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Mieczyslaw Pokorski *Editor*

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Preface

The book series Neuroscience and Respiration presents contributions by expert researchers and clinicians in the multidisciplinary areas of medical research and clinical practice. Particular attention is focused on pulmonary disorders as the respiratory tract is upfront at the first line of defense for organisms against pathogens and environmental or other sources of toxic or disease-causing effects. The articles provide timely overviews of contentious issues or recent advances in the diagnosis, classification, and treatment of the entire range of diseases and disorders, both acute and chronic. The texts are thought as a merger of basic and clinical research dealing with biomedicine at both the molecular and functional levels and with the interactive relationship between respiration and other neurobiological systems, such as cardiovascular function, immunogenicity, endocrinology and humoral regulation, and the mind-to-body connection. The authors focus on modern diagnostic techniques and leading-edge therapeutic concepts, methodologies, and innovative treatments. The action and pharmacology of existing drugs and the development and evaluation of new agents are the heady area of research. Practical, data-driven options to manage patients are considered. New research is presented regarding older drugs, performed from a modern perspective or from a different pharmacotherapeutic angle. The introduction of new drugs and treatment approaches in both adults and children is also discussed.

Body functions, including lung ventilation and its regulation, are ultimately driven by the brain. However, neuropsychological aspects of disorders are still mostly a matter of conjecture. After decades of misunderstanding and neglect, emotions have been rediscovered as a powerful modifier or even the probable cause of various somatic disorders. Today, the link between stress and health is undeniable. Scientists accept a powerful psychological connection that can directly affect our quality of life and health span. Psychological approaches, which can decrease stress, can play a major role in disease therapy.

Neuromolecular and carcinogenetic aspects relating to gene polymorphism and epigenesis, involving both heritable changes in the nucleotide sequence and functionally relevant changes to the genome that do not involve a change in the nucleotide sequence, leading to disorders, are also tackled.

Clinical advances stemming from molecular and biochemical research are but possible if research findings are translated into diagnostic tools, therapeutic procedures, and education, effectively reaching physicians and patients. All this cannot be achieved without a multidisciplinary, collaborative, bench-to-bedside approach involving both researchers and clinicians. The role of science in shaping medical knowledge and transforming it into practical care is undeniable.

Concerning respiratory disorders, their societal and economic burden has been on the rise worldwide, leading to disabilities and shortening of life-span. COPD alone causes more than three million deaths globally each year. Concerted efforts are required to improve this situation, and part of those efforts are gaining insights into the underlying mechanisms of disease and staying abreast with the latest developments in diagnosis and treatment regimens. It is hoped that the articles published in this series will assume a leading position as a source of information on interdisciplinary medical research advancements, addressing the needs of medical professionals and allied health care workers, and become a source of reference and inspiration for future research ideas.

I would like to express my deep gratitude to Paul Roos, Tanja Koppejan, and Cynthia Kroonen of Springer Nature NL for their genuine interest in making this scientific endeavor come through and in the expert management of the production of this novel book series.

Mieczyslaw Pokorski

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Sociodemographic and Clinical Determinants of Quality of Life of Patients with Non-small Cell Lung Cancer

Mariusz Chabowski, Jacek Polański, Grzegorz Mazur, Dariusz Janczak, and Joanna Rosińczuk

Abstract

Non-small cell lung cancer (NSCLC) is a serious health problem. Identifying factors affecting quality of life (QoL) may help modify risk factors and improve survival. The study included 180 patients treated for NSCLC in the Lower Silesian Center of Lung Diseases between January and December 2015. QoL was assessed with QLQ-C30 and QLQ-LC13 scales. General physical functioning was measured with the ECOG Performance Status scale. The clinical and sociodemographic data were retrieved from medical records. The influence of clinical and sociodemographic factors on QoL was examined. NSCLC reduced the global QoL (47.1 ± 23.4) and emotional functioning (57.8 ± 28.8); cognitive functioning was affected in least (76.0 ± 21.0). The patients reported fatigue (42.2 ± 26.2), sleep problems (42.0 ± 30.8), cough (49.8 ± 24.0), and taking analgesics (50.3 ± 37.1) as the most limiting factors. The worsening of a health condition expressed by the length of malignant disease; the presence of comorbidities, metastases, the cluster of symptoms, worse spirometric indices, and living alone had a negative influence on QoL. In conclusion, patients with NSCLC experience reduced QoL and emotional functioning. Proper treatment of comorbidities and symptom management may improve QoL in these patients.

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Keywords
Cognitive functioning • NSCLC • Performance status • Physical functioning • Quality of life • Socioeconomic factors

1 Introduction

Lung cancer is a serious health care problem worldwide. Since 1985, it is one of the most common cancers worldwide. It belongs to the most frequently diagnosed malignancies with 1.6 million, i.e., 13% of total new cancer cases as well as to one of the most fatal ones with 18% of total cancer deaths (1.4 million). About 1 out of 5 cancer deaths are from lung cancer. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined. Despite of advances in diagnosing and treatment, survival rate remains low. The overall 5-year survival rate reaches only about 15% even in the well developed countries (Didkowska et al. 2016; Ridge et al. 2013; Dela Cruz et al. 2011).

Patients with lung cancer experience reduced level of quality of life (QoL), which is even lower than in patients with other malignant diseases. Patients report the presence of many distressing symptoms, which can appear before diagnosis and continue throughout the course of the disease and its treatment limiting their daily functioning. Reduced QoL is a recognized factor for worse prognosis in this group of patients (Arraras et al. 2016; Gupta et al. 2012; Braun et al. 2011). Therefore, identification of factors that negatively affect QoL, especially areas that may worsen survival, may help to improve treatment outcomes. Additional treatment aimed to modify risk factors affecting QoL might be added to current treatment protocols in patients with lung cancer and reduced QoL. For this reason, the aim of our study was to evaluate the impact of selected sociodemographic and clinical factors on QoL in patients with lung cancer.

2 Methods

The study included 180 patients with histologically confirmed non-small cell lung cancer (NSCLC) who were treated in the Lower Silesian Center of Lung Diseases between January and December 2015. Clinical and sociodemographic data was obtained from a self-reported questionnaire and patients' medical records. All patients gave a written informed consent for participation in the study and answering the questionnaires. The study was approved by the Bioethics Committee at Wroclaw Medical University (no. 507/2015) and was carried out according to the guiding principles of the Declaration of Helsinki.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) is the most frequently used in clinical trials and is often combined with supplementary cancer-specific modules (Zikos et al. 2014; Aaronson et al. 1993). The scale is also validated for the use among Polish patients (Tomaszewski et al. 2013). For this reasons, we chose QLQ-C30 along with QLQ-LC13 module. The QLQ-C30 is a 30-item questionnaire including the assessment of global health status, functioning scales (physical, life role, cognition, emotional, and social), and symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems). For the assessment of typical symptoms appearing in lung cancer patients, the QLQ-LC13 module was used (Bergman et al. 1994). Scores obtained from the QLQ-C30 and LC13 scales were linearly converted to a 0–100 scale. For the global health status and functioning scales, higher scores indicate better QoL, while for the symptom scales higher scores indicate greater symptom burden, thus worse QoL. General physical functioning was assessed with

Table 1 Characteristics of the study group

Variable		n (%)
Gender	Female	82 (45.6)
	Male	98 (54.4)
Marital status	In a relationship	105 (58.3)
	Living alone	75 (41.7)
Education	Primary	15 (8.3)
	Vocational	88 (48.9)
	Pre-university	59 (32.8)
	University degree	18 (10.0)
Source of income	Permanent employment	53 (29.4)
	Allowance, pension, retirement	121 (67.2)
	Relatives' dependent	6 (3.3)
Comorbidities	Lack of comorbidities	59 (32.8)
	One coexisting disease	81 (45.0)
	Two coexisting diseases	38 (21.2)
	Three coexisting diseases	2 (1.1)
Metastases	Free from metastases	117 (65.0)
	Metastases to one organ	43 (23.9)
	Multi-organ metastases	20 (11.1)
Treatment	Surgery only	72 (40.0)
	Other treatment	108 (60.0)
Performance status	Grade 0	33 (18.3)
	Grade 1	79 (43.9)
	Grade 2	58 (32.2)
	Grade 3	9 (5.0)
	Grade 4	1 (0.6)

ECOG Performance Status scale (Oken et al. 1982).

Data were reported as means ± SD. The Shapiro-Wilk test was used to analyze the data distribution. For two groups, comparison of quantitative variables with normal distribution was carried out with Student's *t*-test and for variables with distribution other than normal, the Mann-Whitney U test was used. For three or more groups, comparison of quantitative variables with normal distribution was carried out with analysis of variance (ANOVA) and for variables with distribution other than normal, the Kruskal-Wallis test was used. In case of significant differences, Tukey's HSD (honest significant difference) *post-hoc* test was used for normal distributions or the Mann-Whitney test with a Bonferroni adjustment for distributions other than normal. Correlations between two quantitative variables of normal distributions were analyzed with Pearson's coefficient and between two quantitative variables of distribution other than normal with Spearman's coefficient. The criteria for statistical significance were set at $p < 0.05$. Statistical analysis was carried out with the R Project for Statistical Computing v3.2.1.

3 Results

The patients' mean age was 62.7 ± 9.7 (range 25–87 years). Pulmonary function tests revealed following results: forced expired volume in one second (FEV1) 2.38 ± 0.80 L, forced vital capacity (FVC) 3.06 ± 0.96 L, and FEV1/FVC (%) 79.5 ± 20.4. The mean number of symptoms presented by patients was 2.8 ± 1.4. Clinical and sociodemographic patients' data are presented in Table 1.

The overall mean score of QoL was 47.1 ± 23.4. In the QLQ-C30, the greatest

Table 2 The overall quality of life score in the study group calculated on the basis of QLQ-C30 and QLQ-LC13 questionnaires

	Mean	SD	Median	Min	Max	Reference values[a] Mean (SD)
QLQ-C30 functioning area						
Global	47.1	23.4	41.7	0	100	58.8 (22.5)
Physical	72.4	17.8	73.3	13.3	100	78.4 (19.3)
Life role	66.1	26.8	66.7	0	100	60.7 (33.1)
Emotional	57.8	28.8	50.0	0	100	68.1 (24.2)
Cognitive	76.0	21.0	83.3	16.7	100	84.0 (21.1)
Social	65.6	32.7	66.7	0	100	73.6 (28.9)
QLQ-C30 symptom area						
Fatigue	42.5	26.2	44.4	0	100	40.4 (27)
Nausea/vomiting	12.5	18.1	0	0	66.7	9.7 (18.3)
Pain	36.3	23.1	33.3	0	100	29.7 (30.3)
Dyspnea	41.9	23.9	33.3	0	100	38.5 (31.7)
Sleep disturbance	42.0	30.8	33.3	0	100	32.4 (32.7)
Appetite loss	31.7	28.3	33.3	0	100	27.9 (33.5)
Constipation	17.8	26.5	0	0	100	17.4 (27.9)
Diarrhea	8.9	21.9	0	0	100	6.8 (17.4)
Financial problems	34.3	31.8	33.3	0	100	12.8 (25.8)
QLQ-LC13						
Dyspnea	34.3	22.9	33.3	0	100	–
Coughing	49.8	24.0	33.3	0	100	–
Hemoptysis	14.1	20.5	0	0	100	–
Sore mouth and tongue	7.4	15.6	0	0	66.7	–
Dysphagia	13.2	20.1	0	0	100	–
Peripheral neuropathy	11.9	18.9	0	0	100	–
Hair loss	11.7	23.2	0	0	100	–
Chest pain	23.0	25.0	33.3	0	100	–
Pain in arm or shoulder	12.6	22.3	0	0	100	–
Other pain sites	24.3	27.7	33.3	0	100	–
Taking analgesics	50.3	37.1	62.5	0	100	–

[a]According the EORTC QLQ-C30 reference values (Gupta et al. 2012)

limitations were observed for global health status (47.1 ± 23.4) and emotional functioning (57.8 ± 28.8), while the lowest for cognitive functioning (76.0 ± 21.0). The smallest symptom burden was observed in case of diarrhea (8.9 ± 21.9) and nausea (12.5 ± 18.1), while the biggest – in case of fatigue (42.2 ± 26.2) and sleep problems (42.0 ± 30.8). Additionally, QLQ-LC13 showed that patients are the most limited by taking analgesics (50.3 ± 37.1) and coughing (49.8 ± 24.0). Scores for the QLQ-C30 and the QLQ-LC13 are presented in Table 2.

Age was positively correlated with emotional functioning and a greater use of analgesics, while negatively – with symptoms such as nausea/vomiting and problems with sleeping. Length of cancer disease had a significant impact on many dimensions of QoL. Longer disease affected negatively the global health status and limited role, emotional, cognitive, and social functioning. Along with progression of cancer disease, patients reported increased fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, financial problems, as well as QLQ-LC13 scale symptom intensity such as dyspnea, coughing, dysphagia, and peripheral neuropathy. The intensity of hemoptysis and the amount of analgesics taken was correlated negatively with the length of the disease. The number of hospitalizations had a positive influence on

global health status and on emotional, cognitive, and social functioning. Frequent hospitalizations increased symptoms such as constipations, hemoptysis, and hair loss, while decreased sensation of pain.

The number of coexisting diseases varied from none to three in a patient and it affected QoL. Because three diseases were reported only in two cases, they were included in the group of patients with two coexisting disease for further analysis. Patients suffered from diabetes, ischemic heart disease, renal insufficiency, rheumatoid arthritis, heart failure, asthma, and chronic obstructive pulmonary disease. Patients without any comorbidities presented better role, emotional, cognitive, social functioning ($p < 0.001$ in all areas), physical functioning ($p = 0.007$), and had a better global health status than those with one or more comorbidities ($p < 0.001$). Patients burdened with more than one comorbidity reported more intensive sensations of fatigue and dyspnea than those without comorbidities ($p < 0.001$). Patients burdened with two or three coexisting diseases reported a greater degree of nausea/vomiting, coughing, sore mouth and tongue, dysphagia, and other pain sites than patients without coexisting diseases ($p = 0.001$, $p = 0.001$, $p = 0.021$, $p = 0.025$, $p = 0.005$, respectively). Patients with comorbidities, irrespective of the number of comorbidities, reported greater sensation of pain, insomnia, appetite loss, financial problems, and dyspnea than those without comorbidities ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$ and $p = 0.001$, respectively). Patients with two or three comorbidities reported constipation more often than those with one comorbidity ($p = 0.047$). When evaluating the development of metastases, only multi-organ metastases affected QoL intensifying fatigue, pain, and pain in the chest compared with patients free of metastases ($p = 0.046$, $p = 0.050$, $p = 0.033$, respectively). The number of symptoms reported by patients affected QoL in many areas and was significantly correlated with 17 out of the 26 scales. A greater number of symptoms decreased all areas of functioning and increased the intensity of many symptoms. Correlation coefficients describing the impact of the number of symptoms on QoL domains are presented in Table 3.

The type of treatment had an extensive influence on the level of QoL. Patients treated by surgery alone had higher global health status, physical and emotional functioning, but worse role, cognitive and social functioning than patients who were undergoing other types of treatment ($p < 0.001$ in all areas). Patients after surgical treatment reported a significantly lower intensity of all symptoms, except hemoptysis, and took fewer analgesics than patients undergoing other types of treatment.

Spirometric indices also affected QoL. FEV1 was negatively correlated with the sore mouth and tongue, and with the hair loss. FVC was negatively correlated with the intensity of the following symptoms: dyspnea, sore mouth and tongue, dysphagia, and hair loss. The greatest influence on QoL occurred in case of FEV1/FVC ratio. It was significantly positively correlated with global health status and nearly all areas of functioning. A negative correlation was revealed for pain, insomnia, financial problems, and a positive one for hemoptysis. The correlation coefficients for FEV1/FVC ratio are presented in Table 3.

Due to a small number of patients who had performance status of grade 3 and 4, the patients with performance status of grade ≥ 2 were allocated to one group. A degree of disability had a great impact on many areas of QoL. Patients with performance status of grade 0 and 1 had not only a higher level of global health status, role and cognitive functioning ($p < 0.001$ for all areas), but also a reduced sensation of peripheral neuropathy, chest pain, and other pain sites ($p = 0.025$, $p = 0.001$, $p = 0.025$, respectively). Patients with performance status of grade 0 reported a significantly better physical functioning than those with performance status of grade 1, who in turn reported a significantly better physical functioning than those with performance status of grade 2–4 ($p < 0.001$). Similar relations were observed for fatigue and taking analgesics, where patients with performance status of grade 0 reported the lowest score and those

Table 3 Correlation coefficients describing the relationships between quality of life areas and selected factors

Scale	Age	Disease length	No. of hospitalizations	FEV1/FVC	No. of symptoms
QLQ-C30 functioning area					
Global	−0.006 (0.935)	−0.409 (<**0.001**)	0.191 (**0.010**)	0.194 (**0.009**)	−0.209 (**0.005**)
Physical	−0.123 (0.099)	−0.144 (0.054)	−0.01 (0.892)	0.089 (0.237)	−0.295 (<**0.001**)
Life role	0.050 (0.501)	−0.42 (<**0.001**)	0.11 (0.141)	0.166 (**0.026**)	−0.257 (<**0.001**)
Emotional	0.161 (**0.031**)	−0.472 (<**0.001**)	0.287 (<**0.001**)	0.293 (<**0.001**)	−0.221 (**0.003**)
Cognitive	−0.068 (0.363)	−0.269 (<**0.001**)	0.190 (**0.011**)	0.185 (**0.013**)	−0.219 (**0.003**)
Social	0.143 (0.055)	−0.439 (<**0.001**)	0.286 (<**0.001**)	0.234 (**0.002**)	−0.199 (**0.007**)
QLQ-C30 symptom areas					
Fatigue	−0.025 (0.739)	0.325 (<**0.001**)	−0.091 (0.223)	−0.178 (**0.017**)	0.298 (<**0.001**)
Nausea/vomiting	−0.150 (**0.044**)	0.327 (<**0.001**)	−0.005 (0.948)	−0.027 (0.724)	0.189 (**0.011**)
Pain	−0.052 (0.485)	0.309 (<**0.001**)	−0.200 (**0.007**)	−0.156 (**0.037**)	0.263 (<**0.001**)
Dyspnea	−0.050 (0.508)	0.199 (**0.008**)	−0.103 (0.168)	0.021 (0.776)	0.334 (<**0.001**)
Insomnia	−0.155 (**0.038**)	0.446 (<**0.001**)	−0.086 (0.252)	−0.170 (**0.023**)	0.321 (<**0.001**)
Appetite loss	−0.086 (0.250)	0.306 (<**0.001**)	0.082 (0.276)	−0.102 (0.175)	0.128 (0.088)
Constipation	−0.047 (0.528)	0.121 (0.107)	0.180 (**0.016**)	0.061 (0.415)	0.027 (0.718)
Diarrhea	−0.013 (0.861)	0.005 (0.950)	0.074 (0.327)	−0.031 (0.683)	0.031 (0.677)
Financial problems	−0.129 (0.084)	0.486 (<**0.001**)	−0.145 (0.052)	−0.200 (**0.007**)	0.154 (**0.038**)
QLQ-LC13 symptom areas					
Dyspnea	0.052 (0.484)	0.190 (**0.011**)	−0.033 (0.657)	−0.062 (0.409)	0.299 (<**0.001**)
Coughing	−0.043 (0.566)	0.236 (**0.001**)	−0.101 (0.176)	0.014 (0.852)	0.318 (<**0.001**)
Hemoptysis	0.068 (0.365)	−0.163 (**0.029**)	0.187 (**0.012**)	0.149 (**0.046**)	0.273 (<**0.001**)
Sore mouth and tongue	0.095 (0.206)	0.084 (0.264)	0.092 (0.219)	−0.067 (0.368)	0.103 (0.167)
Dysphagia	0.020 (0.793)	0.264 (<**0.001**)	0.028 (0.706)	0.030 (0.689)	0.204 (**0.006**)
Peripheral neuropathy	−0.088 (0.239)	0.166 (**0.026**)	0.081 (0.283)	−0.048 (0.524)	0.002 (0.982)
Hair loss	−0.005 (0.949)	−0.009 (0.901)	0.400 (<**0.001**)	0.070 (0.347)	0.021 (0.782)
Chest pain	−0.127 (0.089)	0.102 (0.174)	0.052 (0.484)	0.004 (0.962)	0.164 (**0.028**)

(continued)

Table 3 (continued)

Scale	Age	Disease length	No. of hospitalizations	FEV1/FVC	No. of symptoms
Pain in arm or shoulder	−0.003 (0.965)	0.014 (0.852)	0.145 (0.052)	−0.088 (0.242)	−0.078 (0.295)
Other pain sites	0.102 (0.171)	0.245 (**0.001**)	−0.127 (0.089)	−0.178 (**0.017**)	0.117 (0.119)
Taking analgesics	0.157 (**0.035**)	−0.205 (**0.006**)	−0.023 (0.760)	0.105 (0.159)	0.028 (0.710)

Values in bold indicate statistical significance

with performance status of grade 2–4 the highest ($p < 0.001$ for both scales).

Patients who were living alone presented with significantly worse physical ($p = 0.006$) and cognitive ($p = 0.013$) functioning, more often complained of dyspnea ($p = 0.021$), and more frequently took analgesics ($p = 0.003$) than patients living in a relationship. Unemployed patients were taking analgesics more often than those who had a stable employment ($p = 0.007$). Gender and education had no significant influence on any of the dimensions of QoL and did not affect significantly any of the symptoms analyzed related to lung cancer.

4 Discussion

In this study we found that NSCLC patients demonstrated a reduced QoL. The patients' score was worse than Scott et al.'s (2008) reference in all QLQ-C30 items except for role functioning. Lung cancer affected the most global health status (mean score of 47.1) and emotional functioning (mean score of 57.8); both differed the most from the reference values, while the least differed cognitive functioning. Our patients complained the most about fatigue, sleep problems, coughing, and an increased need for taking analgesics. Financial problems showed the biggest difference from the reference values. Worsening of health condition expressed by the length of the malignant disease, the presence of comorbidities and metastases, the number of symptoms related to malignant disease, worse spirometric parameters, and living alone all had a negative influence on QoL and increased the intensity of the symptoms presented.

Diagnosis and treatment of NSCLC decreases QoL and affects daily functioning. The outcomes of the present study showed a much greater decrease in QoL in patients from our institution than in other centers, but NSCLC affected similar QoL areas. Limitations in global health status (mean score of 60.0) and emotional functioning (mean score of 64.1) among Spanish patients with advanced NSCLC patients were reported by Arraras et al. (2016). In Brazilian patients subjected to chemotherapy, the biggest decrease was observed in global health status (mean score of 58.3) and emotional functioning (mean score of 66.9) (de Oliveira et al. 2013). Similar areas were affected in Chinese patients after lung resection (emotional function – 45.6 and global health status – 58.3) (Li et al. 2013). Braun et al. (2011), however, observed the biggest impairment in role functioning (mean score of 58.9). A greater decrease in QoL observed in our study may be explained by a worse financial condition reported by the patients. A lack of resources may directly limit treatment options, reduce participation in social life, or even lead to poverty. The score concerning financial problems in our study was 21.5 points over the reference value. Also, over 40% of our patients were living alone.

QoL is affected not only after diagnosis and during the course of treatment, but also after successful treatment in long-term survivors. Rauma et al. (2015) assessed patients with a

median follow-up of 5 years and found the biggest score reduction in global health status (mean score of 66.4) and physical functioning (mean score of 67.4). The observation of QoL during 5 years after stereotactic radiotherapy in stage I NSCLC showed that all areas of QoL changed with time. In the global health status, improvement was observed after 18 months following surgery, but it returned to the baseline values at the end of the follow-up period. A slight improvement was also observed in physical functioning. The level of emotional functioning rose significantly after 1 year and then dropped, but remained at a higher level than that before surgery (Ubels et al. 2015). We measured QoL only once during the present study; thus, we were unable to observe changes. Nevertheless, the length of the disease was significantly correlated with a drop in QoL level, and the longer the disease lasted the greater was the intensity of cancer symptoms.

General health condition related to both progression of cancer and health status affects QoL. Griebsch et al. (2014) investigated QoL in patients with lung cancer before and after progression. They found a significantly poorer QoL in patients at the time of progression than in patients without progression. Some researchers report no correlation between the occurrence of metastases and QoL or fatigue, despite that the presence of a metastatic disease shortens survival (Li et al. 2012; Henoch et al. 2007; Brown et al. 2005). In the present study, patients with multiorgan metastases were significantly more limited by fatigue, pain, and pain in the chest than patients without metastases.

The burden of comorbidities is not directly related to cancer disease, but comorbidities limit treatment options, increase possibility of drug adverse effects or drug interactions, and increase treatment complications. The assessment of general health status and comorbidity burden is crucial in patients with NSCLC, because the median age at diagnosis currently varies from 63 to 70 years of age (Leduc and Quoix 2016). The mean age of our patients was 62.7 years. In the literature, several scales are used to evaluate heath condition in elderly cancer patients, including Comprehensive Geriatric Assessment, Charlson comorbidity index, performance status, and Katz's basic Activities of Daily Living. Maione et al. (2005) found that performance status was significantly correlated with QoL, and patients with performance status of grade 2 had lower scores in all scales than patients with grade 0–1. Efforts have been made also by other researchers to assess the heath condition in elderly patients in order to administer treatment that will improve survival and reduce toxicity and side effects of treatment (Corre et al. 2016; Ngeow et al. 2010). In the present study, we used a simple number of coexisting chronic diseases and performance status. Our outcomes are in line with findings from the literature and suggest that the greater number of comorbidities and the greater level of disability both had a significant impact on QoL, reducing nearly all areas of QoL and increasing patients burden with symptoms related to cancer (Wang et al. 2015; Larsson et al. 2012; Maione et al. 2005). Additionally, poor lung function reduced global health status and nearly all areas of functioning, and increased the intensity of symptoms related to cancer.

