Poznan University of Medical Sciences
Poland

JMS Journal of Medical Science

previously Nowiny Lekarskie

Founded in 1889

2017
Vol. 86, No. 1

QUARTERLY

Indexed in:
Polish Medical Bibliography, Index Copernicus,
Ministry of Science and Higher Education, Ebsco, Google Scholar

eISSN 2353-9801
ISSN 2353-9798

www.jms.ump.edu.pl

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37a Przybyszewskiego Street
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PUBLISHER
Poznan University of Medical Sciences

eISSN 2353-9801
ISSN 2353-9798

Publishing Manager: Grażyna Dromirecka
Technical Editor: Bartłomiej Wąsiel
Proofreader: Jan Jaroszewski

WYDAWNICTWO NAUKOWE UNIWERSYTETU MEDYCZNEGO IM. KAROLA MARCINKOWSKIEGO W POZNANIU
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Ark. wyd. 10,8. Ark. druk. 11,0.
Zam. nr 98/17.

The Editorial Board kindly informs that since 2014 *Nowiny Lekarskie* has been renamed to *Journal of Medical Science*.

The renaming was caused by using English as the language of publications and by a wide range of other organisational changes. They were necessary to follow dynamic transformations on the publishing market. The Editors also wanted to improve the factual and publishing standard of the journal. We wish to assure our readers that we will continue the good tradition of *Nowiny Lekarskie*.

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CONTENTS

ORIGINAL PAPERS

BRIEF REPORT

REVIEW PAPER

THOUSAND WORDS ABOUT...

CASE STUDY

ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.193

Factors associated with overhydration in peritoneal dialysis patients

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ABSTRACT

Aim. Overhydration is a prevalent problem in peritoneal dialysis (PD) patients. The aim of the study was to evaluate the effect of several factors on the development of overhydration in PD patients.
Material and Methods. The study was performed on 74 PD patients, who were divided into two groups according to bioimpedance analysis hydration status (OH_{BIA}): Group A OH_{BIA} < 1.1 L (n = 40) and Group B OH_{BIA} ≥ 1.1 L (n = 34). The assessments of the adequacy of the dialysis dosage were based on the Kt/V ratio as well as weekly creatinine clearance. To evaluate the permeability of the peritoneal membrane a standard peritoneal equilibration test was used.
Results. A statistically significant difference between the groups was found in: the average age of patients (53 ± 18 vs. 62 ± 14 years; p < 0.03), the prevalence of diabetes (27.5% vs. 55.9%; p < 0.02) and residual diuresis (1.7 ± 0.8 vs 1.2 ± 0.9 L; p < 0.05). There was no statistically significant difference in gender distribution, although attention is paid to the greater participation of male in overhydrated group. The study found no statistically significant differences between PD vintage, type of PD, assessment of adequacy of PD and other parameters describing the PD method. Logistic regression model selected diabetes (p < 0.03) as a significant risk factor for the occurrence of hypervolemia.
Conclusions. Diabetes and older age are potential predisposing factors for the development of overhydration in PD patients. Overhydrated PD patients may have relatively high parameters regarding adequacy of dialysis therapy. Probably the most important protective factor in PD patients is residual diuresis.

Keywords: peritoneal dialysis, bioelectrical impedance analysis, state of hydration.

Introduction

Several years ago peritoneal dialysis (PD) was generally regarded as treatment, that could prevent the development of overhydration. However, recent studies have brought attention to the importance of overhydration also in PD patients [1]. Devolder et al. [2] compared hydration status of patients on hemodialysis and peritoneal dialysis, and showed that overhydration occurred more frequently in PD patients [2]. Similar results were obtained by van Biesen et al., who reported that overhydration in PD patients was more frequent than in patients on hemodialysis [3].

In PD patients, overhydration occurs mostly as a result of excessive sodium and fluid intake with insufficient elimination from the body [4, 5]. The problem of hypervolemia relates, in particular, to patients without

residual diuresis, in whom the dialysis method itself turns out to be insufficient in relation to fluid intake [5]. The study by Koning et al., showed a statistically significant correlation between the state of hydration and residual renal function [5]. Similarly, the EuroBCM study demonstrated the development of overhydration in patients with less residual diuresis [1]. The other potentially cause of overhydration in PD patients is loss of peritoneal ultrafiltration capacity [5]. Unfortunately, ultrafiltration and the efficacy of peritoneal dialysis gradually decrease during therapy. Impaired peritoneal ultrafiltration is a serious problem and important limitation of peritoneal dialysis [6]. However, there are probably more factors responsible for water excess in PD patients [4, 5].

Overhydration has numerous clinical consequences. Probably, even subclinical overhydration, which does not manifest with clinical symptoms, can result in numerous complications [1]. That is why it is important to objectively assess the hydration status, find factors responsible for overhydration and prevent hypervolemia.

Aim

The aim of our study was to evaluate association of selected factors with the hydration status of patients on peritoneal dialysis.

Material and Methods

This cross-sectional study was performed on 74 PD patients. The study protocol was approved by the institutional ethics committee (decisions No. 424/13). All patients were informed about the course of the study and gave written informed consent for participation in the study.

Inclusion criteria for the study were: age above 18 years, consent for participation in the study and a minimum 3-month period of treatment with peritoneal dialysis. Exclusion criteria were: presence of acute active inflammatory processes, and status after amputation of upper or lower limb or presence of a cardioverter-defibrillator (because of bioimpedance method used in the study).

Complete medical history from each patient was collected. Clinical assessment of hydration status was based on the presence of dyspnoea, peripheral oedema, jugular vein distension and blood pressure measurement.

Hydration status was also assessed by bioimpedance spectroscopy (BIA) using the Body Composition Monitor (BCM) (Fresenius Medical Care, Germany). The measurements were performed under standardized conditions in the supine position after a 2-minute rest. The OH reference values range from -1.1 L to +1.1 L. The reference values were determined on the basis of bioimpedance studies conducted on a population of 1247 people of Caucasian race [7].

According to bioimpedance analysis hydration status (OH_{BIA}) patients were divided into 2 subgroups:

- Group A: $OH_{BIA} < 1.1$ L (n = 40)
- Group B: $OH_{BIA} \geq 1.1$ L (n = 34).

Peritoneal membrane function was measured with the peritoneal equilibration test (PET) during a 4-hour dwell using 2.27%-glucose dialysate [8]. The assessments of the adequacy of the dialysis dosage were made based on the size ratio Kt/V as well as weekly creatinine clearance [9, 10].

Statistical analyses were performed with STATISTICA 10.0 PL (StatSoft Polska, Kraków, Poland). Analyzed data were presented as means and standard deviations or percentage. All results were considered significant at $p < 0.05$. Normality of the distribution was tested with the Shapiro-Wilk test. The data with a normal distribution were analyzed with parametric methods (t-student test). The data that did not follow a Gaussian distribution were analyzed with the Mann-Whitney test. Categorical data were analyzed with the χ^2 test or the Fisher-Freeman-Halton test. The relationship between variables was analyzed with the Spearman's rank correlation coefficient and by multivariate linear regression.

