PNEUMON

QUARTERLY MEDICAL JOURNAL

PELLHIN THORACIC SOCIETY

TRIMHNH NITIPH N KATOSZH

HEALHNH HNEUMOLOKH H NTAIPHE

OFFICIAL JOURNAL OF THE

HELLENIC THORACIC SOCIETY

(HTS)

ISSN 1105-848X
e-ISSN 1791-4914

www.pneumon.org
www.mednet.gr/pneumon
www.hts.org.gr
www.indexcopernicus.com
www.scopus.com
www.embase.com
www.scolar.google.gr
www.doaj.org

ADDRESS:
PNEUMON
Medical Journal
Athens Chest Hospital (Sotiria)
152 Messogion Ave.
Athens 11527 - Greece
Tel.: 210-7487723
e-mail: pneumon@hts.org.gr

FREE ONLINE ACCESS

ANNUAL SUBSCRIPTIONS
Inland ............................................. € 20
Members of HTS and GBS ......... € 20
Interns-Medical Students ......... € 20
Medical Societies ................. € 20
Medical Libraries ................. € 20
Abroad .............................................. € 50

Editorial Board

Editor-in-Chief: Demosthenes Bourou, MD, PhD, FCCP, FERS, FAPSIR (Greece)
Associate Editors: Joanna Floros, PhD (USA)
Stelios Loukidis, MD FCCP (Greece)
Argiris Tzouvelekis, MD, PhD, MSc (Greece)

International Board

Philippe Astoul (France)
Mehta Atol C (USA)
Robert Baughman (USA)
Semra Bilaceroglou (Turkey)
Marisa Bonsignore (Italy)
Philippe Camus (France)
John Catravas (USA)
Ivane Chkhaidze (USA)
Carlos Robalo Cordeiro (Portugal)
Ulrich Costabel (Germany)
Elisabeth Fireman (Israel)
Talmadge King Jr. (USA)
Meinhard Kneussl (Austria)
Michael Kreuter (Germany)
Richard Light (USA)
Andrew G. Nicholson (UK)
Dario Olivieri (Italy)
F. Rodriguez Panadero (Spain)
Panos Pantelidis (UK)
Martin Petrek (Czech Republic)
UBS Prakash (USA)
Ganesh Raghu (USA)
Paola Rotoli (Italy)
Athol Wells (UK)
W. Wuys (Belgium)

National Board

Antonis Antoniadis (Serres)
Aikaterini Dimakou (Athens)
George Dimopoulos (Athens)
Marios Froudarakis (Alexandroupolis)
Mina Gaga (Athens)
Demetrios Georgopoulos (Heraklion)
Kostas Gourgouliannis (Larisa)
Likourgos Kolilekas (Athens)
George Kolios (Alexandroupolis)
Stavros Konstantinidis (Alexandroupolis)
Stavros Konstantopoulos (Ioannina)
Theodoros Kontakiotis (Thessaloniki)
Nikolaos Koulouris (Athens)
Antonia Koutsoukou (Athens)
Katerina Malagari (Athens)
Efronis Manali (Athens)
Despina Papakosta (Thessaloniki)
Spyros Papiris (Athens)
Nikolaos Siafakis (Heraklion)
Konstantinos Sprioopoulos (Patras)
Paschalis Steiropoulos (Alexandroupolis)
Michael Toubmis (Athens)
Nikolaos Tzanakis (Heraklion)
Vasileios Tzilas (Athens)
## Contents

### Editorial

Homeopathy and acupuncture: Do they have place in respiratory medicine  
R. Pechlivanidou, A. Antoniadis ................................................................. 9

### Original Articles

Prognostic factors affecting smoking cessation
A real-life study in a population of Greek smokers visited a smoking cessation clinic  
S.-C. Kotoulas, A. Stefanidou, E. Chatzopoulos, K. Fekete-Passa,  
K. Domvri, I. Grigoriou, P. Argyropoulou-Pataka, A. Pataka ........................................... 12

Quality of sleep in patients with end-stage renal failure  
V. Tsoulosis, A. Dardas, D. Tsavlis, S. Papakatsika,  
A. Gavriilidou, P. Konstantinidou, D. Anestakis, P. Steiropoulos ..................... 23

### Case Reports

“Metsovo Lung” with benign pleural calcifications: A CXR image with complimentary information from Ultrasound Elastography  
E. Manos, N. Palatianos, P. Panagou .......................................................... 31

The spectrum of CNS clinical manifestations in patients with small cell lung carcinoma presented through two case reports  
K. Natsis, R. Pechlivanidou, D. Nouvakis, V. Drampa,  
E. Papamichalis, H. Mourtzinos, A. Antoniadis ........................................... 34

Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: Report of two cases  
A. Flevari, S. Argentos, S.E. Orfanos, E. Stagaki, A. Frogoudaki,  
D. Konstantonis, A. Pappas, A. Armaganidis, A. Anthi .......................................... 43

### Images in Pulmonology

Pneumocystis jiroveci (PJP) lung infection on the ground of achalasia of esophagus  
E. Pasparaki, E. Bibaki, S. Kourmiotaki, E. Ferdoutsis, G. Meletis ................................. 48

### Eις ΜνήΜην

Σε ανάμνηση… Στέλιου Μιχαηλίδη, Δ/ντού Πνευμονολόγου ΕΣΥ, FCCP  
Β. Πολυχρονόπουλος, Κ. Γουργουλιάνης .......................................................... 49
Homeopathy and acupuncture: Do they have place in respiratory medicine

Rouzana Pechlivanidou, Antonis Antoniadis
Pneumonology Department of General Hospital of Serres, Greece

Key words:
- Complementary and alternative medicine
- Homeopathy
- Acupuncture
- Respiratory medicine

According to the U.S. National Library of Medicine, complementary and alternative medicine (CAM) or “complementary health approaches” are “a group of diverse medical and health care practices and products that are not presently considered to be part of conventional medicine”. It is used alongside modern medicine (complementary medicine) or as an alternative to it (alternative medicine).

This article will review international database for two methods of CAM: homeopathy and acupuncture.

Homeopathy is an alternative approach based on the belief that pharmaceutical substances, which are manufactured in a particular way and which are used in very small quantities, treat physical and mental illnesses.

From its first appearance, homeopathy’s popularity has fluctuated, reaching its heyday in the 19th century when schools of homeopathy, institutes, as well as hospitals, were created. Yet, in the last decade, it has been severely criticized by scientists. From 2000 on, there have been hundreds of studies and reviews on the effectiveness of homeopathy, comparing it to a placebo, to the drugs used in classical medicine, and the comparison of different methods used in homeopathy.

While some studies have shown positive results regarding the effectiveness of homeopathy for treatment of respiratory tract infections, allergic rhinitis, chronic asthma, IPF and lung cancer, they were not evaluated either due to the small number of participants or the poor quality of trials. What is more, publication bias was ascertained.

On the contrary, other studies, reviews and meta-analyses did not find enough evidence that homeopathic medicinal products are more effective than a placebo.

Consequently, in 2017, Great Britain’s National Health Service begins to discourage the use of homeopathic medication, characterizing homeopathy as a form of treatment devoid of “robust evidence of clinical effectiveness”.

In addition, in 2015 NHMRC (National Health and Medical Research Council) in Australia, after the analysis of 57 systematic reviews based on only major, good quality studies, concluded that homeopathy does not differ from placebos regarding its effectiveness due to the fact that “there were no health conditions for which there was reliable evidence that ho-
meopathy was effective"15. The Australian government stops insurance reimbursement for 17 CAM, including homeopathy.

However, in Switzerland, in 2017, the country’s government announced that four methods of alternative medicine, which included homeopathy, would be covered by basic health insurance coverage on condition that it is “practiced by conventional medical practitioners who have an additional qualification in one of the four disciplines”16.

The conflict regarding homeopathy continues. J.E. Prousky supports that it is not the homeopathic remedy itself, but the homeopathic consultation process as a psychotherapeutic technique that can provide a therapeutic result, given that it includes the recording of a detailed individual and family history, regular follow-up and a trusting relationship between patient and therapist17.

Some researchers are looking into the application of homeopathic remedies for non-complicated respiratory infections in order to avoid inappropriate use of antibiotics18.

Yet, it must be noted that the World Health Organization does not recommend the use of homeopathic remedies for diarrhea and flu in infants, and warns against their use in the treatment of serious diseases, such as HIV, tuberculosis and malaria.

**Acupuncture** is a key component of Chinese traditional medicine and it is defined as the stimulation of specific points on the body using a variety of techniques such as needling, moxibustion, cupping, acupressure, and newer techniques like electroacupuncture and the use of lasers on acupuncture points.

Acupuncture has been used in China and other Asian countries for approximately 4000 years and has become a popular form of alternative medicine in America and Europe as a treatment for a vast list of diseases, particularly for pain conditions. Hundreds of studies have been conducted on the effectiveness of acupuncture on respiratory diseases (bronchial asthma, COPD, infections, allergic rhinitis and cystic fibrosis)19,21-24. Attempts have been made to investigate the biological effects of acupuncture mechanisms25,27.

Nevertheless, opinions on acupuncture are divided, and quite a few scientists support that the positive results of this method are based on a powerful placebo effect25,27 and they accuse acupuncturists of publication bias28 and poor study design.

One of acupuncture use is for smoking cessation through the implementation of techniques such as needling, acupressure and the use of lasers on acupuncture points. Some studies have shown positive effects29,30, whereas the Cochrane Review, in 2014, uncovered that acupuncture is less efficient in comparison with nicotine substituting treatment and that its effect is similar to a placebo31.

Various acupuncture techniques have exhibited different complications. In 2013, a systematic review19 compiled the adverse side-effects from case reports. The most frequent complications were skin infections (bacterial and viral), organ injuries (pneumothorax, central or peripheral nervous system trauma, heart and major vessel trauma), burns and hemorrhaging complications. It is reported that complications were most frequently associated with the experience of the acupuncturist and a lack of compliance with sterilizing techniques.

**In conclusion**, complementary and alternative medicine (CAM) is widely implemented on a global scale. The clinical findings regarding the effectiveness of these two CAM techniques (homeopathy and acupuncture) are controversial. The existing database does not support the use of these methods to treat respiratory diseases. Furthermore, it must be emphasized that with the implementation of these methods, one runs the risk of delaying treatments recommended by classical medicine, with negative consequences that may entail for the patient’s health. In addition, these CAM methods can provoke serious complications, especially when practiced by incompetent practitioners. In any case, neither the ERS nor the ATS include these techniques in the guidelines pertaining to the treatment of any respiratory diseases.

**REFERENCES**

6. Beghi G, Morselli-Labate A. Does homeopathic medicine have a preventive effect on respiratory tract infections? A real life
17. Prousky J. Repositioning individualized homeopathy as a psychotherapeutic technique with resolvable ethical dilemmas. Journal of Evidence-Based Integrative Medicine 2018; 23.
SUMMARY
BACKGROUND: Smoking is a chronic disease not only responsible for numerous premature deaths every year, but also for substantial financial burden on health systems. Greece is still one of the leading countries in European Union (EU) in prevalence and incidence of smoking, a fact leading to even higher rates of morbidity and mortality and increases the cost of healthcare. The aim of this study is to identify predictors which play a role in a successful smoking cessation effort in three and six months, in Greek patients, who visited a smoking cessation clinic. METHODS: The research designed as a "case – control" study. Participants were patients who visited the smoking cessation clinic and agreed to take part in the research, answered all the questions needed and could be re-evaluated after three and six months. Out of 231 patients who visited the clinic during a year, 100 fulfilled the above criteria and were divided into two groups; those who succeeded in smoking cessation and those who failed; Fagerström (FNDT), Minnesota (MNWS) and Rosenberg questionnaires, along with questions about epidemiologic and other features were used to evaluate the patients. Multivariate regression analysis was performed to identify predictors which played a role in successful smoking cessation. RESULTS: Among various characteristics examined, multivariate regression analysis indicated that "difficulty in concentration" of the MNWS as well as the whole score of MNWS and FNDT and the reduced number of cigarettes after work independently predicted smoking cessation. CONCLUSIONS: This research confirms that the answers of smokers in both MNWS and FNDT should be taken under consideration for personalized medicine in smoking cessation treatment. Moreover, smoking cessation programs at workplaces should be implemented, because it seems that the increased number of cigarettes at work associates with higher smoking cessation success rates. Pneumon 2019, 32(1-2):12-22.
INTRODUCTION

Smoking is one of the major causes of premature death worldwide, creating apart from health problems significant increase of the financial burden on health systems. In 2011, World Health Organization (WHO) reported that diseases associated with smoking are responsible for a very large proportion of deaths worldwide. Nicotine addiction is defined as highly controlled or compulsive use of tobacco products, with tolerance to nicotine. Various pharmacological therapies have been developed for smoking cessation. More specifically a) Nicotine replacement therapy (NRT), which act on nicotinic receptors, b) Bupropion hydrochloride, a substance that acts as a selective inhibitor of the reuptake of catecholamines (noradrenaline and dopamine), and c) Varenicline, a partial agonist of the nicotine, which selectively binds to α4β2 nicotine receptors and competes nicotine for binding them.