Socio-economic factors play an important role in maintaining good QoL. Age, marital status, possibilities to receive support, and education determine financial condition. Montazeri et al. (2003) reported that patients of lower socioeconomic status experienced more health problems, and reduced functioning and global health status at the beginning of the observational period, but at 3 months after initial treatment the results were inconclusive. In the Ngeow et al.'s (2010) study, patients over 70 years of age showed a longer median survival, less risk of dying, and a better response to treatment than patients below 70 years of age. Braun et al. (2011) found that younger patients with NSCLC had a better physical functioning while worse emotional and social functioning (mean age of 58.3). Larsson et al. (2012), who investigated a study sample with the median age of 66 years, found that younger age inversely affected the role functioning, cognitive functioning, and social and emotional functioning. Additionally,

younger age was correlated positively with financial problems. Li et al. (2012) found that financial problems had a significant impact on survival in NSCLC patients without surgery. Yun et al. (2016) found that monthly income affected QoL and had an independent prognostic value of survival. The association between younger age, poor financial condition, and decreased QoL may be explained by reduced working possibilities in the group of cancer patients who are before the age of retirement. In the present study, despite the mean age was similar to other reports from literature, the level of QoL was lower and the burden of financial problems was higher. The literature comparison of the financial problems scores is as follows: de Oliveira et al. (2013) – 26.6; Larsson et al. (2012) – 12.0; Aaronson et al. (1993) – 8.5; our present study – 34.3. This comparison is alarming and indicates that Polish patients with lung cancer need special attention and require additional social and financial support.

The type of treatment in cancer patients depends on disease stage. Surgery alone or in combination with other treatments is often chosen for patients with early stage NSCLC. Thus, surgery is associated with better outcomes and prognosis than other treatment options in lung cancer patients, although lung operations are often complex and burdened with high risk of complications. Less invasive, thoracoscopic surgery interventions are associated with less postoperative pain and better QoL than open thoracotomy (Bendixen et al. 2016). Li et al. (2012) found that factors affecting survival are different in patients with surgery and without surgery. In NSCLC patients with surgery, emotional functioning, pain burden, and nausea/vomiting were associated with survival, whereas in those without surgery, social functioning, fatigue burden, appetite loss, and financial problems shortened survival. Among operated patients, risk of postoperative complications increased in patient over 70 years of age, and the appearance of complications negatively affected patients' long-term survival and QoL (Rauma et al. 2016). The present study confirmed previous findings on better QoL in patients undergoing surgery than other types of treatment. Patients treated by surgery alone reported a higher global health status and lower burden with disease related symptoms.

We conclude that patients with lung cancer experience a reduced QoL, especially in the area of global health status and emotional functioning. Improvements in health condition, proper treatment of comorbidities, and interventions for symptom management all improve QoL in patients with lung cancer.

Conflict of Interests The authors declare no conflicts of interest in relation to this article.

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Obstructive Sleep Apnea and Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) often accompanies obstructive sleep apnea (OSA). A causative connection of the two disease entities is uncertain. However, eliminating OSA improves the prognosis of CKD patients. In the present study we examined a possible relationship between OSA and CKD, and whether there would be a mutual enhancing interaction in the severity of the two diseases. The study was of a retrospective nature and encompassed 382 patients over the period of 1 January 2014–30 June 2015. The OSA diagnosis was supported by a polysomnographic examination in 363 (95.0%) patients. Blood samples were taken for the determination of kidney function indices. The influence on OSA and CKD of comorbidities also was examined. We found a high probability of a simultaneous occurrence of OSA and CKD; with the odds ratio of 3.94 (95% CI 1.5–10.3%; $p = 0.005$). The 363 patients with OSA were stratified into 73 (20.1%) mild, 98 (27.0%) moderate, and 192 (52.9%) severe OSA cases according to the apnea-hypopnea index. CKD was found in 43 (58.9%) patients with mild OSA, 73 (74.5%) with moderate OSA, and 137 (71.4%) with severe OSA. Most OSA patients also suffered from hypertension and obesity. For comparison, CKD was detected in 7 (36.8%) out of the 19 patients without OSA ($p < 0.003$). We conclude that CKD develops significantly more often in patients with OSA than in those without it, and CKD frequency increases with the severity of OSA.

Keywords

Apnea-hypopnea index • Chronic kidney insufficiency • Comorbidities • Obstructive sleep apnea • Renal function

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1 Introduction

Obstructive sleep apnea (OSA) is a disease caused by repetitive breathing pauses during sleep, which trigger a subthreshold wake-up reaction due to a temporary shortage of oxygen to the organs. This results in various symptoms, such as pronounced daytime sleepiness, cardiovascular impairment, and other potentially serious secondary diseases (Chokorverty 2010). One of those disorders is chronic kidney disease (CKD). A number of studies have shown that OSA is particularly common in patients with advanced CKD (Fleischmann et al. 2010; Iseki et al. 2008). The original guidelines of the Kidney Disease Improving Global Outcomes (KDIGO) state that CKD should be defined based on a reduced glomerular filtration rate (GFR) or markers of kidney damage for at least three months. In addition, the cause of kidney disease, the magnitude of albuminuria, and the degree GFR impairment should be defined (Inker et al. 2014).

The cause-and-effect relationship and the nature of the potential association between the two diseases remains unclear. Thus, a thorough understanding of these two disease entities is essential. One possible feature linking the two diseases is increased arterial blood pressure. Enhanced blood pressure is one of the most important risk factors for the development of CKD (Chang et al. 2016; Sarnak et al. 2003). OSA often results in increased blood pressure (Meng et al. 2016), which could damage the kidneys with time (Archontogeorgis et al. 2016).

In the present study, we attempted to get an insight into the nature of the potential association between CKD and OSA. Further, we wished to examine the possibility of mutually enhancing interaction of disease severity, also taking into account the influence of comorbidities.

2 Methods

The implementation of the study was approved by the Ethics Committee of Witten/Herdecke University in Witten, Germany. Written informed consent by the study participants was waived due to a retrospective nature of the study. All personal information of the population investigated was removed prior to data analysis.

2.1 Study Design and Setting

We reviewed the data of all patients who were screened for OSA in the sleep laboratory of the Department of Pneumology of the HELIOS Clinic in Wuppertal of the Witten/Herdecke University in Germany in the period of 1 January 2014–30 June 2015. The HELIOS Clinic Wuppertal is the largest hospital in the Bergisch Land region lying in the state of North Rhine-Westphalia in Germany, with 967 beds and 26 departments. Each year, this hospital treats around 550 inpatients in the sleep laboratory. The data were collected in Excel file and evaluated after the completion of collection.

2.2 Obstructive Sleep Apnea (OSA)

There were 382 adult patients admitted to the sleep laboratory with a suspicion of having OSA during the study period who underwent a polysomnographic examination (Sleep Diagnostic System ALICE 4, Heinen + Löwenstein, Bad Ems, Germany), a gold standard for OSA diagnosis (Escourrou et al. 2015). OSA was confirmed in 363 (95.0%) patients according to standards of the WHO International Statistical Classification of Diseases (ICD G47.31) (WHO 2016). This classification defines OSA as 10 or more breathing pauses per hour of sleep, each lasting for 10 or more seconds. The patients displayed a number of other typical for OSA symptoms such as are loud snoring, headaches, daytime sleepiness and fatigue, impaired concentration, dry mouth, impotence, and depression (Pagel 2007). The severity of OSA was classified on the basis of apnea-hypopnea index (AHI), i.e., the number of apnea and hypopnea events *per* hour of sleep, calculated by dividing the number of events by the number of sleep hours. OSA was

Table 1 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

CKD-EPI formula			
a	White/other	Male	141
		Female	144
	Black	Male	163
		Female	166
b		Male	0.9
		Female	0.7
c	Male	Serum creatinine $\leq$0.7 mg/dL	−0.411
		Serum creatinine >0.7 mg/dL	−1.209
	Female	Serum creatinine $\leq$0.7 mg/dL	−0.329
		Serum creatinine >0.7 mg/dL	−1.209

stratified into mild (AHI 5–14), moderate (AHI 15–29), and severe (AHI $\geq$30) form of disease (Ho et al. 2015). Comorbidities, other than CKD, and duration of a hospital stay were also compared among the four study groups. Nineteen patients with AHI of less than five, considered free of the disease, were assigned to the control group.

2.3 Chronic Kidney Disease (CKD)

Blood samples were collected in all patients to determine the indices of kidney function. CKD was defined as a slow, progressive loss of kidney function, with unspecific symptoms, for over three or more months (ICD N18.1–N18.5) according to the guidelines of Kidney Disease Improving Global Outcomes (KDIGO 2013). CKD was divided into six degrees of severity based on the estimated glomerular filtration rate (eGFR): Stage 1 (normal) – GFR above 90 mL/min/1.73 m^2; Stage 2 (mildly decreased) – GFR of 60–89 mL/min/1.73 m^2; Stage 3a (mildly to moderately decreased) – GFR of 45–59 mL/min/1.73 m^2; Stage 3b (moderately to severely decreased) – GFR of 30–44 mL/min/1.73 m^2; Stage 4 (severely decreased) – GFR of 15–29 mL/min/1.73 m^2; and Stage 5 (kidney failure) – GFR less than 15 mL/min/1.73 m^2 (WHO 2016).

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for age, gender, race, and different doses of serum creatinine (Scr) for women and men: eGFR (mL/min/1.73 m^2) $= a \times (Scr/b)^c \times (0.993)^{Age}$ (Table 1) (National Kidney Foundation 2002). The serum creatinine (norm 0.5–1.1 mg/dL) was assessed using an Monovette® 4.7 mL blood collection system (Sarstedt AG & Co; Nümbrecht, Germany), including lithium heparin and an enzymatic colorimetric assay kit, and a COBAS® 6000 c501 analyzer (F. Hoffmann-La Roche Ltd; Mannheim, Germany).

2.4 Statistical Elaboration

Categorical data were expressed as percentages and continuous data as means $\pm$ standard deviations (SDs). Odds ratio (OR) was calculated to determine the likelihood of OSA and CKD coexistence. The 95% confidence intervals (CI) were calculated for OSA severity. Significance of gender differences and comorbidities was calculated using a 4 by 2 Chi^2 test. One-way ANOVA for four independent samples was used to assess differences in age, duration of hospital stays, AHI, eGFR, and in the serum creatinine among the four study groups. A p-value <0.05 defined the statistically significant differences.

3 Results

Of the 382 patients screened for OSA, 73 (19.1%; 95%CI 15.2–23.1%) had mild OSA, 98 (25.7%; 95%CI 21.3–30.0%) had moderate OSA, 192 (50.3%; 95%CI 45.3–55.3%) had

Table 2 Interrelationship between obstructive sleep apnea (OSA) and chronic kidney disease (CKD) severity stages

	Total of 382 patients				
	Control	Diagnosed OSA			
	AHI <5	AHI 5–14	AHI 15–29	AHI >30	p<
Patients (*n*; %)	19 (5.0)	73 (19.1)	98 (25.7)	192 (50.3)	
Male (*n*; %)	11 (57.9)	47 (64.4)	62 (63.3)	146 (76.0)	**0.050**
Female (*n*; %)	8 (42.1)	26 (35.6)	36 (36.7)	46 (24.0)	**0.050**
Age (*year*)	56.0 ± 17.7	63.6 ± 14.6	63.5 ± 13.4	64.7 ± 13.2	0.065
Hospital stay (*days*)	1.9 ± 0.8	2.3 ± 0.8	2.3 ± 0.8	2.6 ± 1.0	**0.001**
AHI (*events/h*)	2.0 ± 1.6	10.1 ± 3.5	22.0 ± 4.5	58.3 ± 24.3	**0.001**
eGFR (mL/min/1.73 m^2)	84.1 ± 27.8	80.6 ± 23.0	73.7 ± 24.3	72.0 ± 25.8	**0.026**
Mean					
eGFR >90 mL/min/1.73 m^2 (*n*; %)	12 (63.2)	30 (41.1)	25 (25.5)	55 (28.7)	**0.003**
CKD					
eGFR – 60–89 mL/min/1.73 m^2 (*n*; %)	6 (31.6)	31 (42.5)	48 (49.0)	83 (43.2)	0.520
eGFR – 45–59 mL/min/1.73 m^2 (*n*; %)	0	7 (9.6)	14 (14.3)	29 (15.1)	0.216
eGFR – 30–44 mL/min/1.73 m^2 (*n*; %)	0	3 (4.1)	8 (8.2)	15 (7.8)	0.420
eGFR – 15–29 mL/min/1.73 m^2 (*n*; %)	1 (5.3)	2 (2.7)	3 (3.1)	4 (2.1)	0.845
eGFR <15 mL/min/1.73 m^2 (*n*; %)	0	0	0	6 (3.1)	0.110
Serum creatinine (0.5–1.1 mg/dL)	0.8 ± 0.3	0.9 ± 0.3	2.0 ± 10.1	1.2 ± 1.0	0.452

Data are means ± SD, except gender and eGFR subgroups data that concern the number of patients (*n*)
AHI apnea-hypopnea index, *eGFR* estimated glomerular filtration rate
Note: Significant *P* values shown in bold

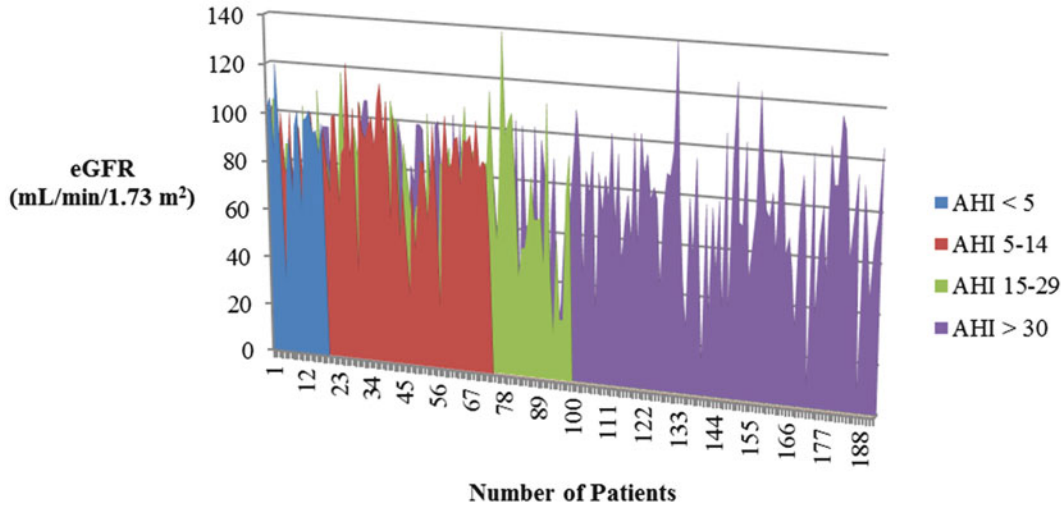

Fig. 1 Number of patients with chronic kidney diseases calculated after estimated glomerular filtration rate (eGFR) in patients with obstructive sleep apnea (OSA) categorized according to the apnea-hypopnea index (AHI) and without OSA (AHI <5)

severe OSA, and 19 (5.0%; 95%CI 2.8–7.2%) did not have OSA (Table 2). Males comprised a total of 266 (69.6%) patients, and predominated in each study group (Table 2). There were no appreciable age differences among the four groups of patients, although younger patients tended to have less OSA. Significant differences were observed regarding the duration of a

hospital stay; hospitalization was longer in patients with severe OSA. The OR for the coexistence of OSA and CKD in all study patients was 3.9 (95%CI 1.5–10.3%; $p = 0.005$). There was a significant difference in the mean eGFR, with lower values for the patients with severe OSA (Fig. 1 and Table 2). There were significantly fewer cases of OSA in patients with normal eGFR. However, no eGFR-dependent differences were found concerning OSA among the CKD stages in the groups studied. No difference was found in the mean serum creatinine value among the four study groups (Table 2).

The most frequently observed comorbidities were hypertension and obesity, with rare cases of coronary artery disease, myocardial infarction, asbestosis, Ormond's disease, sarcoidosis, urinary incontinence, hyperparathyroidism, hypothyroidism, chronic sinusitis, anxiety, stroke, dementia, depression, mania, multiple sclerosis, and polytoxicomania (Table 3).

4 Discussion

The majority of patients with OSA also suffered from CKD. In contrast, most patients without OSA had normal eGFR values. It can be said that the two diseases may be present together. A causative link between the two diseases has yet to be determined. It can also be assumed that OSA and CKD mutually negatively influence each other, although a few scientific studies have been carried out on this topic. One such study has shown that patients with OSA have an increased risk of developing CKD (Lee et al. 2015). While OSA is determined on the basis of pauses in breathing during sleep, CKD is a disorder in which there is an ongoing damage of renal function, and it is a major health problem worldwide (Kalamas and Niemann 2013). The relation between OSA and CKD is unclear. For this reason, screening kidney function indices values for the detection of CKD is essential for a proper treatment of OSA patients (Galbraith et al. 2016). In the present study, majority of OSA patients had a mild form of CKD, which is line with former findings that OSA patients have increased risk for the occurrence of early stages of CKD (Chu et al. 2016; Sim et al. 2009). Remarkably, the present study failed to demonstrate an increasing number of patients with OSA in advanced stages of CKD, but the most severe OSA coincided with the most severe CKD. The latter might have to do with a sometimes late detection of OSA. In contrast, another study has suggested that OSA is an independent risk factor for the advancement of CKD (Kanbay et al. 2012), which would form a plausibly causative link between the two diseases. This conclusion was based on the enhancing effect of hypopnea in OSA, which leads to oxygen desaturation during sleep, an increase of cytokine levels and insulin resistance. The same factors have been found to play a role in the progression of CKD in patients with OSA (Kanbay et al. 2012). Another study has shown an association between OSA severity and renal dysfunction, conspicuously even in patients without hypertension or diabetes (Chou et al. 2011). In the present study, the number of patients with diabetes was underrepresented in all four groups. Although the proportion of patients with severe OSA was largest, there was no real increase in the incidence of severe OSA alongside CKD severity. Accordingly, there was no association between OSA severity, assessed by AHI, and renal function impairment, assessed by eGFR.

As previously reported, sleep disorders are often observed in dialysis patients in advanced stages of renal disease. The prevalence of OSA in hemodialysis patients is as high as 24%, compared with the 16% in non-dialyzed patients with CKD (Ezzat and Mohab 2015). In the present study, proportion of dialysis patients was low at 1.3%, and all these patients had a severe OSA.

The relationship between OSA and hypertension has long since been known. There are several mechanisms that explain this relationship, primarily repeatable increases in sympathetic activity during apneic episodes. The main features of hypertension in OSA patients are high prevalence, diastolic and nocturnal predominance, and a frequent non-dipper status (Baguet et al. 2009). Therefore, hypertension accompanies OSA, particularly a long-lasting and severe OSA, as was also shown in the present

Table 3 Comorbidities stratified by the apnea-hypopnea (AHI) index in the patients studied

	Total of 382 patients				
	Control	Diagnosed OSA			
	AHI <5	AHI 5–14	AHI 15–29	AHI >30	p<
Patients (*n*; %)	19 (5.0)	73 (19.1)	98 (25.6)	192 (50.3)	
Cardiovascular diseases (*n*; %)					
Cardiac arrhythmia	1 (5.3)	7 (9.6)	10 (10.2)	28 (14.6)	0.437
Coronary artery disease	2 (10.5)	5 (6.9)	16 (16.3)	44 (22.9)	**0.016**
Hypertension	10 (52.6)	37 (50.7)	62 (63.3)	153 (79.7)	<**0.0001**
Myocardial infarct	1 (5.3)	1 (1.4)	0	0	**0.013**
Peripheral arterial occlusive disease	0	1 (1.4)	3 (3.1)	4 (2.1)	0.792
Recent deep vein thrombosis	0	0	0	2 (1.0)	0.575
Recent myocardial infarction	0	0	1 (1.0)	7 (3.7)	0.189
Pulmonary diseases (*n*; %)					
Asbestosis	0	6 (8.2)	0	0	<**0.0001**
Asthma	5 (26.3)	9 (12.3)	12 (12.2)	22 (11.5)	0.321
COPD	3 (15.8)	14 (19.2)	18 (18.4)	36 (18.8)	0.989
Emphysema	0	3 (4.1)	3 (3.1)	7 (3.7)	0.838
Lung cancer	0	1 (1.4)	0	3 (1.6)	0.615
Obesity-hypoventilation syndrome	0	2 (2.7)	0	2 (1.0)	0.353
Ormond's disease	1 (5.3)	0	0	0	**0.0003**
Pulmonary embolism	0	0	1 (1.0)	1 (0.5)	0.813
Sarcoidosis	1 (5.3)	0	0	1 (0.5)	**0.028**
Recent lung and pleural empyema	0	0	0	7 (3.7)	0.070
Recent pulmonary embolism	0	2 (2.7)	1 (1.0)	2 (1.0)	0.664
Recent tuberculosis	0	0	2 (2.0)	0	0.120
Gastrointestinal diseases (*n*; %)					
Diabetes mellitus	2 (10.5)	16 (21.9)	25 (25.5)	51 (26.6)	0.432
Esophageal cancer	0	0	1 (1.0)	0	0.406
Gastroesophageal reflux disease	2 (10.5)	4 (5.5)	4 (4.1)	8 (4.2)	0.628
Hypercholesterolemia	1 (5.3)	1 (1.4)	2 (2.0)	3 (1.6)	0.699
Hyperlipidemia	0	0	7 (7.1)	10 (5.2)	0.101
Obesity	3 (15.8)	21 (28.8)	40 (40.8)	123 (64.1)	<**0.0001**
Kidney diseases (*n*; %)					
Acute urinary tract infection	0	0	0	1 (0.5)	0.807
Benign prostatic hyperplasia	1 (5.3)	1 (1.4)	2 (2.0)	10 (5.2)	0.355
Bladder cancer	0	1 (1.4)	1 (1.0)	0	0.461
Diabetic nephropathy	0	0	0	1 (0.5)	0.804
Dialysis	0	0	0	5 (2.6)	0.171
Hyperuricemia	0	3 (4.1)	2 (2.0)	2 (1.0)	0.369
Prostate carcinoma	0	1 (1.4)	2 (2.0)	2 (1.04	0.857
Renal cysts	0	0	1 (1.0)	0	0.406
Urinary incontinence	0	0	10 (10.2)	0	<**0.0001**
Thyroid diseases (*n*; %)					
Goiter	0	0	0	1 (0.5)	0.804
Hyperparathyroidism	0	0	0	14 (7.3)	**0.002**
Hypothyroidism	4 (21.1)	9 (12.3)	9 (9.2)	1 (0.5)	<**0.0001**
Ear, nose, and throat disease (*n*; %)					
Chronic sinusitis	1 (5.3)	0	0	1 (0.5)	**0.028**

(continued)

Table 3 (continued)

	Total of 382 patients				
	Control	Diagnosed OSA			
	AHI <5	AHI 5–14	AHI 15–29	AHI >30	p<
Neurological diseases (*n*; %)					
Anxiety	0	0	33 (34.0)	0	**<0.0001**
Epilepsy	0	0	3 (3.1)	2 (1.0)	0.301
Parkinson's disease	0	1 (1.4)	0	0	0.237
Polyneuropathy	0	1 (1.4)	1 (1.0)	1 (0.5)	0.871
Multiple sclerosis	1 (5.3)	1 (1.4)	0	0	**0.013**
Restless legs syndrome	0	1 (1.4)	0	1 (0.5)	0.655
Schizophrenia	0	0	1 (1.0)	0	0.401
Recent stroke	1 (5.3)	3 (4.1)	6 (6.1)	10 (5.2)	0.952
Past stroke	0	5 (6.9)	0	0	**<0.0001**
Psychiatric diseases (*n*; %)					
Alcoholism	1 (5.3)	3 (4.1)	1 (1.0)	2 (1.0)	0.224
Dementia	0	0	5 (5.1)	2 (1.0)	**0.042**
Depression	3 (15.8)	7 (9.6)	0	9 (4.7)	**<0.0001**
Former smoker	1 (5.3)	0	5 (5.1)	11 (5.7)	0.234
Mania	0	10 (13.7)	0	0	**<0.0001**
Polytoxicomania	0	0	0	14 (7.3)	**0.002**
Smoker	4 (21.1)	9 (12.3)	9 (9.2)	22 (11.5)	0.518
Gynecological disease (*n*; %)					
Breast cancer	1 (5.3)	0	0	2 (1.0)	0.094
Skin diseases (*n*; %)					
Allergy	0	0	1 (1.0)	3 (1.6)	0.689
Eczema	0	1 (1.4)	1 (1.0)	5 (2.6)	0.696
Hypothermia	0	0	2 (2.0)	3 (1.6)	0.633
Psoriasis	1 (5.3)	0	4 (4.1)	2 (1.0)	0.110

COPD chronic obstructive pulmonary disease
Note: Significant *P* values shown in bold

study. Another study has also reported an increase in the frequency of hypertension based on OSA severity (Bayram et al. 2007). Further, in that study hypertension was found in about 37% of 209 OSA positive *versus* 7% of 54 OSA negative patients, which amounted to a remarkably significant difference. Obesity is another major factor in both OSA and CKD (McClellan and Plantinga 2013; Arens and Marcus 2004); the present findings confirmed a high percentage of the overweight among patients suffering from severe OSA. According to a study of Knorst et al. (2008), body mass index offers the best assessment of the effect of obesity on OSA severity.