Results

Characteristics of patients

The study group consisted of 40 females and 34 males. The age of patients ranged from 24 to 88 years. The mean age of the patients was 56.9 ± 16.6 years. Patients < 65 years made up 62.2% (n = 46). The causes of chronic kidney disease (CKD) were: diabetic kidney disease (n = 22; 29.7%), hypertensive nephrosclerosis (n = 17; 23.0%), chronic glomerulonephritis (n = 17; 23.0%), chronic tubulointerstitial nephritis (n = 6; 8.1%), other causes including polycystic kidney disease, status after nephrectomy and multiple myeloma (n = 12; 16.2%). Diabetes was present in 30 (40.5%) patients. The average dialysis vintage was 31.7 ± 22.2 months. In the study group: 58 (78.4%) participants were treated by continuous ambulatory peritoneal dialysis (CAPD) and 16 (21.6%) were using automated peritoneal dialysis (APD) cycler.

Characteristics of the subgroups were presented in **Table 1**. There was no statistical difference in gender distribution between the subgroups, although there was larger proportion of male in group B. A statistically significant difference was found regarding the mean age of patients ($p < 0.03$). In group A, patients' age ranged from 24 to 88 years. The mean age of the patients was 52.9 ± 17.7 years, wherein patients <65 years accounted for 72.5% (n = 28). In group B, patients' age ranged between 30 and 84 years. The mean age of the patients was 61.6 ± 14.2 years; and patients <65 years made up 50.0% (n = 17). A statistically significant difference was also demonstrated regarding the etiology of CKD ($p < 0.03$). In group A, the most common etiological factor of CKD was glomerulonephritis (n = 12; 30.0%) whereas in group B, the most common etiological factor was diabetic nephropathy (n = 16; 47.1%). The two groups also differed in terms of prevalence of diabetes, both type 1 and type 2 ($p < 0.02$). Diabetes was diagnosed in 27.5% (n = 11) of patients in group A and 55.9% (n = 19) of patients in group B. There was also statistically significant difference in residual diuresis between the two study groups ($p < 0.05$). In group A, almost all of the patients had adequate residual diuresis (n = 37; 92.5%).

We found no statistically significant differences between dialysis vintage, type of peritoneal dialysis, parameters of adequacy of peritoneal dialysis or other features describing the method of dialysis (**Table 2**). Whereas higher mean D/P creatinine values by PET were observed in patients in group B, the difference was not statistically significant.

Hydration status

In the whole study group, one or more clinical features of overhydration were found in 19 (25.7%) patients, while bioelectrical impedance criteria for overhydration were met by a 34 (46.0%) of the patients. Frequency of clinical symptoms of overhydration differed significantly ($p < 0.001$) between the two subgroups. Peripheral edema occurred in 7.5% (n = 3) of patients in group A and in 47.1% (n = 16) of patients in group B. Detailed results obtained with the BIA method in both subgroups were shown in **Table 3**.

Table 1. Characteristics of subgroups

	Group A	Group B	P value
Number of Patients	40	34	NS
Gender	25 (62.5%) women; 15 (37.5%) men	15 (44.1%) women; 19 (55.9%) men	NS
Age (years)	52.9 ± 17.7	61.6 ± 14.2	< 0.03
Etiology of CKD	6 (15.0%) diabetes 10 (25.0%) hypertension 12 (30.0%) glomerulonephritis 12 (30.0%) other	16 (47.1%) diabetes 7 (20.6%) hypertension 5(14.7%)glomerulonephritis 6 (17.7%) other	< 0.03
Presence of Diabetes	11 (27.5%)	19 (55.9%)	< 0.02
Diuresis (mL/day)	1662.5 ± 846.3	1224.2 ± 927.5	< 0.05

Values are expressed by mean and standard deviations

Table 2. Characteristics of dialysis methods

	Group A	Group B	P value
Duration of dialysis therapy (mc)	31.1 ± 23.1	32.3 ± 21.6	NS
Type of peritoneal dialysis	9 (22.5%) APD; 31 (77.5%) CAPD	7 (20.6%) APD; 27 (79.4%) CAPD	NS
Glucose Load (g/week)	979.5 ± 283.9	930.3 ± 283.8	NS
patients using or amino acids	8 (20.0%)	4 (11.8%)	NS
D/P creatinine in PET	0.62 ± 0.09	0.66 ± 0.11	NS
Types of peritoneal transport	1 (2.5%) H 14 (35.0%) HA 21 (52.5%) LA 4 (10.0%) L	2 (5.9%) H 16 (47.1%) HA 12 (35.3%) LA 3 (8.8%) L	NS
Kt/V (l/week/1.73 m^2)	2.91 ± 0.89	2.74 ± 0.87	NS
Creatinine clearance (l/week/1.73 m^2)	99.3 ± 35.6	100.4 ± 39.2	NS
Ultrafiltration(ml/day)	1133.3 ± 503.8	1266.7 ± 614.8	NS
GFR (ml/min/1.73 m^2)	6.6 ± 4.8	7.0 ± 5.2	NS

Values are expressed by mean and standard deviations

Table 3. Indices of hydration status obtained by the bioelectrical impedance method

	Group A	Group B	P value
OH_{BIA} (ml)	227.0 ± 2030.8	3544.1 ± 2095.0	< 0.001
OH_{BIA} (%)	0.1 ± 3.0	5.0 ± 3.0	< 0.001
TBW (L)	33.6 ± 6.6	36.5 ± 7.2	NS
ECW (L)	15.0 ± 2.3	19.0 ± 3.9	< 0.001
ICW (L)	18.6 ± 5.2	17.5 ± 3.7	NS

Values are expressed by mean and standard deviations.
Abbreviations: OH_{BIA}, overhydration according to bioelectrical impedance analysis; TBW, total body water; ECW, extracellular water; ICW, intracellular water; all according to according to bioelectrical impedance analysis.

Factors associated with overhydration

We analyzed the associations of OH_{BIA} with age, gender, co-existence of diabetes and residual urine volume. Overhydrated patients were significantly older ($p < 0.04$) and older age was associated with more frequent diagnosis of diabetes ($p < 0.001$). There was no statistically significant difference in the assessment of hydration status, age, residual diuresis or presence of diabetes between the genders. Fluid overload ($OH_{BIA} \geq 1.1$ liters), was more common among patients with diabetes ($p < 0.05$). The risk of fluid overload in patients with diabetes was more than three times higher than that of those without diabetes while presence of diabetes did not associate with volume of residual urine. Using a logistic regression model diabetes ($p < 0.03$) was found as significant risk factor for overhydration.

Discussion

The results of the current study indicate that subclinical signs of overhydration, that can be detected by bioimpedance analysis, are very common in peritoneal dialysis patients. Overhydration in that group of patients were associated with older age, diabetes and low residual renal function.