Epidemiologic factors affect smoking cessation. Aged patients, especially those older than 60 years old are more likely to quit smoking. Gender seems to associate with varying degrees of success, depending on the quitting method selected. Patients of lower socioeconomic strata are at increased risk of relapse and the same applies for patients with basic education compared to those of university degree. Smoking cessation is more likely for working men compared to those who are unemployed, while for women the opposite applies. Married smokers are twice as likely to quit compared to singles, something that also applies for senior executives related to other workers. Incentives, disincentives, and/or support activities in workplaces related to smoking cessation are very helpful, particularly among middle and heavy smokers. On the other hand, increased use of alcohol reduces the probability of a successful smoking cessation. Patients with coronary heart disease, who have undergone intervention in their coronary artery, have higher success rates of smoking cessation. Patients with reduced Forced Expiratory Volume in 1 second (FEV1) have better chance smoking cessation compared to those with normal FEV1. The coexistence of depression reduces the likelihood of a successful smoking cessation effort in patients with chronic respiratory problems.

Withdrawal symptoms assessed with questionnaires as the Minnesota Nicotine Withdrawal Scale (MNWS) are associated with a successful smoking cessation. Nicotine addiction, usually measured by the Fagerström Nicotine Dependence Test (FNDT) has been related with the degree of the successful smoking cessation. Additionally, the degree of self-esteem measured with Rosenberg self-esteem scale (RS) at the beginning of a smoking cessation attempt seems to play a role in successful quitting.

The aim of the study was to identify predictors which play a role in successful smoking cessation in three and six months, in patients who visited a smoking cessation clinic in Greece during one year.

METHODS

Subject evaluation

Patients filled out a questionnaire (age, gender, Body Mass Index (BMI), parental smoking status, educational status, work status, working and workplace related factors, marital status, living with other smokers, smoking after workout, usage, type and amount of alcohol consumption, pregnancy smoking status for women, age of start and duration of smoking, number of daily cigarettes, number of packyears, nicotine content of cigarettes, previous cessation efforts, psychiatric, respiratory, cardiovascular or other co-morbidities) and the MNWS, FNDT and RS (Table 1). Subsequently, the doctor suggested a smoking cessation therapy. Finally, patients were given brochures with useful information, and contact numbers for further information or psychological support. A psychologist was part of the team and participants had a free session during their visit. Moreover, the psychologist’s telephone number was given to patients, to communicate if they needed further assistance. Patients were monitored by telephone at 10 days, 1, 3 and 6 months after their first visit to the smoking cessation clinic. After excluding the patients who did not want to take part in the research, those who did not answered all the questions and those who could not be re-evaluated, 100 patients were included in the research (Figure 1). The protocol was approved by the local ethics committee and all the patients gave their informed consent to participate in the study.

Questionnaires used

Fagerström Nicotine Dependence Test (FNDT) consists of the following six questions: 1) the time between waking up in morning and first cigarette of the day, 2) the difficulty of non-smoking in places where smoking is forbidden, 3) if the most difficult cigarette to avoid is the first of the day or any other, 4) the number of daily cigarettes, 5) the frequency of smoking at morning compared with that of afternoon, 6) if an illness prevents from smoking or not.
**TABLE 1. Characteristics of the population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>49.87 (± 10.64)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27.90 (± 4.78)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Primary education graduates</td>
<td>10</td>
</tr>
<tr>
<td>High school graduates</td>
<td>17</td>
</tr>
<tr>
<td>Senior high school graduates</td>
<td>26</td>
</tr>
<tr>
<td>Technological Institute graduates</td>
<td>28</td>
</tr>
<tr>
<td>University graduates</td>
<td>19</td>
</tr>
<tr>
<td><strong>Work status</strong></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>62</td>
</tr>
<tr>
<td>Unemployed</td>
<td>21</td>
</tr>
<tr>
<td>Pensioner</td>
<td>17</td>
</tr>
<tr>
<td><strong>Age of start smoking</strong></td>
<td>18.84 (± 6.19)</td>
</tr>
<tr>
<td><strong>Years of smoking</strong></td>
<td>31.05 (± 10.92)</td>
</tr>
<tr>
<td><strong>Daily number of cigarettes</strong></td>
<td>27.43 (± 14.59)</td>
</tr>
<tr>
<td><strong>Packyears</strong></td>
<td>44.36 (± 29.61)</td>
</tr>
<tr>
<td><strong>Daily number of cigarettes in work</strong></td>
<td>15.98 (± 11.90)</td>
</tr>
<tr>
<td><strong>Daily number of cigarettes out of work</strong></td>
<td>13.14 (± 9.24)</td>
</tr>
<tr>
<td><strong>Presence of comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
</tr>
<tr>
<td><strong>Psychiatric comorbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>No</td>
<td>82</td>
</tr>
<tr>
<td><strong>Psychiatric condition</strong></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>2</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>3</td>
</tr>
<tr>
<td><strong>Minnesota total score</strong></td>
<td>16.1 (± 9.2)</td>
</tr>
<tr>
<td><strong>Fagerström total score</strong></td>
<td>6.35 (± 2.3)</td>
</tr>
<tr>
<td><strong>Rosenberg total score</strong></td>
<td>19.8 (± 5.6)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Counseling</td>
<td>5</td>
</tr>
<tr>
<td>Nicotine replacement therapy</td>
<td>39</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2</td>
</tr>
<tr>
<td>Varenicline</td>
<td>54</td>
</tr>
</tbody>
</table>

*SD: standard deviation
*BMI: Body Mass Index
Scores under 3 indicate low nicotine dependence; scores 4-5 indicate moderate nicotine dependence and scores 6-10 high level of dependence.

Minnesota Nicotine Withdrawal Scale (MNWS) consists of nine questions. Each question measures the intensity of withdrawal symptoms from nicotine in smokers who abstained or significantly decreased smoking for 24 hours. Those symptoms are 1) desire to smoke, 2) irritability, frustration, anger, 3) Anxiety, 4) Difficulty to concentrate, 5) worry, 6) increased appetite or weight gain, 7) discomfort or depressed mood, 8) insomnia or sleep disorders, 9) awakening at night to smoke. The patients answer to every question at a scale from 0 to 4, with 0 meaning "none", 1 meaning "very lightly", 2 meaning "lightly", 3 meaning "mediocre" and 4 meaning "intensely". From the sum of the answers results a total score, with the higher score showing greater intensity of withdrawal symptoms.

Rosenberg self-esteem scale (RS) consists of 10 questions. Five of them express positive feelings and the other five negative ones. Patients answer with: "I absolutely disagree", "I disagree", "I agree", "I absolutely agree". For every positive feeling question those answers corresponding to a score from 0 to 3 and for every negative feeling question to a score from 3 to 0 respectively. From the sum of the answers results a total score, with the higher score showing higher degree of self-esteem.

**Statistical analysis**

Statistical analysis was performed using the SPSS software, version 20 of the IBM Company. Continuous variables are presented as mean value ± 1 standard deviation (mean±SD) and categorical variables as % percentage.

**FIGURE 1.** Study flowchart.
values. For the detection of statistical significance for variables as prognostic factors of smoking cessation at three and six months, univariate logistic regression and then the multivariate logistic regression to the ratio of the inverse probability (Backward LR) were used. In the univariate logistic regression all the population’s characteristics as age, gender, BMI, parental smoking status, educational status, work status, working and workplace related factors, marital status, living with other smokers, smoking after workout, usage, type and amount of alcohol consumption, pregnancy smoking status for women, age of start and duration of smoking, number of daily cigarettes, number of packyears, nicotine content of cigarettes, previous cessation efforts, psychiatric, respiratory, cardiovascular or other co-morbidities and their answers of MNWS, FNDT and RS were included. In the multivariate logistic regression we included those factors that were statistical significant in the univariate logistic regression. For the detection of statistically significant factors for the relapse after the first three months, the smoking area was used.

To compare the group of smokers who relapsed after three months, with the other two groups (never quitters and quitters for six months or more), two dummy variables were created with reference to the group of interest and then were compared using univariate and multivariate logistic regression (Binary Logistic). Additionally, we performed the above analyses after adjusting for gender, number of daily cigarettes categorized at 0–10, 11–20, 21–30 and more than 30 cigarettes per day and treatment received(type and compliance). P<0.05 was considered statistically significant.

RESULTS

The basic characteristics of the smokers included in the analysis are presented in Table 1. Counseling was provided to all patients and only 5 of them did not receive any pharmacological treatment. Combination treatment with NRT and Varenicline or Bupropion was not used. Varenicline and Bupropion doses were applied according to guidelines. Patients received NRTs according to their nicotine dependence (cigarettes/day) i.e. patch with different dosages and additionally inhalers and chewing gums when needed. Therefore, the patients could not be stratified according to the pharmaceutical dosage they received.

In the univariate model, the number of cigarettes per day was a significant predictor of smoking cessation both for three and six months (OR = 1.034, P = 0.044 and OR = 1.625, P = 0.044) respectively. However, this did not apply in the multivariate analysis; adjusted for the factors that were statistical significant in the univariate models for three and six months respectively. For smoking cessation at three months those factors were: The questions about 1) desire to smoke, 2) difficulty to concentrate, 3) discomforted or depressed mood, 4) irritability, frustration, anger, 5) insomnia or sleep disorders, 6) awakening at night to smoke and 7) the total score of the MNWS, the questions about 8) the time between waking up in morning and first cigarette of the day, 9) the difficulty of non-smoking in places where smoking is forbidden, 10) the number of daily cigarettes and 11) the total score of FNDT as an absolute number and 12) by categories, 13) the daily number of cigarettes as an absolute number and 14) the number of cigarettes out of workplaces. For smoking cessation at six months those factors were: 1) The use of alcohol, 2) the number of cigarettes out of workplaces, 3) the question about difficulty to concentrate and 4) the total score of the MNWS and the questions about 5) the time between waking up in morning and first cigarette of the day, 6) the difficulty of non-smoking in places where smoking is forbidden, 7) the number of daily cigarettes and 8) the total score of FNDT as an absolute number and 9) by categories. The daily number of cigarettes tends to show a statistical significance in predicting the risk of relapse to smoking at six months after a successful smoking cessation effort at three months (P = 0.069). There were no significant outcomes when this factor adjusted for gender.

The distribution of daily cigarettes during work time, appeared to play a role in smoking cessation efforts. As the number of cigarettes smoked outside the workplace reduced, the likelihood of successful smoking cessation increased both in three (OR = 1.094, P = 0.027) and six months (OR = 1.118, P = 0.019) in the univariate model. This relationship remained in the multivariate model for three months (aOR = 1.105, P = 0.044) (Table 2), but not for six. Working status such as employment, unemployment or pension did not seem to constitute a predictor for smoking cessation or relapse. There was also no association between working status(i.e. employment, unemployment) and withdrawal symptoms after abstinence or decreased smoking for at least 24 hours.

Nicotine dependence assessed by the FNDT was a statistically significant factor for successful smoking cessation in six months (aOR = 1.417, P = 0.007) (Table 2) and also for the prediction of relapse in six months after a successful smoking cessation for three months (aOR =
In the univariate logistic regression the first, the second and the fourth question of the FNDT, were statistically significant factors for smoking cessation at three and six months (OR = 1.679, P = 0.034 and OR = 2.149, P = 0.004 for three and six months for question 1 respectively, OR = 2.616, P = 0.032 and OR = 4.281, P = 0.008 for three and six months for question 2 respectively and OR = 1.661, P = 0.023 and OR = 1.625, P = 0.044 for three and six months for question 4 respectively). However, no significant associations were found in the multivariate analysis. Additionally, no significant relationships were found when factors from FNDT were adjusted for gender and treatment received.

Withdrawal symptoms assessed by the MNWS associated with reduced likelihood of successful smoking cessation in three months were: "difficulty in concentration" (OR = 1.559, P = 0.003 and in multivariate analysis aOR = 2.207, P = 0.020), "depressed mood" (OR = 1.422, P = 0.014 and in multivariate analysis aOR = 1.748, P = 0.08), "waking up to smoke" (OR = 1.910, P = 0.027 and in multivariate analysis aOR = 3.864, P = 0.07), and the total score of the questionnaire (OR = 1.073, P = 0.006 and in the multivariate analysis aOR = 0.833, P = 0.025) (table 2). The withdrawal symptom that increased the risk of relapse in six months after successful smoking cessation in three months was the "difficulty in concentration" that significantly increased the risk of recurrence and the protection factor of recurrence in the multivariate analysis (aOR = 0.711, P = 0.05 and aOR = 1.481, P = 0.012 respectively) (table 2). There was no significant association between the withdrawal symptoms assessed or the total score of the MNWS with the type of treatment used. There was a trend of higher MNWS score for patients non-compliant to treatment (P = 0.14), but this trend was not observed for any specific treatment (P = 0.285 for Varenicline and P = 0.387 for NRT). Similarly, there was no association between any specific withdrawal symptom and non-compliance in all or a specific smoking cessation treatment.