A limitation of the present study was that only patients who had the clinical symptoms of OSA were investigated in the sleep laboratory. Patients with CKD, without OSA symptoms, were not examined. The effects on CKD of OSA treatment generally were not investigated either. Finally, a causative link between OSA and CKD was not determined as only a descriptive data evaluation was conducted.

In conclusion, coexistence of OSA and CKD is highly likely as GFR appreciably decreases with increasing OSA severity. CKD frequency increases with the severity of OSA. Hypertension and obesity are the most common comorbidities in OSA and CKD.

Conflicts of Interest The authors declare no competing interests in relation to this article.

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Mortality Due to Nosocomial Infection with *Klebsiella pneumoniae* ESBL$^+$

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Abstract

Klebsiella pneumoniae is one of the most important hospital pathogens, particularly concerning the multidrug-resistant strain ESBL$^+$. The aim of this study was to evaluate nosocomial infections with *K. pneumoniae* ESBL$^+$ in the context of infection location, risk factors, and prognosis. This hospital study was conducted retrospectively and covered a 3 months' period. The infection with *K. pneumoniae* ESBL$^+$ was diagnosed in 36 patients (19 women and 17 men) of the mean age of 74.2 $\pm$ 14.8 years. The number of infected patients amounted to 2.2% of all patients admitted to Czerniakowski Hospital in Warsaw, Poland, over the study time. Twenty of these patients died (13 women and 7 men), representing 14% of all hospital deaths at the time. The infection with *K. pneumoniae* ESBL$^+$ occurred most frequently in the department of internal diseases, and rarely in neurology or intensive care wards. Bacteria was most often isolated from the urine, with the most distinct association between the use of urinary catheters and death ($p = 0.019$). We conclude that infections with *K. pneumoniae* ESBL$^+$ were associated with over 55% mortality and usually occurred in the setting of internal diseases. Deaths due to *K. pneumoniae* ESBL$^+$ infection were significantly related to the use of urinary bladder catheters.

Keywords

Antimicrobial therapy • *Klebsiella pneumoniae* ESBL$^+$ • Mortality • Multidrug resistance • Nosocomial infections • Prognosis • Risk factors

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1 Introduction

Klebsiella spp. are one of the most important hospital pathogens (Tumbarello et al. 2006; Schwaber et al. 2006; Superti et al. 2009). These Gram-negative, non-motile, encapsulated bacteria of the Enterobacteriaceae family are found not only in humans but also in other mammals such as swine, horses, and in the environmental sources such as soil, surface waters, sewage, and plants (Podschun and Ullmann 1998). *K. pneumoniae* and *K. oxytoca* are the most important members of the Klebsiella genus in humans. *K. pneumoniae*, a facultative anaerobic bacteria, is a saprophyte present on the skin, in the upper airways, and in the intestinal tract. Colonization with *Klebsiella* rods can last for a long time in hospitalized individuals and in favorable conditions leads to infection (Ludden et al. 2015; Birgand et al. 2013). The most common are respiratory and urinary tracts infections (ECDC 2012). The bacteria is also associated with opportunistic infections, especially in newborns, cancer patients, diabetics, alcoholics, and in the hospitalized patients with catheters in blood vessels or bladder (Podschun and Ullmann 1998). The infection spreads easily from patient to patient, often *via* the hands of healthcare workers, and leads to local hospital outbreaks (Sekowska et al. 2012). The risk factors of severe infections caused by *K. pneumoniae* are the following: prolonged hospitalization, severity of illness, longer time in the intensive care unit, intubation and mechanical ventilation, arterial or urinary catheterization, and previous antibiotic therapy (Pitout and Laupland 2008; Tumbarello et al. 2007). *K. pneumoniae* is the second most common Gram-negative bacteria, after *E. coli*, which causes bloodstream infections. The mortality rate for pneumonia caused by *K. pneumoniae* is substantial, even when optimal antibiotic therapy is applied (ECDC 2012).

Multi-drug resistance of the *Klebsiella* pathogens raises a real problem. Strains which produce extended-spectrum beta-lactamases (ESBL) are resistant to penicillins, cephalosporins, and monobactams (Lautenbach et al. 2001). Since the first isolation of these strains in Germany in 1983 (Knothe et al. 1983), they have rapidly become an emerging public-health concern in many countries (Superti et al. 2009; Tumbarello et al. 2006). Resistance to the beta-lactam antibiotics due to the action of beta-lactamases has quickly emerged because of inappropriate use and overuse of antibiotics, mainly broad-spectrum cephalosporins (Bradford 2001; Paterson et al. 2001). Carbapenems are the first choice in ESBL$^+$ infections treatment. Unfortunately, new beta-lactamases – carbapenemases and metallo-beta-lactamases, both of which can hydrolize carbapenems, have appeared, causing serious problems in successful treatment of *K. pneumoniae* infections, even in high-developed countries (Nordmann 2014; Steinmann et al. 2011). That is why *K. pneumoniae* ESBL$^+$ strains are so-called emergency pathogens and every infection must be registered. In view of the steadily increasing rate and severity of infections, the aim of the present study was to evaluate nosocomial infections with *K. pneumoniae* ESBL$^+$ specifying the location of changes, risk factors, and prognosis.

2 Methods

The study protocol was approved by the ethics committee of Warsaw Medical University in Poland. In a retrospective approach, infection cases were defined as all patients who were hospitalized between January 1 and March 31 of 2013 at Czerniakowski Hospital in Warsaw and from whom *K. pneumoniae* ESBL$^+$ was isolated from clinical specimens during the hospital stay.

The study included 36 patients (19 women and 17 men), aged 74.2 ± 14.8 (men 72.4 ± 16.3 years and women 75.7 ± 13.4 years). Seventy five percent of the patients were over 65 years of age. One of the patients was homeless, and two were admitted from nursing homes. The medical records of the

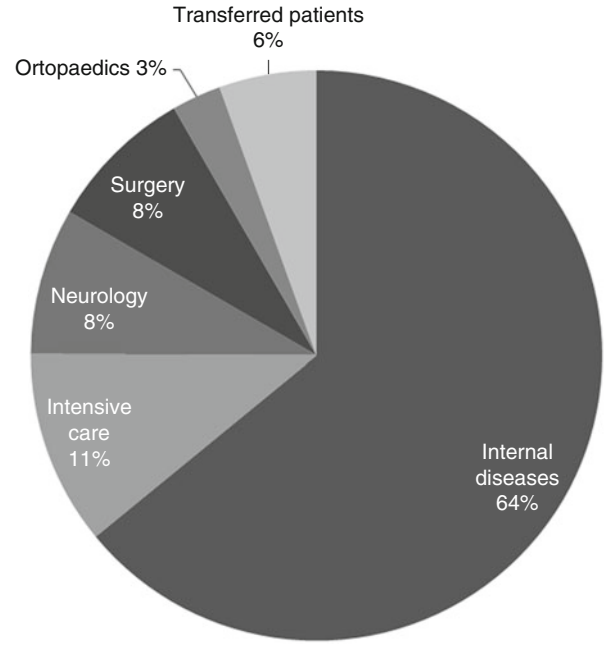

Fig. 1 Incidence of *Klebsiella pneumoniae* ESBL$^+$ infections in hospital wards

patients were retrieved and reviewed. The information was gathered about the wards in which the infection occurred, the site of infection, applied treatment, co-morbidities, and other possible factors which could contribute to the infection. The antibiotic therapy was evaluated in particular. It was categorized as either adequate – compatible to antibiogram or inadequate – incompatible or without treatment. An attempt was made to establish risk factors leading to infection or death. Co-morbidities, demographic, and iatrogenic factors were all considered. Data was entered into a database using Medcalc v4.16. The Chi^2 test was used for the statistical elaboration of categorical variables. A p-value of <0.05 was used to define statistically significant differences.

3 Results

K. pneumoniae ESBL$^+$ was found in 36 patients (2.2% of all hospitalizations over the study time evaluated). Twenty of them died, which comprised 14% of all hospital deaths at that time. A number of infections were multi-organ septic infections (17%). The most frequent site of infection was urinary tract (64%), followed by respiratory tract (22%). Fourteen percent of cases were recognized as colonization and left without treatment. The bacteria were found in the following sites: urine (28), respiratory secretions (7), blood (4), surgical wounds (2), and in the pleural effusion (1).

The affected patients were mostly hospitalized in the general medicine (23 patients), intensive care (4), neurology (3), and surgery (3) wards (Fig. 1). No infection was found in the ophthalmology and ear-nose-throat wards. In a few cases, it was hard to define the actual ward in which the infection started due to patient transfers from one to another ward.

All patients had co-morbidities (Table 1). The most common were the following: cardiovascular diseases (arterial hypertension, heart ischemic disease, heart failure, and deep vein thrombosis), acute or chronic kidney disease (almost two thirds of the patients), and chronic pulmonary diseases (asthma and chronic obstructive pulmonary disease). Liver disorders, assessed with liver function tests, and gastroenterological diseases (peptic ulcers, gastritis, gastroesophageal reflux

Table 1 Co-morbidities in patients with *Klebsiella pneumoniae* ESBL$^+$ infection[a]

Co-morbidities	n (%)
Cardiovascular diseases	33 (92)
Kidney diseases	25 (69)
Pulmonary diseases	15 (42)
Digestive and liver diseases	13 (36)
Malignancy	12 (33)
Diabetes	12 (33)
CNS damage	12 (33)
Obesity or overweight	12 (44)[a]
Protein-energy wasting	9 (33)[a]
Alcoholism	4 (11)

[a]Data available for 27 patients

disease, and acute pancreatitis) were less common. Diabetes, malignancies (lymphoma and lung, pancreas, or colorectal cancers) and a central nervous system damage (stroke, dementia, or subdural hematoma) were found in one third of the patients. Nutrition disorders – overweight, obesity, and malnutrition were noted in 77% of the patients. Eleven percent of the patients were alcohol abusers. A few individuals had endocrine or autoimmune diseases.

The patients received medications such as: proton pump inhibitors – 81%, systemic steroids (orally or intravenously) – 33%, antibiotics (in 6 months period before hospitalization) – 53%. Seventy eight percent of the patients had urinary catheters, while 31% had some other indwelling devices, mostly central venous catheters. Urinary tract infections caused by *K. pneumoniae* ESBL$^+$ were more common when kidney failure co-existed ($p < 0.001$). Also, chronic pulmonary diseases played a part in more frequent ESBL$^+$ occurrence in respiratory system infections in the observed group ($p < 0.001$). There were no other diseases or risk factors connected with the incidence of ESBL$^+$ infection.

Only did 17 patients (55%) received adequate antibiotic therapy. Eleven of them died (65%), including two patients who died less than 48 h after the first dose of targeted antibiotic. Thirty two percent of the patients received inadequate therapy. In this group, mortality rate was very high as it amounted to 90% (9 deaths). Five patients were left with no antibiotic therapy; they were recognized as colonized by *K. pneumoniae* ESBL$^+$. Three patients were transferred to other hospitals: one to the urology department due to hematuria, one to the respiratory ward due to lung cancer, and another one to the rehabilitation center due to previous stroke. One other patient was transferred to a nursing home. The status and further treatment of the transferred patients remained unknown.

Overall mortality in the group studied was 64%. Twenty patients died, including 13 women (76%) and 7 men (37%). A statistical relationship was found between deaths and the use of urinary catheters ($p = 0.019$). No relationship was found between deaths and other catheters, particularly those indwelling blood vessels ($p = 0.08$). Nor was there any relationship between deaths and renal, lung, or liver diseases, as well as malignancies, diabetes, central nervous system diseases, malnutrition, and obesity during *K. pneumoniae* ESBL$^+$ infection.

4 Discussion

A very high morality concerning *K. pneumoniae* ESBL$^+$ infection is alarming. The infected patients comprised only 2% of the hospitalized patients at the time, but the death percentage in relation to all hospital deaths amounted to 14%. This demonstrates the severity of *K. pneumoniae* ESBL$^+$ infections. Sixty four percent of the infected adults died, but in a group with a verified patient's follow-up this percentage rose to 74%. Although 55% of patients obtained an appropriate antibiotic, 65% of them died. On the other side, 32% of patients did not receive adequate treatment and 90% of those died. Tuon et al. (2011) have presented similar mortality rates. In that study, 53% of patients received treatment compatible with the antibiogram and the mortality was 51%. Tumbarello et al. (2007) have shown that inadequate antibiotherapy was a significant predictor of mortality (OR – 6.28). Those authors show that 60% of hospitalized patients died in a group receiving inaccurate antibiotic treatment, while only 19% died of those with adequate treatment. According to a

retrospective evaluation by Kim et al. (2002), 55% of hospitalized patients are treated incorrectly. Patients with infections caused by beta-lactamase producing pathogens are more likely to receive inadequate empirical antibiotherapy (Lee et al. 2012). In patients with bacteremia, outcomes are worse (Tuon et al. 2011). When hospitalized individuals are given an antibiotic incompatible with the antibiogram, the mortality rate reaches 93%, while it is 82% in targeted antibiotherapy. Treating infections caused by *K. pneumoniae* ESBL$^+$ is hard due to multidrug resistance of the pathogen. Carbapenems are the first choice antibiotics; their use is connected with lower mortality (Paterson et al. 2004). According to Du et al. (2002), inadequate antibiotherapy is an isolated mortality risk factor, which is why the early empirical use of carbapenems is extremely important.

According to the current research, many hospitalized patients are not adequately treated despite the knowledge that treatment incompatible with the antibiogram for *K. pneumoniae* ESBL$^+$ infections often results in patient's death. One of the reasons is the cost of carbapenems which is a few times higher than that of other common antimicrobials that are used instead. The use of expensive, targeted medicines is all too often delayed until the very end. In the present study, almost all patients who were not given appropriate antibiotic died. If the aim of treatment is to save those infected with *K. pneumoniae* ESBL$^+$, targeted antibiotherapy with carbapenems should be commenced at onset of therapy. Another problem may lie in the doctors' management of *K. pneumoniae* ESBL$^+$ infections, which not always follows the antibiogram results. To avoid civil or penal responsibility it is crucial to tighten hospital regulations to identify and avoid the potential non-adherence to evidence based medicine.

Another issue lies in the identification of in-hospital multi-drug pathogenic risk factors. In the present study, association between death and urinary catheterization in *K. pneumoniae* ESBL$^+$ infected individuals was found. Bladder catheterization has also been identified in previous studies as a *K. pneumoniae* ESBL$^+$ infection risk factor (Tuon et al. 2011; Demirdag and Hosoglu 2010; Schwaber et al. 2006). Since this procedure is one of the most frequent and overused in hospital wards, it is extremely important to strictly follow the current recommendations for urinary catheterization. Retaining a urinary catheter in a non-critical patient may lead to *K. pneumoniae* ESBL$^+$ infection and consequently death. Although no association between central venous catheterization and death was found in the present study, other authors have found it in larger groups of patients (Schwaber et al. 2006; Tuon et al. 2010; Lautenbach et al. 2001). The use of a central venous line ought to be restricted to explicit instances since prolonged catheterization may lead to dangerous infectious complications inclusive of *K. pneumoniae* ESBL$^+$.

Sekowska et al. (2014) have reported a high incidence of ESBL strains among *K. pneumoniae* obtained from the gastrointestinal tract of ICU patients. In the present study, over 80% of hospitalized patients were given proton pump inhibitors, while only a third of them had gastroenterological diseases which really required this kind treatment. These medications are recognized as a risk factor promoting *K. pneumoniae* ESBL$^+$ gastrointestinal tract colonization, with a nascent systemic infection (Ben-Ami et al. 2006). Likewise, Wielders et al. (2017) have found that proton pump inhibitors enhance almost twofold risk of infection with extended spectrum beta-lactamase-producing bacteria. A routine use of proton pump inhibitors in hospitalized patients may thus be life-threatening. The overuse of antibiotics is another risk factor for *K. pneumoniae* ESBL$^+$ infection (Lin et al. 2013; Lautenbach et al. 2001). That seems confirmed in the present study where more than 50% of infected patients were given antibiotics within a 6-month period before hospitalization.

Unexpectedly, we found that mortality was relatively higher in women (76%) than men (37%). Ben-Ami et al. (2006) have demonstrated that men are more likely to become infected, which in that study was not associated with a greater mortality rate. Other studies have failed

to demonstrate an association between *K. pneumoniae* ESBL$^+$ infection and gender (Kang et al. 2004; Lautenbach et al. 2001), albeit Salsano et al. (2016) have reported that female gender is a predisposing factor for this infection. The problem is obviously multi-factorial so further studies, involving larger samples of patients, are necessary.

Previous studies underscore age as an independent risk factor for *K. pneumoniae* ESBL$^+$ infection (Prestes-Carneir et al. 2015; Yang et al. 2014; Lin et al. 2013). We confirmed that in the presented study as 75% of patients were of advanced age that also was the main cause of co-morbidities; almost every patient had a cardiovascular disease (92%). Schwaber et al. (2006) have stated that two co-existing diseases is enough to enhance risk for *K. pneumoniae* ESBL$^+$ infections. In a similar to ours sample size of adults (mean age 74 $\pm$ 14 years), the most frequent co-morbidities were the following: cardiovascular diseases (72%), malignancies (34%), and diabetes (30%). Nevertheless, those patients were seemingly not as ill as the patients of the presented study.

In the present study, urinary tract infections caused by *K. pneumoniae* ESBL$^+$ were observed more often when kidney failure co-existed (69%). Likewise, pneumonia caused by *K. pneumoniae* ESBL$^+$ was concomitant in patients with chronic pulmonary diseases (asthma, COPD). Comparable results have been reported by Lee et al. (2012), with infections mainly in the urinary (64%) and respiratory tracts (22%). Lautenbach et al. (2001) have demonstrated that 51.5% of *K. pneumoniae* ESBL$^+$ infected patients had urinary tract infection, 9.1% had respiratory tract infection, 15.2% had surgical wound infection, 12.1% had central venous line infection, 9.1% had bacteraemia, and 3.0% had abdominal infection. This raises a question of whether these statistics accurately reflect the frequency of infection at the sites or, perhaps, the ease of sampling for microbiological testing. It is easier to acquire sterile material from the urinary tract or blood vessels than from the respiratory tract. In the presented study, the main material which the pathogen was isolated from urine, as it also was in previous studies (Sekowska et al. 2012; Shanthi and Sekar 2010; Empel et al. 2008).

In the present study, *K. pneumoniae* ESBL$^+$ infections were most often found in the internal medicine ward (64%), ICU (11%), and the surgery ward (8.3%). These wards were also mentioned as the most often affected with the infection in previous studies (Empel et al. 2008; Tumbarello et al. 2006). Somehow different percentages have been reported by Lautenbach et al. (2001): ICU – 39.4%, general medicine – 27.3%, and surgery ward – 18.2%, and by Paluchowska et al. (2012): ICU – 42%, neurology – 16%, and general medicine ward – 11%. In this last report, the pathogen was isolated from the respiratory tract (46%), urine (27%), and blood (12%). *K. pneumoniae* ESBL$^+$ infections seem to clearly predominate in the wards where most patients are of advanced age with co-morbidities, and are frequently malnourishes with deficiency of proteins. In the present study, a third of hospitalized patients were malnourished, 10% were long-term residents of care facilities or homeless. In addition, cramped hospital conditions and shortages of nurses and ancillary staff often induce the necessity of urinary catheterization or setting venous lines outside strict medical recommendations. Mendelson et al. (2005) have reported increased incidence of *K. pneumoniae* ESBL$^+$ cultured from urine in long-term residents of care facilities. Such patients are consequently predisposed to develop an infection.

We conclude that hospital infections with *K. pneumoniae* ESBL$^+$ are associated with high mortality (64–90%). Deaths are related to age, gender, and catheterization of the bladder or other sites. Infections occur primarily in the general medicine ward and foremost concern the urinary tract. Prompt and adequate actions should be implemented in hospitals to decrease a high mortality liked to *K. pneumoniae* ESBL$^+$ infections.

Conflicts of Interest The authors declared no competing interests in relation to this article.

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Echocardiographic Assessment in Patients with Granulomatosis with Polyangiitis

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Abstract

Granulomatosis with polyangiitis (GPA) is one of the most common forms of systemic vasculitis, which usually involves the upper and lower respiratory tract, but it may affect also multiple organs. The aim of the study was an echocardiographic evaluation of cardiac involvement in GPA patients during remission. Eighty eight patients with GPA were evaluated in the study. The control group consisted of 40 age and sex-matched patients without a previous history of cardiovascular disease. We found that there were no differences between GPA and control groups regarding left atrial enlargement and interventricular septal hypertrophy. In one GPA patient, all heart chambers were enlarged. Left ventricle systolic function was decreased (LVEF $\leq$ 50%) in eight patients with GPA, and left ventricle wall motion abnormalities were observed in 12 patients. Left ventricle relaxation dysfunction, mitral valve and tricuspid valve regurgitation were observed with the same frequency in both GPA and control groups. Aortic regurgitation was the single abnormality that occurred significantly more often in the GPA group than in controls (28% *vs*. 7.5%; $p = 0.03$). Pericardial effusion was observed in three GPA patients and in none from the control group. We conclude that the most common echocardiographic manifestation in GPA patients in remission was aortic valve regurgitation. However, cardiac involvement in such patients is rather rare and in the majority of cases clinically insignificant.

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Keywords
Aortic valve regurgitation • Cardiac involvement • Echocardiography • Granulomatosis with polyangiitis • Remission • Vasculitis

1 Introduction

Granulomatosis with polyangiitis (GPA) is one type of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), which also includes microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (Ntatsaki et al. 2014). AAV usually presents with life-threatening pulmonary haemorrhage or kidney failure and has a mortality rate of 28% over 5 years (Lionaki et al. 2009). ANCAs with specificity for proteinase-3 or myeloperoxidase are the hallmarks of AAV and play an important role in disease diagnosis and progression (Flossmann et al. 2011).

GPA is one of the most common forms of systemic vasculitis, with a reported annual incidence of 11 cases per million (Watts et al. 2012). GPA usually involves the upper and lower respiratory tract and renal systems, where necrotizing glomerulonephritis and pulmonary capillaritis are often detected. However, it may also affect other organ systems. Cardiac involvement in GPA occurs in approximately 6–44% of cases and is secondary to necrotizing vasculitis with granulomatous infiltrates (Koyalakonda et al. 2010; Grant et al. 1994). The two most common cardiac manifestations are coronary arteritis and pericarditis, which account for approximately 50% of cases, but myocarditis, endocarditis, and conduction system disturbances are also described (Colin et al. 2015; Florian et al. 2011; Morelli et al. 2000).

Cardiac involvement is an independent predictor of mortality in GPA patients. The overall mortality rate of GPA with cardiac involvement has been reported to be between 15% and 45% (Guillevin et al. 2011; Oliveira et al. 2005). The estimates of frequency of cardiac involvement in GPA vary widely. Recently, in a North American retrospective study, cardiac abnormalities, defined as any documented history of cardiac disease, deemed to be secondary to GPA, were found only in 3.3% of patients and there was no association with a higher rate of relapse or premature death (McGeoch et al. 2015). However, in a European study, cardiac involvement, defined as abnormalities in electrocardiography or echocardiography, has been reported in 46% of GPA patients. In that study, cardiac manifestation is related to increased all-cause and cardiovascular mortality (Hazebroek et al. 2015). The literature concerning cardiac involvement in GPA is limited and is based mostly on case reports and a few retrospective studies. The range of cardiac abnormalities in GPA patients vary significantly between studies, which may be explained by differences in disease activity, selection bias, and differences in applied diagnostic methods. There is a lack of prospective studies to define the true prevalence of cardiac involvement in GPA patients. Further, there are only a few studies that involved GPA patients in the remission period. Therefore, the aim of the present study was the echocardiographic evaluation of cardiac involvement in GPA patients.

2 Methods

2.1 Study Population

The study protocol was approved by the Ethics Committee of the Medical University of Warsaw in Poland. In this prospective cohort study, 88 consecutive GPA patients (28 men and 60 women, mean age 49 ± 24 years) were

evaluated. The patients were hospitalized in the Department of Family Medicine, Internal and Metabolic Diseases of the Medical University of Warsaw between February 2013 and August 2016. All of them were diagnosed with GPA according to the current guidelines (Ntatsaki et al. 2014). The mean duration of the disease was 99 ± 54 months. All the patients were in sustained remission after immunosuppressive treatment. Most of the patients (88.6%) were on maintenance treatment during the echocardiographic assessment; 78 patients were treated with prednisolone (5–15 mg *per* day) and 20 patients simultaneously received cyclophosphamide (50–100 mg *per* day). The control group consisted of 40 age and sex-matched subjects (14 men and 26 women; mean age 45 ± 18 years) without previous history or symptoms of a cardiovascular disease.

2.2 Echocardiographic Assessment

M-mode and two-dimensional standard echocardiography (Mindray M7, Shenzhen Mindray Bio-Medical Electronics Co., Shenzhen. China) followed by pulsed and continuous-wave Doppler recordings were performed in all patients by the experienced cardiologist. The heart chamber diameter, left and right ventricle systolic and diastolic function, valvular changes, and pericardial effusion were assessed. Left ventricular ejection fraction (LVEF) was obtained by the biplane Simpson method. Reduced LVEF was defined as <50% of the norm (Ponikowski et al. 2016). Peak systolic right ventricular pressure was estimated from the maximal tricuspid regurgitant blood flow velocity. Five consecutive measurements were averaged for each parameter. Mitral and tricuspid regurgitation were defined as grade >2 and aortic valve regurgitation as any regurgitant jet.