The results of our study are consistent with previous studies, showing a high prevalence of fluid overload in PD patients, ranging from 22% to 72% in different studies [1, 2, 11, 12]. Devolder et al. [2] reported that more than 22% of PD patients showed clinical features of overhydration. In the study of European Body Composition Monitoring (EuroBCM) [1] overhydration in BIA was present in more than 53% of the patients. Furthermore, in the study by Kwan et al. [12] comprising of 122 asymptomatic PD patients, showed that in BIA overhydration was present in over 72% of patients. Also Juan-Garcia et al. [11] pointed out that the BIA method allows for identification of fluid excess in a greater number of patients than clinical evaluation. In addition, Duman et al. [13] in their work showed that the BIA better correlated with results of echocardiography than result obtained by clinical evaluation. Thus, it seems that due to the prevalent of subclinical state of overhydration in PD patients, the BIA is a better criterion for assessing fluid status than clinical evaluation in that group of patients.

In our study attention was drawn to the larger percentage of male in the group of overhydrated patients, which - although the difference was not statistically significant - may suggest that male gender is a predisposing factor for the development of overhydration. Many authors draw attention to the male gender as a risk factor for development of overhydration in patients on PD. Van Biesen et al. in their work showed a statistically significant relationship between gender and the state of hydration, indicating that male gender is a risk factor for the development of overhydration [1]. Similar results were presented by Kwan et al. [12], stating that fluid overload assessed by bioelectrical impedance, was more frequent among men. Furthermore, Tang et al. [14] found that male gender was associated with a higher incidence of fluid overload in both clinical assessment and examination by bioelectrical impedance.

Our study demonstrated a statistically significant difference regarding the mean age of patients in both groups, which may indicate age as one of the factors predisposing to overhydration. The results of our study are consistent with the literature. In the EuroBCM study [1] it was shown that there was a relationship between hydration status and age of the patients. Similarly, Demirci et al. [15] in their work pointed out, that overhydrated patients were characterized by older age. Also, the study by Guo et al. [16] demonstrated a statistically significant correlation between age and the state of hydration.

Our study also highlights differences in the pathogenesis of chronic kidney disease in both groups. In the overhydrated patients, diabetic nephropathy was the most common diagnosis, whereas other causes of chronic kidney disease were more frequent in patients with normal hydration status. Differences also included the frequency of co-existence of diabetes as an addi-

tional diagnosis in both groups. This may indicate diabetes as one of the risk factors for overhydration. Our results confirm those previously obtained by the others [1, 17, 18]. The EuroBCM study demonstrated a relationship between the prevalence of diabetes and overhydration in PD patients [1]. The same relationship was found in a study conducted in a group of patients on hemodialysis therapy [19]. Moreover, the relationship has also been shown in another study, involving pre-dialysis patients [18]. The study by Hung et al. [18] included 338 patients diagnosed with chronic kidney disease in stages 3 to 5. When overhydration was assessed by BIA, it was found that over 50% of patients were overhydrated and a statistically significant correlation between the presence of diabetes and the state of hydration was found [18]. This may indicate diabetes as an additional risk factor for the development of overhydration also in earlier stages of chronic kidney disease and regardless of the type of renal replacement therapy [18]. Although the exact mechanisms for the development of these complications in diabetes are not known.

Another factor, which seems to have an impact on the development of overhydration in PD patients is residual diuresis. In the EuroBCM study [1] it was shown that there is a tendency for development of overhydration in patients with reduced residual diuresis. Similarly, in the study by Konings et al. [5] a statistically significant relationship between the state of hydration and the residual kidney function was found. It appears that in the case of PD patients, residual diuresis plays a critical role in the state of hydration of an individual. However, the results of several studies suggest that the benefits of preservation of residual renal function in PD surpass the regulation of hydration alone [20].

The average time on dialysis therapy in the study group was 31.7 ± 22.2 months and did not differ significantly between the subgroups. The results of our study are consistent with those obtained in the EuroBCM study [1], in which the average duration of dialysis was approximately 33 months and comparable in the overhydrated and normovolemic groups. However, it seems that when observed for a longer period of time, the dialysis vintage may play an integrative role in the development of overhydration, due to ultrafiltration failure in patients on prolonged PD therapy, as pointed out by Matsuda et al. [21].

Our study also draws attention to the lack of differences between groups in terms of the method of PD (CAPD vs. APD). Similar findings can be found in literature. Cnossen et al. for example compared the state of hydration in groups of patients treated with CAPD and APD systems and found no statistically significant difference between the groups [22]. Similarly, in earlier study by Davenport et al., the authors did not demonstrate any significant relationship between the state of hydration and the type of PD [23]. Thus, it seems that both of these methods are equally effective in regulating the body's hydration status.

There was also no significant difference in the adequacy of PD. Moreover, it was observed that in overhydrated patients the parameters for adequate dialysis therapy were relatively high. The results of our study are consistent with the results obtained by Van Biesen et al. [1]. In addition, in a study by Asqhar et al. [24], composed of 68 stable patients on PD, the authors showed no differences in Kt/V and the average weekly creatinine clearance in overhydrated patients and those with a normal hydration state. This may indicate that patients on PD who are overhydrated can have relatively satisfactory parameters of adequate PD.

Higher mean values of D/P creatinine in PET in overhydrated patients were observed, although it did not reach statistical significance. However, a statistically significant correlation was found between the values of D/P creatinine in PET and the relative and absolute state of hydration in BIA. The results of our study are probably due to the relatively short period of dialysis therapy in our group of patients. Perhaps with a longer period of observation differences between the groups would be more pronounced, because time of PD seems to be the deciding factor affecting the type of peritoneal transport. Our results are only partially in line with those obtained in the EuroBCM study [1] in which the authors demonstrated a relationship between the state of hydration and type of peritoneal transport, as well as a tendency for development of overhydration in the group with fast peritoneal transport. However, in the study by Konings et al. [5], the results were dependent on the duration of the test, which seems to confirm the effect of time- dependency in this regard. The results from the initial time point in the cross-sectional study showed no statistically significant correlation between the state of hydration and the results of PET, whereas the long-term follow-up showed a statistically significant correlation between the values of D/P creatinine and the state of hydration when assessed by bioelectrical impedance [5].

