Original Article

Bronchial hyperreactivity in perimenstrual asthma is associated with increased Th-2 response in lower airways

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Background: perimenstrual asthma (PMA) is a commonly observed, usually difficult-to-treat asthma phenotype. The mechanisms underlying this phenomenon remain unexplained. The aim of the study was to assess the degree of airway hyperresponsiveness and its relationship to proinflammatory cytokines concentration in lower airways of PMA compared to non-PMA patients.

Methods: Premenopausal women with regular menstrual cycles diagnosed as: PMA (n=12), non-PMA asthmatics (n=9), and healthy controls (n=10) were prospectively followed for 10 weeks over two consecutive menstrual cycles. The bronchial responsiveness (BR) test to methacholine was performed in each subject prior to the study. The serum for total immunoglobulin E (IgE) concentrations was taken and sputum was induced in the 26th day of each of the two cycles. Sputum concentration of eotaxin, IL-4 and IL-10 were measured by ELISA.

Results: Levels of BR to metacholine as well, as total blood IgE concentrations in PMA subjects were significantly higher than in non-PMA asthmatics and healthy controls (P=0.001, P=0.022 respectively) and correlated with each other (P=0.030; r =–0.65). Sputum eotaxin and IL-4 concentrations in luteal phase were increased in PMA patients when compared with non-PMA asthmatics (P=0.016; P=0.041, respectively) and healthy subjects (P<0.001 both cytokines). No differences for the sputum levels of IL-10 among studied groups were seen.

Conclusions: BR level in perimenstrual asthma is higher than in non-PMA asthmatics and correlates with increased total IgE serum concentration. The increased level of BR in PMA patients is associated with a shift in the type-1/type-2 cytokine balance toward a type-2 response.

Keywords: Bronchial hyperreactivity; cytokines; perimenstrual asthma

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Introduction

Asthma, one of the most common chronic respiratory diseases might deteriorate during perimenstrual period, representing a phenomenon known as perimenstrual asthma (PMA) (1). PMA occurs in 8.2% to 57% of asthmatic women in childbearing age (2-4) and has often more severe course than other asthma phenotypes (5-7). However, current knowledge about the pathogenesis

of PMA is incomplete and inconsistent. Most, but not all (8) data, obtained from studies conducted so far underlie the hypothesis, that links cycle-related changes of female steroid sex hormones with changing concentrations of proinflammatory mediators in both, peripheral blood and lower airways of patients with PMA (9-11).

Increased bronchial hyperreactivity has been suggested as one of the most important background factors for the exacerbation of asthma during perimenstrual period (12). Tan *et al*. demonstrated that airway responsiveness to adenosine 5'-monophosphate (AMP) in asthmatic women was highest during the premenstrual period (13). Previously performed studies showed, that both, estrogen and progesterone are involved in modifying airway responsiveness (14-19) which may suggest, that PMA exacerbations could be triggered by some characteristic pattern of female sex hormones concentrations during perimenstrual period. According to some studies, PMA also seems to be closely linked to some atopy markers. In study by Pereira-Vega *et al.* all women diagnosed with PMA had total blood immunoglobulin E (IgE) values increased above normal (20).

Data obtained in human asthma patients indicate the important role of eotaxin, IL-4 and IL-5 in mediating airway hyperresponsiveness and inflammatory cell recruitment into lower airways (21-23). However, data regarding the concentrations of inflammatory markers in lower airways of PMA patients are extremely scarce. In their study Nakasato *et al.* revealed that serum levels of leukotriene C4 (LTC4) [but not IL-1beta, IL-4, IL-5, IL-6, Granulocyte-macrophage colony-stimulating factor (GM-CSF), histamine, LTB4 and PAF] were significantly higher during perimenstrual exacerbations of asthma than after recovery (11). De Oliveira found less inflammatory cells in the airways of ovariectomized rats, than in the healthy controls (24). In this study, administration of estradiol was associated with the influx of inflammatory cells into the bronchoalveolar lavage and increased release of IL-1β and tumor necrosis factor (TNF) by (bronchoalveolar lavage) BAL cells (24). Similarly, progesterone administration significantly increased the release of IL-10, IL-1β, TNF by BAL cells. Oguzulgen revealed higher levels of exhaled air nitric oxide (eNO) concentration and increased induced sputum eosinophil count before the expected menstruation in PMA patients (25).