Self-esteem at the beginning of the smoking cessation effort was assessed by RS. Although a tendency of higher successful rates was found in patients with higher self-esteem, this was not statistically significant (P = 0.12).
Many other factors concerning the population’s baseline characteristics as age, gender, BMI, parental smoking status, educational status, working and workplace related factors other than number of cigarettes at work, marital status, living with other smokers, smoking after workout, usage, type and amount of alcohol consumption, pregnancy smoking status for women, age of start and duration of smoking, number of packyears, nicotine content of cigarettes, previous cessation efforts, psychiatric, respiratory, cardiovascular or other co-morbidities, were analyzed, but there was no significant relationship between them and the success in smoking cessation effort.

The treatment received by the patients did not affect significantly the success of the smoking cessation neither at three months (P = 0.823), nor at six months (P = 0.575). Moreover, there was no significant relationship between the treatment and the prediction of relapse in six months after a successful smoking cessation of three months (P = 0.915).

Out of five patients who received only counseling, two quit smoking in 3 months but one of them relapsed at 6 months. The two patients that received bupropion did not quit smoking neither at 3 nor at 6 months. From 39 patients that received NRT 14 (35.9%) quit smoking after 3 months, but 4 (10.3%) relapsed at 6 months. From the patients receiving varenicline, 21 out of 54 (38.9%) quit smoking at 3 months, but 5 (9.3%) relapsed at 6 months.

Finally, a subgroup analysis according to gender and treatment for smoking cessation was performed. None of the factors analyzed predicted smoking cessation at three or six months or relapse at six months after a successful smoking cessation effort of three months, when adjusted for gender or treatment received.

**DISCUSSION**

The main outcome of this study was that in Greek population of a smoking cessation clinic, smoking out of the workplace and difficulty in concentration affected smoking cessation and abstinence. Additionally, as found in previous studies, the total score in both MNWS and especially in FNDT were prognostic factors of smoking cessation and relapse.

In this study we scrutinized the role of a wide variety of epidemiological characteristics in smoking cessation. Gender and age associate with varying degrees of success. Additionally, smokers with higher degree of education are more likely to quit smoking and less likely to relapse compared to those of lower degree of education. Married smokers are more likely to quit smoking compared to those who are single. Increased use of alcohol reduces a successful smoking cessation attempt, while psychiatric co-morbidities have the opposite effect. In our study, we did not discover any significant relationship between all the above mentioned factors and the success rate of smoking cessation. Perhaps this is due to the relatively small number of the participants. Moreover, in the gender subgroup analysis no significant relationship was found.

A novel finding of the study was that smokers who smoked more in their workplaces were more likely to quit. Numerous studies have found that actions in workplaces encouraging employees to abstain from smoking are very supportive in smoking cessation, especially among middle and heavy smokers. This was also confirmed by three recent published Cochrane systematic reviews. Our study is the first, connecting the effect of smoking at workplace with the success rate of smoking cessation in a population of Greek smokers. This finding supports the need of smoking abstinence in workplaces for successful smoking cessation. Greece is the country with the highest rate of non-compliance with the laws of restrain tobacco use in public places in EU and based on our results, smoking cessation programs in workplaces should be encouraged.

In our study there was no association between working status (i.e. employment, unemployment) and success rate of smoking cessation effort. The effect of working status in smoking cessation is debatable. There is evidence that smoking cessation was more likely for working men compared to those who are unemployed, while for women the opposite applied. However, in another study, unemployment more strongly associated with persistent daily smoking among women than among men. In a more recent study smoking relapse after percutaneous coronary intervention in Chinese patients was more likely in those who were employed. Perhaps those controversial results are due to illegible confounding factors.

There is strong evidence supporting the validity and reliability of the MNWS for the evaluation of withdrawal symptoms. In the current study, we found that concentration problems assessed by MNWS, constitutes a key factor that hardens smoking cessation even with different pharmacological treatments.
Pharmacological treatments present different success rates in smoking cessation. In a systematic review all three pharmacological treatments were evaluated. It seems that higher doses or extended duration of therapy for NRT and Varenicline were associated with higher success rates of smoking cessation whereas for bupropion data are conflicting. Combination of Varenicline with either of the other two therapies had higher success rates compared with monotherapy something that not apply for the combination of NRT and Bupropion. Finally, a pre-cessation treatment with nicotine patches or with varenicline increased abstinence rates and retreatment with varenicline was efficacious in smokers who have previously taken it. Most studies conclude that Varenicline may be more effective in smoking cessation than NRT or Bupropion; however, two large studies including more than 35,000 smokers combined, found no statistical important differences between the three treatment options.

Our study was a retrospective research of factors affecting smoking cessation in a smoking cessation clinic. There were no differences between Varenicline and NRT in smoking cessation success rate, something that has also been observed in previous studies with much bigger number of participants. Bupropion was used in only two patients with psychiatric background after conciliation with their Psychiatrist, as it seems that it has the same efficacy in smokers with psychiatric disorders. Counseling alone was used in only five patients with low nicotine addiction. Furthermore, in the subgroup analysis adjusted for treatment received, no association was found between any of the factors studied and smoking cessation at three or six months or relapse at six months after a successful smoking cessation effort of three months.

Finally, we investigated the role of self-esteem, at the beginning of a smoking cessation attempt, thus the information they provided represented their current status at that time, something that minimized the recall bias, with the exception of nicotine withdrawal symptoms that were given retrospectively. Another weak point of the study was the inability to assess the compliance of the participants with the smoking cessation therapy. Additionally the follow-up was based on telephone interview and this could be regarded as another limitation of the study. This fact obliged us to evaluate participants’ answers about the outcomes of the smoking cessation effort rather than biochemical examinations which are more objective than self-assessment (cotinine was not measured).

CONCLUSIONS

This study verifies the outcomes of many previous studies that Minnesota Nicotine Withdrawal Scale and Fagerström Nicotine Dependence Test are valid predicting factors of smoking cessation and relapse. A new finding was that difficulty in concentration as a withdrawal symptom is an independent predictor of continuous abstinence failure. Moreover, this study evinced that smokers who smoke more at their workplaces and less out of them are more likely to quit smoking, therefore smoking cessation incentives at workplaces should be taken under more serious consideration.

FUNDING

This paper was not funded.

DECLARATION OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
ΠΕΡΙΛΗΨΗ
Μελέτη προγνωστικών παραγόντων που επηρεάζουν τη διακοπή καπνίσματος σε έναν πληθυσμό Ελλήνων καπνιστών στην καθημερινή κλινική πράξη ενός ιατρείου διακοπής καπνίσματος

Σεραφείμ-Χρυσοβαλάντης Κωτούλας1, Αιμιλία Στεφανίδου1, Ευάγγελος Χατζόπουλος1, Καταλίν Φέκετε-Πασσά1, Κωνσταντίνος Α.Κ. Βαυτίδης2, Φανέλ Μακάριος1, Παρασκευή Αργυροπούλου-Πατάκα1, Αθανασία Πατάκα1

1 Μονάδα Αναπνευστικής Ανεπάρκειας, Αριστοτελείο Πανεπιστήμιο Θεσσαλονίκης, Π.Γ.Ν. “Γ. Παπανικολάου”, Εξοχή, Θεσσαλονίκη, 2 Πνευμονολογικό Τμήμα, Αριστοτελείο Πανεπιστήμιο Θεσσαλονίκης, Π.Γ.Ν. “Γ. Παπανικολάου”, Εξοχή, Θεσσαλονίκη

Υπόβαθρο: Το κάπνισμα είναι μια χρόνια νόσος, υπεύθυνη όχι μόνο για αναρίθμητους πρόωρους θανάτους κάθε χρόνο, αλλά και για σημαντικό οικονομικό βάρος στα συστήματα υγείας. Η Ελλάδα είναι ακόμη μια από τις πρώτες χώρες στην Ευρωπαϊκή Ένωση (ΕΕ) στην επίπτωση και συχνότητα του καπνίσματος, παράγοντας που οδηγεί σε ακόμη μεγαλύτερο ρυθμό νοσηρότητας και θνητότητας και αυξάνει το κόστος της φροντίδας υγείας.

Μέθοδοι: Η έρευνα σχεδιάστηκε ως μελέτη "ασθενών – μαρτύρων". Οι συμμετέχοντες ήταν ασθενείς που επισκέφτηκαν ένα ιατρείο διακοπής καπνίσματος και συμφώνησαν να πάρουν μέρος στην έρευνα, απάντησαν όλες τις ερωτήσεις που χρειάστηκαν και μπορούσαν να επανεκτιμηθούν μετά από τρεις και έξι μήνες. Από τους 231 ασθενείς που επισκέφτηκαν το ιατρείο κατά τη διάρκεια ενός χρόνου, 100 πληρούσαν τα ανωτέρω κριτήρια και χωρίστηκαν σε δύο ομάδες: Αυτούς που κατάφεραν να διακόψουν το κάπνισμα και αυτούς που απέτυχαν. Τα ερωτηματολόγια Fagerström (FNDT), Minnesota (MNWS) και Rosenberg (RS), μαζί με ερωτήσεις που αφορούσαν επιδημιολογικά και άλλα χαρακτηριστικά, χρησιμοποιήθηκαν για την αξιολόγηση των ασθενών.

Αποτελέσματα: Μεταξύ των διαφόρων χαρακτηριστικών που εξετάστηκαν, η πολυπαραγοντική ανάλυση παλινδρόμησης υπέδειξε ότι "δυσκολία στη συγκέντρωση" από το ερωτηματολόγιο Minnesota όπως και το συνολικό σκορ των ερωτημάτων Minnesota και Fagerström και ο μειωμένος αριθμός τσιγάρων μετά τη δουλειά αποτελούν ανεξάρτητους προγνωστικούς παράγοντες διακοπής καπνίσματος, πραγματοποιήθηκε πολυπαραγοντική ανάλυση πολυδρόμησης.

Συμπεράσματα: Η έρευνα αυτή επιβεβαιώνει ότι οι απαντήσεις των καπνιστών στα ερωτηματολόγια Minnesota και Fagerström πρέπει να λαμβάνονται υπόψη για εξατομικευμένη ιατρική στη θεραπεία διακοπής καπνίσματος. Επιπλέον, η μεγαλύτερη ποσοστο καπνιστών επιτυχούσε καπνιστών στους χώρους εργασίας, επειδή φαίνεται ότι ο αυξημένος αριθμός τσιγάρων στην εργασία σχετίζεται με υψηλότερα ποσοστά επιτυχούς διακοπής του καπνίσματος.


Λέξεις - Κλειδιά: Ιδιοπαθής πνευμονική ίνωση, θεραπεία, αποζημίωση, επίπτωση στον προϋπολογισμό

REFERENCES
40. McLeish AC, Farris SG, Johnson AL, Bernstein JA, Zvolensky MJ. An examination of the indirect effect of anxiety sensitivity
in terms of asthma and smoking cessation processes. Addict Behav 2015;50:188-91.


58. Hagen G, Wisløff T, Klemp M. Cost-Effectiveness of Varenicline, Bupropion and Nicotine Replacement Therapy for Smoking Cessation [Internet]. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2010 May. Report from Norwegian Knowledge Centre for the Health Services (NOKC) No. 10-2010.


60. van de Graaf RC, van Schayck OC. [Helping people to give up smoking: efficacy and safety of smoking cessation interventions]. Ned Tijdschr Geneeskd. 2017;161:D1131.


Quality of sleep in patients with end-stage renal failure

Vasileios Tsousis1, Athanasios Dardas2, Drosos Tsavis3, Sofia Papakatsika1, Anna Gavriilidou1, Polyanthi Konstantinidou4, Daxakis Anestakis4, Paschalis Steiropoulos5

1Pulmonary Department, General Hospital Papageorgiou, Thessaloniki, Greece
2Laboratory of Immunology - Histocompatibility, General Hospital Papageorgiou, Thessaloniki, Greece
3Laboratory of Experimental Physiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
4Laboratory of Forensic and Toxicology, Department of Autopsy Histopathology, Aristotle University of Thessaloniki, Greece
5Department of Pulmonology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

Key words:
- Restless Legs Syndrome,
- End-Stage Renal Disease,
- Sleep Quality

Abbreviations
RLS: Restless Legs Syndrome
PSQI: Pittsburgh Sleep Quality Index
CKD: Chronic Kidney Disease
IRLSSG: International Restless Legs Syndrome Study Group
PTH: Parathyroid Hormone
HTC: Hematocrit
B2M: B2 Microglobulin

Correspondence:
Drosos Tsavis
Laboratory of Experimental Physiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
e-mail: dr.tsavis@yahoo.com

SUMMARY
INTRODUCTION: Restless syndrome (RLS) is a common disorder of the lower limbs, characterized by an intense need for continuous movement and accompanied usually by unpleasant sensations. In patients with End-Stage Renal Disease (ESRD) under hemodialysis and under peritoneal dialysis, the syndrome has not been thoroughly studied, particularly in the Greek population. The aim of the study was to assess the prevalence of RLS in ESRD. MATERIALS AND METHODS: ESRD patients underwent laboratory examinations and completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire. It is a cross sectional study and the syndrome RLS was diagnosed according to the International Restless Legs criteria. RESULTS: RLS prevalence was 30% among ESRD patients with a higher prevalence among patients under peritoneal dialysis. The value of urea, β2-microglobulin and parathyroid hormone was related to the scores of the individual components of the PSQI questionnaire. Gender was not statistically associated with the presence of RLS. CONCLUSIONS: The current study demonstrated that 3 out of 10 patients with ESRD suffer from RLS, with the relative risk being increased in patients with high levels of parathyroid hormone. No association was found between hematocrit levels and hemodialysis characteristics. The value of urea, β2-microglobulin and parathyroid hormone was related with the scores of the individual components of the PSQI. Pneumon 2019, 32(1-2):23-30.

