reported previously. The lower rate of PMA found in this study is likely due to the study method used, namely self-reports of PMA. Both physicians and their female asthma patients should pay attention to the current lack of patient knowledge relating to PMA. An interesting observation in this study was that there was a significant increase in the incidence of AIA among patients in the PMA group compared with the non-PMA group, indicating that the clinical similarity between PMA and AIA may provide a new insight into the mechanism of PMA.

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