Conclusions

Overhydration in bioimpedance analysis was present in 46% of PD patients, despite absence of clinical markers of fluid overload in over half of these patients,

suggesting that the bioelectrical impedance method may be a more sensitive method. Older age and diabetes appeared as potential predisposing factors for the development of overhydration. In contrast, residual diuresis in patients on PD plays an important protective role against the development of overhydration. Interestingly, it seems that the parameters of peritoneal dialysis are less critical for the regulation of hydration status in these patients. The PD patients who are significantly overhydrated (OH_{BIA} > 1.1 L) may have relatively high parameters regarding adequacy of dialysis therapy.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2017-01-08
Acceptance for publication: 2017-03-30

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ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.196

Surgery of early stage breast cancer in older women – multicenter study and review of 143 cases

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ABSTRACT

Most of breast cancers are diagnosed in females over 50 years of age, however it is found that about 30% of the disease diagnosed with women above 70 years. Generally speaking, those patients is treated with a smaller range of treatment which usually offered to the younger group of patients. Despite the presence of many comorbidities, however the patient may still have a good physiological reserve, which make offering a radical surgery of the cancer very possible. Age should not be a determinant for quality of care in breast cancer. In this paper, we looked to 143 breast cancer patients with age >70 years had been operated. The oldest was 86. ASA assessment tool used Pre-operatively. Mastectomy done in 70% where 30% underwent Breast Conservation Surgery. Axillary surgery done in 94% of cases (52% Sentinel lymph node biopsy and 42% axillary clearance). The histology of the removed cancers showed invasive ductal carcinoma in 76% of cases, invasive lobular carcinoma in 11%, with DCIS in 06%. After surgery, every patient has been offered the individual suitable adjuvant treatment as chemotherapy, radiotherapy, Herceptin or hormonal manipulation. As those patients can stand the radical surgery and live with a good life quality after treatment, we advise to extend the screening program beyond the current recommended age. Also we recommend further research to understand more about the biology of the breast cancer in the older age group and disseminate geriatric assessment tool as Adult Co-morbidity Evaluation (ACE-27) to provide a proper evaluation of the patient status prior to final management decision.

Keywords: breast cancer, mastectomy, breast conservation surgery.

Introduction

Most of breast cancers are diagnosed in females over 50 years of age, however most of the screening programs covers the women age group between 50 to 70 years of age. In UK, any lady over 70 can self-refer for a screening mammogram [1]. Looking to breast cancer incidence, it is found that about 30% of the disease diagnosed with women above 70 years, however in general this population is dealt with less active treatment [2].

With modern medicine and improved the care level, the life span of the population is increasing. Accordingly, the number of older age group patients with cancer will considerably increase by the time, as the incidence of cancer in general is elevated 11-fold after the age of 65 years compared to adults up to 65 years [3]. Also, breast cancer in older individuals will be increasingly encountered in daily clinical practice. Management options and decisions should not be based on age alone. Physiological reserve, comorbidities, physical impairments and social factors that might impact on their diagnosed cancer care, all should considered [4]. This indicates the need for looking up and plan the future of adequate management of the cancer in the older age group. The primary treatments for early breast cancer are surgery, adjuvant radiotherapy and adjuvant systemic therapy. This paper discusses the surgical management of breast cancer in seniors.

In 1981, Herbman et al showed that older women with early stage breast cancer could tolerate radical breast and axillary and had a considerable long-term survival [5]. Many authors today asking "Should we?", we are asking "Why not?". We believe a potential curative treatment should be offered to any patient regardless age, providing that this patient is fit enough for the procedure. The cancer treatment should decrease not only the associated anxiety and unpleasantness but also the morbidity produced. Certainly any successful management will have a tremendous impact on the patient health, physical performance, psychological relief,social life as well as life expectancy. Also this will influence the life of the people surrounding the patients, this included their families as well as their carers.

Aim

To describe the age-specific surgical choice pattern in the older age group with early breast cancer breast and to elucidate the challenge of providing optimum early cancer surgical treatment for elder patients.

Material and Methods

We are presenting a series of 143 women aged 70 years and above who has been diagnosed with early breast cancer and received treatment for between 2011–2016 (**Figure 1**). The minimum age was 70 and the oldest patient was aged 89 years. The average age was 77, the median 73 and the mode 70. 100 patients had been operated at Basildon & Thurrock University Hospital – Essex England (BTUH)and other 43 at Wielkopolska Oncology Centre in Poznan Poland (WCO). The paper explored the surgical procedures has been performed in all patients, the use of pre-operative assessment tool as well as the immediate postoperative outcome. The updated medical records of all the cases has been analysed

Results

This group, had a higher proportion of mastectomy surgery (70%) than Breast Conservation Surgery BCS (30%).Mastectomy with axillary node clearance was done in 36% of cases, where mastectomy and sentinel lymph node biopsy in 32%. Only 20% of BCS cases had axillary node clearance (**Figure 2**). One postoperative mortality recorded at BTUH, it was due to a cardiac event two weeks after the surgery.

The age group specific distribution indicates that, there are 47% of the patients are below 80 and had mastectomy and only 20% of the group who are under 80 and had BCS. To attain a loco-regional disease con-

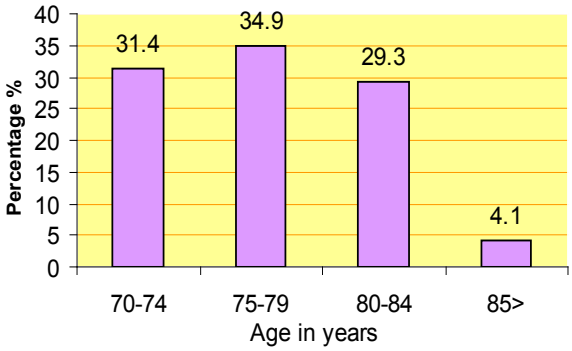

Figure 1. Age group distribution of 143 patients operated on, with breast cancer

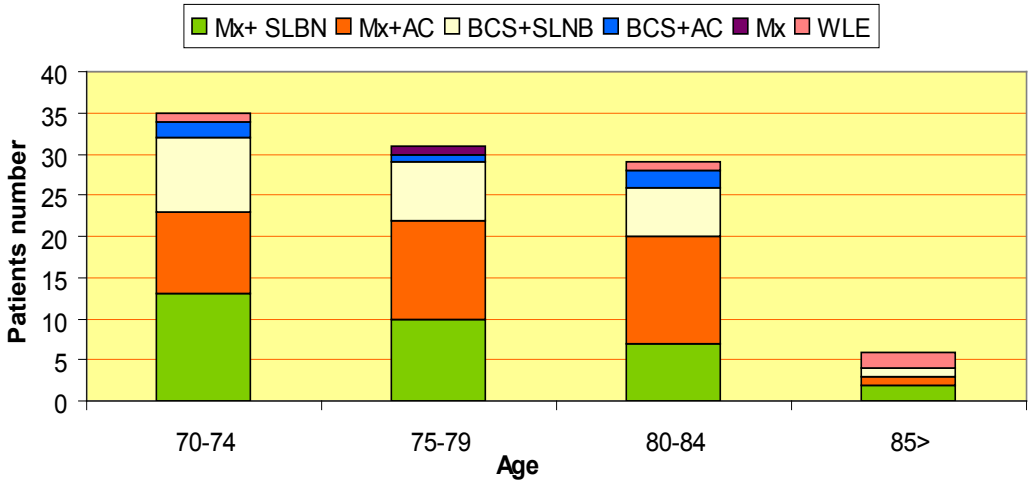

Figure 2. Surgical procedure by age @ diagnosis. Mx: mastectomy, AC: axillary clearence, BCS: breast conservative surgery, SLNB: sentinel lymph node biopsy