INTRODUCTION
Restless Legs Syndrome (RLS) is a common neurological disorder characterized by lower limb paresthesia. Predominant theories on the pathophysiology of the syndrome include dysfunction of the dopaminergic system and iron deficiency. It occurs mainly in the evening hours, causing arousals and disrupting the sleep architecture. The diagnosis is based on the International Restless Leg Syndrome Study Group (IRLSSG) criteria and
its impact on the general population in Greece is 3.9%, similar to that of South Eastern Europe. Chronic Kidney Disease (CKD) is a progressive, irreversible reduction of renal function, while End-Stage Renal Disease (ESRD) is defined by glomerular filtration rate (GFR) <15ml/min, or when mechanical support of renal function is required (kidney transplantation, dialysis). Recent studies, using the IRLSSG criteria, reveal a close relationship between ESRD and RLS, probably due to iron deficiency anemia, inadequate rehabilitation treatment and secondary hyperparathyroidism frequently present in patients with severe nephropathy. The development of micro-inflammation favors the onset of the syndrome and results in insomnia, decreased sleep quality, poor quality of life, and increased use of sleeping medications. These conditions may ultimately lead to cardiovascular complications and reduced survival. The purpose of the present study was to record and describe the epidemiological characteristics of RLS in patients with ESRD undergoing hemodialysis and peritoneal dialysis. Secondary objectives of the study were to establish possible predisposing factors of the syndrome in the various subgroups of patients.

MATERIAL AND METHODS

The study included a total of 100 patients with ESRD (65 men and 35 women), 74 under artificial kidney (hemodialysis) and 26 under peritoneal dialysis. Included patients were on rehabilitation therapy at the Nephrology Clinic of General Hospital "PAPAGEORGIOU" Thessaloniki. Patients were divided into four groups according to the form of renal recovery and whether diabetic nephropathy was present. Analytically:

• Group 1 (DM): Artificial kidney patients without diabetic nephropathy (N = 59)
• Group 2 (PD): Patients under peritoneal dialysis without diabetic nephropathy (N = 19)
• Group 3 (DMDR): Artificial kidney patients with diabetic nephropathy (N = 15)
• Group 4 (PDDR): Peritoneal dialysis patients with diabetic nephropathy (N = 7)

All patients underwent laboratory blood testing for the hematocrit, urea, β2-microglobulin and parathyroid hormone (Immulate 2000 analyzer, SIEMENS®) and completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire. The Diagnosis and Severity Scale that which was distributed and supplemented in one single visit to the Nephrology Clinic with a personal interview.

The PSQI measures the quality of sleep in adults over the last month evaluating components. It includes seven components: 1) Subjective sleep quality, 2) sleep latency, 3) sleeping period, 4) average sleep efficiency, 5) sleep disorders, 6) use of sleep medications, 7) daily dysfunction. Each item is weighted on a 0–3 scale. The overall PSQI score is then calculated with the sum of the seven component scores, providing a total score ranging from 0 to 21 with lowest scores suggesting a better quality of sleep. The Diagnostic and Gravitational Restlessness Syndrome Scale was established in its final form in 2012 by the International RLS Study Group (IRLSSG). The basic criteria for diagnosis are four: 1) the need for legs movement due to an unpleasant sensation, 2) the onset or worsening of an uncomfortable sensation in the legs at rest, 3) the improvement or complete relief of symptoms after movement, 4) aggravation of symptoms and tendency to move in the afternoon or evening compared with the rest of the day. Diagnosis of RLS requires the presence of all criteria. The severity of RLS is determined by ten questions with scores ranging 0 to 4 and is related to the subjective assessment of sleep quality due to the symptoms of restless legs as well as the incidence of symptoms in the daily activities and the patient’s psycho-emotional state. Scores from 1 to 10 indicates mild syndrome, 11 to 20 moderate, 21 to 30 severe and 31 to 40 the most severe syndrome. A statistical analysis was done with the SPSS22.0 statistical software, and the MS Excel accounting software. A statistical significance level was set at 0.05. The statistical methods used were: binomial control, Pearson coefficient and Spearman coefficient. The linear regression model and control X were applied.

RESULTS

Results demonstrated a statistically significant increase in RLS prevalence in patients receiving peritoneal dialysis treatment (groups 2 and 4) (p <0.05). RLS was not predominant in patients undergoing artificial kidney therapy (groups 1 and 3). A comparison was made between artificial kidney and peritoneal dialysis for the presence and severity of RLS. Results showed increased rates of RLS among patients receiving peritoneal dialysis compared with those of patients treated with artificial kidney (Figure 1).

There was a correlation of the renal recovery method with the RLS severity, which revealed significant statistical dependence and in particular patients on peritoneal
dialysis exhibit much higher rates of moderate degree of RLS severity compared with those of the artificial kidney patients (Table 1 and Figure 2).

A binomial control (NPar Test) was performed in order to estimate RLS in the study population divided into Group 1 (kidney patients with RLS) and Group 2 (kidney patients without RLS). It has been shown that the prevalence of RLS in end-stage renal disease was significantly higher compared with RLS prevalence in the general population (p <0.001) (Table 2).

The quantitative variables studied are listed in Table 3, which includes mean values and standard deviations.

**TABLE 1.** RLS severity rates relative to the type of renal recovery.

<table>
<thead>
<tr>
<th>Mild RLS</th>
<th>Moderate RLS</th>
<th>Severe RLS</th>
<th>Very severe RLS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2</td>
<td>17</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

**TABLE 2.** Results of NPar test.

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>RLS Existence</th>
<th>N</th>
<th>RLS% in End Stage Renal Disease</th>
<th>RLS% in general population</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>YES</td>
<td>30</td>
<td>0.30</td>
<td>0.390</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>NO</td>
<td>70</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>100</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The investigated laboratory indicators were linearly related to the seven classes of PSQI. The correlation was plotted at the linearity level with the aid of the Pearson coefficient, but the Spearman coefficient was based on the order of the values. There was a statistically significant positive correlation between the increase in urea value and the second category of the PSQI questionnaire, or else the category referring to the difficulty of sleep initiating (Table 4 and Figure 3, 4). Additionally, a statistically significant positive correlation was found between the increase in the PTH value and the fifth category of the PSQI questionnaire, or else the category referring to the
presence of sleep disorders (Table 5 and Figure 5, 6). There was a statistically significant correlation between the increase in the β2 microglobulin value and the third category of the PSQI questionnaire referring to sleep duration (Table 6 and Figure 7, 8). Finally, no significant correlation emerged between the hematocrit and the individual classes of PSQI (Table 7 and Figure 9, 10).

**DISCUSSION**

The importance of sleep for the normal functioning of the body is fundamental. During this time, vital functions...
and consciousness are both reduced in order to enable reposal and the ability to cope with metabolic needs during vigilance. Sleep deprivation adversely affects quality of life, reduces performance in daily activities, causes sleepiness and malaise and leads to both physical and emotional disturbances. In recent years, interest has grown over the pathophysiology of sleep, because it has become common knowledge that its disorders lead with

<table>
<thead>
<tr>
<th>TABLE 6. Correlation between β2 microglobulin serum levels and components of PSQI questionnaire.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQ1</td>
</tr>
<tr>
<td>r</td>
</tr>
<tr>
<td>0.119</td>
</tr>
<tr>
<td>0.237</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 7. Correlation between hematocrit levels and components of PSQI questionnaire.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQ1</td>
</tr>
<tr>
<td>r</td>
</tr>
<tr>
<td>-0.068</td>
</tr>
<tr>
<td>0.504</td>
</tr>
</tbody>
</table>

**FIGURE 7 and 8.** Correlation between β2 microglobulin serum levels and PSQI total score.

**FIGURE 9 and 10.** Correlation between hematocrit levels and PSQI total score.
This study was designed for patients with ESRD. These patients have special human body functioning due to renal insufficiency but also due to the consequences resulting from renal recovery, whether treated with artificial kidney, or undergoing peritoneal dialysis. Results from the current study suggest that RLS, which is a kinetic disorder of the lower limbs during sleep, is present in significantly higher percentage of 30% among patients with ESRD, compared to the proportion in the general population in Greece which is estimated at approximately 3.9%. This prevalence is similar to other studies, although a wide range of RLS prevalence has been acknowledged. It is worth mentioning that in a study conducted in Greece, the reported prevalence of RLS in patients on renal replacement therapy was 26.6% (154 out of 579 hemodialysis patients). Araujo et al in a study of 400 hemodialysis patients from Brazil reported RLS prevalence of 21.5%. Al-Jahdali et al in a study from Saudi Arabia reported a 50.2% prevalence of the syndrome. Gigli et al from Italy evaluated the prevalence of RLS at 21.5% and La Manna et al at 31.5%. Moreover, Cengic et al in a study conducted in found that the prevalence of RLS in HD patients was 20.5%, while in a study from Japan that included 490 hemodialysis patients, the reported prevalence of RLS was 12.2%. Finally, in Glasgow, Siddiqui et al in a study including 227 hemodialysis patients estimated the prevalence at 45.8%. Thus, one could argue that the prevalence of RLS reported in the current study (30%) is the average of the international bibliography.

Additionally, some interesting results, reported for the first time in the Greek population, emerge in our study. According to these, the proportion of with RLS was higher in patients on peritoneal dialysis and moderate in severity, while the proportion of RLS in patients under treatment with artificial kidney was lower, but of increased severity. The fact that the percentage of patients who had RLS was higher in patients on peritoneal dialysis is in agreement with the study of Losso et al, where 50% of patients under peritoneal dialysis had RLS while the prevalence of RLS among patients on artificial kidney therapy was 23%. In our study, the respective percentages were 58% and 25%, and thus are in accordance with the existing data.

An important finding in our study is that also parathyroid hormone levels increased in line with the risk of RLS occurrence. This finding is consistent with previous data, and in the study of Gade et al there was also a significant correlation between parathyroid hormone levels and the risk of RLS. These results are confirmed by the work of Santos et al who reported a decrease in the prevalence of RLS from 52% to 21% in ESRD patients under hemodialysis after parathyroidectomy, which caused a decrease in parathyroid hormone serum levels.

The B2-microglobulin has been shown to be positively associated with PSQI Questionnaire component 3, relative to, the duration of sleep. A positive correlation between the increase of the urea serum levels and the PSQI component No 2, which refers to the difficulty of initiating sleep was also observed. The abnormally elevated urea value may reflect only partial renal rehabilitation. End-stage renal disease and renal recovery have been shown to be associated with increased rates of sleep disorders compared to the general population. Consequently, our finding regarding the association of increased urea serum levels and the increased likelihood of presenting RLS, is consistent with previous observations. Of note, this is the first time that such an observation has been reported in a Greek population of end stage renal disease patients.

Significant positive correlation between the increase in the serum levels of parathyroid hormone and PSQI component 5, or else the component relative to the presence of sleep disorders was also observed. Accordingly to previous observations regarding urea serum levels, as well as the significant pathological increase of parathyroid hormone is the result of extraterritorial clearance. Previous studies reported a correlation between increased parathyroid hormone levels and augmented risk of RLS. As a result, while RLS rate increase in this specific population, it is perfectly reasonable to expect a greater proportion of sleep disorders, something which has been clearly demonstrated in the present study. It is worth mentioning that this is the first time that an association between PSQI component 5 and parathyroid levels is reported in a Greek population of end stage renal disease patients.

The type of renal recovery of every patient with end-stage renal failure proved to be unrelated to sex. Men and women follow dialysis by artificial kidney and peritoneal dialysis, similar to the current study, after medical recommendation and with respect to the personal desire of the patient.

It is worth mentioning that the prevalence and severity of RLS is significantly reduced in patients who have undergone kidney transplantation, while exhibiting correlations, such as with hemoglobin or ferritin serum levels are similar to the non-uremic form of the syndrome. It is also known that kidney transplantation significantly
improves secondary hyperparathyroidism, neuropathy and amyloidosis of hemodialysis, decreasing β2-microglobulin levels and generally the «uremic profile» exhibited by hemodialysis patients. It could therefore be assumed that the inability of conventional dialysis to eliminate all «uraemic toxins» makes this theory a potential pathogenetic mechanism of the RLS, as this improves along with their removal by kidney transplantation14.