2.3 Statistical Elaboration

Continuous data were presented as means ±SD and categorical data as percentages. Differences between the study and control groups were evaluated with Student's *t*-test. Difference in LVEF were evaluated with Chi squared test with Yates' correction or with Fisher's exact test. A p-value of <0.05 defined statistically significant differences. Statistical evaluation was performed with the statistical analysis system – commercial SAS v9.2 package (Cary, NC).

3 Results

There were no significant differences between the GPA and control groups in the mean results of basic echocardiographic parameters (Table 1). The frequency of deviations from the norm concerning the specific variables in both groups

Table 1 Echocardiographic variables in the granulomatosis with polyangiitis (GPA) and control groups

Variable	GPA	Control	p
Ao (mm)	31.6 ±3.2	30.7±3.0	ns
LA (mm)	35.8 ±3.4	35.2±3.2	ns
IVS (mm)	10.6 ±2.0	10.2±1.6	ns
PW (mm)	10.3 ±1.6	10.7±1.4	ns
LVDd (mm)	44.6 ±4.3	45.5±4.2	ns
LVSd (mm)	23.6 ±1.9	25.1±2.1	ns
RV (mm)	28.1 ±3.2	30.2±2.8	ns
PA (mm)	19.3 ±1.6	18.7±1.9	ns
VCI (mm)	16.5 ±2.0	15.8±1.8	ns
PAT (ms)	131.0 ±16.6	128.0±13.4	ns
RVSP (mmHg)	32.0 ±3.9	31.2±2.8	ns
LVEF (%)	63.0 ±5.9	65.0±3.8	ns

Data are means ±SD. *Ao* ascending aorta, *LA* left atrium, *IVS* intraventricular septum, *PW* posterior wall, *LVDd* left ventricle diastolic diameter, *LVSd* left ventricle systolic diameter, *RV* right ventricle, *PA* pulmonary artery, *VCI* vena cava inferior, *PAT* pulmonary acceleration time, *RVSP* right ventricle systolic pressure, *LVEF* left ventricle ejection fraction; *ns* non significant

Table 2 Comparison of echocardiographic abnormalities between the granulomatosis with polyangiitis (GPA) and control groups

	GPA n (%)	Control n (%)	p
Left atrium enlargement	7 (8.0%)	2 (5%)	ns
Interventricular septum hypertrophy	34 (38.4%)	11 (27.5%)	ns
Left ventricle ejection fraction < 50%	8 (9.1%)	0	ns
Left ventricle wall motion abnormalities	12 (13.6%)	0	ns
Left ventricle relaxation dysfunction	15 (17.0%)	5 (12.5%)	ns
Aortic valve stenosis	4 (4.5%)	0	ns
Aortic valve regurgitation	25 (28.4%)	3 (7.5%)	0.03
Mitral valve regurgitation	9 (10.2%)	3 (7.5%)	ns
Tricuspid valve regurgitation	8 (9.1%)	3 (7.5%)	ns
Pericardial effusion	3 (3.4%)	0	ns

ns non significant

is compared in Table 2. Left atrium (LA) enlargement was observed in 8.0% of GPA patients and interventricular septum (IVS) hypertrophy in 38.4% of patients. Systolic left ventricle function was decreased (LVEF <50%) in 9.1% of GPA patients, and left ventricle wall motion abnormalities were described in 13.6% of patients. Dysfunction of left ventricle relaxation was observed in 17.0% patients. Aortic valve regurgitation was seen in 28.4%, mitral valve regurgitation in 10.2%, and tricuspid regurgitation in 9.1% of patients. Aortic valve stenosis was observed in 4.5% of patients. Pericardial effusion was described in 3.4% of GPA patients. Only did aortic regurgitation occur significantly more often in the GPA than that in the control group; 28.4% *vs.* 7.5%, respectively ($p = 0.03$). None subject from the control group had any left ventricle systolic function abnormalities.

The GPA patients with aortic valve regurgitation tended to be older (mean age of 52 ± 20 *vs.* 49 ± 24 years) and had a shorter disease duration (94 ± 49 *vs.* 99 ± 54 months) compared with the other GPA patients ($p > 0.05$). Eighty percent of GPA patients with aortic valve regurgitation suffered from multi-organ organ damage.

4 Discussion

The majority of previous studies investigating the prevalence of cardiac involvement in GPA patients, have dealt with symptomatic patients in acute phase of the disease, when pericarditis and coronary arteritis are the most common cardiac manifestations (Florian et al. 2011; Morelli et al. 2000). Furthermore, different diagnostic methods have been used to evaluate cardiac manifestations such as ECG, Holter ECG, echocardiography, magnetic resonance imaging (MRI), or coronarography (Hazebroek et al. 2015; McGeoch et al. 2015). Echocardiography is a safe and easily accessible method that may be used in all patients. In a study by Hazebroek et al. (2015), GPA patients in remission were investigated, but the number of 41 participants was rather small. Oliveira et al. (2005) have conducted a retrospective echocardiographic evaluation of GPA patients and demonstrate a high prevalence of abnormalities; 26 (36%) of the 73 patients had changes that could be directly attributed to the disease. Since various methodological and disease-related differences may blur the true rate of cardiac manifestations in GPA, in the present study we chose to investigate the echocardiographic prevalence of cardiac abnormalities in a large, prospective, and well-defined population of GPA patients being in sustained remission, irrespective of symptoms. We found a small percentage, mostly within single digits, of various usually coexisting echocardiographic abnormalities, with aortic valve regurgitation and intraventricular septum hypertrophy being the leading abnormalities seen in

approx. 30% of patients each. Possibly, the number of abnormalities could actually be greater had the more comprehensive and accurate methods, such as MRI and the like, been employed for assessment, as reported in other studies (Hazebroek et al. 2015; Mavrogeni et al. 2009).

Cardiac valvular involvement in GPA patients may potentially be fatal (Yanda et al. 1989). The most frequent valvular presentation is aortic valve regurgitation, followed by mitral valve regurgitation (Lacoste et al. 2011); the findings that we confirmed in the present study. In contrast, aortic and mitral valve stenosis are extremely rare. Several mechanisms responsible for these valvular lesions have been proposed such as leaflet thickening, valvular perforation, or endocardial masses. Singh et al. (2014) have described a case of a 47 years old male with aortic involvement during GPA. The patient presented with mild aortic valve stenosis and moderate regurgitation due to the aortic valve mass lesion; the abnormality responded to immunosuppressive treatment. Unfortunately, in some cases of GPA patients with myxoid degeneration of valves, initiation of treatment fails to suppress the valvular changes. Davenport et al. (1994) have described two patients with aortic valve disease that progressed despite clinical remission after treatment initiation of non-cardiac manifestations of ANCA-associated vasculitis. Although aortic valve involvement appears to be more frequent, a mass lesion of the mitral valve is also seen in GPA. Dupuy et al. (2009) have described a case of a patient with severe mitral valve regurgitation caused by anterior leaflet perforation due to GPA infiltrates, which required surgical mitral valve replacement. Espitia et al. (2014) have reported a case of a 60 years old woman with severe inflammatory aortic and mitral valvular involvement with histopathological valvular lesions typical for GPA, which at presentation, misleadingly, suggested infectious endocarditis.

In the present study, aortic regurgitation was present more often in GPA patients than in controls. In the majority of patients, aortic valve regurgitation was mild and not clinically significant. In a Hazebroek et al.'s study (2015), aortic regurgitation was present only in 5% of GPA patients, but the authors considered the regurgitation of grade 3 or more, while in the present study we took into account the regurgitation of any degree. McGeoch et al. (2015) have described a low incidence of any valvular disease (1.6%) in GPA, but there were only 17 patients with cardiac involvement in that study. Aortic valve regurgitation may lead to heart failure and may necessitate valve replacement therapy (Davenport et al. 1994; Yanda et al. 1989). Therefore, careful echocardiographic monitoring and prompt treatment may delay symptom development and the need for surgery.

Pericarditis is one of the most common cardiac manifestation in the acute phase of GPA (Florian et al. 2011). It is usually asymptomatic, or may be manifested by chest pain or dyspnea (Koyalakonda et al. 2010; Grant et al. 1994; Goodfield et al. 1995). Pericardial effusion can be due to the disease itself or due to uremia in case of renal failure (Yildizer et al. 1996; Meryhew et al. 1988). In the present study, pericardial effusion was an uncommon finding accounting for 3.4% of GPA patients. In all these patients, it was mild and clinically irrelevant. Likewise, Hazebroek et al. (2015) have reported that pericardial effusion is a rare accompaniment of GPA; found only in 4% of GPA patients. In a retrospective study by McGeoch et al. (2015), pericarditis was the most common cardiac manifestation found, with the incidence of 6.35%. That study, however, included patients at any stage of the disease. In another retrospective study, Oliveira et al. (2005) have reported pericardial effusion in 5.8% of patients.

Coronary artery involvement in GPA patients is characterized by coronary arteritis, subsequent coronary artery thromboembolism, coronary arteries dilatation, and accelerated development of atherosclerosis (Mavrogeni et al. 2009; Parry et al. 2000). Morbini et al. (1998) have reported an elderly female without clinical signs from the cardiovascular system who developed cardiac arrest and died, and who suffered from clinically unrecognized systemic autoimmune inflammatory disorder with necrotizing arteritis. The autopsy showed findings typical of GPA and

systemic arteritis with fibrinoid necrosis. In a study by Cocco and Gasparyan (2010), ischemia in GPA patients was due to the involvement of small vessels secondary to the vasculitic process rather than atherosclerosis, as it responded to immunosuppressive therapy with reversal of ischemic changes.

Since life expectancy in GPA patients has gotten extended, longer duration of inflammation and treatment with corticosteroids may accelerate the development of atherosclerosis in patients of younger age compared to the remaining population at large. There are several reports that described patients with GPA and myocardial infarction (Salazar-Exaire et al. 2012; De la Prada et al. 2003; Lawson and Williams 1996; Papo et al. 1995). In the present study, systolic left ventricular function was reduced in 9.0% of GPA patients and left ventricle wall motion abnormalities were described in echocardiography in 13.6% of these patients. Likewise, in a study by Hazebroek et al. (2015), 10% of GPA patients had general left ventricle wall motion abnormalities. In a retrospective study from the Mayo Clinic in the US, left ventricular systolic dysfunction with decreased ejection fraction was found in 15.2% of 85 GPA patients (Oliveira et al. 2005). In the Danish National Hospital register, patients had an increased rate of myocardial infarction within 5 yr of diagnosis of GPA when compared with the population at large (Faurschou et al. 2009).

GPA should be included in the differential diagnosis when soft tissue thickening involves the coronary arteries or endocardium, even when no pulmonary or airway findings are identified (Dewan et al. 2015). In addition, risk stratification using cardiac imaging is recommended in all GPA patients, irrespective of symptoms or ECG abnormalities (Hazebroek et al. 2015; Oliveira et al. 2005). It would be also recommended to perform echocardiographic monitoring of GPA patients, which would begin in the acute phase and be continued during remission.

We conclude that echocardiographic abnormalities in GPA patients remaining in sustained remission are rare and in the majority of cases are of little or no clinical insignificance. The most common cardiac manifestation in these patients is aortic valve regurgitation. Echocardiography is a helpful tool in the diagnosis of cardiac involvement in GPA patients and should be performed routinely even in patients asymptomatic from the cardiologic standpoint.

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Conflict Interest The authors declare no conflict of interest in relation to this article.

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Lung Lesions During Fever of Unknown Origin

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Abstract

Fever of unknown origin (FUO) remains one of the most difficult diagnostic challenges. The causes of FUO can be various diseases located in different organs. The aim of the study was to determine the prevalence and nature of pulmonary lesions during FUO. One hundred and sixty one patients with FUO participated in this prospective study. We performed a detailed comprehensive history, physical examination, and a wide spectrum of tests. The most common causes of FUO were infections (39%), autoimmune conditions (28%), and neoplasms (17%). Lung lesions were found in 30% of patients. In this group 35% were infections, 30% autoimmune diseases, and 4% cancer. Among patients with respiratory infections, there were cases of tuberculosis, atypical pneumonia, lung abscess, and bronchiectases. Autoimmune pulmonary lesions were observed during vasculitis and systemic lupus. The causes of FUO in the group of patients with lung lesions were also pulmonary embolism, sarcoidosis, and pulmonary fibrosis. Chest CT played an important role in the diagnosis of the causes of FUO with pulmonary manifestations. Pulmonary lesions are a common cause of FUO. Most FUO with pulmonary lesions are recognized during infections and autoimmune diseases. An important part of diagnosing FUO is a detailed evaluation of the respiratory system.

Keywords

Computed tomography • Diagnostics • Fever of unknown origin • Infection • Lung lesions • Malignance

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1 Introduction

Fever is a thermoregulatory disorder that is manifested as an increased body temperature

greater than 38 °C. It is one of the most common responses to viral, bacterial and fungal infections, the presence of allergens, foreign bodies, and other external or internal pyrogenic factors (Kluge 2015). The definition of fever of unknown origin was proposed for the first time in 1961 by Petersdorf and Beeson (1961). It required fulfilling the following criteria: fever ≥38.3 °C lasting for more than 3 weeks or recurring, a failure to establish a cause, or the diagnosis is unclear despite routine diagnostic tests for 7 days (≥3 days in the hospital or during ≥3 outpatient visits). In 1991, Durack and Street (1991) proposed a new definition of fever of unknown origin, and the criteria they presented are currently in use to this date. They distinguished four types of causes of fever of unknown origin: classic FUO, neutropenic/immune-deficient, nosocomial, and human immunodeficiency virus-associated. Causes of classic FUO and their frequency vary widely depending on the results of research study (Cunha et al. 2015; Cunha 1996). Infectious diseases are causes of classic FUO in 25–50%, neoplasms in 5–25%, autoimmune diseases 15–40%, other causes 5%, and unknown causes 5–10% (Arnow and Flaherty 1997). The most important infectious causes are abscesses of the lungs, abdominal cavity and pelvis, tuberculosis, endocarditis, complications of urinary tract infections, prostatitis, biliary tract infections, peritonitis, osteomyelitis, inflammation of the teeth, periodontitis and sinusitis, malaria, zoonotic infections (Q fever, brucellosis), viral infections (Epstein-Barr virus, cytomegalovirus), parasitic infections (*Entamoeba histolytica, Toxoplasma gondii*), and fungal infections (*Candida albicans)* (Cunha 2007a; Tanoue and Mark 2003; Sood et al. 1997). Proliferative hematologic diseases (lymphoma, leukemia or myeloma) and solid tumors (e.g., kidney tumors) are the common neoplasmic causes of FUO (Cunha 2007b; Sørensen et al. 2005). Autoimmune causes of FUO include connective tissue diseases and primary systemic vasculitis such as Still's disease, systemic lupus erythematosus, rheumatoid arthritis, giant cell arteritis, Takayasu arteritis, ANCA-associated vasculitis, microscopic polyangiitis, Churg-Strauss syndrome, polyarteritis nodosa (Cunha 2007a; Sørensen et al. 2005; Mert et al. 2003). Other causes of FUO are drug-induced after antibiotics, nonsteroidal anti-inflammatory drugs, interferon-α, anticonvulsants, quinidine and anti-thyroid drugs, endocrine diseases (hyperthyroidism, pheochromocytoma), sarcoidosis, Crohn's disease and ulcerative colitis, histiocytosis, and disorders of the thermoregulation center in the hypothalamus (Cunha et al. 2015). FUO remains one of the most difficult diagnostic challenges for the clinician because of the diversity of disease entities causing it and a wide-array of expensive and lengthy diagnostic procedures. The diagnostics are based on a comprehensive history, physical examination, and appropriate laboratory tests and imaging. The cause of FUO can be various diseases located in different organs, including the lungs. The causes of FUO have changed in the past 50 years. Decreases in infectious diseases and cancer have been observed. This is due to the dynamic development of modern diagnostics techniques such as molecular and immunological methods, CT, and PET, which enables a more accurate diagnosis. At the same time, however, a significant increase in the number of patients remaining in observation without an established diagnosis (up to 30%) has been observed (Mansueto et al. 2008), which underscores the persisting difficulty in identifying the cause of FUO. In the present study, therefore, we seek to determine the prevalence and nature of pulmonary lesions during FUO.

2 Methods

The study was approved by the Ethics Committee of Warsaw Medical University in Poland. This prospective study, consisted of 894 patients hospitalized for fever between January 2004 and December 2010 at the Department of Family and Internal Medicine and Metabolic Diseases at the Czerniakowski Hospital of Warsaw Medical University in Poland. From this group, 161 patients (81 females and 80 males) met the

criteria for classic FUO according to Durack and Street's (1991) definition. The mean age of the patients was 57 ± 19 years (minimum 19 – maximum 88 years). One fourth of patients were younger than 40 years old and another one fourth were older than 70 years old. After analyzing the education of the patients involved, 56 patients had secondary education, 46 had vocational education, 37 had some form of higher education, and 23 patients had a primary education. The starting point of the study was the hospitalization with a diagnosis of FUO. The end of the study, the so-called primary endpoint, was the identification of the agent causing the fever and establishing a definitive diagnosis. Secondary endpoints were to evaluate the incidence of lung lesions in the course of FUO and assess the usefulness of individual studies in the diagnosis of FUO.

In all patients, a detailed comprehensive history was conducted. Attention was particularly given to: age, gender, medical history, habits, recent travel, exposure to animals, work environment, family history, and drugs. The next step was daily physical examination, with emphasis on skin and mucous changes, lymph nodes, lymphatic system, abdominal palpation for masses or organomegaly, cardiac murmurs, lung examination, and joint changes.

The next stage of diagnosis was appropriate laboratory and imaging studies. Each patient underwent the following laboratory tests: complete blood count (manual smear), the parameters of inflammation (C-reactive protein – CRP, erythrocyte sedimentation rate – ESR, and fibrinogen), parameters of renal function (creatinine, estimated glomerular filtration rate – eGFR), urinalysis, proteinogram, and blood cultures. Depending on the clinical condition, additional microbiological tests of urine and sputum were performed. In the whole study group, chest X-ray and abdominal ultrasound were performed. In the absence of diagnosis, diagnostic imaging was widened to include more precise imaging techniques such as computed tomography – CT, magnetic resonans imaging – MRI, and positron emission tomography – PET. For some patients confirming the final diagnosis required specific serological tests such RF, ANA, pANCA, or cANCA and histopathological evaluation including trepanobiopsy.

3 Results

In the study group of 161 patients with FUO, the cause of fever was determined in 153 of them, which represents 95% of the group. The most common cause of FUO was infectious disease, which accounted for 60 patients. Followed by other causes of FUO: autoimmune disease consisted of 43 patients, neoplasms of 26 patients, and other miscellaneous diseases of 24 patients. In 8 patients, a definitive diagnosis was never established. In 4 patients, a spontaneous remission of body temperature was observed, with the average time of fever of 7 days, and in 2 patients fever during hospitalization did not occur. Two patients had not consented to further diagnostic testing.

In the group of 153 patients who had established a definitive cause of FUO, in 46 lung lesions were discovered, which represents 30% of the group. The most common cause of FUO in the group with lung lesions was infectious diseases, which accounted for 16 patients. Followed by other causes of FUO: autoimmune disease consisted of 14 patients, neoplasm of 2 patients, and other diseases of 14 patients. In the group of all patients with FUO, a similar percentage of fever was observed for infection and autoimmune diseases. Important differences were observed for neoplasm and the miscellaneous group (Fig. 1).

Among patients with respiratory infection there were two cases of tuberculosis, seven cases of atypical pneumonia (*Legionella pneumophilla* – 5, *Chlamdia* spp. – 2), five patients with lung abscess, and two patients with bronchiectases. Autoimmune pulmonary lesions were observed in 30% of the group. In this group, the most often recognized was vasculitis with pulmonary manifestations (11 patients) and systemic lupus (3 patients). The diagnosis of lung cancer was established in two patients. In one case, it was small-cell lung cancer and in the

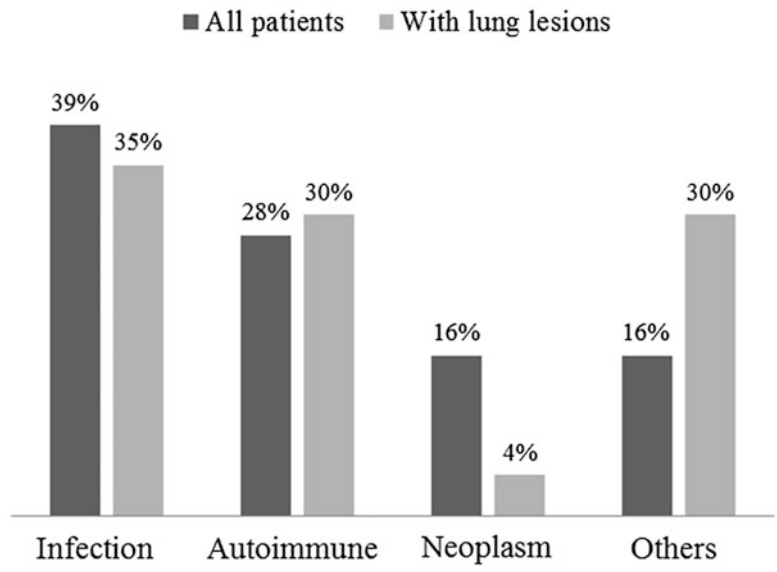

Fig. 1 Causes of fever of unknown origin in the whole group investigated and in patients with changes in the lungs

other, non-small- cell lung cancer. The last group, the so-called "other reasons" of FUO, accounted for about 30%. In this group, six patients were diagnosed with embolism, five patients with sarcoidosis, and three patients with pulmonary fibrosis were found.

The analysis of the usefulness of particular additional tests in making a final diagnosis revealed that the most useful study in patients with pulmonary lesions was the CT scan. It contributed to the diagnosis in 60% of patients. In the group of infectious diseases, CT was the key in making a diagnosis in 66% of patients. Another important study to help in the diagnosis in this group were serological and microbiological tests. In patients with lung neoplasm, tomography remained a necessary diagnostic tool in conjunction with histopathology. In the group of autoimmune diseases, CT was a useful diagnostic tool in 64% of patients. The useful tests in diagnosis in this group were also: serological tests (22%) and histopathology (14%). In the group of extrapulmonary FUO results of the evaluation of diagnostic usefulness were different (Fig. 2). CT has been key in making a diagnosis in 24% of patients. In the group of infectious diseases, the most useful were microbiological tests (38%) and CT (34%). In the cancer group, helpful were histopathological examination, including bone marrow biopsy (67%) and CT (33%).

4 Discussion

Fever of unknown origin can be observed in more than 200 diseases (Cunha 2007a). It is the subject of many studies consisting of significant sample size, similar to that of the present study on FUO, such as 154 patients in Turkey (Kucukardali et al. 2008), 164 in Romania (Baicus et al. 2003), 192 in Italy (Sica et al. 1999), and 199 in Belgium (Knockaert et al. 1996). However, there are no studies assessing the presence of lung lesions in the literature in this group of patients. The most of the studies focus on the evaluation of lung lesions stemming primarily from infectious causes. In the study group, pulmonary lesions were significant; they were found in 30%, indicating the need for careful evaluation of the lungs.

In this research, similar to other studies of FUO, the main causes of fever (25–50%) were infections (Bleeker-Rovers et al. 2007; Mourad

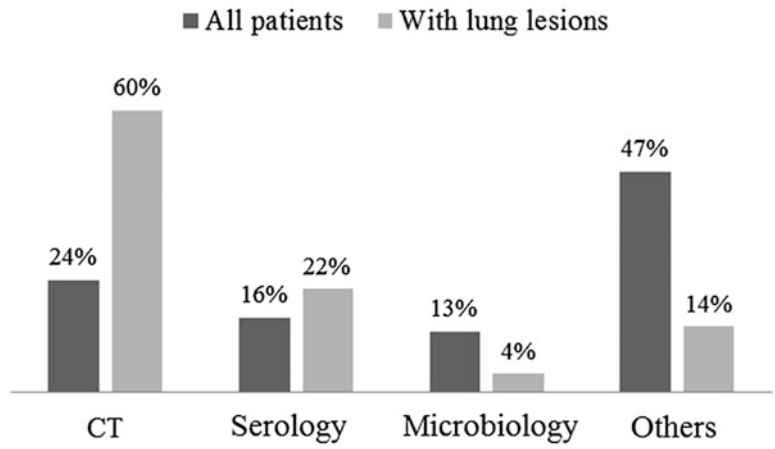

Fig. 2 Essential methods for establishing the cause of fever of unknown origin *CT* computed tomography

et al. 2003). The most commonly reported causes of infections (abscess, tuberculosis, endocarditis, and pneumonia) were similar to most studies conducted so far. The analysis of patients with lung lesions revealed that most often infection agents were atypical pneumonia caused by *Legionella pneumophila* and *Chlamydia pneumoniae*. Very often patients with outpatient respiratory infections are treated initially as pneumococcal pneumonia with beta-lactam antibiotics. The problem of atypical pneumonia is due to diagnostic difficulties and the lack of response to beta-lactam antibiotic therapy. Clinical presentation may not be different from "typical" pneumonia and radiological changes remain unspecific. Serological tests often remain the basis of diagnosis. However, it is necessary to wait 4 weeks for the results. Modern methods such as genetic, PCR techniques often remain unused because of cost and lack of availability. In addition, culture is possible only in highly specialized centers. Other authors also emphasized diagnostic problems in this group of patients (Muñoz-Gómez and Cunha 2015). Lack of clinical improvement after the use of first line antibiotics leads doctors to further research the causes of failure. Therefore, in the case of serious infection we should start treatment with a combination of beta-lactams and macrolides in accordance with applicable recommendations (NICE 2014).