Since progesterone has been proved to directly enhance T cell differentiation into Th2 cells (26) and increased concentrations of Th2-derived cytokines (e.g., IL-4, IL-5) as well as eotaxin are believed to participate in the development of airway hyperresponsiveness, we hypothesized that increased concentration of these cytokines in lower airways of PMA patients (caused by higher progesterone concentration in luteal phase of the cycle) is responsible for asthma deterioration during this period. To test this hypothesis we measured levels of these cytokines in lower airways of PMA patients in luteal phase of menstrual cycle and compared them with non-PMA asthmatics and healthy controls.

Methods

Study population

A three-arm, case-control clinical study (women in childbearing age with PMA *vs.* non-PMA asthmatics *vs.* healthy control group) was designed. The informed, written consent was obtained from all study participants. The study was approved by ethics committee of the Medical Faculty, Silesian Medical University, Katowice, Poland.

Thirty one premenopausal women with regular menstrual cycles from the outpatient pulmonology and gynaecology units of the Central Clinical Hospital of the Silesian Medical University and from neighbouring allergy outpatient clinic were screened for PMA symptoms. Of these, 12 fulfilled entry criteria and were recruited to PMA group. PMA was diagnosed on the basis of typical clinical history of asthma [mild to severe according to current GINA recommendations (27), confirmed by the positive metacholine challenge test] with cyclical clinical asthma deterioration during luteal phase and/or during the first days of menstruation and/or ≥20% reduction of peak expiratory flow (PEF) values up to 5 days before, or during menstruation, for at least 5 consecutive years. PMA patients were all treated according to current GINA guidelines (27) and were told not to withdraw any asthma controlling drugs during the study. Other exclusion criteria for entry were: (I) age <18 and >45 year; (II) irregular menstrual cycles (cycle-to-cycle variability >3 days); (III) use of oral contraceptives in a period shorter than 6 months before recruitation; (VI) pregnancy and breast-feeding; (V) current smoking and/or history of >5 pack-years; (VI) history of infection for 4 weeks prior to the recruitation and in course of the study; (VII) any chronic diseases other than asthma; (VIII) poor patient compliance.

Each out of the nine non-PMA asthmatics recruited in the study had a typical clinical history of asthma [mild to

severe according to current GINA recommendations (27), confirmed by the positive metacholine challenge test] with no exacerbations of clinical symptoms and/or PEF reduction 5 days before, or during menstruation.

Ten control subjects volunteered to take part in the study. They had no symptoms and no history of asthma or any other chronic disease and did not use any local or systemic medication.

Exclusion criteria for both, non-PMA asthmatics and healthy controls were the same as for the PMA patients.

Study design

Each of the women recruited to one of the three groups studied has prospectively been followed for 10 weeks over two consecutive menstrual cycles. At least 2 months prior to study, bronchial responsiveness (BR) to metacholine was performed in each subject. All women completed asthma symptom questionnaire, asthma control test and recorded PEF twice daily during both menstrual cycles. Total IgE serum concentrations as well, as sputum induction were determined in the 26th day of each, of the two cycles. Sputum concentration of eotaxin, IL-4 and IL-10 were measured by sandwich ELISA test. The averaged results obtained from two consecutive cycles have been subjected to statistical analysis.

Lung function and metacholine challenge test

Lung function was measured with dry spirometer (MasterLab, Jaeger, Germany) according to the recommendations of the European Respiratory Society (28).

Bronchial hyperreactivity in metacholine challenge testing was assessed according to the protocol described by Hargreave *et al.* (29).

Sputum induction and analysis

Sputum was induced by hypertonic saline inhalation (3%, 4% and 5% for 7 min) by an ultrasonic nebulizer device (Thomex MB, Medbryt, UK) and processed according to a method previously described (30).