Overall, the results of this study are considered significant. Some of these are, of course, already mentioned in the previous studies and the fact that the prevalence of RLS reported in our study is similar, leads to further enhance the viewpoint of previous researchers. However, some statistical correlations were made for the first time and yielded results with statistical significance that has not been reported again in the past. This fact proves that the specific field of RLS in patients with ESRD remains partially unexplained and further studies are needed to illuminate this multi-faceted syndrome in this particular population group.

**REFERENCES**

"Metsovo Lung" with benign pleural calcifications:
A CXR image with complimentary information from Ultrasound Elastography

Emmanouil Manos¹, Nektarios Palatianos², Panagiotis Panagou³

¹Pulmonary Clinic, General Hospital of Lamia, ²Radiology Department, IASIS Medical Institution of Lamia, ³Pulmonary Department, IASIS Medical Institution of Lamia

SUMMARY
Metsovo lung was an epidemic lung disease resulting from domestic asbestos exposure in Metsovo area of northwestern Greece, that declined after white wash ceased to be used after 1985. This exposure to thin tremolite fibers caused an epidemic of malignant mesothelioma and benign pleural calcifications in almost 80% of those above 70 years of age. A case of Metsovo lung in an asymptomatic Albanian older woman that lived in an area outside Metsovo is described, along with thoracic ultrasound and elastographic findings that were compatible with a benign domestic exposure to asbestos.


"Metsovo Lung" was an epidemic of lung disease resulting from domestic exposure to asbestos in Metsovo (a village in Northwest Greece). Most of the inhabitants had previously been exposed to a whitewash derived from local soils, containing tremolite asbestos. This substance caused an epidemic of malignant mesothelioma (MM) that reached an incidence of 300 times more than expected in populations not exposed to asbestos. It was accompanied by pleural calcifications (PCs) in almost 50% of the adult population, increasing to 80% in those above 70 years old (confirmed in a field study in Metsovo and 3 neighboring villages around Ioannina - the capital of Northwest Greece's Province)¹². Both conditions had declined significantly since whitewash ceased to be used after 1985. Transbronchial lung biopsies from Metsovites with extensive PCs revealed long thin tremolite asbestos fibers, in spite of their minuscule size.

Elastography-based imaging techniques have received substantial attention in recent years, for a non-invasive assessment of tissue’s mechanical properties. They take advantage of changed soft tissue elasticity in various pathologies to yield qualitative and quantitative information that can be
used for diagnostic purposes. UltraSound Elastography (USE) provides complementary information to conventional US by adding stiffness as an another measurable property to current US techniques. The assessment of tissue stiffness through palpation is based on the fact that mechanical properties of tissues are changing as a result of various diseases and situations. A higher tissue stiffness translates into a higher elasticity modulus, and as a result, during tissue palpation, tumors are felt as tissues harder than the surrounding normal areas.

Harder tissues deform under compression less than softer tissues. Their pre- and post-compression US images are similar and thus, better correlated. On the other hand, softer tissues undergo greater deformation under compression and their images differ, indicating a lower degree of correlation. The stiffness of investigated tissue can be assigned by different color-coded or gray-scales depending of US transducer. So, because of the nonlinear behavior of various tissues, the initial compression should be very gentle, in order not to reduce the difference in the effective stiffness.

A 77-years old female patient living in Koritsa village outside Metsovo area presented for evaluation with a working diagnosis of possible TBC. In CXR image (Figure 1) can be seen calcified pleural plaques, bilateral and relatively symmetrical, due to asbestos exposure. In US image (Figure 2) are observed two calcified pleural plaques and in compression USE (Figures 3, 4) calcified pleural plaques are shown with acoustic echoes of benign etiology (light blue color).
ΠΕΡΙΛΗΨΗ

«Πνεύμονας Μετσόβου» με καλοήθεις υπεζωκοτικές επασβεστώσεις: Ακτινογραφία θώρακα και συμπληρωματικές πληροφορίες από την Υπερηχογραφική Ελαστογραφία

Εμμανουήλ Μάνος1, Νεκτάριος Παλατιανός2, Παναγιώτης Πανάγου3

1Πνευμονολογική Κλινική Γενικού Νοσοκομείου Λαμίας, 2Ακτινολογικό Τμήμα, Ιατρικό Διαγνωστικό Κέντρο Λαμίας «ΙΑΣΗ», 3Πνευμονολογικό Τμήμα, Ιατρικό Διαγνωστικό Κέντρο Λαμίας «ΙΑΣΗ»

Ο «Πνεύμονας Μετσόβου» αποτέλεσε μια επιδημία πνευμονικής νόσου που οφείλεται στην εγχώρια έκθεση στον αμίαντο στην περιοχή του Μετσόβου. Οι περισσότεροι από τους κατοίκους είχαν εκτεθεί στο παρελθόν σε ασβέστη που προέρχεται από τοπικά εδάφη, που περιέχουν τρεμολίτη (αμίαντο). Αυτή η ουσία προκάλεσε επιδημία κακοήθους μεσοθηλιώματος του υπεζωκοτικές και έφτασε να είναι 300 φορές μεγαλύτερη από την αναμενόμενη, σε σχέση με πληθυσμούς που δεν εκτέθηκαν σε αμίαντο. Συνοδεύτηκε από υπεζωκοτικές ασβεστώσεις σε ποσοστό σχεδόν 50% του ενήλικου πληθυσμού αγγίζοντας το 80% σε ηλικίες άνω των 70 ετών. Οι διαβροχικές βιοψίες των πνεύμων των ασθενών αποκάλυψαν μακριές λεπτές ίνες τρεμολίτη, παρά το μικροσκοπικό τους μέγεθος. Περιγράφεται περίπτωση ασυμπτωματικού ασθενούς με πνεύμονα του Μετσόβου. Παρουσιάζονται υπερηχογραφικές εικόνες των επασβεστώσεων και περαιτέρω ανάλυση με ελαστογραφία, όπου διαπιστώθηκε η καλοήθης παθολογία των υπεζωκοτικών βλαβών.


Λέξεις - Κλειδιά: Αμίαντος, Πνεύμονας Μετσόβου, Υπεζωκοτικές Επασβεστώσεις, Υπερηχογραφική Έλαστογραφία

REFERENCES


The spectrum of CNS clinical manifestations in patients with small cell lung carcinoma presented through two case reports

Konstantinos Natsis¹, Rouzana Pechlivanidou², Dimitrios Nouvakis¹, Vasiliki Drampa³, Evangelos Papamichalis¹, Harilaos Mourtzinos¹, Antonis Antoniadis²

¹Neurology Department of General Hospital of Serres, Greece
²Pneumonology Department of General Hospital of Serres, Greece

Key words:
- Small cell carcinoma
- Paraneoplastic
- Hypercoaguable state
- Stroke

Correspondence to:
Antonis Antoniadis
Director of Pneumonology Clinic
General Hospital of Serres, Greece
Tel.: +30 23210-94425
Fax: +30 23210-94604
E-mail: antonisant100@gmail.com

SUMMARY
Lung cancer is one of the most common neoplasms in the world. In particular, small cell lung carcinoma (SCLC) is one of the most aggressive neoplasms with poor prognosis. Central and peripheral nervous system involvement is very common in this type of cancer due to cerebral metastases, spinal cord compression or even complications from treatment (either chemotherapy or immunotherapy). Paraneoplastic neurological syndromes and hypercoagulability syndrome are two complicated conditions which connect small cell carcinoma and nervous system. In this article, an extensive reference is made to the two latter situations through the description of two incidents: one with subacute cerebellar degeneration and one with hypercoagulable syndrome and multiple ischemic strokes in patients with SCLC. Pneumon 2019, 32(1-2):34-42.

INTRODUCTION
Globally, lung cancer is the most common cancer in men and the fifth most common malignancy in women¹. Small cell lung carcinoma (SCLC) comprises 13% of all lung cancers. Its incidence has fallen during the last few years due to the reduction of smoking rates². It is a very aggressive cancer, with most patients (60-70%) exhibiting a widespread disease, thereby reducing survival rates to 20% and 2% at 7 months and 5 years respectively³. The central nervous system is frequently affected in patients with SCLC. Neurological dysfunction can occur due to brain metastases, spinal cord compression, post-treatment complications, nutritional and metabolic causes. Two important but more complex interactions between CNS and lung cancer relate to paraneoplastic neurologic disorders and hypercoagulable states, which will be presented below through two clinical cases.

The term Paraneoplastic neurological disorders (PNDs) refers to a
group of syndromes that can affect either the central or the peripheral nervous system and are caused by cancers not located within the aforementioned structures. Their pathophysiology is different from metastases or other cancer complications such as metabolic deficits, infections and coagulopathy. They are associated with various types of tumours, the most common being SCLC. Although they were considered rare syndromes, PNDs are more frequent than previously thought. Our understanding of the underlying pathophysiology has increased through years of observation and now PNDs are considered to have an autoimmune mechanism. This notion is supported by the detection of specific antineuronal antibodies in the CSF and serum of patients with PNDs. Although the classic concept is that these disorders occur exclusively with the co-occurrence of cancer, a few patients with clinical PNDs and specific antineuronal antibodies fail to demonstrate any evidence of tumour presence, despite extensive work-up and follow up imaging. This leads to the reasonable conclusion that PNDs should be considered as autoimmune disorders with a high risk of cancer, rather than a clinical manifestation of the latter.

The interrelationship between a stroke and cancer is complex and not completely understood. The two entities can occur independently in a given patient or cancer may lead to stroke via various mechanisms such as hypercoagulability, non-bacterial thrombotic endocarditis, direct tumor compression of blood vessels and treatment-related effects that can increase the risk of stroke. It is therefore important, especially in cryptogenic strokes, to be aware of this relationship and guide the appropriate workup for occult malignancy under the right clinical circumstances in a stroke patient.

**CASE 1**

A 66-year old female patient complained of dizziness, somnolence and generalized weakness for 20 days. She was admitted to our clinic for evaluation of her symptoms. She was a smoker and was receiving anti-hypertensive drugs for the last 5 years. No other medical problems or previous hospital stays were mentioned. Her family history was unremarkable. Body temperature and serum glucose were also normal. The first step in the evaluation of this patient was a CT scan which was normal. Meanwhile, she reported that the feeling of dizziness was getting worse. Examination of the CSF via lumbar puncture revealed a mild pleiocytosis (290/mm³ -90% lymphocytes), mild elevated total protein: 71,7 mg/dL and normal glucose values: 64 mg/dL. The next day the patient reported nausea and began vomiting. Her neurological examination at that point revealed a truncal ataxia, difficulty in gait and nystagmus with a changing fast phase, indicative of a central etiology of her symptoms. MRI of the brain was negative for any structural causes. A second lumbar puncture was conducted but failed to reveal any CSF changes. Serologic examination, CSF PCR, blood-CSF cultures and autoantibodies for autoimmune encephalitis (anti-NMDA, anti-LG1, anti-CASPR2) were negative. Meanwhile the patient became lethargic and laboratory studies showed a moderate hyponatremia. A paraneoplastic disorder was suspected at this stage. Cancer markers (CA 19-9, CEA, CA-125) were negative. CT of the chest revealed a mass located on the upper lobe of the right lung, with enlargement of mesothoracic lymph nodes (Figure 1). Bronchoscopy and lung biopsy that were performed revealed SCLC. Testing of CSF paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Ri, anti CV2-CRMP5, anti-VGCC) was negative. The patient received a 5-day regimen of intravenous Ig (total dose 2g/kg) but failed to show any significant improvement. She was referred to an oncological center for further evaluation and treatment.

**CASE 2**

A 61-year old male patient suddenly developed weakness and numbness in his right hand along with articulation problems and was admitted for further evaluation. He was a smoker (1 pack/day) and 3 months before he had developed deep venous thrombosis of his right leg, for which he was receiving anticoagulation treatment with rivaroxaban. His brain MRI revealed multiple acute infarcts located in the cerebellum, left occipital and parietal lobe (Figure 2). U/S examination of the carotid and vertebral arteries was normal, as well as his ECG and transthoracic ultrasonography. Rivaroxaban was replaced with low molecular weight heparin (LMWH-tinzaparin 175 mg/kg) and due to his stable medical condition, the patient was discharged and arranged for follow up after 1 month. However, he was admitted in our clinic after 5 days, due to severe dysarthria. Tinzaparin was increased to 200 mg/kg and aspirin 80 mg daily was added to the treatment regimen. The next day the patient complained of dyspnoea and he was evaluated by a pneumonologist. His chest CT revealed a mass located in the right lung and enlarged mesothoracic lymph nodes (Figure 3). Via bronchoscopy the mass turned out to be a SCLC. LMWH was stopped 2 days prior to the procedure and was re-
established 5 days later. Meanwhile the patient developed severe chest pain and after cardiological evaluation, he was diagnosed with myocardial infarction. He was admitted to the ICU, where he was stabilized and was later discharged with dual antiplatelet therapy (clopidogrel 75 mg/d plus aspirin 100 mg daily) and cessation of LMWH. The next day he was transferred to the ER with intense abdominal pain, confusion and a reduced level of consciousness. CT of the brain revealed multiple bilateral acute infarcts located bilaterally in the subcortical white matter and CT of the abdomen demonstrated infarcts located on the spleen and both kidneys (Figure 4). Additionally, his ECG revealed acute extensive myocardial infarction and he was immediately transferred to the ICU where he passed away after 12 hours.