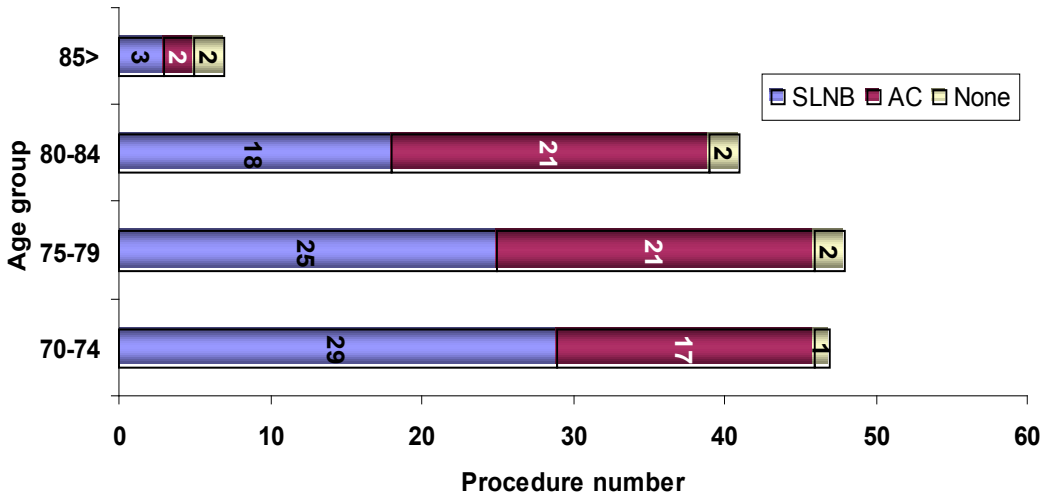

Figure 3. Axillary surgery in 143 breast cancer patients > 70

Table 1. Histology of breast cancer in 143 patients aged > 70

Histological type	Basildon % (N)	Poznan % (N)	Total % (N)
Invasive ductal carcinoma	52 (75)	23 (33)	76 (108)
Invasive lobular carcinoma	09 (13)	02 (03)	11 (16)
DCIS	03 (05)	03 (04)	06 (09)
Mixed	02 (03)	0.6 (02)	03 (05)
Others	02 (03)	0.6 (02)	03 (05)

trol, axillary node surgery also was an essential part of management. 52% of patients had sentinel lymph node biopsy only, 42% went through axillary clearance either with or without sentinel lymph node biopsy. The other 7% had no axillary surgery (**Figure 3**). The procedures used in the sentinel lymph node biopsy are blue dye as well as intra-dermal radio-colloid techniques.

The histology of the removed cancers showed invasive ductal carcinoma in 76% of cases, invasive lobular carcinoma in 11%, with DCIS in 06% (**Table 1**). The results indicate that elderly women can tolerate standard surgical procedures, go through uneventful early post operative period and survive disease-free interval for many years.

Discussion

It was presumed that elderly patients have simultaneous health problems that override the life-threatening risks associated with breast cancer. This idea in the past has often resulted in deprivation of these patients from optimum treatment of breast cancer.

Studies found that, the life expectancy of patients with breast cancers dying of other causes to be indistinguishable from that of the sex/age-matched population without breast cancer [6]. In a large study conducted in USA, it is found that women age ≥ 80 years with breast cancer receive less aggressive treatment and are more likely to die from breast cancer [7].

The published date indicates that breast cancer older age group patients do not necessarily always present with more locally advanced disease. The cancer is amenable to resection in a good number of cases. In literature it is mentioned that the older age group, presents with higher disease stages compared to younger patients. The cancer detected by clinical signs and imaging in 82% and 18%, respectively [4]. The issue of comorbidities is important in this age group. As we know, coexisting illnesses increase dramatically with age. this may include chronic obstructive airway disease, hypertension, cardiac diseases. Thrombo-embolic disease, diabetes and cerebro-vascular accidents. All these conditions independently limit their functional capacity, affects recovery, increase the risk of death and shorten life expectancy. It is not only the presence of chronic diseases can affect the treatment of a such patients, the older age group also has less use of screening mammography, lower diagnostic activity, and lower treatment activity. Careful patient assessment and selection prior to surgery is very crucial element when we think about surgery as a part of the management. In both canters we used ASA physi-

cal status classification system to assess the patients preoperatively. Some centres already using Adult Co-morbidity Evaluation (ACE-27) Tool to assess the patients [8].

Breast Conservation surgery had been introduced 35 years ago to minimise the physical and outcome of removing the whole breast. 1n 1970s, the clinical trials indicated equivalent survival when comparing mastectomy with BCS and adjuvant radiotherapy to the breast. Despite the fact that,the rate of local recurrence in the BCS and radiotherapy group were higher.The patients who developed local disease recurrence were treated by a mastectomy. Breast radiotherapy is widely accepted as gold standard treatment for patients with early breast cancer underwent BCS [9]. The performed surgical techniques in our series indicated clearly the predominance of mastectomy (70%) over BCS (30)%. This reflects many aspects as disease nature, tumour size, breast size, multi-focality or fitness for adjuvant treatment. Other factors that may affect decision are, the patient choice, as many of patients have fear of recurrence or prefer not to have radiotherapy after BCS. As we know the aims surgery to achieve good local control of both the primary tumour as well regional nodes. The axillary procedures doesn't affect the surgical time or surgery associated risk significantly, in the other hand improves the overall outcome of breast cancer management. Still we can see that the invasive ductal carcinoma is the most common malignant neoplasm of breast, consisting 75% to 80% of breast cancers [10].

Conclusions

The older age group ob breast cancer patients should have the same treatment offered to the younger counterparts. Close collaboration with geriatricians, anaesthetist, patient family and other health professionals to assess the patient status and limitations associated, all should be integral part of the decision-making process. This enables, proper management choices to be offered as well as delivery of adequate care to elderly patients with breast cancer. Establishing recommendations for management of older individuals with breast cancer is challenging, however more researches are needed to know more about the nature and behaviour of breast cancer in this group.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2017-01-16
Acceptance for publication: 2017-03-30

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ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.160

Major adverse cardiovascular events in patients after acute myocardial infarction treated invasively and different patterns of glucometabolic disturbances evaluated at mid-term follow-up

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ABSTRACT

Aim. To assess the impact of glucometabolic status (GS) evaluated at hospital discharge and at mid-term follow-up visit (FU-visit) on major adverse cardiovascular events (MACE) in patients (pts) with acute myocardial infarction (AMI) treated invasively.

