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ORIGINAL ARTICLE

Seasonal Variability of the Methacholine Challenge Test

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Background. Since the intensity of some variables that influence bronchial hyper-responsiveness (BHR) varies across different seasons of the year, the percentage of positive methacholine challenge test (MCT) is theoretically subjected to seasonal variation. This study has looked at the seasonal variability of MCT among young adults with suspected asthma. **Methods.** The number of MCT performed and its corresponding proportion of positive results were retrospectively evaluated and compared for different seasons over a 5-year period. **Results.** Overall 645 subjects (mean age 21.4 ± 2.3 yr) underwent MCT during the study period. Two-hundred nine MCTs (34.2%) were performed in the winter, significantly higher when compared to any other season of the year. Positive MCT (defined as $PC_{20} < 16$ mg/mL) was noted in 163 patients (25.2%). The proportion of positive MCTs has shown significant seasonal trend, ($p < 0.0001$, chi-square test for trend), it was significantly higher in the winter and in the spring (32.2% and 32.4%, respectively) when compared with the summer (13.4%). **Conclusions.** This study showed a significant seasonal variability for both pattern of referral to MCT and the seasonal prevalence of BHR young adults. These findings probably reflect seasonal variation in the intensity of external stimuli that involve in the pathogenesis of BHR, such as allergens burden and respiratory tract infections across the year. We suggest that interpretation of a positive MCT as predictive of BHR and of asthma should take into account the observed seasonal variability of the test.

Keywords bronchial hyperresponsiveness; asthma; methacholine challenge test

INTRODUCTION

One of the key features of asthma is reversible airflow obstruction, and demonstrating this phenomenon by pulmonary function testing is a key step in the diagnostic algorithm (1). In undetermined cases, indication for bronchial hyper-reactivity (BHR) during a challenge test is required to establish the diagnosis. In this setting, exercise and the methacholine challenge test (MCT) are widely used (2). Although the sensitivity of MCT can be very helpful in excluding the diagnosis of asthma, this test has a relatively high rate of false-positive results and relatively poor specificity (1,3).

Some factors that are involved in the pathogenesis of BHR and hence may influence the results of the MCTs are subjected to seasonal variability. For example, in asthmatic subjects, the proportion of positive tests is lower during seasons of low allergen burden with exceptionally lower figures recorded during the summer remote from the allergy season (4–6). Conversely, a higher percentage of BHR in asthmatic patients were recorded during the winter while episodes of upper airway infections are particularly common (7–9).

Based on this data, we hypothesized that the proportion of positive MCT, corresponding to the prevalence of BHR in a population of subjects with symptoms suggestive of asthma, would be susceptible to seasonal variability too.

METHODS

The study was conducted in the pulmonary outpatient clinic situated in a 900-bed tertiary university-affiliated medical center. The study cohort included all consecutive pa-

tients that were referred to the pulmonary function testing laboratory during 5 years, between January 2004 until December 2008 for evaluating the possibility of asthma because of symptoms consisting of cough and/or unexplained episodes of wheezing and/or dyspnea. All had normal baseline spirometry, forced expiratory volume in the first second (FEV_1) values range between 80% to 120% of predicted values, and lack of significant response defined as greater than 12% improvement in the FEV_1 values after administering of bronchodilators (salbutamol 200 μ g). Smokers were excluded to reduce to minimum the risk of false-positive MCT. Asymptomatic army recruitments scheduled to serve in the elite combat unit that underwent MCT as a part of selection were excluded from the study too because they underwent MCT in an intent to disclose occult BHR, which is not of clinical relevance to this study. Since all army recruits to elite units undergo MCT, we did not want to include those asymptomatic healthy subjects in the analysis. The prevalence of positive MCT in asymptomatic army recruits is less than 1%; no significant seasonal trend was noted (Fruchter, Yigla : unpublished data).

Approval for the study was obtained from the local Review Board. There was no need for informed consent as no information that would allow personal identification was used.