**DISCUSSION**

Paraneoplastic cerebellar degeneration (PCD) constitutes one of the most common PNDs. It is most commonly associated with SCLC, breast and gynaecological cancer, as well as Hodgkin's lymphoma\(^6\). The syndrome develops subacutely over several days or weeks and is often preceded by a viral like illness or nausea-vomiting-dizziness that is often attributed to a peripheral vestibular process\(^5\). These symptoms are followed by difficulty in gait,
generalized ataxia, diplopia, dysarthria and nystagmus. Some patients may also report blurry vision.

The initial brain MRI is usually normal, but in later stages of the disease it may exhibit diffuse cerebellar atrophy. Another helpful diagnostic tool in this case is fluorodeoxyglucose-PET which in the early phases of the disease will demonstrate cerebellar hyper- and later on hypometabolism. The pathologic hallmark of PCD is extensive loss of Purkinje cells that can be associated with inflammatory infiltrates located in the cerebellar cortex, deep cerebellar nuclei and inferior olivary nuclei. As with other paraneoplastic syndromes, PCD shares an autoimmune basis for its pathogenesis. An increasing number of immune responses and specific autoantibodies regarding PCD have been recognized. Some of those are specifically associated with cerebellar dysfunction, while others are not specific and mostly represent a tumor-induced immune response. Anti-Yo (associated with breast or gynaecological cancer) and anti-Tr (associated with Hodgkin's lymphoma) are commonly encountered in PCD and are highly specific of this syndrome.

Patients with SCLC may exhibit various autoantibodies in association with paraneoplastic cerebellar degeneration. 41% of these patients are positive for autoantibodies.
against voltage-gated calcium channels (anti-VGCC). In this setting, Lambert-Eaton myasthenic syndrome may co-exist with PCD. Another 23% of patients exhibit anti-Hu antibodies, while a minority develops autoantibodies against various antigens such as collapsin-response mediator protein 5 (anti-CV2/CRMP5), amphipysin and Purkinje cell cytoplasmic antigen type 2 (anti-PCA2)\textsuperscript{13,14}.

There is no standardized treatment for this condition. Case studies have shown some benefit, especially in the early stages of the disease with immunotherapy such as corticosteroids, plasma exchange, intravenous immunoglobulin, cyclophosphamide, and tacrolimus\textsuperscript{15}. However, because of early, irreversible neuronal loss most patients with PCD do not improve with any of these treatments. Treatment of the tumour remains the most important step in disease stabilization and halting neurological deterioration.

The most common causes of a stroke in cancer patients are traditional cerebrovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus and smoking\textsuperscript{16-18}. However, cryptogenic strokes, meaning that no cause for them was identified despite thorough investigation, appear to be more prevalent in patients with cancer such as SCLC, suggesting an association between the two\textsuperscript{16}. In one study, 67% of strokes in cancer patients appear as multiple embolic infarcts in neuroimaging, suggesting
that clot formation and subsequent embolization may be the prevailing mechanism. It is therefore hypothesized that in a subgroup of patients, a stroke may be caused by mechanisms specifically linked to their underlying malignancy. We will present each one of them in the following section.

**Hypercoagulability:** The most important mechanism that SCLC can lead to a stroke is via abnormal coagulation cascades. Coagulation disorders such as disseminated intravascular coagulation (DIC) are more commonly seen in stroke patients with cancer than those without. Furthermore, cancer patients with a cryptogenic stroke were found to have elevated D-dimer levels compared to non-cancer patients. Tumor cells can release pro-coagulant molecules such as tissue factor (TF) and cancer pro-coagulant (CP). TF is a protein that binds to factor VII and potentiates the coagulation cascade, leading to thrombosis. It has been found in high concentrations in symptomatic atherosclerotic plaques, leading to the hypothesis that it plays an important role in plaque destabilization and emboli formation. CP is a cysteine proteinase that is released by the majority of cancers. It leads to thrombin formation via activation of factor X to Xa. Other pro-coagulant cytokines that are secreted by malignant cells are tumor necrosis factor-α (TNF-α), IL-1 and IL-6. These cytokines induce vascular endothelial
cells, monocytes and cancer cells to release TF, thereby potentiating thrombin formation. They also inhibit protein C, a natural brake in the coagulation cascade. Finally, platelet aggregation seems to play an important role as well, being the result of multiple mechanisms such as cytokine release and elevated levels of von-Willebrand factor.

**Venous-to-arterial embolism:** Hypercoagulability usually manifests as deep venous thrombosis and pulmonary embolism. However, these venous clots can lead to stroke via venous-arterial shunting, a process that is known as paradoxical emboli. It is hypothesized that this shunting can occur via a patent foramen ovale (PFO). The risk that PFO alone plays in stroke appearance is not well established, however, when combined with an increased rate of pelvic thrombosis it seems to increase stroke risk. It is a fair assumption to assume that increased clot formation can lead to increased paradoxical embolization.

**Nonbacterial thrombotic endocarditis:** Another common mechanism relating to stroke and cancer is nonbacterial thrombotic endocarditis (NBTE), previously known as marantic endocarditis. In NBTE, sterile vegetations develop in the cardiac valves, mainly the aortic and the mitral, and can lead to a stroke through embolization. These vegetations result from abnormal fibrin attachment to previously undamaged valves in areas with high blood flow, thus creating a suitable substrate onto which platelets can adhere. Transesophageal echocardiography (TEE) is thought to be more sensitive than transthoracic echocardiography (TTE) in detecting valvular vegetations, although it is not routinely performed in stroke patients. Up to 50% of patients with NBTE in the context of cancer can present with a stroke, mainly of embolic origin. Diffusion pattern MRI in these patients demonstrates multiple widely distributed small and large vessel infarcts.

**Direct Tumor Effects:** SCLC can lead to a stroke through direct vessel compression from brain metastases. This compression can result from either direct tumor invasion of the vessel or via vasogenic edema, leading to cerebral ischemia and infarction in the territory distal to the affected vessel. It is also worth mentioning that this compression, apart from ischemia, can also lead to a hemorrhagic stroke. This hemorrhagic conversion of brain metastases is exceedingly rare in cases of SCLC and is more commonly associated with melanoma and renal cell carcinoma.

Other rare causes of direct cancer effects leading to a stroke include embolism to the brain from metastasis in the heart. Again, this is more commonly associated with melanomas, although in rare cases it can be present in patients with SCLC.

**Treatment-related stroke:** Some chemotherapeutic agents have also been associated with an increased risk of stroke, such as cisplatin, methotrexate and L-asparaginase, however the mechanisms of this adverse action are poorly understood.

It is extremely important that the clinician be aware of some stroke characteristics that should prompt additional workup for occult malignancy. Cryptogenic strokes, multiple embolic infarcts on neuroimaging (large cortical strokes), absence of traditional risk factors, clinical signs such as clubbing and elevated D-dimer levels are some clues that may indicate the presence of an underlying tumor such as SCLC. In these cases, additional diagnostic tests such as TTE (with or without bubble study), coagulation profile and full body FDG-PET may be needed in order to detect an occult cancer and the mechanism responsible for stroke appearance.

These patients present a major therapeutic problem. There are no specific guidelines regarding secondary prevention. The first important step is to address common cerebrovascular risk factors such as hypertension and hyperlipidemia and treat those conditions first. Anticoagulants, mainly LMWH, may be superior to anti-platelet medication in reducing the risk of stroke recurrence in cancer patients, however it should be noted that this group of medications increase the risk of systemic and intracranial bleeding in cancer-stroke patients. Depending on the underlying mechanism of a stroke (et NBTE and patient characteristics (increased bleeding risk) and pending randomized clinical trials, an individualized approach continues to be the mainstay of treatment for those patients.

**CONCLUSION**

SCLC can present with various neurological complications, the most common being brain metastases. Apart from those, CNS involvement may be associated with metabolic and nutritional deficits as well as treatment-related complications. Two important mechanisms of CNS dysfunction in these patients include paraneoplastic neurologic disorders and cancer-related stroke. The clinician must be aware of these conditions, guide appropriate workup when necessary and immediately begin treatment in order to prevent neurological deterioration and achieve patient stabilization.
ΠΕΡΙΛΗΨΗ

Το φάσμα των κλινικών εκδηλώσεων από το ΚΝΣ σε ασθενείς με μικροκυτταρικό καρκίνο του πνεύμονα, μέσα από την παρουσίαση δύο περιστατικών

Κωνσταντίνος Νατσής1, Ρουζάνα Πεχλιβανίδου2, Δημήτριος Νουβάκης1, Αντώνη Αντωνιάδης2,
1Νευρολογική Κλινική, 2Πνευμονολογική Κλινική, Γενικό Νοσοκομείο Σερρών

Ο καρκίνος του πνεύμονα είναι μια από τις πιο συχνές νεοπλασίες παγκοσμίως. Ειδικότερα το μικροκυτταρικό καρκίνο του πνεύμονα αποτελεί μια από τις πιο επιθετικές νεοπλασίες με κακή πρόγνωση. Η συμμετοχή του κεντρικού και περιφερικού νευρικού συστήματος είναι πολύ συχνή στον συγκεκριμένο τύπο καρκίνου και μπορεί να αφορά εγκεφαλικές μεταστάσεις, συμπίεση του νωτιαίου μυελού ακόμα και επιπλοκές από τη θεραπεία (είτε χημειοθεραπεία είτε ανοσοθεραπεία). Δύο από τις πιο περίπλοκες όμως καταστάσεις που συνδέουν το μικροκυτταρικό καρκίνωμα με το νευρικό σύστημα είναι τα παρανεοπλασματικά νευρολογικά σύνδρομα και το σύνδρομο υπερπηκτικότητας. Στο παρόν άρθρο γίνεται μια εκτενής αναφορά στις δύο τελευταίες καταστάσεις μέσα από την περιγραφή δύο περιστατικών: ένα με υποξεία παρεγκεφαλιδική εκφύλιση και ένα με σύνδρομο υπερπηκτικότητας και πολλαπλά ισχαιμικά εγκεφαλικά επεισόδια σε ασθενείς με μικροκυτταρικό καρκίνο του πνεύμονα.


Λέξεις - Κλειδιά: Μικροκυτταρικό καρκίνωμα; παρανεοπλασματικά, σύνδρομο υπερπηκτικότητας, ΑΕΕ

REFERENCES


Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension

Report of two cases

Case Report

ABSTRACT
Langerhans cell histiocytosis (LCH) is a multisystemic disease affecting mainly the skeleton and the lungs. It is an uncommon interstitial lung disease whose radiological findings are characterized by centrilobular nodules and cysts of varying sizes of mid to upper lung distribution. Pulmonary LCH can be associated with pulmonary hypertension (PH) which is often severe. We report two cases with Pulmonary Langerhans cell histiocytosis who were referred to our pulmonary hypertension clinic because of echocardiographic signs of severe PH. Right heart catheterization confirmed the presence of precapillary PH in both patients; however in one patient the severity of PH was disproportional to lung disease, as revealed from pulmonary function tests and highresolution computed Tomography chest findings, suggesting pulmonary vascular involvement. We would like to emphasize the wide spectrum of Pulmonary LCH-associated PH and the rationale to treat some patients with specific PAH medication.


INTRODUCTION
Langerhans cell histiocytosis (LCH) is a smoke related multisystemic disease, with an estimated annual incidence of 4 cases per million population of children under the age of fifteen. It has a wide spectrum of clinical and pathological findings because of the invasion of a clonal growth of a differentiated cell of the monocyte-macrophage line (Langerhans cell) to various tissues. Approximately 60% of adults have lung-only disease, namely pulmonary LCH (PLCH), which is an uncommon cause of chronic interstitial lung disease (ILD). Among patients with PLCH, symptoms and signs of pulmonary hypertension (PH) of variable severity are common. PH due to chronic lung diseases is usually moderate, mean Pulmonary Artery Pressure (mPAP) rarely exceeds 35 to 40 mm Hg, and is related to altera-
tions in blood gases, abnormal pulmonary mechanics and relatively subtle vascular remodelling.

We present two cases with PLCH referred to our Pulmonary Hypertension clinic, in order to show the wide spectrum of PLCH- associated pulmonary hypertension, the multifactorial mechanisms of PH development and the need to treat some patients with specific PAH medication.

CASE REPORTS

Patient A, a 51 years-old female with a smoking history of 70 pack-years and active smoker, was diagnosed with PLCH two years before admission. The diagnosis was based on clinical and radiological findings and documented by positive immunocytochemical and cytofluorimetric study for CD1a cluster (5.4%) in bronchoalveolar lavage fluid. She was referred to our PH clinic because of clinical deterioration (WHO functional class III) and echocardiographic findings of severe PH (RVSP 60mmHg). She was receiving oxygen 12 hours per day for the last 6 months.