Material and Methods. Study encompassed 368 AMI-pts treated invasively, in whom GS was assessed by 2-hour post load glycemia at hospital discharge and at FU-visit after 6 months. Patients were divided into two groups with respect to GS at hospital discharge: abnormal glucose tolerance (AGT, n = 149), normal glucose tolerance (NGT, n = 219). Each of those groups was divided into two subgroups with respect to GS at FU-visit: persistent AGT (pAGT, n = 101), transient AGT (tAGT, n = 48), newly detected AGT (newAGT, n = 114), persistent NGT (pNGT, n = 105). Median follow-up duration after FU-visit was 24.5 months.

Results. There was a trend towards more subjects with MACE in AGT than NGT group (24.2% vs. 16%; p = 0.051). More AGT-pts were hospitalized due to decompensated heart failure (6% vs. 0.5%; p = 0.002). However, there were no significant differences in MACE between subjects with pAGT and tAGT, including heart failure hospitalizations. Among NGT-pts there were no significant differences in particular MACE between newAGT-pts and pNGT-pts.

Conclusions. In AMI-pts treated invasively, who had abnormal glucose tolerance at hospital discharge, the improvement in glucometabolic status after 6 months was not related to lower risk of hospitalization due to decompensated heart failure.

Keywords: abnormal glucose tolerance, coronary artery disease, mortality, oral glucose tolerance test, heart failure hospitalization.

Introduction

Two-hour post load glycemia (2h-PG) is a well established parameter used to evaluate glucometabolic status and predict long-term prognosis in patients with coronary artery disease or acute myocardial infarction (AMI) [1–7]. Abnormal glucose tolerance (AGT) was associated with major cardiovascular events (MACE) in patients with stable angina or AMI [1–7]. Nevertheless, those studies did not show that any of the particular adverse events, except all-cause mortality, was related to long-term higher event rate in patients with AGT. Recently, it has been shown, that the initial risk stratification based on 2h-PG obtained at hospital discharge improved after reevaluation of glucometabolic status by oral glucose tolerance test repeated 6 months after AMI [7]. The study showed, that the risk of any-cause death was higher in patients with persis-

tent AGT, but the differences in MACE were non-significant with respect to changes in glucometabolic status [7]. Therefore, the aim of the presented study was to analyze particular MACE in patients with different glucose abnormalities evaluated at mid-term follow-up visit (FU-visit) with respect to glucometabolic status at hospital discharge.

Materials and Methods

Study population

The presented analysis was a part of a single centre, observational study prospectively enrolling AMI patients treated with percutaneous coronary intervention (PCI) between January 2012 and December 2013 who survived in-hospital period and were discharged to ambulatory care. Patients, in whom diabetes mellitus was diagnosed before admission or discovered by elevated fasting glycaemia ≥7 mmol/l on at least two occasions during hospitalization were excluded from the study. Repeated OGTT and other laboratory tests, electrocardiogram, echocardiography were planned as a part of follow-up visit on an outpatient basis approximately 6 months after AMI. Study population encompassed 368 consecutive AMI survivors in whom oral glucose tolerance test (OGTT) was performed at hospital discharge, and who completed FU-visit. Patients were followed and data considering remote MACE defined as the occurrence of death or any of the following events: either recurrent myocardial infarction, repeated percutaneous coronary intervention, coronary artery by-pass grafting, hospitalization for heart failure or stroke were collected. Median follow-up duration after FU-visit was 24.5 months. The enrollment of patients into the study was presented in detail elsewhere [7].

Definitions of glucometabolic status

Abnormal glucose tolerance (AGT) at discharge was defined as 2h-PG ≥ 7.8 mmol/l. Patients with 2h-PG < 7.8 mmol/l were classified as having normal glucose tolerance (NGT) at discharge. Persistent AGT (pAGT) at FU-visit was defined as 2h-PG ≥ 7.8 mmol/l detected at discharge and 2h-PG ≥ 7.8 mmol/l or antidiabetic pharmacotherapy at FU-visit. Transient AGT (tAGT) at FU-visit was defined as 2h-PG ≥ 7.8 mmol/l detected at discharge and no antidiabetic pharmacotherapy at FU–visit with 2h-PG < 7.8 mmol/l. Newly detected AGT (newAGT) at FU-visit was defined as 2h-PG < 7.8 mmol/l at discharge but 2h-PG ≥ 7.8 mmol/l or antidiabetic pharmacotherapy at FU-visit. Persistent NGT (pNGT) at FU-visit was defined as 2h-PG < 7.8 mmol/l at discharge and without antidiabetic pharmacotherapy at FU-visit with 2h-PG < 7.8 mmol/l.

Patients were divided into two groups with respect to glucometabolic status at hospital discharge: AGT (n = 149) and NGT (n = 219). Each of those groups was divided into two subgroups with respect to glucometabolic status at FU-visit: pAGT (n = 101), tAGT (n = 48), newAGT (n = 114), pNGT (n = 105).

Definition of AMI

Clinical AMI criteria evaluated on admission were: chest pain persisting > 20 minutes, ST segment elevation of at least 0.1 mV in two or more contiguous electrocardiographic leads or non-diagnostic electrocardiogram (without persistent ST segment elevation, left bundle branch block or acute ischemic changes) with enzymatic confirmation of AMI.

Ethics

All clinical data were obtained as the result of the diagnostic procedures and therapy, which were in accordance with the appropriate guidelines. All patients provided informed written consent for hospitalisation, invasive treatment, and use of their data for research purposes. Follow-up visit was performed on an outpatient basis as a routine follow-up. Remote follow-up was performed by telephone contact with patients or their families as well as during routine ambulatory visits. The study protocol was in line with ethical standards and was approved by the Institutional Review Board.

Statistical analysis

Continuous parameters were expressed as means with standard deviations unless otherwise specified, categorical variables were presented as numbers and percentages. Comparative analyses between groups were performed using Student's t-test for continuous variables and Chi-square or Fisher's exact test, as appropriate, for dichotomous parameters. Log-rank tests were used to compare cumulative survival. All tests were double-sided. P value < 0.05 was considered statistically significant. All analyses were performed using the software package Statistica (version 6.1, StatSoft Inc., Tulsa, OK, USA).

Results

Comparative analysis of demographic, clinical and laboratory data between patients with AGT and NGT at discharge who completed FU-visit.

Patients who had AGT at discharge, compared to patients with NGT, were older, more often had arterial hypertension and atrial fibrillation/flutter, had worse renal function. The proportion of patients with prior myocardial infarction, presence of NYHA class ≥ 2 as well as mean left ventricle ejection fraction was similar between two groups, however patients with AGT had more often severe left ventricle dysfunction or moderate/severe mitral regurgitation. Differences in pharmacotherapy were related to comorbidities, especially arterial hypertension and reduced left ventricle ejection fraction. Therefore, patients with AGT were more often treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, diuretics and aldosterone receptor antagonists. Detailed data were presented in **Table 1**.