The diagnosis of typical pneumonia normally takes less than 2 weeks to establish, and so it does not meet the definition of FUO. Previous studies emphasized infections due to cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in addition to atypical infections (Kucukardali et al. 2008). This was not observed in the present study, but we cannot forget them in the differential diagnosis.

Another group of infections sometimes overlooked in routine diagnostics is tuberculosis (Tanoue and Mark 2003; Sood et al. 1997). In patients with no risk factors (the homeless, malnourished, poor housing conditions, and treated with immunosuppressants) and no specific clinical signs, diagnosis can be difficult. In this study tuberculosis was recognized in six patients, in two of them it was the pulmonary localization. In many studies, the leading cause of infectious FUO is tuberculosis. It represents up to 60% of the causes of infectious FUO (Moawad et al. 2010), and in other research 40% (Kucukardali et al. 2008) and 20% (Baicus et al. 2003). These differences depend on a local epidemiological situation. In the case of tuberculosis, diagnosis is difficult due to the long waiting time for test results. We expect up to 3 months for the result of culture on classical Löwenstein-Jensen solid medium, and 3 weeks when liquid media such as Middlebrook are used (Augustynowicz-Kopeć et al. 2013). An additional difficulty is the

problem of obtaining a specimen when the patient does not have a productive cough or in extra-pulmonary cases of tuberculosis. In developed countries, the incidence of tuberculosis significantly decreased, therefore tuberculosis may rarely be the cause of FUO, especially when there are no apparent risk factors.

In the case of persistent fever, we should consider lung abscess. It is a complication of pneumonia, particularly in patients with swallowing disorders, alcohol abuse, and impaired consciousness. In most studies, abscesses are one of the main causes of infectious FUO, but abdominal locations are more frequent. In a study of Cunha (2007a), extra-pulmonary abscesses were observed in eleven patients, and lung abscesses in five. Early signs and symptoms of lung abscess cannot be differentiated from pneumonia and include fever with shivering, cough, night sweats, dyspnea, weight loss and fatigue, chest pain, and sometimes anemia (Kuhajda et al. 2015). To confirm the diagnosis, it is often necessary to perform a CT scan because the classical radiological examination of the lungs remains insufficient.

In previous studies concerning FUO, attention was not drawn to patients with infected bronchiectases. Bronchiectases may be a result of prolonged respiratory infections, easily occurring in damaged airways (Chalmers et al. 2015). These patients are predisposed to recurrent infections that can occur with prolonged fever. The key diagnostic method for bronchiectases is imaging studies such as high-resolution computed tomography (Altenburg et al. 2015).

In most studies, autoimmune disease ranks second in the causes of prolonged fever (15–40%) (Bleeker-Rovers et al. 2007; Mourad et al. 2003). Systemic autoimmune diseases such as vasculitis and collagen diseases are characterized by chronic inflammation. Pulmonary manifestations are typical for many of them (Lambin et al. 2001). We should especially consider vasculitis (diagnosed in 11 patients in the present study) and systemic lupus (in 3 patients) when we find changes in the lungs (diffuse alveolar hemorrhage, nodular or cavitary changes). In the pathogenesis of systemic vasculitis, the genetic, environmental (viral or bacterial infections) and iatrogenic factors are taken into account (Millet et al. 2014). Pulmonary lesions may also be present in the course of Still's disease, systemic lupus erythematosus, and giant cell arteritis, which are the most common causes of fever in most studies (Cunha et al. 2006; Mert et al. 2003; Akar et al. 2002).

Neoplasm is another group of illnesses which cause prolonged fever (5–25%) (Bleeker-Rovers et al. 2007; Mourad et al. 2003). The proliferative hematological processes are especially common (Sørensen et al. 2005). Fever may be the only leading symptom and the first symptom in Hodgkin lymphoma (Cunha 2007b) and may be accompanied by lymphadenopathy, night sweats, weight loss, splenomegaly, and hepatomegaly. In the present study, neoplasms with lung lesions were rare; they were diagnosed in only two patients. This is because the common reason of FUO are hematologic diseases, such as lymphoma, leukemia, or myeloma (Cunha 2007a; Sørensen et al. 2005). Trepanobiopsy and PET/CT diagnostic methods remain helpful in this group (Meller et al. 2007). However, cases of persistent fever in the course of lung neoplasm have also been described (Zee and Soo 2010; Kim et al. 2007). In persons with lung cancer it is necessary to perform tomography of the chest and lung biopsy with histopathological evaluation.

In the present study, the most frequently diagnosed among the so called "other reasons" were: ulcerative colitis, pulmonary embolism, pulmonary fibrosis, and sarcoidosis. These results are similar to the majority of studies. Although in some studies, depending on the geographical location, Mediterranean fever or drug fever dominated in this group (Kucukardali et al. 2008). In the case of sarcoidosis, diagnostic difficulties may be due to an unusual clinical course, no lung changes in X-ray study (approximately 5%), and the need to perform a lot of research in highly specialized centers (Verschakelen 2005). A widening of diagnostics, performing special studies such as high-resolution computed tomography (HRCT) allows the detection of changes in the lungs (Chiles

2002). In many cases, it is necessary to perform invasive diagnostic tests – transbronchial, open lung biopsy, or lymph nodes biopsy under ultrasound control (ATS 2000). For the explanation of the cause of interstitial pulmonary changes it may be helpful to perform a bronchoalveolar lavage (Welker et al. 2004). However, the obtained material requires assessment in experienced pulmonary centers. It is also necessary to exclude other diseases causing the formation of granuloma. Diagnosis of sarcoidosis often requires several weeks from onset of symptoms such as fever, erythema nodosum, and arthritis. Sarcoidosis fever occurs mainly in acute forms with Löfgren's syndrome (Mañá et al. 1999). In the course of lung fibrosis, symptoms of respiratory disease such as dry cough and shortness of breath may be accompanied by systemic symptoms such as fever, malaise, arthralgia, myalgia, and weight loss (ATS/ERS/WASOG 1999). In the present study, patients with pulmonary lesions and FUO accounted for 6.5% of cases with pulmonary fibrosis.

Pulmonary embolism accounts for 4% of FUO in the elderly (Tal et al. 2007). These individuals may not present with classic signs and symptoms of dyspnea, chest pain, symptoms of pneumonia, or heart failure. Studies also describe cases of fever in the course of deep vein thrombosis and emphasize the role of ultrasound examination in the diagnosis (Mourad et al. 2003; AbuRahma et al. 1997).

According to the most proposed diagnostic algorithms, the final diagnosis of FUO requires the implementation of many diagnostic tests. Diagnosis usually includes numerous tests: laboratory, images, and invasive. In the present study, all patients required the implementation of a number of laboratory tests, which helped in targeting further diagnosis, like in most other studies (Kucukardali et al. 2008; Bleeker-Rovers et al. 2007; Mourad et al. 2003). However, in the presented group of patients with pulmonary lesions, the key role of CT was demonstrated for the diagnosis of the fever cause. In the survey, it was especially helpful in infectious reasons, particularly with lung lesions – diagnostic yield of about 60%. The role of CT was also emphasized by other authors. In the Mourad et al. (2003) study, the diagnostic yield of CT was about 20%. In the diagnosis of an abscess with a suspicion of malignancy, its usefulness was underlined. The classic chest radiogram is often insufficient to visualize changes in the lungs, and that is when CT is necessary. Furthermore, CT is available and non-invasive. According to other authors it seems that these should be compulsory tests for patients with prolonged fever. However, in the last decade studies highlight the usefulness of other imaging methods such as: 2-[(18)F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) or (111)In-labeled leukocyte scintigraphy (Seshadri et al. 2008; Meller et al. 2007). Such methods provide essential diagnostic information of high clinical meaning, particularly in the case of inflammatory and unknown or miscellaneous diseases (Kubota et al. 2011; Jasper et al. 2010). However, it is not widely available, especially in smaller diagnostic centers, and it is costly. In the present study, PET led to diagnosis in only one patient – the patient with vasculitis; which also was likely influenced by the fact of low availability of this method.

Microbiological tests must be repeated and remain an essential part of the diagnosis in FUO, especially among infectious causes and lung lesions. There is a consensus that microbiological tests remain the basic investigation in any patient with FUO (Kucukardali et al. 2008; Bleeker-Rovers et al. 2007; Mourad et al. 2003). Diagnosis of tuberculosis, which remains a common cause of FUO, is based among other things, on microbiological testing in both pulmonary and extra-pulmonary manifestations.

Another important group of helpful studies are serological tests. In the present study, such tests were particularly valuable in the diagnosis of autoimmune diseases both in the whole group and in the group with lung lesions. Serological tests are especially suitable in patients with vasculitis (Brown 2006), but also in the diagnosis of atypical respiratory infections (Muñoz-Gómez and Cunha 2015). Additionally, further diagnostics are required, e.g., bronchofiberoscopy, to differentiate from other diseases

such as cancer, tuberculosis, or ANCA-associated vasculitis. In the case of finding thick-walled cavitary lesions, differential diagnosis of lung abscess *vs*. tuberculosis or neoplasm should be considered (Cunha et al. 2010). Numerous previous studies show that despite the progress of knowledge, diagnosis of prolonged fever remains a big challenge for doctors of many specialties, including pulmonologists (Vanderschueren et al. 2003). An important part of diagnosing FUO is a precise evaluation of the respiratory system because lung lesions are a common cause of FUO; they are observed in one third of patients with this diagnosis. Most FUO with lung lesions are recognized in the course of infections and autoimmune diseases. CT of thorax plays an important role in the diagnosis of the causes of FUO with pulmonary manifestations.

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Importance of GOLD Guidelines for Chronic Obstructive Pulmonary Disease

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Abstract

In December 2011, a major revision of GOLD 2011 guidelines was published based on the evidence-based medicine. The goal of GOLD 2011 is to determine the severity of the disease, its impact on the patient's health, and the risk of future events; all of which eventually guide therapy. A combined COPD assessment according to GOLD 2011 considers the patient's level of symptoms, spirometry abnormalities, risk of exacerbation, and the presence of comorbidities. GOLD 2011 stratifies patients into four basic groups labeled A, B, C, and D. The aim of the present study was to assess the importance of updated GOLD guidelines for the diagnosis, treatment, and prevention of COPD. We found that the multicomponent 2011 guidelines offer a significant advantage over the previous monocomponent COPD assessment according to GOLD 2006 in terms of disease control and therapy management, with patients enjoying better spirometry values and a higher arterial oxygen content considered the primary outcomes of interest.

Keywords

Comorbidities • COPD • Exacerbations • GOLD guidelines • Spirometry • Symptoms

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1 Introduction

In 1998, in cooperation with the National Heart, Lung and Blood Institute of the National Institutes of Health in Bethesda, Maryland, and the World Health Organization in Geneva, the Global Initiative for Chronic Obstructive Lung Disease was implemented (GOLD 2011). In 2001, GOLD published the first report called the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (COPD). This report summarized the then state of COPD. It provided the information on COPD for pulmonary specialists and other physicians. GOLD 2001 was then updated every year in July 2003, July 2004, and then July 2005, each update included the knowledge and progress in the understanding the disease and its management from the past January to December period (GOLD 2011). In January 2005, the GOLD Science Committee prepared an updated and a revised version of GOLD 2006 based on spirometric classifications of stages I-IV of COPD (GOLD 2006). From 2006 to 2010, GOLD guidelines were updated only once.

In 2009, the GOLD Science Committee recognized new information, based on the evidence-based medicine, concerning the diagnosis and treatment of COPD, which led to a significant revision of GOLD guidelines published in December 2011 (GOLD 2011). According to those latest guidelines, the goal of combined COPD assessment is to define the severity of the disease, its impact on the patient's health, and the risk of future events such as exacerbations, hospital admissions, or death, in order to eventually guide therapy. A combined COPD assessment ought to take into account the following aspects of the disease: patient's symptoms, spirometric abnormalities, risk of exacerbations, and the presence of co-morbidities (GOLD 2011).

Clinical diagnosis of COPD should be considered in each patient with dyspnea, chronic cough or sputum production, and the risk factors in anamnesis, for instance smoking cigarettes. The guidelines suggest to assess the patient's intensity of symptoms with Modified British Medical Research Council (mMRC) or COPD Assessment Test (CAT) questionnaires. The mMRC assesses only the impact of dyspnea (Nishimura et al. 2002; Bestall et al. 1999), whereas the CAT questionnaire provides a more comprehensive assessment of symptomatic COPD status (Jones et al. 2009). Spirometry examination involves the inhalation application of the standardized dose of a short-acting bronchodilator. The GOLD guidelines suggest that the post-bronchodilator forced expiratory volume in one second (FEV_1) <80% of the predicted value in combination with a FEV_1/forced vital capacity (FVC) ratio <70% confirms the presence of airflow limitation and thus the diagnosis of COPD. COPD patients are classified according to the post-bronchodilator spirometric value of FEV_1 into four grades termed GOLD 1, GOLD 2, GOLD 3, and GOLD 4. The latest GOLD publication recommends the use of a new staging system that classifies COPD patients into A, B, C, and D groups, taking into account not only spirometric indices but also obstruction degree, frequency of exacerbations, and the scores of the quality of life questionnaires outline above (GOLD 2011). After the major 2011 GOLD revision, guidelines were updated on the yearly basis in January 2013, January 2014, January 2015, and lately in December 2015 (GOLD 2015).

An exacerbation of COPD is an acute event characterized by a worsening of the respiratory symptoms such as cough, sputum, dyspnea, or a heavy pressure feeling on the chest (Celli and Barnes 2007; Burge and Wedzicha 2003; Rodriguez-Roisin 2000). Exacerbations of symptoms in COPD patients are often triggered by bacterial or viral infections, environmental pollutants, or some unknown factors. Exacerbations increase hyperinflation and gas trapping resulting in decreased expiratory flow and increased dyspnea (Parker et al. 2005).

STAGE		
I	Mild	FEV_1 / FVC < 0.70 $FEV_1 \geq 80$ % predicted
II	Moderate	FEV_1 / FVC < 0.70 $50\% \leq FEV_1 < 80$ % predicted
III	Severe	FEV_1 / FVC < 0.70 $30\% \leq FEV_1 < 50$ % predicted
IV	Very Severe	FEV_1 / FVC < 0.70 $FEV_1 < 30$ % predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Fig. 1 Mono-component COPD assessment according to (GOLD 2006) based on spirometric classification, with the severity assessed from to the level of post-bronchodilator forced expiratory volume in one second (FEV_1); stages I, II, III, and IV. *FVC* forced vital capacity

GOLD	Symptoms: mMRC 0-1, CAT < 10	Symptoms: mMRC ≥ 2, CAT ≥ 10	Exacerbations / year
4 / 3	C	D	≥ 2 hospitalizations
2 / 1	A	B	1 or 0 hospitalizations

GOLD 1: $FEV_1 \geq 80$ % predicted
GOLD 2: $50\% \leq FEV_1 < 80$ % predicted
GOLD 3: $30\% \leq FEV_1 < 50$ % predicted
GOLD 4: $FEV_1 < 30$ % predicted or $FEV_1 < 50$ % predicted plus chronic respiratory failure

Fig. 2 Combined COPD assessment according to (GOLD 2011) based on patient's symptoms, severity of spirometric abnormalities, and the risk of exacerbations; groups A, B, C, and D. FEV_1 forced expiratory volume in one second, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *mMRC* Modified British Medical Research Council, *CAT* COPD Assessment Test

COPD may initiate or worsen co-morbidities such as ischemic heart disease, heart failure, diabetes mellitus, metabolic syndrome, osteoporosis, depression, and others. Co-morbidities can occur in patients in all COPD grades concerning airflow limitation (Agusti et al. 2010) and increase the frequency of hospitalization and mortality (Mannino et al. 2008). Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange (Barr et al. 2010).

The aim of the present study was to assess the importance of GOLD guidelines for the diagnosis, treatment management, and prevention of COPD, and to evaluate the advantages of most recent combined COPD assessment according to GOLD 2011 with the past mono-component COPD assessment according to GOLD 2006.

2 Methods

The study protocol was approved by the institutional Ethics Committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia. All the patients enrolled into the study were hospitalized at the Department of Pneumology and Phthisiology of the University Hospital with the diagnosis of COPD. The patients with the mono-component COPD assessment according to the GOLD 2006 guidelines were divided into the stages I, II, III, and IV (Fig. 1) and with the combined COPD assessment according to the GOLD 2011 guidelines into the A, B, C, and D groups (Fig. 2).

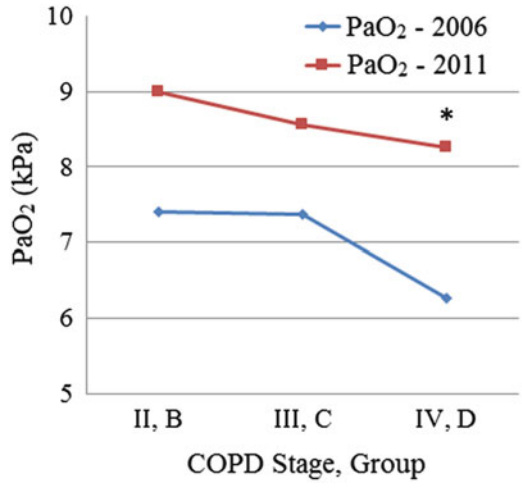

Fig. 3 Partial pressure of arterial oxygen (PaO_2) in patients with the mono-component COPD assessment according to GOLD 2006 (stages II, III, and IV) and in patients with the combined COPD assessment according to GOLD 2011 (groups B, C, and D). *p < 0.05 for the difference between group D and stage IV

In the group with the mono-component COPD assessment, there were 35 patients (25 men, mean age – 71.9 ± 8.1 years; 10 women, mean age – 71.8 ± 8.2 years) with positive current smoking anamnesis in 18 patients. Patients were divided as follows: stage I (2 patients), stage II (16 patients), stage III (8 patients), and stage IV (9 patients). In the group with the combined COPD assessment, there were 49 patients (38 men, mean age – 68.6 ± 9.5 years; 11 women, mean age – 70.3 ± 11.6 years) with positive current smoking anamnesis in 31 patients. Patients were divided as follows: group A (0 patents), group B (7 patients), group C (16 patients), and group D (26 patients). In the patients of both groups the following parameters were considered; anamnestic data, clinical symptoms, laboratory parameters, spirometric examination, exacerbations, comorbidities, treatment management, and mortality. These parameters were compared between the patients with the mono-component COPD assessment according to GOLD 2006 (stages I, II, III, and IV) and the patients with the combined COPD

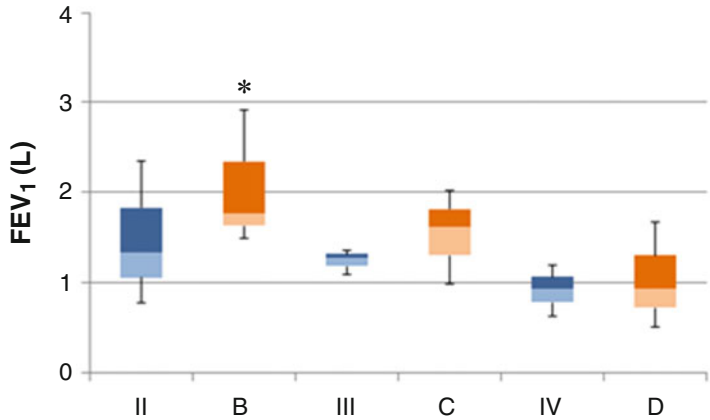

Fig. 4 Spirometric examination of forced expiratory volume in 1 second (FEV_1) in patients with the mono-component COPD assessment according to GOLD 2006 (stages II, III, and IV) and in patients with the combined COPD assessment according to GOLD 2011 (groups B, C, and D). X-axis represents different stages of the disease according to GOLD 2006 or different groups of patients according to GOLD 2011; y-axis represents FEV_1 expressed by medians and interquartile scatter. *p < 0.05 for the difference between group B and stage II

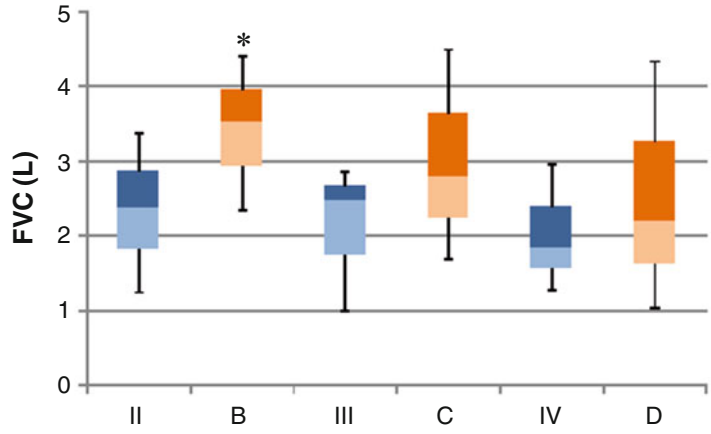

Fig. 5 Spirometric examination of forced vital capacity (FVC) in patients with the mono-component COPD assessment according to GOLD 2006 (stages II, III, and IV) and in patients with the combined COPD assessment according to GOLD 2011 (groups B, C, and D). X-axis represents different stages of the disease according to GOLD 2006 or different groups of patients according to GOLD 2011; y-axis represents FVC expressed by medians and interquartile scatter. *$p < 0.05$ for the difference between group B and stage II

assessment according to GOLD 2011 (groups A, B, C, and D). One-way analysis of variance (ANOVA) and a chi-squared test were used for the statistical elaboration of results. A p-value <0.05 defined the statistically significant differences between the two modes of COPD assessment.

3 Results and Discussion

The patients with the combined COPD assessment according to GOLD 2011 had more optimal values of the parameters examined compared with those who had the mono-component COPD assessment according to GOLD 2006. The former patients had a significantly higher average partial pressure of arterial oxygen ($p < 0.05$) (Fig. 3) and a lower partial pressure of carbon dioxide. They also had a significantly higher FEV_1 (Fig. 4), FVC ($p < 0.05$) (Fig. 5), lower number of exacerbations leading to hospitalizations, and a lower use of theophylline treatment ($p < 0.05$).

The presence of comorbidities such as ischemic heart disease, arterial hypertension, myocardial infarction, gastric ulcer disease, stomach cancer, diabetes mellitus, osteoporosis, chronic renal insufficiency, depression, or bronchogenic carcinoma, except the arrhythmias, dyslipidemia, or cardiac failure, was lower in patients with the combined COPD assessment according to GOLD 2011. The survival rate and average age at death were higher in patients with the combined COPD assessment according to GOLD 2011.

COPD is a leading cause of morbidity and mortality worldwide associated with a significant economic and social burden (Murray and Lopez 2013; Mathers and Loncar 2006; Lopez et al. 2006). Limited available COPD morbidity databases indicate that morbidity due to COPD increases with age (Schirnhofer et al. 2007; Menezes et al. 2005; Fukuchi et al. 2004). Morbidity from COPD may be affected by other comorbidities, e.g., cardiovascular disease, diabetes mellitus, and so forth, which are closely related to COPD. The mortality data are still affected with under-recognition and under-diagnosis of COPD (Talamo et al. 2007). The Global Burden of Disease Study has projected that COPD, which ranked sixth as a cause of

death in 1990, will become the third leading cause of death worldwide by 2020 (Lozano et al. 2012). Another projection has estimated that COPD will be the fourth leading cause of death in 2030 (Mathers and Loncar 2006). The increased mortality can be due to expanding epidemic smoking, reduced mortality from other common causes, aging of the world population, as well as under-recognition of COPD.

There is evidence that COPD has the rising trend, with a higher prevalence COPD in smokers and ex-smokers than in non-smokers, in those over 40 yr than under 40 yr of age, and in men than women (Halbert et al. 2006; Fukuchi et al. 2004). Our present study is in line with this distribution taking into account the positive smoking anamnesis, patients' age, and gender. Cigarette smoke and other noxious environmental particles are the most common risk factor for COPD and the elimination of this risk would be an essential step forward toward for COPD prevention and control (Salvi and Barnes 2009).

A cardinal symptom of COPD is dyspnea. Chronic cough is often the first symptom of COPD (Georgopoulas and Anthonisen 1991). Initially, cough may be intermittent, later every day and often throughout the day. Chronic cough may also be unproductive (Burrows et al. 1965). Sputum production in COPD patients is usually of small quantities after coughing bouts. Patients with COPD can have also nonspecific symptoms such as wheezing and chest tightness. Additional features in severe and very severe COPD are fatigue, weight loss, and anorexia (Schols et al. 1993). All these symptoms were demonstrated in our present study in patients of all stages and all groups, and the main symptom was dyspnea.

Peripheral airway obstruction caused by inflammation, fibrosis, and luminal exudates correlates with the decline in FEV_1 and FEV_1/FVC ratio characteristic of COPD (Hogg et al. 2004). Airway obstruction traps the air during expiration, resulting in hyperinflation. Emphysema is associated with gas exchange abnormalities as the impairment of gas transfer of oxygen and carbon dioxide results in hypoxemia and hypercapnia. In the present study, we found that the average values of PaO_2 and $PaCO_2$ as well as spirometric FEV_1 and FVC were more optimal in patients with the combined COPD assessment according to GOLD 2011 compared with GOLD 2006. The data of patients classified according to GOLD spirometric grades show the increased risk of exacerbations, hospitalizations and deaths with worsening airflow limitation (Hurst et al. 2010; Decramer et al. 2009; Jenkins et al. 2009). In our present study, the number of COPD exacerbations increased directly with the disease progression in all stages and all groups of patients. The patients with the combined COPD assessment treated according to GOLD 2011 guidelines had fewer exacerbations leading to hospitalizations.