Measuring cytokine levels

Sputum eotaxin, IL-4, and IL-10 concentrations were measured by ELISA kits (R & D Systems, McKinley Place N. E. Minneapolis, USA) according to the manufacturer's protocol.

Statistics

Statistical evaluation was performed with software package (Statistica 6.0). Kolmogorov-Smirnov test was used to test variables for normal distribution. Student *t* test or Wilcoxon test were used to determine the differences between parameters in the different phases of the menstrual cycle. Inter-group comparisons were performed using Kruskal-Wallis ANOVA and Mann-Whitney U test. Spearman`s rank correlation test was used to evaluate correlations between different parameters. P values of <0.05 were accepted as statistically significant.

Results

Baseline characteristics, PC20 and total serum IgE

Baseline characteristics of all patients included is summarised in *Table 1*. Groups were comparable with respect to age, smoking status and FEV_1%VC values. Asthma control measured by asthma control test (medians and ranges are in brackets) was significantly (P<0.05) worse in PMA group: 17 points (11–23 points) than in non-PMA asthmatics: 22 points (19–25 points), while the average daily use of inhaled steroids in PMA patients was significantly higher than among non-PMA asthmatics [800 *vs.* 400 mcg budesonide (BUD)/day, P<0.05] (31).

In metacholine challenge test PC_{20} values were significantly lower in both, PMA and non-PMA asthmatics, than in healthy control group (P=0.001). When compared to non-PMA asthmatics, PC_{20} values to metacholine in PMA group was also significantly lower (P=0.044; *Table 1*).

Inter-group comparisons revealed significant differences in total serum IgE level (P=0.022), with a higher total IgE concentration in PMA, than in non-PMA asthmatics (P=0.032; *Table 1*). In PMA group total IgE concentration in luteal phase of the menstrual cycle was reversely correlated with PC_{20} values (P=0.030; r =–0.65) (*Figure 1*).

Induced sputum cytokine levels

Measurable concentrations of eotaxin and IL-4 were found in all sputum samples assayed. Sputum IL-10 levels were undetectable in one person in PMA group and in one non-PMA asthmatic. Sputum cytokine levels in groups studied are presented in *Table 2*.

Sputum eotaxin and IL-4 concentrations in luteal phase of the menstrual cycle in PMA subjects were significantly higher than in non-PMA asthmatics (P=0.016; P=0.041,

Table 1 Characteristics of the participants (n=31)*

Characteristics	PMA patients (n=12)	Non-PMA asthmatics (n=9)	Healthy subjects (n=10)	P**
Age [years]	28.6 [20–39]	30.8 [22–43]	32.1 [22–45]	0.86
PC_{20} metacholine (mg/mL)	1.09 (0.05–4.3)	1.8*** (0.11–6.11)	>25	0.001
FEV_1 (% PRED)	92.10 (36.3–121.3)	96.89 (83.2–115.7)	105.4 (108.3–119.0)	0.038
FEV_1%VC (%)	73.2 (41.2–96.9)	80.5 (62.6–98.4)	93.1 (81.8–97.5)	0.421
Total serum IgE (IU/mL)	725.1 (3.1–4,557)	649.9**** (35.5–3,284)	57.4 (44–195.0)	0.022

*, data are expressed as medians and ranges (maximal and minimal values are in brackets); **, P values for inter-group comparisons (Kruskal-Wallis ANOVA); ***, P=0,044 for PMA-non-PMA asthmatics differences (Man-Whitney U test); ****, P=0.032 for PMA-non-PMA asthmatics differences (Man-Whitney U test). PC_{20}, provocating concentration of metacholine, which caused a 20% decrease of FEV_1 value; FEV_1, forced expiratory volume in 1 s (percentage of predicted value); VC, vital capacity; IgE, immunoglobulin E; PMA, perimenstrual asthma.