Comparative analyses of any-cause mortality and major adverse cardiovascular events

There was a trend towards more MACE after the FU-visit in patients with AGT compared to NGT patients (24.2% vs. 16%; p = 0.051). More patients were hospitalized due to heart failure in AGT group compared to NGT (6% vs. 0.5%; p = 0.002). However, there were no significant differences in MACE between subjects with pAGT and tAGT, including heart failure hospitalizations. Among patients with NGT there were no significant differences between newAGT and pNGT with respect to particular MACE. Detailed data were presented in **Tables 2** and **3**.

Table 1. Comparative analysis of demographic, clinical, laboratory and pharmacotherapy data obtained at follow-up visit

Patients' characteristics at FU-visit	AGT at discharge, n = 149	NGT at discharge, n = 219	p value
Age [yrs] ≥ 65 years – n (%)	64 ± 9.4 63 (42.3)	61 ± 10 71 (32.4)	0.004 0.054
Female sex – n (%)	40 (26.8)	52 (23.7)	0.501
CCS class ≥ 2 – n (%)	10 (6.7)	21 (9.6)	0.331
NYHA class ≥ 2 – n (%)	54 (36.2)	66 (30.1)	0.221
Prior MI (before index hospitalization) – n (%)	31 (20.8)	43 (19.6)	0.778
Pre-hospital history of arterial hypertension – n (%)	108 (72.5)	127 (58)	0.004
Atrial fibrillation/flutter – n (%)	23 (15.4)	11 (5)	0.001
eGFR [ml/min/1.73 m^2] < 60 ml/min/1.73 m^2 – n (%)	83 ± 24.5 21 (14.1)	89.9 ± 20.5 14 (6.4)	0.004 0.013
Left ventricle ejection fraction [%] ≤ 35% – n (%)	46.4 ± 8.9 22 (14.8)	47.8 ± 7.4 12 (5.5)	0.109 0.002
Moderate/severe mitral regurgitation – n (%)	15 (10.1)	7 (3.2)	0.006
Anemia – n (%)	13 (8.9)	9 (4.2)	0.340
Fasting glycemia [mmol/l]	5.93 ± 0.8	5.7 ± 0.7	0.003
2h-PG* [mmol/l]	8.34 ± 2.5	7.28 ± 2.5	<0.001
Glycosylated hemoglobin [%]	6 ± 0.5	5.86 ± 0.5	0.004
HDL cholesterol [mmol/l]	1.3 ± 0.4	1.32 ± 0.4	0.576
LDL cholesterol [mmol/l]	2.45 ± 0.9	2.65 ± 1.1	0.065
Triglycerides [mmol/l]	1.4 ± 0.9	1.34 ± 0.8	0.519
Acetylsalicylic acid – n (%)	138 (92.6)	206 (94.1)	0.567
$P2Y_{12}$ receptor inhibitor – n (%)	146 (98)	209 (95.4)	0.187
Beta-adrenergic blocker – n (%)	145 (97.3)	208 (95)	0.274
ACE-I/ARB – n (%)	143 (96)	195 (89)	0.017
Statin – n (%)	141 (94.6)	208 (95)	0.865
Dihydropyridine calcium channel blocker – n (%)	40 (26.8)	40 (18.3)	0.053
Diuretic – n (%)	56 (37.6)	43 (19.6)	<0.001
Aldosterone receptor antagonist – n (%)	46 (30.9)	45 (20.5)	0.024
Antidiabetic pharmacotherapy – n (%)	15 (14.9)	0 (0)	-
Oral hypoglycemic agent – n (%)	13 (12.9)	-	-
Insulin – n (%)	2 (2)	-	-

Values presented as means ± SD or number and percentage of subjects. 2h-PG = two-hour post load glycemia; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; CCS = Canadian Cardiovascular Society grading of angina pectoris; eGFR = estimated glomerular filtration rate; FU-visit = follow-up ambulatory visit; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; NYHA = New York Heart Association Functional Classification; * in patients not treated with antidiabetic medication.

Table 2. Major adverse cardiovascular events after the FU-visit with respect to abnormal and normal glucose tolerance at hospital discharge

Adverse cardiovascular events	AGT at discharge, n = 149	NGT at discharge, n = 219	p value
Myocardial infarction – n (%)	10 (6.9)	8 (3.6)	0.183
PCI – n (%)	15 (10.1)	18 (8.2)	0.544
CABG – n (%)	2 (1.3)	7 (3.2)	0.260
Stroke – n (%)	2 (1.3)	4 (1.8)	0.720
Hospitalization due to heart failure – n (%)	9 (6)	1 (0.5)	0.001
All-cause mortality – n (%)	13 (8.7)	10 (4.6)	0.106
Total adverse events – n (%) *each event was counted only once*	36 (24.2)	35 (16)	0.051

Values presented as number and percentage of subjects. AGT = abnormal glucose tolerance, NGT = normal glucose tolerance, PCI = percutaneous coronary intervention, CABG = coronary artery by-pass graft.

Table 3. Major adverse cardiovascular events after the FU-visit with respect to abnormal and normal glucose tolerance at hospital discharge and at FU-visit

Among patients with abnormal glucose tolerance at discharge			
Adverse cardiovascular events	persistent AGT, n = 101	transient AGT, n = 48	p value
Myocardial infarction – n (%)	6 (5.9)	4 (8.3)	0.588
PCI – n (%)	9 (8.9)	6 (12.5)	0.499
CABG – n (%)	1 (1)	1 (2.1)	0.591
Stroke – n (%)	2 (2)	0 (0)	0.330
Hospitalization due to heart failure – n (%)	5 (5)	4 (8.3)	0.424
All-cause mortality – n (%)	12 (11.9)	1 (2.1)	0.034
Total adverse events – n (%) *each event was counted only once*	25 (24.8)	11 (22.9)	0.808
Among patients with normal glucose tolerance at discharge			
Adverse cardiovascular events	newly detected AGT, n = 114	persistent NGT, n = 105	p value
Myocardial infarction – n (%)	2 (1.8)	6 (5.7)	0.120
PCI – n (%)	10 (8.8)	8 (7.6)	0.758
CABG – n (%)	4 (3.5)	3 (2.9)	0.785
Stroke – n (%)	3 (2.6)	1 (1)	0.356
Hospitalization due to heart failure – n (%)	0 (0)	1 (1)	0.298
All-cause mortality – n (%)	7 (6.1)	3 (2.9)	0.242
Total adverse events – n (%) *each event was counted only once*	19 (16.7)	16 (15.2)	0.774

Values presented as number and percentage of subjects. AGT = abnormal glucose tolerance, NGT = normal glucose tolerance, PCI = percutaneous coronary intervention, CABG = coronary artery by-pass graft.