COPD patients have a variety of comorbidities related to smoking, aging, or COPD itself (Soriano et al. 2005). Comorbidities have a major impact on patients' quality of life and survival (Barnes and Celli 2009). The most frequent comorbidities include cardiovascular diseases, skeletal muscle dysfunction, diabetes mellitus, metabolic syndrome, osteoporosis, depression, lung cancer, and respiratory infections (Decramer and Janssens 2013); all of which were also noted in the present study.

COPD treatment includes nonpharmacological, pharmacological, and surgical management (Barjaktarevic et al. 2015). Preventative management consists of smoking cessation, exercise programs, and influenza and pneumococcal vaccinations. The basis for nonpharmacological management is supplementation of oxygen and pulmonary rehabilitation (Vestbo et al. 2013). COPD is considered a multicomponent disease with systemic effects and comorbidities, therefore pharmacological treatment includes not only bronchodilators but also anti-inflammatory treatment and the management of comorbidities. Surgery in severe COPD consist of lung volume reduction, either open or endoscopic, and in extreme cases also lung transplantation (Barjaktarevic et al. 2015). In the present study, we noted a significant decrease in the use of theophylline for COPD treatment, which is in line with the GOLD guidelines that advocate caution concerning this drug as being less

effective and of less tolerance compared with inhaled long-acting bronchodilators (Rossi et al. 1985).

COPD management according to the past GOLD guidelines was based only on spirometric classification. There is evidence that the level of FEV_1 alone is an inadequate descriptor of disease status. Therefore, a newer management strategy considers a broad disease impact defined by patients' symptoms and the risk of disease progression, particularly reflected by exacerbations. The combined COPD assessment that includes comorbidities, reflects the complexity of COPD better than the mono-component approach of airflow limitation previously used for staging the disease and ought to guide to individualized management (GOLD 2011).

4 Conclusions

The individualized multi-component approach to the diagnosis and treatment of COPD taking into account patients' symptoms, progression risks, exacerbations, and comorbidities as advocated by GOLD (2011) guidelines appears to streamline the diagnostic and therapeutic processes. Therefore, it is superior to older mono-component, spirometry-based guidelines from both medical and socioeconomic standpoint concerning this widespread disease that takes an ever increasing morbid toll on societies. The management of COPD patients should consist of interdisciplinary approach and collaboration.

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Conflict of Interest The authors declare no conflicts of interest in relation to this article.

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Cardiac Arrhythmias in Patients with Exacerbation of COPD

Tomasz Rusinowicz, Tadeusz M. Zielonka, and Katarzyna Zycinska

Abstract

Supraventricular and ventricular arrhythmias are common among patients with chronic obstructive pulmonary disease (COPD). Multiple factors can contribute to the development of arrhythmias in patients with exacerbation of the disease, including: respiratory or heart failure, hypertension, coronary disease and also medications. In the present study we seek to determine the prevalence of cardiac arrhythmias and risk factors among patients with exacerbation of COPD. The study was a retrospective evaluation of 2753 24-h Holter recordings of patients hospitalized in 2004–2016. Exacerbation of COPD was diagnosed in 152 patients and the prevalence of arrhythmias in this group of patients was 97%. The commonest arrhythmia was ventricular premature beats (VPB) – 88.8%, followed by supraventricular premature beats (SPB) – 56.5%. Permanent atrial fibrillation accounted for 30.3% and paroxysmal atrial fibrillation (PAF) for 12.5%. Supraventricular tachycardia (SVT) was noted in 34.2% patients and ventricular tachycardia in 25.6%. Respiratory failure increased the risk of SPB, while heart failure increased the risk of VPB. Treatment with theophylline was associated with a higher proportion of PAF and SVT. In conclusion, COPD exacerbation is associated with a high prevalence of cardiac arrhythmias. COPD treatment and comorbidities increase the risk of arrhythmias.

Keywords

Adverse effects • Arrhythmias • Comorbidities • COPD exacerbation • ECG monitoring • Risk factors

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major global public health problem. COPD is

a common preventable and treatable disease, characterized by persistent airflow limitation, usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs (Sliwinski et al. 2014). In 2020, COPD is projected to rank fifth worldwide in terms of burden of disease and third in terms of mortality. Extra-pulmonary manifestations of COPD include cardiovascular disease, skeletal muscle dysfunction, osteoporosis, metabolic syndrome, depression, and lung cancer (Vestbo et al. 2013b).

Patients with diagnosed COPD and undergoing treatment for the disease are at increased risk of hospitalizations and mortality due to heart diseases. In the retrospective cohort study, the prevalence of cardiovascular diseases was higher in the COPD group than that in the control group (Curkendall et al. 2006). In that study, after adjusting for cardiovascular risk in the COPD group, the odds ratio for arrhythmia prevalence was 1.76. There also was increased risk of hospitalization secondary to cardiovascular causes.

COPD is associated with specific electrocardiographic (ECG) abnormalities and an increased incidence of cardiac arrhythmias such as supraventricur or ventricular premature beats, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, supraventricular tachycardia, and non-sustained ventricular tachycardia (Bhatt and Dransfield 2013). A recent retrospective study has shown that COPD is associated with increased likelihood of atrial fibrillation/atrial flutter and sustained ventricular tachycardia (Konecny et al. 2014).

Patients with COPD are prone to have acute exacerbations of the disease and common causes for this are usually viral infections of the upper respiratory tract or tracheobronchial tree (Sliwinski et al. 2014). In patients with exacerbations multiple factors can contribute to the development of arrhythmias, including the respiratory or heart failure, hypertension, coronary heart disease and the medications such as β-agonists, steroids, theophylline, diuretics, and the others (Falk et al. 2008). The purpose of the present study was to determine the prevalence and peculiar types of arrhythmias and risk factors in patients with COPD exacerbations.

2 Methods

2.1 Study Population

This study was conducted in conformity with the Declaration of Helsinki for Human Experimentation of the World Medical Association. The study, due to a retrospective nature, enjoyed the waiver of ethical permission granted by a local Ethics Committee. We evaluated medical history of 2753 consecutive adult patients who underwent clinically indicated 24-h Holter monitoring at the Internal Medicine Ward of Warsaw Medical University in Poland in 2004–2016. Only were full 24-h recordings considered, which reduced the number of admissible recordings to 2604. From this cohort, 158 patients were identified as diagnosed with a COPD exacerbation. The definition and clinical criteria of the exacerbation were taken as those set by Anthonisen et al. (1987). Data such as relevant demographic variables, comorbid conditions, and medication use at the time of Holter monitoring were collected from the electronic medical records. Incomplete records were discarded. As a result, 152 patients were included in the final evaluation: 47% females and 53% males of the mean age of 75 ± 10 years. Over 50% of the patients were more than 75 years of age. The

Table 1 Baseline characteristics of the study population

All patients (n; %)	152 (100%)
Female	71 (46.7%)
Male	81 (53.3%)
Current smokers	43 (28.3)
Age (year)	75 ± 10
Age > 75 years	80 (52.6%)
Hospitalization length (days)	14 ± 6

Data are means ±SD or number (%)

mean length of a hospital stay was 2 weeks (Table 1).

2.2 Holter Monitoring

Clinical indications for Holter monitoring were arrhythmias detected in routine ECG during the treatment of COPD exacerbations. All recordings were done between the 5th and 10th day after admission. The portable 12-channel Holter monitoring system Hscribe 4 and 5 (Mortara; Milwaukee, WI) was used for the 24-h ECG recording, and the evaluation was always performed by the same physician. The arrhythmias were classified according to the Polish clinical guidelines (Baranowski et al. 2013) as follows:

- The presence of supraventricular premature beats (SPB) or ventricular premature beats (VPB) was considered when the number of extra beats exceeded 100 over the 24-h period;
- Supraventricular tachycardia (SVT) or ventricular tachycardia (VT) was considered as a sequence of more than three supraventricular or ventricular beats at a rate greater than 100 *per* minute;
- Ventricular tachycardia that lasted for less than 30 consecutive beats was termed non-sustained VT (NSVT) and for more than 30 consecutive beats was termed sustained VT (SustVT)

2.3 Data Analysis

Data were presented as means ±SD for continuous variables and frequencies for categorical variables. Student's *t*-test was used for normally distributed variables and a Chi-squared test for the comparison of differences among proportions. A p-value of less than 0.05 defined statistically significant differences.

3 Results

The most of patients showed a coexistence of COPD with heart failure, hypertension, and coronary artery disease (Table 2). More than one third had undergone myocardial infarction or stroke. Thirty percent of patients showed metabolic risk factor such as diabetes mellitus. The frequency of pneumonia and respiratory failure was relatively low. A high frequency of current smokers among patients with COPD exacerbations was quite alarming (Table 1). The treatment choices in COPD exacerbations consisted mostly of ipratropium bromide and β-agonists (Table 2). We also documented a frequent use of theophylline while only one third of patients were treated with systemic steroids. The most commonly used antiarrhythmic drugs were β-antagonists (68%). Other drugs such as digoxin, amiodarone, or verapamil were rarely used. Interestingly, 60% of patients were treated with both β-agonist and β-antagonist.

Holter monitoring revealed that patients with COPD exacerbations experienced an accelerated

Table 2 History of diseases, comorbidities, and medications used at the time of Holter examination

	n (%)
History	
Hypertension	112 (73.7)
Ischemic heart disease	93 (61.2)
Myocardial infarct	38 (25.0)
Stroke	12 (7.9)
Diabetes mellitus	45 (29.6)
Comorbidities	
Heart failure	121 (79.6)
Respiratory failure	26 (17.1)
Pneumonia	19 (12.5)
Medication	
ß-antagonists	104 (68.4)
Digoxin	19 (12.5)
Amiodarone	15 (9.9)
Verapamil	9 (5.9)
Inhaled anticholinergics	144 (94.7)
Inhaled β-agonists	135 (88.8)
Theophylline	56 (36.8)
Systemic corticosteroids	45 (29.6)

heart rate and a greater number of VPB and SPB (Table 3). The prevalence of arrhythmia of any sort was 97% in the patient population studied. The commonest arrhythmia was VPB, followed by SPB, 88% and 56%, respectively (Fig. 1). When a cut-off point was applied at the level of 100 premature beats *per* 24 h, VPB remained the most common arrhythmia. Permanent atrial fibrillation (AF) was present in 31% and paroxysmal AF in 13% of patients. Only had a small proportion of patients the episodes of atrial flutter. SVT was noted in 34% of patients and NSVT in 25%. There were no cases of SustVT.

Table 3 Basic results of Holter monitoring

Average heart rate (beats/min)	85 ± 12
Minimum heart rate (beats/min)	46 ± 11
Maximum heart rate (beats/min)	126 ± 14
Mean VPB/24 h	1870 ± 6605
Mean SPB/24 h	699 ± 2230

Data are means ±SD; *VPB* ventricular premature beats, *SPB* supraventricular premature beats

We further evaluated the prevalence of arrhythmia dependent on comorbidities and medications. The percentage of patients with paroxysmal AF revealed in the 24-h Holter recording was significantly greater among those treated with theophylline (Fig. 2a). Likewise, the theophylline group showed a greater number of VPB ($p < 0.05$) (Fig. 2b). Paroxysmal AF and SPB were recorded more often in the patients with COPD exacerbations who suffered from respiratory failure compared with those without respiratory failure ($p < 0.01$) (Fig. 3a, b).

4 Discussion

Increased mortality in patients with COPD exacerbations has been widely reported. A large Spanish study showed that severe exacerbations of COPD requiring a hospital management are independently associated with all-cause mortality. The mortality risk apparently increases with the frequency of severe acute exacerbations (Soler-Cataluña et al. 2005). Other studies have

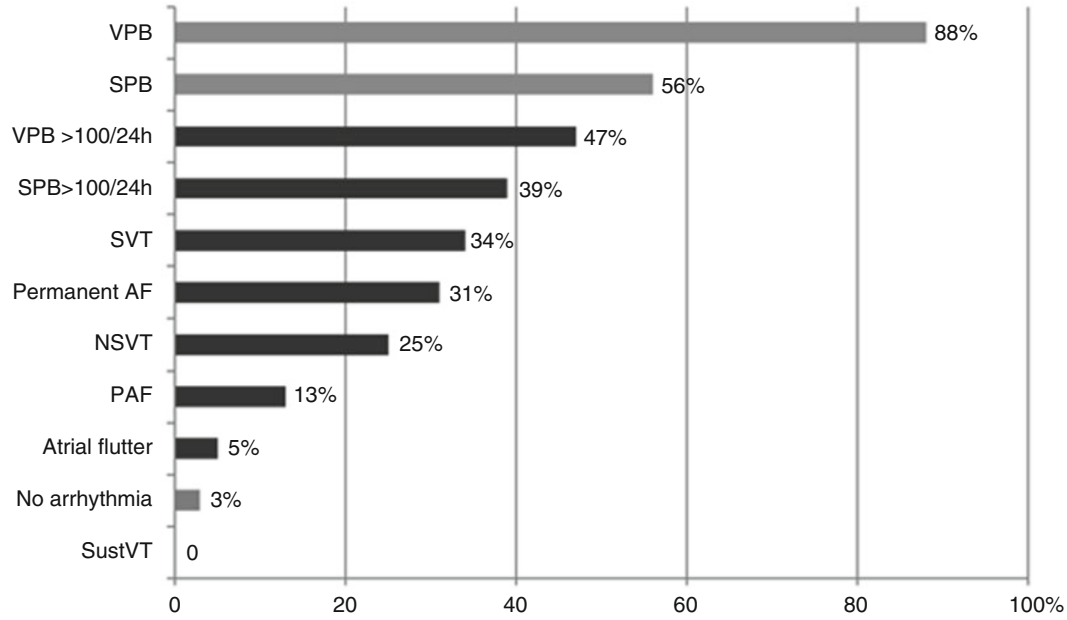

Fig. 1 Prevalence of cardiac arrhythmias in COPD exacerbations. *VPB* ventricular premature beats, *SPB* supraventricular premature beats, *SVT* supraventricular tachycardia, *AF* atrial fibrillation, *NSVT* non-sustained ventricular tachycardia, *PAF* paroxysmal atrial fibrillation, *SustVT* sustained ventricular tachycardia

reported a high mortality rate after admission to hospital with acute exacerbations of COPD. In one of the most important studies, Connors et al. (1996) recorded an in-hospital mortality rate of 11% in patients with acute hypercapnic respiratory failure. Those authors observed that patients presenting with congestive heart failure at onset of acute COPD exacerbation had increased mortality, although the exact underlying reasons remain unclear. An infectious etiology of acute exacerbation does not seem to be a determinant of increased mortality. On the other hand, Fuso et al. (1995), in a retrospective series, showed that atrial fibrillation or ventricular arrhythmias were important determinants of mortality risk.

Increased arrhythmogenicity in COPD patients has been recognized for decades (McCord and Borzak 1998), but a systematic assessment of this phenomenon in COPD exacerbations by means of a continuous ECG monitoring has not yet been often studied. The present findings show an increased number of premature ventricular and supraventricular beats in patients with COPD exacerbations. Although the exact reason for increased atrial and ventricular automaticity in COPD remains open to further investigation, the oxidative stress, low oxygenation, pulmonary hypertension, and the use of β-agonistic bronchodilators are presumed to be liable causative factors (Caglar et al. 2012).

Our present finding that paroxysmal AF is associated with COPD exacerbations corresponds with previous reports, which relied on resting ECG (Shibata et al. 2011; Sidney et al. 2005). We scrutinized the most prominent risk factors for paroxysmal AF such as age, gender, hypertension, coronary disease, heart or respiratory failure, steroid treatment, β-agonists, theophylline, and smoking cigarettes (Benjamin et al. 1994). Many participants of this study were current smokers. The effect of cigarette smoking on the progression of atherosclerotic diseases is established and well-studied. However, the role of cigarette smoking on cardiac arrhythmia is less clearly defined. The mechanisms by which cigarette smoking can

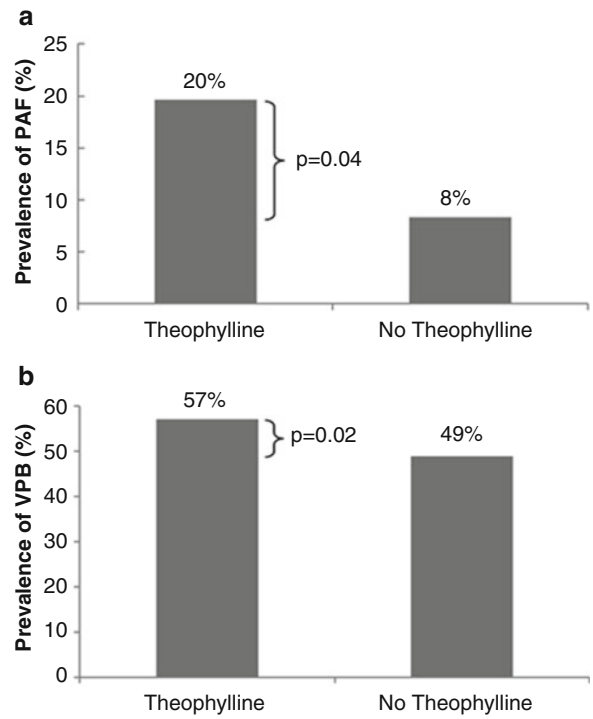

Fig. 2 Prevalence of paroxysmal atrial fibrillation (PAF) (**a**) and of ventricular premature beats (VPB) (**b**) in patients with and without theophylline treatment

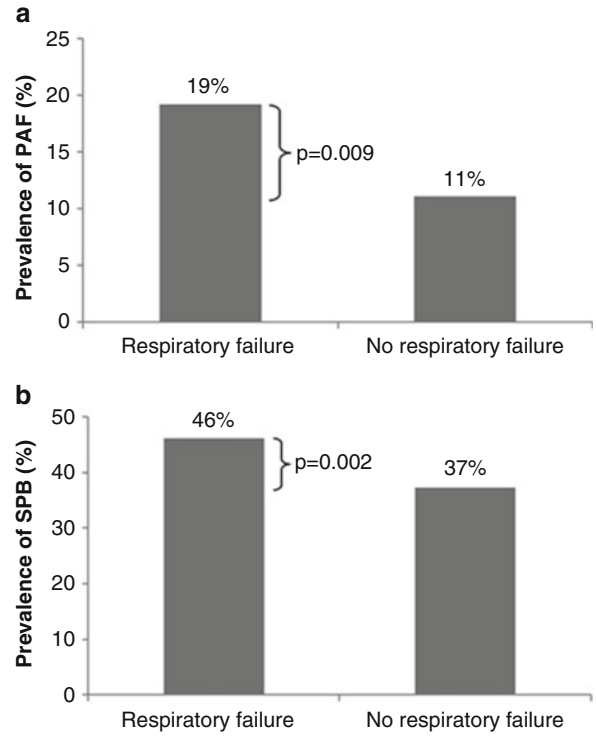

Fig. 3 Prevalence of paroxysmal atrial fibrillation (PAF) (**a**) and of supraventricular premature beats (SPB) (**b**) in patients with and without respiratory failure

contribute to acute vascular events include the following: promoting a hypercoagulable state, increasing myocardial load, carbon monoxide mediated reduction in the oxygen carrying capacity of the blood, endothelial dysfunction, coronary vasoconstriction, and catecholamine release (Benowitz et al. 2002). Some of these mechanisms can also contribute to the development of cardiac arrhythmia but the effect of cigarette-smoking on cardiac arrhythmia is probably a complex one: nicotine along with CO and oxidative stress induce myocardial fibrosis generating remodeling that may promote arrhythmia. Further, tobacco-related coronary arterial disease and COPD with the resulting hypoxia can be additional mechanisms inducing cardiac arrhythmia in smokers. Finally, there is an observation from some animal and cell culture studies that nicotine might, by itself, be arrhythmogenic (D'Alessandro et al. 2012).

Among the risk factors investigated in the present study, the association between paroxysmal AF and COPD exacerbation remained highly significant in the patients treated with theophylline and in those with respiratory failure, which suggests that some other arrhythmogenic factors were at play. According to the GOLD Guidelines for the Diagnosis and Treatment of Patients with COPD, theophylline can be used for treating COPD exacerbations (GOLD 2016). However, use of this agent is considered controversial and theophylline is generally considered to be a third-line treatment option after inhaled β2-agonists and anticholinergic agents because of the frequency, severity and types of adverse events, and its limited clinical efficacy. Concerns regarding theophylline treatment center around its small therapeutic window, wide range of dose-related toxic effects, and the need for close monitoring of plasma concentrations during treatment. The need to monitor the concentration of theophylline during the administration which is not routine, is important especially because the drug is metabolized in the liver by cytochrome P450 isoenzymes. Many drugs interact with theophylline by inhibiting or potentiating its

metabolism, e.g., macrolides and ciprofloxacin, amiodarone, omeprazole, cimetidine, sedatives, and others. The metabolism of theophylline can be also affected by smoking (Khan et al. 2014). Among adverse events associated with theophylline treatment, there is increased risk of developing cardiac arrhythmias, such as sinus tachycardia, supraventricular tachycardia, atrial fibrillation or flutter, ventricular extra-systoles, and tachycardia, particularly at therapy onset or renewed courses of therapy (Barns 2013). In many studies, theophylline has been associated with higher rates of atrial fibrillation and ventricular premature beats (Bittar and Friedman 1991). Of the arrhythmias, atrial fibrillation affects the greatest number of patients, but ventricular arrhythmias may be the most serious of all (Huerta et al. 2005). Among European countries, Poland ranks third, after Croatia and Turkey, with 48.4% use of theophylline in the course of COPD exacerbations, while the European mean use is 14.3% (Roberts et al. 2012). Such frequent use of theophylline is burdened with adverse reactions from the cardiovascular system and should be limited to a necessary minimum.

Hypoxia, which is characteristic for patients with COPD exacerbations, has also been recognized as an initiating and perpetuating factor in cardiomyopathic processes (Konecny et al. 2014). In the acute condition, the dose of administered oxygen may be critical because tissue hypoxia occurs within 4 min of inadequate ventilation due to small tissue reserves of oxygen. In such cases, inspiration of oxygen concentrations of 60–100% for a short time may preserve life until more specific treatment can be introduced (Bateman and Leach 1998). Conversely, high doses of oxygen in patients with COPD who have respiratory failure can reduce the hypoxic drive to breathe and increase ventilation-perfusion mismatching. This can promote carbon dioxide retention and a respiratory acidosis. Hypercapnia can induce increased cardiac output, elevate arterial blood pressure, and increase the tendency to arrhythmias (Terzano et al. 2014). In patients with COPD exacerbations, arterial blood gases or at least transcutaneous capnometry and SaO_2 should be performed to assess the risk of hypercapnic respiratory failure and oxygen supplemented properly. However, it is recognized that doctors prescribe oxygen poorly in many audited countries (Roberts et al. 2012). In New Zealand, oxygen prescribing practice among hospitalized patients has been shown to be poor despite subsequent interventions, including the introduction of local guidelines (Boyle and Wong 2006). In a Canadian study, prescribing practice for therapeutic oxygen was worse than for antibiotics and attributed to the lack of appreciation of oxygen as a medical drug (Small et al. 1992). In the UK, use of oxygen therapy was unsatisfactory prior to the implementation of national guidelines in 2008. Each year since then, the British Thoracic Society has conducted a national audit that has demonstrated a slow but steady improvement in oxygen use (Rudge et al. 2014).

Additional attention must be paid to ischemic heart disease and heart failure among patients with COPD exacerbations. In present study, up to 68% of participants were treated with β-adrenergic antagonists (β-blockers), which differs from the reported general practice. For many years, it has been a common practice to consider COPD as contraindication to the use of β-blockers, based mainly on case reports citing acute bronchospasm following their administration and the most common comorbid conditions necessitating the withholding of β-blockers in elderly patients after myocardial infarction such as COPD and asthma. In the meantime, multiple studies have shown that use of β-blockers, particularly cardioselective β-blockers, is safe in COPD patients and decreases mortality in patients with coronary vascular disease (Albouaini et al. 2007). Currently, β-blockers are underused in patients COPD despite the guidelines, due to perceived risk of bronchoconstriction (Lipworth et al. 2016). Further, β-blockers have more indications for use in COPD than in case of cardiovascular diseases. The use of these drugs in COPD patients has been shown to decrease the number of clinic visits (Barnett et al. 2005). Studies also suggest that β-blockers can be safely used in patients with

COPD and coexistent ischemic heart disease, heart failure, or hypertension during hospitalization for COPD exacerbation (Farland et al. 2013). In addition, long-term treatment with β-blockers increased survival and decreased exacerbations by 21% in patients with COPD without cardiovascular disease. The benefits of β-blockers' use are even higher for patients with COPD and heart failure who enjoy a 55% reduction in exacerbations of the disease (Lahousse et al. 2016).

The ventricular arrhythmogenic substrate in the exacerbation of COPD is increased due in part to a high prevalence of coronary artery disease in this population (Maclay and MacNee 2013). Further, COPD patients suffer from myocardial infarcts even after revascularization, and this risk increases with COPD severity (Konecny et al. 2014). We accounted for coronary artery disease, and a history of myocardial infarct or heart failure in the present study, but the association between them and VPB or NSVT in COPD exacerbation was insignificant.