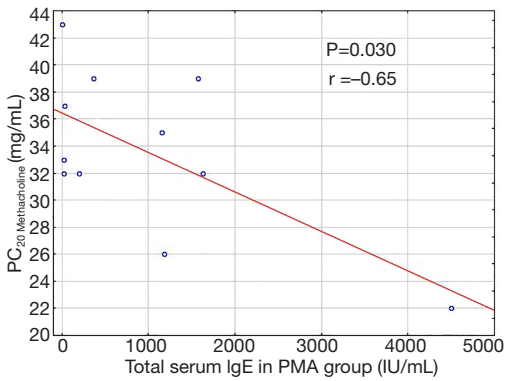

Figure 1 The correlation between total serum IgE concentration with PC20 values in PMA group. IgE, immunoglobulin E; PMA, perimenstrual asthma.

respectively) and healthy control group (P<0.001, both cytokines) (*Table 2*). No differences (P>0.05) were noticed in sputum levels of IL-10 between all groups studied (*Table 2*).

Discussion

PMA is one of the asthma phenotypes wherein the disease worsens cyclically in the luteal or perimenstrual phase of the cycle, leading to a recurrent loss of the disease control. Although, according to the results of epidemiological studies, PMA occurs in 8.2% to 57% of asthmatic women in childbearing age (1-4) and the disease exacerbations have often more severe course, than in other asthma phenotypes (5-7), the phenomenon of PMA still remains unclear. It is suggested that the exacerbations of asthma symptoms in PMA are associated with perimenstrual, increased airway hyperresponsiveness (12,13), dependent on fluctuating concentrations of sex hormones (9-11,14,17-19) and proinflammatory mediators (11,24,25). However, of the few studies conducted so far on the molecular basis of PMA, most focused on the markers of systemic inflammation (11,20) or was carried out in animal models (17,19,24). With this in mind, we designed a study to evaluate the possible involvement of proinflammatory cytokines in lower airways of PMA patients in the development of airway hyperresponsiveness and the co-related disease exacerbation in perimenstrual period. Additionally, in our study we compared markers of inflammation in the lower respiratory tract in patients with PMA and non-PM asthmatics, in order to better understand the molecular basis of PMA phenotype.

To our best knowledge, this is the first study, which demonstrates that PMA phenotype is characterized by a significantly higher degree of airway hyperresponsiveness in luteal phase of the menstrual cycle than other asthma phenotypes. This is consistent with the results of study by Tan *et al.* which revealed that airway responsiveness to AMP in asthmatic women was highest during the premenstrual period (13). However, in this study authors did not analyze the degree of bronchial hyperresponsiveness (BHR) in relation to the presence of cyclical perimenstrual asthma exacerbations. A higher degree of BHR in the luteal phase of the menstrual cycle in PMA women is likely related to different, than observed in other asthma phenotypes, absolute concentrations (or concentration ratio) or greater variability of female sex hormones levels. Previously performed studies show that estrogen and progesterone receptors are widely distributed in the lower

Table 2 Sputum cytokine levels in luteal phase of the menstrual cycle in groups studied

Parameter (pg/mL)	PMA group	Non-PMA asthmatics	Healthy controls
Eotaxin*	162.8 (129.5–180.3)	132.5** (108.3–164.0)	118.3 (105.3–142.8)
IL-4*	5.15 (2.51–193.1)	3.01*** (1.45–4.76)	1.7 (1.11–118.3)
IL-10	17.24 (0.0–183.1)	14.2 (0.0–117.77)	69.95 (0.96–219.72)

Data are expressed as medians and ranges (maximal and minimal values are in brackets). *, P<0.05 for inter-group differences (Kruskal-Wallis ANOVA); **, P=0.016 for PMA-non-PMA asthmatics differences (Mann-Whitney U test); ***, P=0.041 for PMA-non-PMA asthmatics differences (Mann-Whitney U test).

airways (15) and both hormones are involved in modifying airway responsiveness (14). Hellings *et al.* revealed that progesterone increased BHR in a mouse model of allergic asthma (17). On the contrary, estradiol has been shown to reduce BHR by increasing the activity of acetylcholine esterase in bronchial epithelium nerve endings (18) and estrogen replacement therapy in murine model of allergic asthma decreased airway hyperresponsiveness to metacholine in a dose-dependent way (19). Detailed explanation of the impact of the distribution of female sex hormones on the severity of BHR in PMA asthmatics certainly requires further studies. However, our study for the first time highlights the possibility that higher perimenstrual BHR degree in women with PMA (when compared to non-PMA asthmatics) may be responsible for more severe exacerbations and often poorer response to treatment, which, according to many authors (5-7), are characteristic for this phenotype.