METACHOLINE CHALLENGE TEST

After inhaling an initial control solution of isotonic saline solution, patients were administered doubling concentrations of Metacholine, starting from 0.0625 mg/mL, up to 16 mg/mL (if no response), by dosimeter (2). All the spirometries were conducted on the KoKo Pneumotach Spirometer (SUSQUEHANNA MICRO, INC; Red Lion, PA, USA) as previously described (10). The variables measured were forced vital capacity (FVC), FEV_1 , and mid-expiratory flow

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TABLE 1.—Annual average (over 5 consecutive years) of the number of metacholine challenge tests in each quartile and the proportion of positive test results.

Quartiles	Months (Season)	No. of MCT (%)	Positive MCT No. (%)	Average PC ₂₀ (±SD)	Percentage of Subjects with PC ₂₀ = 4 mg/ml (%)
I	January to March (Winter)	209 (32.4%)*	68 (32.5%)**	5.222 ± 4.172	34 (49.2)%
II	April to June (Spring)	140 (21.7%)*	46 (32.8%)**	5.676 ± 4.823	25 (54.3)%
III	July to September (Summer)	160 (24.8%)*	21 (13.1%)**	6.448 ± 5.186	12 (54.5)%
IV	October to December (Fall)	136 (21.0%)*	28 (20.5%)	4.617 ± 4.253	16 (57.1)%
Total		645 (100%)	163 (25.2%)	5.478 ± 4.740	87 (53.3 %)

*I vs. II, $p = 0.001$, I vs. III, $p = 0.049$, I vs. IV, $p < 0.0001$; Chi-square test.

** I vs. III, $p = 0.001$, II vs. III, $p = 0.001$; Chi-square test.

(FEF_{25–75}). During the MCT, FEV₁ values were measured 1 minute after the end of the corresponding inhalation. Each FEV₁ measurement was expressed as a percentage from the baseline record. The provocation concentration of metacholine defined as causing a decrease of 20% in FEV₁ (PC₂₀) was recorded. According to the standard protocol in our institute, all study subjects were instructed to stop any anti-asthma medication before MCT. The washout period was 12 hours for short-term beta-agonists, 48 hours for long-term beta-agonists, and 7 days for inhaled corticosteroids.

SEASONAL VARIABILITY

For each patient the exact date when the MCT was performed was available. Given an 8-week lag between symptoms onset to performing MCT along with the calendar distribution of the seasons in Israel, every single patient was categorized into one of the following four subgroups according to the season when the MCT was performed as described below:

1. Subgroup 1 (winter) – January – March.
2. Subgroup 2 (spring) – April – June.
3. Subgroup 3 (summer) – July 1 – September.
4. Subgroup 4 (fall) – October 1 – December 31.

The total number of the MCTs performed, the percentage of positive tests, as well as the corresponding means of

PC₂₀ were defined for each season. Thereafter, the figures were compared between the different seasons for each year separately and for the whole study period.

DATA ANALYSIS

Continuous variables are expressed as the mean and SD and compared using Mann-Whitney U-statistics. Dichotomous variables are summarized as simple proportions and compared using t tests. Differences in the proportion of positive MCT between seasons were compared by Chi-square test. A p value below 0.05 was considered to be statistically significant. Statistical analysis was performed using MedCalc version 9.0.1.

RESULTS

The cohort consisted of eligible 645 young adult patients (mean age 21.4 ± 2.3 years) of whom 57% were male. The monthly and the quarterly distribution of the MCT are presented in Table 1 and in Figures 1 and 2. The total number of MCT performed in the winter was 209 (32.4%), and these figures were significantly higher when compared with any other season of the year (I vs. II, $p = 0.001$, I vs. III, $p = 0.049$, I vs. IV, $p < 0.0001$).