Patient B, a 37 years-old female, with 40 pack-years smoking history, was diagnosed with LCH at the age of 7. The diagnosis was made by cervical lymph node biopsy and she has had symptoms of diabetes insipidus. She was referred to our PH clinic due to clinical deterioration (WHO functional class III) and echocardiographic findings of severe PH (RVSP 110mmHg). She was not under oxygen therapy.

They were both evaluated with 6-minute walk test (6-MWT), blood tests including specific markers of cardiac dysfunction (N-terminal pro brain natriuretic peptide NT-proBNP and troponin), Pulmonary Function Tests (PFTs) including Diffusion Capacity for carbon monoxide (DLco), high-resolution computed tomography (HRCT) of the lungs and CT angiography, perfusion lung scanning and Right Heart Catheterization (RHC). The results of the diagnostic workup are tabulated in Table 1.

The radiological findings of Patient’s A chest HRCT,

<table>
<thead>
<tr>
<th>TABLE 1. Functional status and main findings of diagnostic workup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient A</strong></td>
</tr>
<tr>
<td>Demographic characteristics, Sex/Age (years old)</td>
</tr>
<tr>
<td>Clinical evaluation</td>
</tr>
<tr>
<td>1. WHO functional class</td>
</tr>
<tr>
<td>2. 6-MWT (m)</td>
</tr>
<tr>
<td>3. Hypoxaemia at rest</td>
</tr>
<tr>
<td>Doppler echocardiography</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
</tr>
<tr>
<td>Tricuspid Regurgitation maximal velocity V’max (m/s)</td>
</tr>
<tr>
<td>PFTs</td>
</tr>
<tr>
<td>FEV1 Liters (% predicted)</td>
</tr>
<tr>
<td>FVC Liters (% predicted)</td>
</tr>
<tr>
<td>FEV1 / FVC</td>
</tr>
<tr>
<td>TLC Liters (% predicted)</td>
</tr>
<tr>
<td>DLco (% predicted) (mmol/min/kPa)</td>
</tr>
<tr>
<td>RHC</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
</tr>
<tr>
<td>PAP (mmHg) Systolic/Diastolic (Mean)</td>
</tr>
<tr>
<td>CO (L/min)</td>
</tr>
<tr>
<td>PVR dyne.s/cm⁵ (Wood Units)</td>
</tr>
</tbody>
</table>

Abbreviations: WHO= World Health Organization; 6-MWT= 6 Minutes Walk Test; RVSP= Right Ventricular Systolic Pressure; V’max= maximal velocity; PFTs= Pulmonary Function Tests; FEV₁= Forced Expiratory Volume in the first second; FVC= Forced Vital Capacity; TLC= Total Lung Capacity; DLco= Diffusing capacity of the lung for carbon monoxide; RHC= Right Heart Catheterization; RAP= Right Ventricular Pressure; PAP= Pulmonary Artery Pressure; CO= Cardiac Output; PVR= Pulmonary Vascular Resistance.
(Figure 1), were strikingly abnormal, showing reticular opacities and multiple thin-walled bilateral cysts of various sizes. The dimensions of cardiac chambers were slightly enlarged. On the contrary, the findings on Patient’s B chest HRCT, (Figure 2), regarding lung parenchyma were far less prominent compared to those of Patient A, showing mosaic attenuation and small thin-walled bilateral cysts. Nevertheless, there was severe enlargement of the cardiac chambers, mainly of the right ventricle.

PFTs for patient A revealed a mixed obstructive-restrictive pattern of moderate severity, whereas for patient B tests revealed an isolated moderately low diffusion capacity disturbance.

RHC confirmed precapillary pulmonary hypertension for both patients. For patient A, RHC (mPAP 36 mmHg, and Pulmonary Vascular Resistance - PVR 6 WU) revealed moderate PH which was in accordance with the severity of the underlying parenchymal lung disease and hypoxaemia, as indicated by HRCT, PFTs and blood gases. For patient B, RHC results (mPAP 66 mmHg, PVR 11.8 WU) confirmed the presence of severe PH which was inconsistent with the underlying relatively mild parenchymal lung disease.

We treated patient B with specific PAH therapy including an endothelin receptor antagonist (ERA) (macitentan 10mg), a phosphodiesterase type 5 (PDE5) inhibitor (tadalafil 40 mg once daily) and subcutaneous infusion of a synthetic analog of prostacyclin (PGI2) (treprostinil up to 50ng/kg/min). Six months later on the follow-up visit, patient’s functional class was improved, recorded as late II, 6-MWT was 502 meters and this improvement was verified by RHC showing a drop in PVR at 8.1 Wood units. There were also no significant side effects except for pain at the site of infusion.

**FIGURE 1.** High Resolution CT (HRCT) axial image of Patient A showing multiple innumerable thin wall cysts, some bizarre shaped with nodules in the intervening lung parenchyma. Cardiac silhouette is of normal size.

**FIGURE 2.** Axial CT image (lung window) of Patient B showing mosaic attenuation, small thin-walled bilateral cysts and severe enlargement of the right cardiac chambers.

**FIGURE 3.** In patient B, coronal reconstruction of high resolution chest CT shows multiple cystic lesions, some bizarre shaped, with an apicobasal gradient distribution and relative sparing of the lung bases and costophrenic angles.
DISCUSSION

PH is a pathophysiological disorder implicated in multiple clinical conditions, often complicating the course of the majority of cardiovascular and respiratory diseases. According to 2015 ESC/ERS guidelines, PH is clinically classified into 5 groups based on the similarity of clinical presentation, pathology, haemodynamics and treatment strategy. PH due to left-sided heart diseases (Group 2) and chronic lung diseases and/or chronic hypoxemia (Group 3) comprise the vast majority of patients.

PH associated with PLCH manifests more commonly and with greater severity than in patients with other diffuse lung disease. LCH is a multisystemic disease, classified in Group 5 WHO classification for PH, which encompasses diseases of unclear and multifactorial mechanisms. It is characterized by aberrant function, differentiation and proliferation of Langerhans histiocytes, which are phagocytic cells with mononuclear morphologic features. The aggregation of these cells in the center of the bronchiole of the lungs forms granulomatous lesions which are responsible for the small irregular or stellate nodules of centrilobular location observed in early stages chest CT. As the disease progresses nodules cavitate and form cysts which finally coalesce to create asymmetrical cysts, so characteristic of LCH. Histopathologic observations have also suggested that in addition to bronchiocentric inflammation and fibrosis, widespread vascular abnormalities are found in the majority of cases. Langerhans' cell granulomas can infiltrate the walls of small and medium-sized pulmonary arteries, primarily in regions of prominent pulmonary histiocytosis X nodules, whereas medial and subintimal wall thickening may occur in areas uninvolved with pulmonary nodules. This pattern shows that among the mechanisms involved in the pathogenesis of PLCH, there is an intrinsic pulmonary vascular disease, which is independent of small airway or lung parenchyma involvement. It has been shown that in ILDs, even at early stages where pulmonary function tests are minimally affected, DLCO and abnormal physiologic dead space ventilation (VD/VT) strongly suggest the presence of pulmonary vascular abnormalities. DLCO was found abnormal in both our cases. For Patient A, the severely reduced DLCO was in accordance with the severity of primary disease as revealed from chest imaging and PFTs. For patient B, whose radiological findings were less striking and PFTs were almost within normal limits, the moderate reduction of DLCO was suggestive of PH existence. Indeed DLCO has been described as the most common indicator of PH coexistence in non end-stage PLCH patients, with inexplicable symptoms and signs. Because PH in PLCH is also encountered prior to end-stage disease, this marker could be useful in guiding diagnosis as well as clinical monitoring of PH; the latter is important since with the advent of specific treatment options, such as endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostanooids clinical improvement has been reported.

Our cases present evidence that the severity of PH in patients with PLCH, does not necessarily correlate with the severity of chest imaging findings or hypoxaemia; there is a rationale of vascular involvement, supporting the use of specific PAH therapy in some cases. Therefore, patients with PLCH and echocardiographic findings of PH should be referred to a PH centre, to undergo all the necessary diagnostic work-up and finally receive the optimum for their case treatment.
Η ιστιοκυττάρωση Langerhans (LCH) είναι μια πολυσυστηματική νόσος, που προσβάλλει κυρίως οστά και πνεύμονες. Αποτελεί σπάνιο αίτιο διάμεσης πνευμονοπάθειας και έχει ως ακτινολογικά ευρήματα κεντρολοβιδιακά οζίδια και διαφορετικού μεγέθους κύστεις, που κατανέμονται στα άνω και μέσα πνευμονικά πεδία. Η πνευμονική ιστιοκυττάρωση μπορεί να σχετίζεται με πνευμονική υπέρταση, που συνήθως είναι βαριάς μορφής. Παρουσιάζουμε δύο κλινικές περιπτώσεις πνευμονικής ιστιοκυττάρωσης, που παραπέμφθηκαν στο τμήμα πνευμονικής υπέρτασης της κλινικής μας επειδή είχαν ηχοκαρδιογραφικά ευρήματα σοβαρής πνευμονικής υπέρτασης. Ο δεξιός καρδιακός καθετηριασμός επιβεβαίωσε την παρουσία προτριχοειδικής πνευμονικής υπέρτασης, καθώς και την παρουσία υπερυθροειδούς πάθησης της προαιρετικής καρδιών.

REFERENCES

Pneumocystis jiroveci (PJP) lung infection on the ground of achalasia of esophagus

Eirini Pasparaki,
Eleni Bibaki,
Sevasti Koumiotaki,
Emmanouil Ferdoutsis,
Georgios Meletis

Pneumonology department, Venizeleio-Pananeio General Hospital of Heraklion, Crete, Greece

A 57 year-old woman, never smoker, with known achalasia of esophagus accompanied by gastroesophageal reflux (GER) was admitted to our hospital due to fever, chronic non productive cough, shortness of breath and weight loss, for at least 6 months. The Chest CT scan revealed ground glass opacities, consolidations and mild bronchiectasis, predominantly in left lower lobe. From the sputum cultures and the PCR, Pneumocystis jiroveci (PJP) was isolated.

Achalasia is a rare motor disorder of the esophagus, characterised by the absence of peristalsis and impaired swallow-induced relaxation, which result in stasis of ingested food in the esophagus and repeated microaspirations, leading to structural abnormalities of the lungs such as bronchiectasis(1).

Lung infection due to PJP is the most common opportunistic infection among persons with HIV infection or severe immunosuppression, however this diagnosis should be included in the differential diagnosis also for immunocompetent patients with structural abnormalities of the lung parenchyma due to swallowing disorders.

REFERENCES:
Σε ανάμνηση…
Στέλιου Μιχαηλίδη
Δ/ντού Πνευμονολόγου ΕΣΥ, FCCP

Είναι πραγματικά ένα παιχνίδι της μοίρας:

Πώς είναι δυνατόν ένα τόσο δημιουργικό μυαλό όπως αυτό του Στέλιου Μιχαηλίδη να χαθεί τόσο γρήγορα, χτυπημένο από την κακοήθεια.

Ανήσυχος, πάντα ανικανοποιητός με τις γνώσεις του, ασχολούμενος πάντα σε βάθος με τα φαινομενικά απλά, αλλά στην πράξη πολύ δύσκολα ερωτήματα, ο Στέλιος μπορούσε να εκλαϊκεύεται τη γνώση που ο ίδιος με θυσίες και πολύ κόπο αποκτούσε.

Απλός και ταυτόχρονα πολυσχιδής, εξαιρετικός συνεργάτης, άοκνος στην καθημερινότητα, δεν γνώριζε ποτέ ορόσημα όταν επρόκειτο για τον ασθενή ή για την εκπαίδευση νέων συναδέλφων. Ο Στέλιος μας ξεσήκωνε συχνά με τις πρωτότυπες σκέψεις του και αλλοίμονο, πάντα φοβόμαστε μην μας κάνει... «απλή» ερώτηση στην Πνευμονολογία, που θα έπρεπε να ψαχνόμαστε για μέρες. Γι' αυτό προτιμούσαμε από τη θέση μας στο Διοικητικό Συμβούλιο της Ελληνικής Πνευμονολογικής Εταιρείας να του αναθέσουμε πρώτοι εμείς τα δυσκολότερα θέματα, από τη φυσιολογία της αναπνοής, τα νοσήματα του υπεζωκότα ή την αγαπημένη του Χρόνια Αποφρακτική Πνευμονική Πνευμονία. Κάθε φορά που βγάζαμε ελάχιστο δρόμο συναδέλφων του, σχεδόν τις ξαναγράφει. Στα συνέδρια που συμμετείχε με τις ομιλίες του γέμιζε τις αίθουσες, αλλά και μετά πρωταγωνιστούσε στο κοινωνικό μέρος, με το πηγαίο χιούμορ του, απολαμβάνοντας την παρέα των αγαπημένων φίλων του.

Ο Στέλιος συνδύαζε τη βαθειά γνώση της Πνευμονολογίας, την αγάπη για τους αρρώστους, με το ανήσυχο ερευνητικό πνεύμα. Ατυχοί όσοι δεν πρόλαβαν να γνωρίσουν έναν εξαιρετικό χαρισματικό δάσκαλο, γιατρό και φίλο.