The results of some former studies suggested, that PMA seems to be closely linked to some atopy markers. In their study Pereira-Vega *et al.* proved that women with PMA had total blood IgE values increased above normal (20). Authors however, did not compare total IgE concentrations between PMA and non-PMA asthmatics. In our study, inter-group comparisons revealed, that women with PMA had significantly higher total IgE serum concentration (when compared to non-PMA asthmatics) which reversely correlated with the PC_{20} value in the bronchial challenge test with metacholine. Given the fact, that women with parasitic diseases and any other chronic diseases, in which total serum IgE is increased above normal values, have been excluded from the study, the obtained results indicate, that PMA phenotype is more strongly associated with atopic mechanisms than other asthma phenotypes. Another possible explanation of these results would be, that in some asthmatic women high propensity to atopy (associated with the increased bronchial reactivity) overlaps with substantial fluctuations in female sex hormones levels during perimenstrual period, leading to a further increase in the degree of BHR, known as perimenstrual asthma.

In our study we demonstrated, that in PMA subjects sputum concentrations of both, eotaxin and IL-4 during luteal phase of the menstrual cycle were higher than in non-PMA asthmatics. To our best knowledge, this is the first study which assessed markers of inflammation in lower airways of PMA subjects and compared them with other asthma phenotypes. To date, a number of studies have stressed that recruitment and activation of inflammatory cells in asthma is controlled by the release of chemotactic agents, such as eotaxin (32). In a recent meta-analysis (33) increased concentrations of eotaxin have been reported in blood and sputum of asthmatic patients when compared to healthy controls. Sputum eotaxin levels in that study were significantly elevated in unstable (versus stable) asthma patients suggesting, that this chemokine might be a useful biomarker for the assessment of asthma severity and control. Increased sputum eotaxin level in PMA patients during lutheal phase of the cycle in our study is in agreement with the results of the above-mentioned meta-analysis (33) proving once again, that higher concentrations of eotaxin may be associated with the more severe disease course. The increased sputum IL-4 concentration in PMA group found in our study is interesting, especially in the light of the co-existing significantly higher total IgE serum concentration in these patients. It has previously been proved, that in order for a B lymphocyte to switch to IgE synthesis, a signal provided by a Th2 cell in the form of the IL-4/IL-13 is necessary (34). The results of our study not only suggest, that PMA phenotype is associated with the increased IgE synthesis (when compared to other asthma phenotypes) but also with the IL-4 up-regulation in the lower airways of these patients.

Conclusions

Patients with perimenstrual asthma are characterized by a significantly higher degree of bronchial hyperreactivity and higher concentrations of total serum IgE, when compared with non-PMA asthmatics. PC_{20} to metacholine and total serum IgE in these patients are reversely correlated. Higher degree of bronchial hyperreactivity in patients with PMA (as compared to non-PMA asthmatics) is associated with increased concentration of eotaxin and IL-4 in lower airways of these patients suggesting a shift in the type-1/type-2 cytokine balance toward a type-2 response.

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Footnote

Conflicts of Interest: The results of the study were presented during the European Respiratory Society in Munich (Germany), 6-10.09.2014 (Eur Respir J Suppl 2014;44:2).

Ethical Statement: The study was approved by Ethics Committee of the Medical Faculty, Silesian Medical University, Katowice, Poland and it conforms to the provisions of in accordance with the Helsinki Declaration as revised in 2013. The informed, written consent was obtained from all study participants.

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