Data about the seasonal distribution of the diagnostic yield of the MCTs performed (defined as a cutoff of PC₂₀ < 16 mg/mL) and of the severity of the BHR as expressed by the mean PC₂₀ across the different seasons of the year are

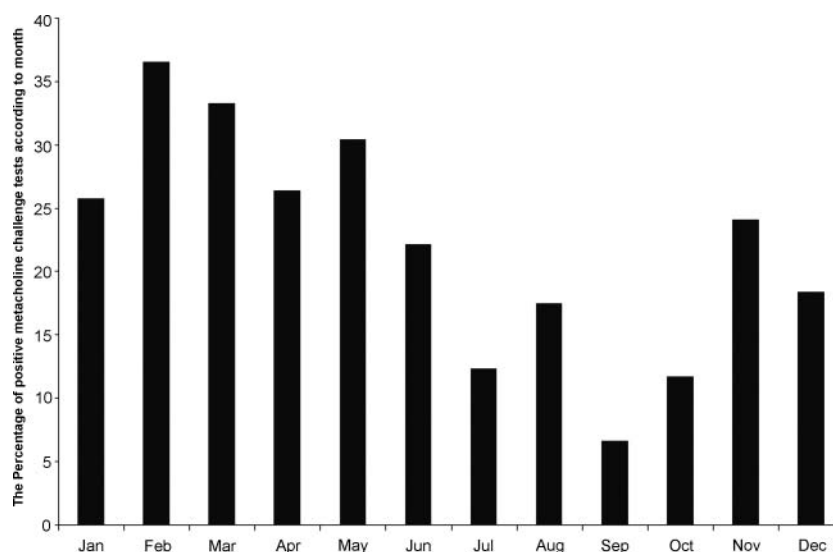


FIGURE 1.—Monthly average of metacholine test results.

The average yearly percentage (across 5 years) of positive metacholine challenge test results according to month of performance.

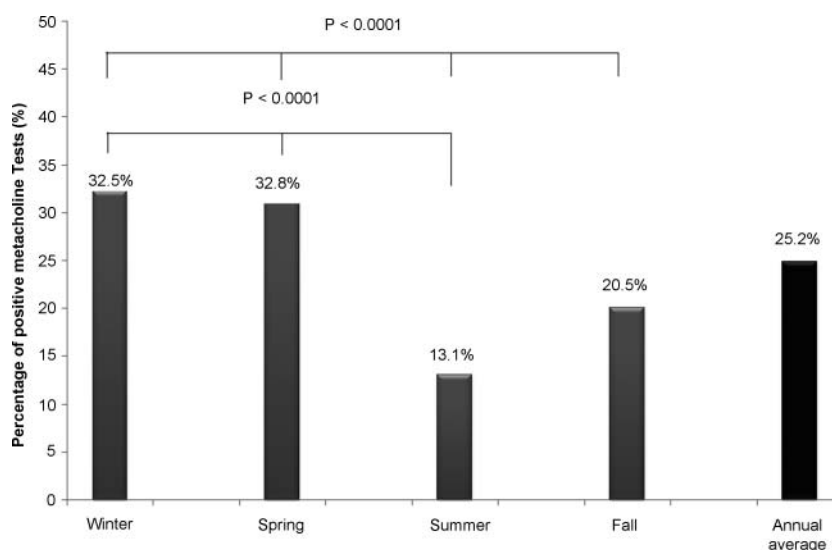


FIGURE 2.—Seasonal average of metacholine test results.

The average yearly percentage (across 5 years) of positive metacholine challenge test results according to season of performance.

presented in Table 1 and Figure 2. Overall, 25.2% of the MCT performed were positive. The percentage of positive MCT varied significantly across the four seasons of each year consistently with a significant seasonal trend for the whole study period (Figure 2) ($p < 0.0001$, Chi-square test for trend).

The frequency of positive MCT results during the summer (13.4%) was significantly lower when compared with any other season of the year ($p < 0.0001$ for comparing of each quartile separately). Conversely, the higher frequency of positive MCT was recorded in the winter and the spring (32.2% and 32.4%, respectively), and these figures were significantly higher when compared to the summer ($p < 0.0001$) and to the fall ($p < 0.0001$).