Στέλιο θα σε θυμόμαστε για πάντα.

Βλάσης Πολυχρονόπουλος
Κώστας Γουργουλιάνης
INSTRUCTIONS FOR AUTHORS

PNEUMON is an open access, single blind peer reviewed, published quarterly in English as the official scientific journal of the Hellenic Thoracic Society, both in print and online. The journal publishes original papers of international interest on laboratory and clinical research that are pertinent to lung biology and disease. Clinical and experimental work dealing with the whole field of respiratory medicine, including allied health, cell and molecular biology, epidemiology, immunology, pathology, pharmacology, physiology, intensive and critical care, pediatric respiratory medicine and thoracic surgery will be considered for publication.

Articles published in PNEUMON address topics related to pneumonology and critical care medicine in the following categories: (1) Editorials, (2) Reviews, (3) Basic and Clinical Research Studies, (4) Case Reports, (5) Special Articles, and (6) Letters to the Editor. Details on the length and number of references for each type of publication can be found at the end of this text.

Editorials, reviews and special articles are published following invitation by the Editorial Board. The Editorial Board reserves the right of publishing other types of papers as well. Papers submitted for publication will not be returned, irrespective of whether they are published or not. Published papers are a literary property of both the authors and the journal and their publication, in part or in whole, without written permission of the Editorial Board is prohibited.

Requirements and Ethics of Publication

Manuscripts containing original material are accepted for consideration if neither the article nor any part of its essential substance has been or will be published or submitted elsewhere. Copies of any closely related manuscripts must be submitted along with the manuscript. PNEUMON discourages the submission of more than one article dealing with related aspects of the same study. Authors are advised to follow the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals,” published by the International Committee of Medical Journal Editors (http://www.icmje.org).

Credit for Authorship

Following the recommendations of the International Committee of Medical Journal Editors, “author” is a person who has participated sufficiently in the work to take public responsibility for portions of the content. Specifically, an author is a person who (1) has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) has drafted the submitted article or revised it critically for important intellectual content, and (3) has provided final approval of the version to be published. Any person who does not meet all three of the listed criteria does not qualify as an author and should not be designated as an author. Importantly, any change in authorship after submission must be approved in writing by all authors.

Human and Animal Study Guidelines

PNEUMON endorses recommendations concerning human research described in the Declaration of Helsinki (World Medical Association Declaration of Helsinki). Recommendations guiding physicians in biomedical research involving human subjects. JAMA1997;277:925-926. Available at: http://www.wma.net/e/policy/b3.htm). Manuscripts that do not conform to these recommendations may not be considered for publication. Manuscripts reporting human research must state within the text that the assignment of the medical intervention is not the discretion of the investigator do not require registration. Further information on this subject can be found on the International Committee of Medical Journal Editors website (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html). Manuscripts that report data from randomized clinical trials, authors should follow the flow diagram and/or checklist of the Consolidated Standards of Reporting Trials (CONSORT) format and provide all the information required (available at: http://www.consort-statement.org accessed November 9, 2008).

Reporting Clinical Trials

PNEUMON requires that investigators register their clinical trials (other than phase 1trials) in a public trials registry (e.g. http://www.clinicaltrials.gov). According to the WHO definition, a clinical trial is “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes”. The name of the registry and the registration number should be clearly stated in the last paragraph of the Abstract and in the Materials and Methods section of the manuscript. Purely observational studies (those in which the assignment of the medical intervention is not the discretion of the investigator) do not require registration. Further information on this subject can be found on the International Committee of Medical Journal Editors website (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html). In manuscripts that report data from randomized clinical trials, authors should follow the flow diagram and/or checklist of the Consolidated Standards of Reporting Trials (CONSORT) format and provide all the information required (available at: http://www.consort-statement.org accessed November 9, 2008). Reporting Other Types of Studies

PNEUMON suggests that authors follow the international standards for other types of publications. For example, (1) meta-analyses and systematic reviews should conform to the QUOROM requirements (Moher D, et al. Lancet 1999; 356:1996-2000); (2) meta-analyses of observational studies in epidemiology should conform to the MOOSE requirements (Stroup DF, et al. JAMA 2000; 2008-2012); (3) studies of diagnostic accuracy should conform to the STARD statement (available at http://www.stard-statement.org; accessed November 9, 2008); and (4) observational studies in epidemiology should conform to the STROBE statement (von Elm E; et al. BMJ 2007;335:806-808).

Conflicts of Interest

A conflict of interest exists if authors or their institutions have financial or personal relationships with other people or organizations that might inappropriately affect, or might reasonably be thought by others to affect, the authors' judgment or actions. Examples of financial conflicts include employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted. Conflicts of interest should be clearly stated in the Title page of the manuscript. If there are no conflicts of interest, authors should state that. For further information on how to report conflicts of interest, authors may refer to “the Lancet’s policy on conflicts of interest” (James A, Horton R. Lancet 2003; 361:8-9) (http://www.icmje.org/conflicts-of-interest/).

Tobacco Policy

PNEUMON will not consider for publication manuscripts that have been supported in whole or in part or sponsored in any way by tobacco companies and associated institutes and organizations.

Publishing & Editorial Issues

- Copyright (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/copyright.html)
● Fees: Free of charge
● Sponsorship or Partnership (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/sponsorship-or-partnership.html)

Advertising
The “PNEUMON” journal is an outstanding place for companies in the respiratory field to promote themselves and their products through advertising. Please contact M. Stefanakis for detailed information: techn@hol.gr

Target area
The “PNEUMON” journal targets a key professional market in the respiratory field, which has about 60 years' experience and extensive circulation.

Advertising policy and disclaimer
The aim of this policy is to ensure that the content of advertising in the “PNEUMON” journal serves the best interests of the readers.
● Advertisements must be legal, decent and accurate and must comply with the relevant laws and regulations.
● Advertisements for products making therapeutic claims but without marketing authorization or CE marking (or local equivalent) should be submitted with all claims substantiated in full length research papers published in peer reviewed journals.
● Readers should immediately be able to distinguish between advertising and editorial content.
● “PNEUMON” journal accepts advertising for products and services that are of interest to users in their personal, as well as professional lives.
● In line with the spirit of the policy on tobacco, “PNEUMON” journal does not accept advertising relating to tobacco products or to products and services from tobacco companies, their foundations, or their wholly owned subsidiaries.
● “PNEUMON” journal does not allow advertising to influence editorial decisions.

Advertising is subject to editorial oversight. Advertising may be refused if it is judged by editors.

The advertiser shall be liable for the content of any of its advertisements published according to its instructions. The advertiser shall indemnify and hold harmless the “PNEUMON” journal against and from any and all claims, damages, liabilities, costs and expenses whatsoever, including reasonable counsel fees, arising from the content of any of its advertisements.

MANUSCRIPT SUBMISSION
All manuscripts and correspondence can be submitted by e-mail to the address pneumon@hts.org.gr. All submissions should include a Cover Letter and a single Manuscript file (including Body of Manuscript, References, Tables, Figure Legends, and Figures). Figures may be submitted also as separate files. All text should be double-spaced using 12-point type face (Arial or Times New Roman) and should be prepared in a word processing format (Microsoft Word preferred; an acceptable alternative would be PDF format). For the suggested length of publications please refer to Table 1. All authors must sign an agreement form (agreement form). The form must be scanned and send by e-mail at the time of the submission of the manuscript.

Cover Letter
All manuscripts should be accompanied by a cover letter, signed by the corresponding author, clearly stating the following:
1. Neither the article nor any part of its essential substance has been or will be published or submitted else where; if papers closely related to the submitted manuscript have been published or submitted for publication elsewhere, the authors should provide details.
2. The clinical relevance of the work described and what it adds to the current literature.
3. Potential significant conflicts of interest.
4. The manuscript has been prepared according to the instructions for authors of PNEUMON and all authors have read and approved the text of the article.
5. If accepted for publication, the copyright will be transferred to PNEUMON Journal.
Failure to provide a cover letter addressing each of the points above will result in the paper being returned to the author. The cover letter must be presented as a separate submission item.

Title page
The title page must contain the following information:
1. The title of the manuscript (no more than 10 words). If it is necessary the title can include a sub-title
2. The full name, institutions, city and country for all co-authors
3. The full name, postal address, e-mail, telephone, and fax numbers of the corresponding author.
4. Conflicts of interest of all authors.
5. Potential funding or grant support of the work described.

A running (short) title.
The total number of words of the manuscript and the abstract.

Abstract
A structured abstract should be provided of up to 250 words. It should consist of three paragraphs, labeled Background, Methods, Results, and Conclusions. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the most important results, and what the authors conclude from the results. Abbreviations should be avoided and, if used, they should be explained the first time mentioned.

Keywords
Up to 5 keywords that reflect the content of the manuscript should be provided. Authors should consult the Medical Subject Headings (MeSH) website (available at http://www.nlm.nih.gov/mesh/meshhome.html; accessed on November 9, 2008).

Abbreviations
Please provide an alphabetical list of all abbreviations used in the manuscript on a separate page. For clarity reasons, please use abbreviations sparingly. When abbreviations are used, they should be explained the first time they are mentioned in the text.

Body of Manuscript
The paper should include the following sections:

Table 1. Suggested Maximum Length Requirements for Submitted Manuscripts
(November 2008)

<table>
<thead>
<tr>
<th>Type of publication</th>
<th>Abstract (words)</th>
<th>Body of Manuscript (words)*</th>
<th>References (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editorial</td>
<td>n/a</td>
<td>1000</td>
<td>15</td>
</tr>
<tr>
<td>Original Research</td>
<td>250</td>
<td>3500</td>
<td>50</td>
</tr>
<tr>
<td>Reviews</td>
<td>250</td>
<td>4500</td>
<td>100</td>
</tr>
<tr>
<td>Case Reports</td>
<td>150</td>
<td>1500</td>
<td>20</td>
</tr>
<tr>
<td>Special Articles</td>
<td>250</td>
<td>2500</td>
<td>50</td>
</tr>
<tr>
<td>Correspondence</td>
<td>n/a</td>
<td>500</td>
<td>5</td>
</tr>
</tbody>
</table>

*excluding References, Tables, Acknowledgements and Figure Legends
n/a: not applicable
Introduction
The rationale for the study should be summarized and relevant background material outlined. The Introduction should not contain findings, methods used or conclusions.

Methods
Methods should be described in adequate detail to assure the reader as to how the results were obtained. In manuscripts reporting human research, the authors should report approval by the Review Board or Ethics Committee and that written informed consent was obtained from patients. The location (city, state, country) of a manufacturer listed in the text should be provided. Units should conform to SI conventions. Generic names of drugs should be used instead of trade names. Statistical methods should be meticulously described and referenced.

Results
Results should be presented in a rational order in the text, tables and figures. The authors should avoid repetitive presentation of the same data in different forms, especially between the text and tables and figures. The Results should not include material appropriate to the Discussion.

Discussion
The discussion should start by presenting the new and most interesting data of the work in relation to any hypotheses made in the Introduction. Any unexpected or contradictory results should be explained or defended. For example, evaluation of methodology and the associations of new information to the existing knowledge in the topic should be discussed. Speculation should be kept to a minimum. The results must not be simply reiterated. New results should not appear in the Discussion. No specific reference to figures and tables should be included in the Discussion.

Acknowledgements
Acknowledge the persons who provided a true contribution and who endorse the data and conclusions. Acknowledge any funding sources.

References
Only published works may be cited as references. Manuscripts accepted but not yet published may be cited designating the accepting journal, followed by the term (in press), and copies of the in-press articles should be provided for reviewer inspection. References should be cited in the manuscript with superscript numerals in the order in which they appear in the text. The full list of references should be provided in numerical order on a separate page at the end of the text. References should include, in order, the following: authors, title, source, year of publication, volume, and inclusive page numbers. All authors should be listed if they are six or fewer; when they are seven or more, list the first three followed by ‘et al.’ Please abbreviate journal names as in Index Medicus (available at http://www.nlm.nih.gov/tsd/serials/ji.html; accessed on November 9, 2008).

The following are sample references:

Numbered references to personal communications, unpublished data, or manuscripts either «in preparation» or «submitted for publication» are unacceptable. If essential, such material can be incorporated at the appropriate place in the text.

Tables
Double-space tables (including any footnotes) should be presented on separate pages, providing a title for each. Any abbreviations used in a Table should be defined in the Table’s footnote.

Figures
Figures may be inserted in the text file or in a separate file (accepted formats are JPEG, TIFF and EPS). Legends for all figures should be included in the file with the text, on a separate page after the Tables, and should not appear on the actual figures. If photographs of patients are used, they should either not be identifiable or the photographs should be accompanied by written permission to use them.

Permission
The manuscript must be accompanied by copies of permission to reproduce previously published material (figures or tables); to use illustrations of, or report sensitive personal information about, identifiable persons; and to name persons in the Acknowledgments section.

Manuscript Submission
You can submit your manuscript using the following online form.
- Site map
- Sign in
- Register
- Contact us
- Email Alerts
© 2011 - 2018 Hellenic Thoracic Society (HTS) - All rights reserved.
Developed by LogicOne