Beside the ischemic heart disease, multiple other possible mechanisms deserve further exploration. In the present study, 89% patients were treated with inhaled β-agonistic medications. These drugs have been shown to modify ventricular refractoriness and although it seems that β-agonists are safe in COPD patients, the results of an ongoing large randomized trial are expected to answer the question of whether these agents are safe in COPD patients who are predisposed to coronary artery disease (Vestbo et al. 2013a). None of the large studies that reported a high rate of cardiovascular morbidity and mortality in COPD patients evaluated to what extent such events can be explained by ventricular arrhythmias. However, since cardiac arrhythmias, in general, were noted in all patients with COPD exacerbations in the present study, attention ought to be directed to the possibility of arrhythmias playing a significant role in the course of the disease.

A retrospective database design of this study is subject to several inherent limitations. The COPD patients varied from non-COPD ones in demographic and comorbid characteristics and no statistical adjustment can fully alleviate the influence of all confounding factors. Further, patients with COPD exacerbations differed from the whole population of COPD patients. That is the likely reason why the demographic and comorbid characteristics of our cohort differed from the previously published large unselected registries of COPD patients, particularly concerning the prevalence of hypertension: 73.7% *vs.* 18–52% and heart failure 79.6% *vs.* 13–50% (Chatila et al. 2008). Because of the retrospective nature of the study, all continuous ECG testing was performed in the context of clinical care, and therefore a potential selection bias could have been introduced. These limitations request more focused future investigations to explore the possible mechanisms linking the COPD exacerbation with arrhythmias.

The novel findings of this study were as follows: (1) exacerbation of COPD was related to the high prevalence of arrhythmias present in a 24-h Holter monitoring; (2) treatment with theophylline was associated with an increase in paroxysmal AF and VPB; and (3) COPD exacerbation accompanied by respiratory failure was a risk factor for PAF and SPB. These findings suggest that an exacerbated COPD is an important risk factor for atrial and ventricular arrhythmias and that the pathophysiological links between COPD and arrhythmias need to be further studied to choose potentially modifiable therapeutic targets.

Conflicts Interest The authors declare no conflict of interest in relation to this article.

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Enzymatic Activity of *Candida* spp. from Oral Cavity and Urine in Children with Nephrotic Syndrome

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Abstract

Oral colonization with *Candida* spp. is not synonymous with a systemic active infection. The aim of the study was to evaluate enzymatic activity of *Candida* strains isolated from the oral cavity in patients with nephrotic syndrome (NS) and to compare it with the activity determined in urine. We studied 32 children with NS and 26 control healthy children. Children with NS were treated with glucocorticosteroids, cyclosporin A, mycophenolate mofetil or azathioprine. In all children, API-ZYM enzymatic tests were performed to evaluate hydrolytic enzymes of *Candida* isolated from the oral cavity and in urine. *Candida* spp. were isolated from the oral cavity in 11 patients with NS (34.4%), all receiving immunosuppressive treatment. All strains produced valine arylamidase, 9 alpha-glucosidase (E16), and 9 N-acetyl-beta-glucosaminidase (E18). A positive correlation between the presence of *Candida* in the oral cavity and E16 and E18 enzymatic activity in both oral cavity and urine was found. A dose of cyclosporin A had an effect on the enzymatic activity ($p < 0.05$).

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We conclude that immunosuppressive treatment of NS in children may predispose to systemic *Candida* invasion. The results of this study suggest that oral candida infection should be monitored in children with nephrotic syndrome, particularly those treated with immunosuppressive agents.

Keywords
Candida spp. • Cyclosporin A • Hydrolytic enzyme activity • Immunosuppressive treatment • Infection • Nephrotic syndrome • Oral candidiasis

1 Introduction

Candida spp. is the most common cause of fungal infections (Richards et al. 2000), leading to a range of life-threatening invasive to non-life-threatening mucocutaneous diseases. *Candida albicans* is the most common infectious agent. This dimorphic yeast is a commensal that colonizes the skin and the gastrointestinal and reproductive tracts.

Candida spp. can be isolated from the oral cavity in about 20–75% of subjects in the general population (Olczak-Kowalczyk et al. 2013; Tarcin 2011; Akpan and Morgan 2002; Cannon et al. 1995; Scully et al. 1994). However, oral colonization with *Candida* spp. is not synonymous with an active infection. In healthy subjects with effective host defense mechanisms, the presence of *Candida* spp. usually does not lead to the development of pathological lesions. Endogenous sites of *Candida* colonization, primarily in the gastrointestinal system, are the major source of generalized infections in immunosuppressed patients (Leroy et al. 2011; Samonis 2004; Richardson and Kokki 1998). It is difficult to distinguish between *Candida* colonization and invasion. *Candida* spp. exist as blastopore phase yeasts (Y), in the pseudohyphal phase (chains of elongated cells), and in the hyphal or mycelial phase (M). The mycelial phase is more pathogenic than the blastopore phase yeast, which is probably related to its ability to break down and penetrate host tissues. An important indicator of invasiveness is the activity of hydrolytic enzymes secreted by *Candida*, such as esterases, glycosidases, and peptidases (Mohan and Ballal 2008; Schaller et al. 2005). The aspartic proteases are particularly important since they catalyze peptide substrates at the site of CO-NH bonds; facilitating *Candida* adhesion, colonization, and tissue penetration, and the phospholipases that hydrolyze membrane phospholipids, contributing to cellular destruction (Naglik et al. 2004). It has also been shown that N-acetyl-β-glucosaminidase and α-glucosidase inhibit neutrophil migration to infection sites. The effect of N-acetyl-β-glucosaminidase on the formation of germ tubes by *Candida* is an established fact. Mattia et al. (1982) and Huang et al. (2010) have proposed that N-acetylglucosamine is a potential inducer of filamentation.

Multiple systemic and local factors predispose to the presence of *Candida* and the development of signs of infection in the oral cavity. Major systemic factors include hormonal disturbances, impaired host defense mechanisms, particularly cellular defenses, negative protein and energy balance, and vitamin D deficiency. Local factors in the oral cavity include the loss of epithelial continuity due to mechanic, infectious, toxic, autoimmune, or cancer-related factors, reduced amount of saliva and decreased salivary pH, the presence of carbohydrates, and abnormal oral flora, e.g., due to the action of antibacterial agents (Olczak-Kowalczyk et al. 2013; Tarcin 2011; Akpan and Morgan 2002; Scully et al. 1994).

Candida spp. is frequently present in the oral cavity in children and adolescents receiving

immunosuppressive therapy. It has been isolated in 45.4% of children with nephrotic syndrome (NS) but oral candidiasis has been diagnosed in only 13.3% (Olczak-Kowalczyk et al. 2013). NS is a clinical condition that may predispose to oral cavity colonization with *Candida* spp. and frank *Candida* infection. Due to proteinuria above 50 mg/kg *per* day that exceeds maximal capacity of the body's compensatory mechanisms, dysproteinemia and hyperlipidemia ensues. An additional factor contributing to impaired host defense mechanisms, primarily regarding cellular immunity, is the use of immunosuppressive agents including glucocorticosteroids, cyclosporin A, cyclophosphamide, azathioprin, and mycophenolate mofetil (Kuźma-Mroczkowska et al. 2016; Eddy and Symons 2003; Zachwieja et al. 2002).

The aim of the present study was to evaluate the enzymatic activity of *Candida* strains isolated from the oral cavity in patients with nephrotic syndrome (NS) and to compare it with the activity determined in the urine.

2 Methods

The study was approved by the Ethics Committee of Medical University of Warsaw in Poland. The study was prospective, cross-sectional, and included clinical and mycological evaluation of the oral cavity and urine.

The study group consisted of 32 children with NS (mean age 10.1 ± 4.8 years, range 3–18 years) with the mean disease duration of 5.1 ± 5.0 years. The control group consisted of 26 healthy children aged 11.2 ± 4.0 (range 3–17 years). Written informed consent from the child and his parents or guardians was obtained from all participants. In the NS group, the recruited children had to be off any medications other than those used for the NS treatment, free of any diseases other than NS, and without antibiotic therapy for 3 weeks preceding study onset. In the control group, children also had to be free of any chronic diseases and drug or antibiotic therapy. Smokers, patients using orthodontic appliances and dental prostheses, with the presence of *Candida* in urine, and treated with antifungal agents were excluded from the study.

2.1 Clinical and Microbiological Evaluation

The information was obtained from available medical records regarding NS treatment, including drugs, doses, and duration. Laboratory tests consisted of serum albumin level (reference range 3.7–5.6 g/dL) and 24-h urinary protein excretion expressed in mg/kg/day, measured with standard laboratory methods. Signs of oral candidiasis were evaluated during dental examination (Kramer et al. 1980; Loe 1967).

Clinical material collected from both patient groups consisted of oral swabs and urine samples cultured onto the Sabouraud agar. Following incubation for 24–72 h at 30 °C, the isolated *Candida*-like fungi were identified using commercial API ID32C kits (bioMérieux; Marcy l'Etoile, France). Test results were read out using the automated ATB Expression System (bioMérieux) (Samaranayake et al. 1986). Enzymatic tests were used to evaluate hydrolytic enzymes of *Candida* spp. isolated from the oral cavity and urine samples. We used the API-ZYM microtest (bioMérieux) with 20 microvials containing 19 substrates to detect 19 hydrolytic enzyme. The enzymes selected for the indication of *Candida* invasiveness were the following: valine arylamidase (E7), alpha-glucosidase (E16), and N-acetyl-beta-glucosaminidase (E18). The intensity of a color reaction was assessed after 5 min using the tables provided along with the kit, with scores ranging from 0 to 5, where 0 is a negative reaction, 1 corresponds to 5 nmol/L, 2 to 10 nmol/L, 3 to 20 nmol/L, 4 to 30 nmol, and 5 to maximum reaction intensity, pointing to high activity, i.e., 40 nmol/L (Reiss and Morrison 1993).

2.2 Statistical Elaboration

Data were presented as means ±SD or proportions. The relationship between variables

was evaluated with the Kendall Tau correlation coefficient and Chi^2 test. A p-values <0.05 defined statistically significant differences. The analysis was performed using a commercial Statistica v10.0 package (StatSoft; Tulsa, OK).

3 Results

Twenty nine out of the 32 children with NS (90.6%) received immunosuppressive treatment in the form of glucocorticosteroids at the mean dose of 33.3 ± 19.9 mg/kg/day, with the mean duration of treatment of 4.0 ± 4.5 years. Glucocorticosteroids monotherapy was used in 13 of those patients, two-drug immunosuppression in another 13 patients (9 patients were treated with glucocorticosteroids and cyclosporin A, and 4 patients with glucocorticosteroids and azathioprin); and triple-drug immunosuppression (glucocorticosteroids, cyclosporin A, and mycophenolate mofetil) in 3 patients. Overall, the mean duration of treatment with cyclosporin A in 12 patients was 3.9 ± 3.0 years; mycophenolate mofetil was used in 3 patients for 14.7 ± 6.7 months, and azathioprin in 4 patients for 8.1 ± 6.0 months. The mean doses of the immunosuppressive drugs during the study time were 134.5 ± 48.0 mg/day, 985.7 ± 427.3 mg/m^2, and 2.1 ± 0.3 mg/kg/day, respectively. Three patients did not receive immunosuppressive treatment. Among the 32 children with NS, proteinuria (73.2 ± 104.2 mg/kg/day) was present in 18 (56.3%) patients and hypoalbuminemia in 5 (46.9%) patients (serum albumin of 3.5 ± 0.8 g/dL).

Candida spp. was isolated from the oral cavity in 11 (34.4%) patients with NS, all receiving immunosuppressive treatment (Table 1). All strains produced valine arylamidase (E7), nine produced alpha-glucosidase (E16), and nine produced N-acetyl-beta-glucosaminidase (E18). A multi-enzyme activity, greater than 40 nmol/L, in the oral cavity was found in 8 patients (72.7%) from whom *Candida* was isolated, including E7 in one patient, E16 in five patients, and E18 in six patients. They were all characterized by a high E16 activity (>40 mmol/L), and two of them had E18 activity in the urine. *Candida* was not present in the oral cavity of another 11 out of the 32 patients with NS who also had E7, E16, and E18 activity in the urine. In the remaining 10 patients with NS, neither *Candida* in the oral cavity nor the hydrolytic enzyme activity in the urine was detected.

Oral candidasis was diagnosed in three (9.4%) patients with NS (Table 1), all having proteinuria; one child was treated with glucocorticosteroids only, one was on two-drug immunosuppression, and one was on triple-drug immunosuppression. In addition, erythematous candidiasis, pseudomembranous candidasis with associated median rhomboid glossitis, and angular cheilitis also were observed.

Candida spp. was not cultured from the urine of any patients with NS. However, a variable hydrolytic enzyme activity was found in the urine of 21 (65.6%) of those patients. A multi-enzyme activity, greater than 40 nmol/L, was noted in 17 (81.0%) of the 21 patients, including E7 in five patients, E16 in 15 patients, and E18 in five patients (Table 1). There were no significant differences in urine enzyme activity between patients with and without *Candida* isolates from the oral cavity. A high *Candida* urine enzyme activity (>40 mmol/L) was seen more frequently in the patients with NS on immunosuppressive therapy compared to control subjects; in 17 out of the 29 *vs*. 2 out of the 26 subjects, respectively ($p = 0.01$).

In the control group, *Candida* spp. was isolated from the oral cavity in 11 (42.3%) subjects, with the following multi-enzyme activity: E7 in ten subjects, E16 in nine subjects, and E18 activity also in nine subjects. *Candida* was not cultured from the urine of any control subjects.

We found an association between the presence of *Candida* in the oral cavity and E16 and E18 enzymatic activities in both oral cavity and urine, while no such relationship was found for E7. The dose and treatment duration with glucocorticosteroids did not have an appreciable influence on the enzymatic activity. However, cyclosporin A dose and duration of treatment

Table 1 *Candida* multi-enzyme activity in patients with nephrotic syndrome and healthy subjects stratified by the polytherapy and the presence of *Candida*

Nephrotic syndrome – 32 patients; n (%)						Control – 26 subjects; n (%)			
Therapy		*Candida* spp. Oral cavity isolates	Oral candidiasis	Candida multi-enzyme activity		*Candida* spp. Oral cavity isolates	Oral candidiasis	Candida multi-enzyme activity	
				Oral cavity (n)	Urine (n)			Oral cavity (n)	Urine (n)
One-drug	13 (44.8%)	4	1	E7 (n = 1)	E7 (n = 5)			E7 (n = 10)	E7 (n = 0)
Two-drug	13 (44.8%)	5	1	E16 (n = 5)	E16 (n = 15)			E16 (n = 9)	E16 (n = 2)
Triple-drug	3 (10.3%)	2	1	E18 (n = 6)	E18 (n = 5)			E18 (n = 9)	E18 (n = 0)
Total cases	29 (90.6%)	11 (34.4%)	3 (9.4%)	11 (34.4%)	21 (65.6%)	11 (42.3%)	0	10 (38.5%)	2 (7.7%)

E7 valine arylamidase, *E16* alpha-glucosidase, *E18* N-acetyl-beta-glucosaminidase

Table 2 Relationship between urinary and oral *Candida* enzyme activities and immunosuppressive treatment assessed by the Kendall Tau correlation coefficient (*r*)

	Urinary *Candida* enzymatic activity			
	≥1 enzyme	E7	E16	E18
Oral *Candida* enzyme activity				
≥1 enzyme	0.385*	0.200	0.430*	0.313*
E7	0.388*	0.249*	0.455*	0.316*
E16	0.325*	0.176	0.468*	0.466*
E18	0.318*	0.114	0.463*	0.308*
Immunosuppressive treatment				
>1 drug	0.021	0.079	0.139	0.060
1 drug	−0.111	−0.118	−0.196	−0.151
2 drugs	−0.169	−0.041	−0.108	−0.014
3 drugs	0.274*	0.178	0.365*	0.111
Cyclosporin A				
Treatment duration	0.247*	0.220	0.295*	0.289*
Dose	0.276*	0.239	0.327*	0.315*

*$p < 0.05$; *E7* valine arylamidase, *E16* alpha-glucosidase, *E18* N-acetyl-beta-glucosaminidase. For cyclosporin A, the mean treatment duration was 3.9 ± 3.0 years and the mean dose was 134.5 ± 48.0 mg/day

did affect the enzymatic activity of E16 and E18 glucosidases (Table 2).

4 Discussion

A frequent presence of *Candida* in the oral cavity in subjects with impaired immune defense mechanisms have been often reported in the literature, e.g., in organ donors treated with immunosuppressive drugs, cancer patients treated with cytotoxic drugs, and patients with AIDS (Olczak-Kowalczyk et al. 2010, 2012, 2013; Florescu et al. 2012; Dongari-Bagtzogol et al. 2009; Alberth et al. 2006; Gülec et al. 2003; Al Mohaya et al. 2002; Macura and Bort 2002). It is also known that the gastrointestinal system, including the oral cavity, is a potential source of fungemia. No studies, however, have reported on the relationship between the presence of *Candida* spp. in the oral cavity and urinary hydrolytic enzyme activity that may be a marker of systemic effects of *Candida*. Thus, we attempted to identify local and systemic factors predisposing to fungal acquisition of pathogenic properties.

Our results indicate that the systemic effects of proteinuria do not predispose to oral colonization with *Candida* in children with NS. Nonetheless, oral candidiasis was seen only in that group of patients. We also failed to find differences in the enzymatic activity between strains isolated from the oral cavity in NS patients and the healthy control subjects. Similar results were reported by Macura and Bort (2002) in HIV-positive subjects and healthy controls. Plomer-Niezgoda et al. (2004) showed different enzymatic biotypes of *Candida*, according to the Williamson classification, in patients receiving immunosuppressive therapy (biotypes C and B) and healthy subjects (biotypes A and B), but both groups showed E7, E16, and E18 activity. The biotypes of *Candida albicans* isolated by Pytko-Polończyk et al. (2008) from the oral cavity of patients with nasopharyngeal cancer who underwent radiation therapy were often characterized by a high activity of the enzymes outlined above. According to Moqbil and Kurnatowski (2012), strains isolated from the oral cavity in patients with malignant tumors of the head and neck before, during and after radiotherapy are characterized by the highest activity of leucine arylamidase, acid phosphatase, and naphthol-AS-BI-phosphohydrolase. In the present study, *Candida* isolated from the oral cavity in NS was more frequently characterized by a high activity of N-acetyl-beta-glucosaminidase (E18) and alpha-glucosidase (E16). High enzyme activity in urine was seen only in the NS group.

More importantly, we showed a significant correlation between the presence and enzymatic activity of *Candida* spp. in the oral cavity and urinary enzymatic activity. Although *Candida* was not isolated from the oral cavity in some patients with NS and urinary enzymatic activity, this may simply indicate other localizations of *Candida*, e.g., more distal sites in the gastrointestinal tract.

The factors increasing the risk of systemic effects of *Candida* seem to include abnormalities resulting from the proteinuria of NS, i.e., hypoalbuminemia, hyperlipidemia, and immunosuppressive treatment, particularly with cyclosporin A, as indicated by positive correlations with urinary enzyme activity. It is also possible that *Candida* present in the oral cavity might increase proteinuria. *Candida* present in the human gastrointestinal tract may have a number of systemic effects, not always related to the signs of infection. *Candida* is known to exert the immunosuppressive and allergizing effects (Goldman and Huffnagle 2009). Further studies are warranted to examine the effects of oral colonization with *Candida* on the renal health in children with NS. Enzymatic testing of urine samples seems helpful in distinguishing mucosal colonization from submucosal and systemic infection. Detection of enzymatic activity characteristic for fungi may indicate an infection but further investigations are necessary.

We conclude that the relationship between enzymatic activity of *Candida* spp. isolated from the oral cavity and from the urine samples in children with NS may indicate systemic *Candida* invasion that may be predisposed to by immunosuppressive treatment, particularly with cyclosporin A.

Competing Interest The authors declare no competing interests in relation to his article.

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Thyroid Autoimmunity in Girls with Turner Syndrome

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Abstract

Turner syndrome is associated with increased incidence of autoimmune diseases, especially those of the thyroid gland. The aim of this study was to assess the prevalence of thyroid autoimmunity among pediatric patients with Turner syndrome. The study was retrospective and included 41 girls with Turner syndrome aged 6–18 years. Free thyroxine (FT4), thyroid stimulating hormone (TSH), anti-thyroid peroxidase (TPO-Ab) antibodies, anti-thyroglobulin (TG-Ab) antibodies, and karyotype were investigated. The correlation between karyotype and incidence of thyroid autoimmunity was also examined. Eleven patients (26.8%) were positive for TPO-Ab and/or TG-Ab. Three girls from that subgroup were euthyroid, 5 had subclinical hypothyroidism, and 3 were diagnosed with overt hypothyroidism. Out of these 11 patients affected by thyroid autoimmunity, 6 girls had mosaic karyotype with X-isochromosome (n = 4) or with deletions (n = 2), and 5 had the 45,X karyotype. The study findings confirmed a high incidence of thyroid autoimmunity in girls with Turner syndrome, but we failed to observe an association between the incidence of thyroid autoimmunity and karyotype. We conclude that it is important to monitor thyroid function in patients with Turner syndrome because they are prone to develop hypothyroidism.

Keywords

Autoimmunity • Hypothyroidism • Karyotype • Thyroid disease • Turner syndrome

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1 Introduction

Turner syndrome is a congenital disorder caused by numerical and/or structural abnormalities of the X chromosome with a prevalence of 1:2500 to 1:3000 live-born girls (Grossi et al. 2013; McCarthy et al. 2008; Menasha et al. 2005). The main clinical features are short stature, gonadal dysgenesis and cardiovascular, renal and otological malformations (Zenaty et al. 2011; Persani et al. 2009; Gravholt 2004). Turner syndrome is associated with an increased incidence of autoimmune disorders, especially those of the thyroid gland and metabolic disorders (Lleo et al. 2012; Invernizzi et al. 2009; Larizza et al. 2009; Mortensen et al. 2009). The most common disorders are Hashimoto's thyroiditis (Gawlik et al. 2011; El-Mansoury et al. 2005; Elsheikh et al. 2001), inflammatory bowel disease, such as ulcerative colitis or Crohn's disease (Hyodo et al. 2009; Scarpa et al. 1996), diabetes mellitus type 1 (Jorgensen et al. 2010), coeliac disease (Bonamico et al. 2002), juvenile rheumatoid arthritis (Zulian et al. 1998), psoriasis, vitiligo, and alopecia areata (Lowenstein et al. 2004; Rosina et al. 2003). Thyroid autoimmunity in Turner syndrome patients may manifest itself as euthyroid autoimmune thyroiditis, subclinical hypothyroidism, or overt hypothyroidism. Early diagnosis of Turner syndrome is crucial as it allows for screening for associated health problems and an early start of growth hormone treatment, which improves final body height. The aim of the present study was to assess the prevalence of thyroid autoimmunity disorders and their potential association with karyotype among pediatric patients with Turner syndrome.

2 Methods

The study was approved by the Bioethics Committee of the Medical University of Warsaw, Poland. This retrospective study was based on the data obtained by reviewing the medical records of 41 girls with Turner syndrome (aged 6–18, mean age 14.2 ± 3.8, median 13.8 years). Turner syndrome was diagnosed in each patient by karyotyping. The serum concentration of free thyroxine (FT4), thyroid stimulating hormone (TSH), anti-thyroid peroxidase (TPO-Ab) antibodies and anti-thyroid thyroglobulin (TG-Ab) antibodies were measured in each patient by chemiluminescence with ARCHITECT i2000SR Immunoassay Analyzer (Abbott; Abbott Park, IL). Thyroid autoimmunity was defined as the presence of TPO-Ab and/or TG-Ab. The study group was divided into two subgroups depending on the presence of thyroid autoimmunity. In the subgroup positive for anti-thyroid antibodies, three clinical variants were distinguished according to concentrations of TSH and FT4: euthyroid with normal concentrations of TSH and FT4, subclinical hypothyroidism, and overt hypothyroidism. Subclinical hypothyroidism was diagnosed in subjects with TSH concentrations of 5–10 mcUI/ml and normal FT4. Diagnosis of overt hypothyroidism was defined as TSH concentration higher than 5 mcUI/ml and FT4 concentration below the normal range. The association between karyotype and incidence of thyroid autoimmunity was also examined.

Data were presented as means ±SD and medians, and minimal and maximal values. Differences between groups were evaluated with a *t*-test. A p-value <0.05 defined statistical significance of inter-group differences. Statistical evaluation was performed with a commercial Statistica 7.1 package (StatSoft Inc., Tulsa, OK).