The mean annual PC_{20} for the study population was 5.18 mg/mL. Of them, 57.25% of had moderate to severe BHR (defined as $PC_{20} \leq 4$ mg/mL). There was no significant difference in the distribution of the severity of the BHR across the different seasons of the year (Table 1).

DISCUSSION

This study has shown a significant seasonal variation for both pattern of referral to MCT, as well as the proportion of BHR defined as positive MCT in young adults with symptoms suggestive of asthma. Over a 5-year period a significantly higher number of patients were referred to MCT during the first quartile of the year. Furthermore, the highest proportion of positive BHR was noted in the first and second quartiles of the year, while the lowest proportion was during the third quartile, and this seasonal variability was statistically significant.

In other words, a single patient with similar typical symptoms such as cough and/or unexplained dyspnea is less likely to receive a diagnosis of asthma in the summer when compared to the winter and/or to the spring.

The 5-years annual frequency of positive MCT at our site was 25.7%. A yearly analysis for each separate year of the

study has shown similar figures that matched data from other studies referring to a population with similar profile (2). This and the criteria for patient's selection ensure that the study population adequately represents the population of patients undergoing MCT for suspected asthma.

The most interesting finding of this study is documentation of seasonal variation in the incidence of BHR, which in this clinical scenario correlates with newly diagnosed cases of asthma that peaks in the winter and spring and is lowest during summer. The winter peak could be a consequence of upper or lower respiratory tract infections, which have been described previously as a cause of BHR de-novo or an event that leads to exacerbation of occult BHR (7–9). Conversely, the spring peak is attributed to heavy allergen exposure, which is particularly common in Israel during this season of the year (4–5) and was found previously to be a major determinant of BHR and asthma particularly in young adults with a positive skin test (11–12). A summer with an incidence of BHR could be attributed to lower allergy burden, chronologically remote from the dominant allergy season (6). Our results suggest that an interpretation of a positive MCT performed during seasons of higher prevalence of externally induced non-specific BHR should be done with caution with respect to the clinical ramifications of a positive test, especially in a subject with low pre-test probability for asthma. Seasonal variability in BHR has been described in young subjects with suspected asthma that underwent exercise challenge testing (13). Exercise induces release of mediators, which in turn induce bronchial smooth muscle contraction. The authors concluded that a positive response to this stimulus depends on the presence active airway inflammation, which is likely to be attenuated when asthma is less active, during summer for example. The relationship between asthma activity and direct provocation tests such as MCT is more complicated because the results of the MCT are less likely to be affected by external stimuli and theoretically are less subjected to seasonal variation.

Studies investigating the effect of asthma status on the results of MCT have yielded conflicting results. Benckhuijsen et al. (14) have found that patients with asthma and house dust mite allergy who lived for 1 month in a hypoallergenic area experienced a decreased BHR to exercise and to 5' adenosine monophosphate challenge, but not to metacholine. Boulet et al. (15) have shown that BHR responsiveness as assessed by repeated MCT was stable throughout the year in asthmatic and among normal subjects. Other studies (5, 6, 16, 17) did show a decreased response to metacholine in patients with allergic asthma during low allergic load periods. However, all of these studies tested the response to MCT in individual patients with established asthma over different external allergic load conditions. Conversely, we tested the response to MCT in subjects with suspected asthma over the different seasons across five consecutive years.

A major limitation of the current study is that the prevalence of atopy in the study population is not known. In a previous report (12) we showed that the prevalence of positive aeroallergen skin-prick test in subjects with positive MCT was 95.4%, and since the study population in the current report was similar we expect the prevalence of atopy to be in the same magnitude. This assumption has to be tested in further studies.

In summary, this study has shown a significant seasonal variability in the response to metacholine, a direct bronchial constrictor challenge test that likely stems from the difference in the external burden of allergens, pollutants, and/or respiratory tract infections. Interpretation of a positive MCT as predictive of BHR should take into account besides the clinical pre-test probability for asthma, the specific season in which it was conducted.

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O. F. and M. Y. have both been actively involved in design and conduct of the research and wrote the manuscript.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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