3 Results

In the whole study group, a non-mosaic karyotype 45,X was found in 14 patients (34.2%), whereas a mosaic karyotype was found in 27 (65.9%) patients. In 11 (26.8%) out of the 41 patients, thyroid autoimmunity was detected. Three patients from this subgroup with thyroid autoimmunity were positive for TPO-Ab antibodies and/or TG-Ab antibodies, with the normal TSH and FT4 levels, five had subclinical hypothyroidism, and three were diagnosed with

Table 1 Characteristics of Turner syndrome patients with thyroid autoimmunity

Patient	Age (years)	Age at onset (years)	Karyotype	Diagnosis
1	16.8	11.0	45,X	H
2	17.5	16.3	mos 46,X,i(X)(q10),9 ph[30]	AT
3	12.3	11.0	mos 45X(70%)/46,Xi(Xq)	AT
4	13.0	2.0	mos 45,X[11]/46,X,i(X)(q10)[11]	H
5	13.0	10.3	45,X	AT
6	17.1	11.0	45,X	H
7	5.8	1.3	mos 46,X,i(X)(q10)	SH
8	18.0	14.8	45,X	AT
9	13.8	8.3	mos 46,X,del (X)(p11.2)	SH
10	18.0	9.0	mos 46,X,del(p11)[50]	SH
11	10.8	10.0	45,X	SH

AT euthyroid thyroid autoimmunity, *H* overt hypothyroidism, *SH* subclinical hypothyroidism

overt hypothyroidism. The mean age at onset of thyroid autoimmunity was 10.4 ± 3.6, median age was 10.3, and age range was 2–16 years. One girl was diagnosed when she was 2 years old, the remaining were more than 8 years old. The oldest age of thyroid autoimmunity diagnosis was 16.3 years. In the subgroup affected by thyroid dysfunction, six patients had mosaic karyotype with X-isochromosome (n = 4) or with deletions (n = 2), and five had the 45,X karyotype. The characteristics of the thyroid autoimmunity subgroup are shown in Table 1. Among Turner syndrome patients without thyroid autoimmunity (n = 30, mean age 13.9 ± 4.3 years), the 45,X karyotype was present only in nine cases (30.0%), whereas 21 (70.0%) patients had mosaic karyotype including: 45,X/46,XX (n = 10, 47.6%), mosaic with ring chromosome X (n = 4, 19.1%), with isochromosome (n = 2, 9.5%), with deletions (n = 2, 9.5%), 45,X/47, XXX (n = 2, 9.5%), and with Y chromosome (n = 1, 4.8%). Considering the small number of patients in the whole study group and in the subgroup with thyroid dysfunction, our results have no statistical significance. Anti-thyroid antibodies were detected in five (35.7%) out of 14 non-mosaic patients. In the group of 27 patients with mosaicism, six (22.2%) were positive for anti-thyroid antibodies. The incidence of thyroid autoimmunity was greater in the patients who had mosaic than non-mosaic karyotype (n = 6, 14.6% *vs.* n = 5, 12.2%).

4 Discussion

Girls with Turner syndrome are at higher risk of developing autoimmune diseases, particularly of the thyroid gland (Kucharska 2014; Invernizzi et al. 2009). Increased incidence of thyroid autoimmunity and hypothyroidism in that group of patients, dependent on age, has been reported in many studies (Grossi et al. 2013; Lleo et al. 2012; Mortensen et al. 2009; McCarthy and Bondy 2008; Medeiros et al. 2000; Chiovato et al. 1996). The study by Radetti et al. (1995), which included nearly 500 girls with Turner syndrome aged 3.6–25.3 years, has found that 22.2% of them are positive for anti-thyroid antibodies and 10% of those also have ultrasound findings typical of thyroiditis. The prevalence of TPO-Ab and/or TG-Ab has been significantly greater in Turner syndrome than that in age-matched female controls. The results by Chiovato et al. (1996) suggest that the prevalence of autoimmunity in Turner syndrome increases significantly after the age of 13 years, with a peak in the third decade of life. The frequency of anti-thyroid antibodies increases from 15% in girls aged below 10 years to 30% in the third decade of life. A clinically relevant autoimmune disease has been diagnosed in 46% of Turner syndrome patients with anti-thyroid antibodies. Patients with Turner syndrome are at higher than average risk of developing an autoimmune disease, not only in adolescence and adult age but also in

childhood. Mortensen et al. (2009) have evaluated the prevalence of autoantibodies related to the organ-specific disease and the association of autoimmunity with karyotype in more than 100 girls with Turner syndrome aged 6–60 years. The authors examined the presence of autoantibodies against gliadin, transglutaminase, adrenal cortex, intrinsic factor, anti-thyroid peroxidase, and glutamic-acid-decarboxylase 65. Their findings show that autoantibodies are present in 58% of all patients, 18% of whom had autoantibodies targeting more than one organ. In that study, TPO-Ab was present in 45% of patients, 33% of whom were clinically hypothyroid and 4% had Graves' disease. TPO-Ab and coeliac disease autoantibodies co-existed in 9% of patients. Those authors also have found that pediatric patients with autoantibodies are significantly older than those without autoantibodies; the youngest girl with autoantibodies was 11 years old.

Our present observations are consistent with those of other authors and confirm a high risk of developing thyroid autoimmunity in girls with Turner syndrome, especially considering a relatively young age of patients in the study group. Thyroid autoimmunity was detected in 26.8% of patients and most of them had subclinical hypothyroidism or overt hypothyroidism. The youngest girl with anti-thyroid antibodies was 5.8 years old and was positive for both TPO-Ab and TG-Ab. The mean age of developing thyroid autoimmunity was 10.4 years old. An earlier long-term follow-up study by Gawlik et al. (2011) also included a group of Polish girls with Turner syndrome of the median age of 10.6 years at baseline. The prevalence of thyroid abnormalities increased during the follow-up. At the end of the observation period of the mean length of 4.6 $\pm$ 3.0 years, 36% of patients were positive for anti-thyroid antibodies and 31.4% had subclinical hypothyroidism. The median age of the occurrence of anti-thyroid antibodies and subclinical hypothyroidism was 14.1 years and 14.8 years, respectively. The youngest patient with hypothyroidism was 1.8 years old and the youngest girl positive for anti-thyroid antibodies was 5.5 years old. Anti-thyroid antibodies were mostly detected after the age of 13 years.

The underlying cause of increased risk of autoimmune diseases in Turner syndrome remains unclear. Elsheikh et al. (2001) have reported a correlation between X-isochromosome and increased prevalence of anti-thyroid peroxidase (TPO-Ab) antibodies. Their study included nearly 150 women with Turner syndrome aged 16–52 years, 41% of whom were positive for anti-thyroid antibodies, and 16% of the positive were hypothyroid and required L-thyroxine treatment. That study also shows that women with an X-isochromosome have a higher risk of developing autoimmune thyroiditis compared with women with other Turner syndrome karyotypes (83% *vs*. 33%, respectively; $p < 0.0001$). Women with an also have a higher risk of hypothyroidism than other karyotypes (37.5% X-isochromosome *vs*. 14% 45,X *vs*. 6% other karyotypes; $p = 0.0034$). These authors conclude that a gene on the long arm of the X chromosome (Xq) may play an important role in the development of thyroid autoimmunity. A later study by Grossi et al. (2013) has confirmed a high frequency of thyroid autoimmunity in Italian patients with Turner syndrome and has found that the frequency of thyroid autoimmunity is statistically higher in the X-isochromosome group. A study by El-Mansoury et al. (2005) has failed to confirm those findings. However the authors have found that hypothyroidism is more common in women with Turner syndrome (25%) than in controls (2%; $p < 0.0001$) and the hypothyroidism prevalence increases with age. They conclude that an elevated TPO-Ab concentration is evenly distributed between the karyotype 45,X and mosaicism; therefore, the risk of developing autoimmune thyroiditis and hypothyroidism is independent of the karyotype. In the study by Gawlik et al. (2011), mentioned above, which concerned the Polish population, the prevalence of thyroid abnormalities was unrelated to the karyotype. A study by Aversa et al. (2015) has also confirmed that the risk of subclinical hypothyroidism, overt hypothyroidism, or hyperthyroidism in Turner syndrome is independent of the

karyotype. The authors' findings are that 67.7% of the girls who had presented with subclinical hypothyroidism became overtly hypothyroid later on. They speculate whether most women with Turner syndrome are destined to develop hypothyroidism with time.

In our present study, the incidence of thyroid autoimmunity was almost equal between mosaic karyotype with isochromosome or with deletions and 45,X karyotype, but considering the relatively small number of patients in the whole study group and in the subgroup with thyroid autoimmunity, our results have no statistical significance. Divergent results of the above-mentioned studies suggest that karyotype is not the only factor that determines the incidence of thyroid autoimmunity in patients with Turner syndrome. Kucharska (2014) in a review discussing reasons for a greater incidence of autoimmune thyroid diseases in women emphasises the role of not only genetic factors linked to sex chromosomes, but also hormonal and environmental factors. There are genes located on the X chromosome that are important for the regulation of the immune response. The author suggests that in girls with Turner syndrome haplo-insufficiency of X-linked genes, skewed X chromosome inactivation, and maternal/paternal origin of X chromosome may be the main factors responsible for a greater incidence of autoimmune thyroid diseases. That might explain the lack of an association between the risk of thyroid autoimmunity and karyotype in girls with Turner syndrome. It seems that while assessing the risk of autoimmune thyroiditis in such patients, the family history should also be considered. Since the risk of thyroid autoimmunity increases in subsequent decades of life, thyroid function must be checked regularly in girls and women with Turner syndrome.

5 Conclusions

The incidence of thyroid autoimmunity is high in girls with Turner syndrome. In the present study, thyroid autoimmunity was confirmed in 26.8% of patients. It is essential to monitor thyroid function in patients with Turner syndrome as they are prone to develop subclinical or overt hypothyroidism early on. Thyroid function should be checked at a regular basis as soon as Turner syndrome is diagnosed.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Preventive Chair Massage with Algometry to Maintain Psychosomatic Balance in White-Collar Workers

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Abstract

People working at computers often suffer from overload-related muscle pain, and physical and mental discomfort. The aim of the study was to evaluate the effectiveness of chair massage, conducted in the workplace among white-collar workers, in relieving symptoms of musculoskeletal strain related to prolonged sitting posture. The study was conducted in 124 white-collar workers, 55 women and 69 men, aged 33.7 ± 7.6 years. Subjects were randomly assigned to three groups: chair massage program, relaxing music sessions, and a control group, each of four-week duration. Each group was evaluated before and after the program completion. Pain perception was assessed algometrically as a threshold for compression pain of neck muscles, measured in kg/cm^2. The relaxation level was assessed from the heart rate variability. We found that the chair massage increased both the pain threshold in all tested muscles ($p < 0.001$) and the relaxation level from 31.9% to 41.6% ($p < 0.05$). In the group with music sessions, muscle pain threshold remained unchanged, except for the trapezoid muscle where it decreased ($p < 0.05$), while the relaxation level increased from 26.0% to 33.3% ($p < 0.05$). In both massage and relaxing music groups, there was a significant decrease in muscle tension ($p < 0.01$). Changes in the control group were inappreciable. We conclude that the chair massage performed in the workplace is an effective method

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for prevention of musculoskeletal overstrain related to prolonged sitting posture. The program seems worth implementing in various occupational environments.

Keywords
Algometry • Health prevention • Massage • Pain threshold • Relaxation • White-collar workers

1 Introduction

The occurrence of overstrain-related muscle pain, and physical and mental distress is common among people working at computers (Brandt et al. 2014; Eijckelhofa et al. 2014; Ayanniyi et al. 2010; Strøm et al. 2009; Szeto et al. 2009). It is therefore worthwhile to develop preventive methods that could mitigate the work-related distress. Different massage routines of muscle therapy has hitherto been investigated (Cook et al. 2015; Cheng and Huang 2014; Topolska et al. 2012; Back et al. 2009; Moyer et al. 2004), but the study paradigms are all too often of subjective nature; thus the hard evidence of beneficial effects is hard to come across. One of the more objective methods is a musculoskeletal massage with the use of a specially adapted chair, the so called 'chair massage' taking place directly in the workplace (Cabak et al. 2016; Stephens 2005). The algometry method employed in chair massage assesses compression sensitivity of selected muscles as matched to the psychosomatic equilibrium assessed, in turn, from the level of relaxation and heart rate variability (HRV) (McCraty 2002a, b).

Algometry is the precise and reliable method of a measurement approved and verified by researchers (Aboodarda et al. 2015; Takamoto et al. 2015; Andrzejewski et al. 2010; Farasyn et al. 2008; Chesterton et al. 2007). It is used for the diagnostics of tissue dysfunction, both before and after treatment consisting of various forms of massage. The method defines the threshold of muscle pain in response to treatment, which makes it useful in the monitoring of treatment effectiveness (Fischer 1987).

Recording of the difference between muscle tension and relaxation and the level of naturally occurring beat-to-beat heart rate variability (HRV) is the non-invasive assessment of the autonomic nervous system activity and the indication of a psychosomatic equilibrium. HRV is useful in the assessment of a variety of functional disorders, for instance, chronic fatigue syndrome, particularly related to the workplace, which could run a surreptitious course, but lead to a whole range of detriments such as decreases in productivity, job satisfaction, effectiveness in communication, or workers' health. The optimal level of HRV, on the other side, reflects the resistance, agility, vitality, and the ability to cope with stress. It should be recognized, however, that both low and high extremes of HRV, strongly departing from the average level usually point to the presence of unbearable chronic stress, neural exhaustion, mental and physical fatigue, and the enhanced risk of subsequent health problems (McCraty 2002a, b).

Psychosomatic equilibrium that accompanies the feeling of positive emotions involves balanced cognitive, emotional, and behavioural processes, which enables the physiological alignment of body systems. That forms the basis of psychosomatic entirety (Bedell and Kaszkine-Bettag 2010; McCraty and Zayas 2014; McCraty 2002a, b) and is highly desirable among white-collar workers exposed to both somatic and mental overload.

The aim of the present study was to evaluate the effectiveness of the chair massage program conducted in the workplace among people with muscolo-skeletal overloads, based on the measurement of muscle pain sensitivity and the level

of psychosomatic equilibrium. In addition, we seek to define the most effective from the psychosomatic standpoint form of relaxation during work breaks.

2 Methods

The project was conducted as part of the statutory research program run by the Academy of Physical Education in Warsaw, Poland, and was approved by the Academy's Senate Committee for Scientific Research (SKE 01–50/2014).

2.1 Study Participants

The is a prospective observational study study that was conducted in 124 office workers, 55 women and 69 men of the mean age of 33.7 ± 8.3 years. Subjects were randomly assigned to the following groups: Group 1 – exposed to the chair massage; Group 2 – exposed to the relaxing music, and Group 3 – the control group. The participation criteria were as follows: good general health, office work in a sitting position for at least 8 h a day, minimum 1 year office work experience, working age, no acute diseases, and no contraindications for chair massage. Table 1 shows details of the subjects' characteristics in each group (Table 1).

2.2 Study Design

The study program lasted 4 weeks and was performed in the subjects' work offices twice a week on Tuesday and Friday afternoon. In Group 1 and 2, the implemented program consisted of eight interventions, each lasting 15 min twice a week. The control group – Group 3 – had 15-min work breaks instead, with the participants leaving the workplace and assuming the body position different from that during the worktime.

2.3 Instrumentation

The assessment of muscle pain threshold was performed using Pain Test FDX 50 – Force Gage Wagner pressure algometer (Wagner Instruments; Greenwich, CT). This technique assessed the first perception of a painful stimulus in response to compression of three neck muscles performed at 6 bilateral pain triggering sites: descending part of the trapezoid muscle, the supraspinatus muscle, and the levator scapulae muscle. The unit of measurement was kg/cm^2.

The health of the autonomic nervous system expressed by HRV and an individual's ability to handle stressful challenges was assessed with the em-Wave device (Heart Math Inc.; Boulder Creek, CA). The level of relaxation level was assessed from the measurement of changes in the galvanic skin response (McCraty 2002a, b). Rating of physiological and emotional reactions takes place through the use of self-breathing skills and muscle relaxation ability. During the test, the sensor was clipped to the subject's earlobe to record heart rate (HR), HRV, breaths, and muscle relaxation. The recordings started after 6 min of rest in the sitting posture and were performed twice; the day before the commencement of the study program, taken as the baseline level, and at the program completion 4 weeks later. The levels of relaxation and tension were expressed as the percentage of changes and HR rate as the number of beats/min.

2.4 Interventions

The subjects of Group 1 underwent a series of eight 15-min sessions of massage for the relaxation purpose, based on the concept of chair massage concept (Cabak et al. 2016; Stephens 2005). The massage was performed by hand through thin clothing while the subject was sitting in a specially designed massage chair. It covered the interscapular area around the spine, consisting of the erector spinae muscles, the neck and shoulder

Table 1 Characteristics of the study participants

	Group I (n = 44)	Group II (n = 41)	Group III (n = 39)
Age (years)	33.3 ± 8.3	32.8 ± 10.6	35.1 ± 11.7
BMI (kg/m^2)	25.8 ± 4.3	23.0 ± 4.2	22.5 ± 3.7
Number of hours at the desk *per* day	8.5 ± 1.5	8.4 ± 1.1	9.2 ± 1.5
Office work duration (years)	9.5 ± 8.1	9.3 ± 9.7	11.5 ± 9.5

Data are means ±SD; *BMI* body mass index

muscles, and the entire area of the upper limbs and hands. Each massage session ended with passive stretching and relaxing of the upper limbs. The massage technique use were kneading, compression, and shaking. The program also included a brief assessment of the most overloaded and painful points. Massage was always performed by the same certified physiotherapists in the company conference room.

The subjects of Group 2 underwent a series of relaxing music sessions using a similar time schedule as that for Group 1. The sessions consisted of listening to classical music, recommended for individuals performing mental work, in the most comfortable position of their choice for 15 min, individually through headphones (Hughes 2001). The control subjects of Group 3 were asked to move freely outside the workplace during 15-min breaks through study duration.

Data were presented as means ±SD for continuous variables and as percentages for categorical variables. The mean algometric values were submitted to a mixed-design analysis of variance (ANOVA) comparing the mean differences between groups that were split on two factors or independent variables, with one between-subjects variable (group) and two within-subjects variables (experimental condition, i.e., before and after physiotherapy, and muscle side, i.e., left and right corresponding muscles. This split-plot ANOVA was followed by *post hoc* Tukey's test. In addition Pearson's Chi-squared test for independence and Wilcoxon's signed-rank test were used as required. A p-value <0.05 defined statistically significant changes.

3 Results

Since we did not note any appreciable gender-related differences in the test results, data for men and women were combined and evaluated as a whole. Table 2 shows the results of the pain threshold measurements in each group before onset and after completion of the month-long physiotherapeutic program. The greatest increase in pain threshold, i.e., a decrease in pain perception, was recorded in the group subjected to the chair massage (Group 1) in all three muscles investigated on both sides, where the pain threshold increased, on average, by approx. 1 kg/cm^2 of compressive force used ($p < 0.001$). In Group 2 subjected to music sessions, the pain threshold increased significantly only in the trapezius muscle, whereas in the control group, left without any physiotherapeutic intervention (Group 3), changes were inappreciable.

Pain perception tended to be greater in the left-sided muscles in each group; the difference between both sides assumed statistical significance in the majority of experimental conditions concerning the supraspinatus and levator scapulae muscles ($p < 0.01$).

Table 3 presents the results of psychosomatic evaluation, consisting of changes in relaxation (advantageous) and tension (disadvantageous), conducted with the em-Wave device in all groups. There were significant changes in both relaxation and tension after physiotherapy completion. The level of relaxation increased; the greatest increase occurred in the massage group (Group 1), from 31.9% to 41.5%, and in the

Table 2 Algometric measurements of individual muscle performance, expressed in kg/cm^2, in the study groups before and after completion of the month-long physiotherapeutic program

Muscles examined	Group 1 – Chair massage		Group 2 – Music sessions		Group 3 – Control	
	Left side	Right side**	Left side	Right side**	Left side	Right side**
TRAP						
Before	3.44 ± 1.54	3.69 ± 1.57	3.66 ± 0.64	3.47 ± 0.86	3.88 ± 1.48	4.09 ± 1.62
After	4.40 ± 1.93*	4.51 ± 2.01*	3.88 ± 0.97*	3.95 ± 0.79*	4.17 ± 1.93	4.36 ± 2.30
SUPS						
Before	3.98 ± 1.87	4.16 ± 1.44	3.41 ± 0.97	3.61 ± 0.82	4.60 ± 2.12	4.90 ± 2.03
After	5.07 ± 2.35*	5.25 ± 2.35*	3.79 ± 0.95	3.81 ± 0.98	4.41 ± 1.66	4.78 ± 2.03
LEVS						
Before	3.92 ± 2.08	4.18 ± 2.13	3.47 ± 0.52	3.72 ± 0.64	4.58 ± 2.18	4.63 ± 2.05
After	4.86 ± 2.78*	5.24 ± 3.02*	3.75 ± 1.17	4.00 ± 1.38	4.72 ± 2.26	4.94 ± 2.53

TRAP trapezius muscle, *SUPS* supraspinatus muscle, *LEVS* levator scapulae muscle
Data are means ±SD; *$p < 0.001$ for differences between the corresponding values in a given muscle before and after physiotherapy; **$p < 0.01$ for differences between left and right sided corresponding muscles considering the averaged results of muscle performance before and after physiotherapy in all groups (mixed-design analysis of variance – ANOVA)

Table 3 Evaluation of psychosomatic equilibrium and heart rate in the study groups before and after completion of the month-long physiotherapeutic program

	Group I		Group II		Group III	
	Before	After	Before	After	Before	After
Relaxation (%)	31.9 ± 24.0	41.6 ± 25.4*	26.0 ± 23.6	33.3 ± 20.6*	35.7 ± 28.3	34.2 ± 27.4
Tension (%)	45.7 ± 24.6	35.5 ± 21.6**	55.5 ± 25.4	44.5 ± 20.5**	45.2 ± 24.9	44.6 ± 26.3
HR (beats/min)	71.1 ± 10.7	71.1 ± 10.5	73.5 ± 15.1	70.7 ± 13.5	70.2 ± 13.4	69.3 ± 12.5

Data are means ± SD; *HR* heart rate. The levels of relaxation and tension are derived from the relaxation index computation by em-Wave device's software; *$p < 0.05$ and **$p < 0.01$ for the physiotherapeutic effects

music sessions group (Group 2), from 26.0% to 33.3% ($p < 0.05$) before *vs.* after physiotherapy, respectively. Concomitantly, tension (stress) level decreased in Group 1 and 2 after physiotherapy by 10.0% and 11.0%, respectively ($p < 0.01$). In the control group, relaxation changed inappreciably from 35.7% before to 34.2% after physiotherapy. Changes in HR were inappreciable in all groups.

4 Discussion

The aim of this study was to evaluate the chair massage program designed to reduce the impact of work overloads on psychosomatic status of white-collar workers. The findings expand on our previous study performed in less numerous groups of subject and without the comparison with the relaxation effects of music sessions (Cabak et al. 2016). The massage, music and control groups designed for the present study made it possible to compare various forms of intervention aimed at relieving the musculoskeletal overload. It turned out that the most effective intervention was massage, while relaxation by listening to music could be viewed as complementary to the massage. The work breaks, during which the subjects left the workplace, failed to influence the work tension appreciably. Significantly, our present findings, based on the algometric evaluation, demonstrate a substantial increase in the pain threshold of more than 1 kg/cm^2 concerning the supraspinatus and levator scapulae muscles after chair massage physiotherapy; the effect tantamount to reduced pain sensitivity of these muscles.

The effectiveness of chair massage in the workplace has also been reported by other

authors, employing alternate study designs. Šiško et al. (2011) have concluded that massage performed in white-collar workers in the workplace, twice a week for 15 min, is a more effective intervention than that performed once a week, and is also superior to work breaks alone. The massage reduces the duration and intensity of pain and increases the range of movements in the cervical and lumbar spine. The effectiveness of this type of massage has also been demonstrated in medical and healthcare workers. Engen et al. (2012) have shown that a 15-min massage session once a week for 10 weeks exerts a positive anti-stress influence in the nursing staff. Similar effects have also been noted with 30-min massage sessions in case of sonographers (Engen et al. 2010). Back et al. (2009) have conducted research in a group of 145 healthcare workers with a program consisting of 20-min massage sessions once a week for 4 weeks, performed in a specially prepared room with a relaxing natural light and decor, and soft background music. Those authors pointed to the short-term relaxing effects, suggesting the need for longer and more frequent than once a week sessions. However, Brennan and DeBate (2006) have demonstrated beneficial, anti-stress results after a single 10-min massage session in the nursing staff; the result was appreciably better that obtained with routine coffee breaks at work.

An unexpected finding of the present study was that the corresponding right sided muscles had, nearly uniformly in all groups and conditions, a higher pain threshold. All the subjects investigated were right-handed. Therefore, in all likelihood, the arm-shoulder muscle mass is greater on the side whose muscles are more frequently used and subjected to a greater workload. Further, the muscle use on the active right-hand would be in various movement configurations, as opposed to passive left side, causing dissymmetry in the spread of muscle tension on both sides of the spine. That is an intriguing finding that suggests the pain perception decrease with increasing muscle mass. This issue was beyond the scope of the present research in which muscle mass was not determined. Therefore, further exploration of this unclear phenomenon would be required using a different study design.

Increasing the level of relaxation and reducing tension/stress in white-collar workers subjected to chair massage and music sessions apparently improved the psychosomatic equilibrium. Nonetheless, average heart rate did not change significantly, which demonstrates a degree of heart rate stability, particularly while using this specific massage program. The program was aimed at muscle relaxation and the lack of appreciable heart rate changes may be viewed as an advantageous feature of it. Both 15-min massage bouts and listening to classical music, although causing momentary relaxation and inner calm, seem insufficient stimuli to induce changes in heart rhythm.

The subjects of this study were young people of working age, with no serious health problems and with no relevant pain sensations. Psychosomatic overload accumulates along the aging process and length of work experience, particularly in case of long working hours and stressful job. Therefore, more serious symptoms may mount up. Health prevention programs ought to focus on prophylaxis and minimizing the effects of harmful factors. One of easily accessible and economical preventive interventions could be the chair massage program above proposed. We submit that this kind of massage program be promulgated and implemented among various professions and people in the workplace, and the program ought to be properly matched to current health needs. Chair massage has the potential to become part of preventive programs counteracting the long-term impact of occupational diseases on psychosomatic health, exaggerated by the lack of physical movement during long working hours and work-related distress.

5 Conclusions

- Chair massage is an effective form of prevention and alleviation of musculoskeletal pain and discomfort, and of mental distress in white-collar workers;

- Classical music sessions could complement the chair massage;
- Preventive health programs ought to focus on expanding generally available, economical activities that are implementable in the workplace.

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