Discussion

In patients with AMI the relation of glucose abnormalities with adverse treatment outcome is undisputed [1, 2, 4–6, 8]. However, some studies showed that in patients during stable condition disturbances in glucose metabolism, which had been detected at hospital discharge, were predominantly transient [9–12]. Nevertheless, the prognosis in patients after AMI with respect to changes in glucometabolic status has not been widely studied. Recently it has been shown, that in patients who completed mid-term follow-up visit after AMI, reassessment of glucometabolic status by oral glucose tolerance test improved long-term risk stratification. Patients with abnormal glucose tolerance at discharge in whom glucometabolic profile improved had similar mortality to subjects with persistent normal glucose tolerance [7]. The presented study was undertaken to widen the scope of previously published data. It showed, that patients with AMI and abnormal glucose tolerance at hospital discharge had higher risk of hospitalization due to decompensated heart failure compared to patients with normal glucose tolerance. The risk was irrespective of changes in glucometabolic status after 6 months. Therefore, in the light of the results of previously cited study, one can conclude, that although the risk of death is lower when glucometabolic profile improves, the risk of hospitalization due to heart failure remains unchanged and high. There are several, although only hypothetical explanations of those observations. One of them, is that larger infarct size and acute hemodynamic derangement in the course of AMI is associated with insulin resistance, which resolves in stable condition. Patients with tran-

sient pattern of abnormal glucose tolerance may have increased risk of heart failure because of initial myocardial injury. Knudsen et al. showed, that patients with abnormal glucose regulation detected in-hospital had higher troponin peak value during AMI than patients with dysglycemia classified with respect to glucose metabolism after 3 months [10]. Hyperglycemia was associated with higher troponin levels, probably as a consequence of more extensive myocardial damage, and patients with hyperglycemia presented with larger infarct size compared with normoglycemic subjects [13]. Underlying microangiopathy of myocardial tissue may contribute to subsequent adverse remodeling of the heart in patients with hyperglycemia [14–16]. One should know, that the cut-off point for diabetes mellitus on 2h-PG value was primarily determined based on the prevalence of microvascular disease, especially diabetic retinopathy. Abnormal glucose tolerance in the presented study population of patients after AMI was not related to macrovascular complications, however the increased risk of heart failure hospitalization may be considered as a result of myocardial microangiopathy [17]. One cannot exclude that patients who recovered to normal glucose regulation were adherent to lifestyle modification, which may have caused decrease in insulin resistance. It has been shown, that very low-calorie diet, in some patients with diabetes mellitus, was associated with significant glucometabolic improvement, and some authors concluded that type 2 diabetes mellitus was a potentially reversible condition [18].

On the biological level, 2h-PG is associated with insulin resistance and decreased beta cell function of the pancreas, which contribute to hyperglycemia, oxidative stress and eventually endothelial dysfunction [1, 10, 19–20]. Prolonged and recurrent post-prandial hyperglycemia may play an important role in the development and progression of atherosclerosis [20]. Disturbed glucose metabolism in myocardial cells may also play role [14–16]. Therefore 2h-PG may be a direct therapeutic target in the treatment of cardiovascular disease [21–24].

Clinical implications

The major clinical implication of the presented study was, that patients, who had had overt manifestation of abnormal glucose tolerance during in-hospital period, and in whom a transient pattern of AGT was observed after 6 months did not have reduced risk of heart failure hospitalizations. Abnormal glucose tolerance detected during hospitalization due to AMI, even if transient following the acute period, has significant prognostic value. Therefore, the study emphasized the important role of oral glucose tolerance test performed during in-hospital and post-hospital period.

Study limitations

The study was nonrandomized and observational and encompassed relatively low number of patients.

Conclusions

In patients with AMI and abnormal glucose tolerance at discharge, who were treated invasively, the improvement in glucometabolic status after 6 months was not related to lower risk of hospitalization due to decompensated heart failure.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-1-20
Acceptance for publication: 2017-03-27

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ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.132

Assessment of women's awareness about reproductive and breast cancers

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ABSTRACT

Introduction. The aspect of prevention and treatment of malignant tumours is a key problem of public health in Poland, posing a great challenge for the health care system. A perfect method of fighting against neoplasms is prevention. Its widespread use may allow reduction in the risk of developing cervical and breast cancer.
Aim. The aim of the paper was to assess women's awareness about prophylaxis and risk factors related to the development of reproductive and breast cancers among women subject to the survey.
Materials and Methods. The analysis comprised a group of 154 women at the age from 17 to 70. The study was conducted between 17 March and 30 July 2015. The research tool used in the study was an independently prepared survey questionnaire.
Results. The biggest group of respondents (48.70%) was made up of women at the age from 20 to 30. 68.83% of the women had a secondary level education, 42.20% were women from cities of between 51,000 to 100,000 inhabitants and only 1.94% represented large cities of over 500,000 inhabitants. A change in the size or shape of the breast (88.96%) and changes in the look of the nipple (86.36%) were quoted as the most frequent symptom of breast cancer.
Conclusions. The knowledge about reproductive organs and breast cancer prevention among women is not fully satisfactory and needs to be broadened. Media (internet, television) were the most popular source of information on cancer prevention among the respondents. It is necessary for family doctors and midwives to intensify health-care activities aimed especially at women who are the age associated with an increased risk for cancer.

Keywords: cancer, risk factors, prevention.

Introduction

Breast cancer is the most frequently diagnosed malignant tumour among women in Poland. It accounts for about 20% of the total number of cancers affecting women [1].

Up until now the direct cause of the development of breast cancer has not been identified. The most important risk factors include female sex, age and the occurrence of breast cancer in relatives in the first and second degree of consanguinity [2]. Women with a BRCA1 gene mutation have about 45–90% higher risk of developing breast cancer [3], and the risk of ovarian cancer stands at the level from 16 to 60% [4]. In comparison, in women with a BRCA2 gene mutation the risk of developing breast and ovarian cancer is 31–56%

and 11–27% respectively [5]. Besides, the formation of breast neoplasms is significantly influenced by a particular lifestyle, which is a combination of many factors such as the type of diet followed, especially rich in animal fats, tobacco smoking, drinking alcohol or insufficient physical activity.

Another risk factor related to developing breast cancer is the early age of the first menstrual period and the late age of the last menstrual period. Getting the first period before the age of 16 causes the risk of breast cancer to rise by about 75%. Likewise, the first delivery at the age of 35 and later increases this risk as many as 2.6 times [6]. On the contrary, late first menstrual cycle, full-term pregnancy before the age of 20, breastfeeding and taking physical exercise decrease the probability of getting cancer [7].

Observations carried out over the past few years confirm that the most substantial role in the development of cancer of the female reproductive system is played by the sexual activity of both women and men. It is particularly visible in the case of cervical cancer. Many studies [8–10] show that apart from HPV, which is the main factor in the aetiology of cervical cancer, other elements favourable for the development of the condition are tobacco smoking, lowered immunity, hormonal disorders and vitamin A deficiency. The presence of the HPV virus in 99.7% of the cases of cervical cancer confirms the relationship between an HPV infection and cervical cancer [11].

A perfect method for combating cancer is prevention. It is possible to reduce the risk of cervical, ovarian and endometrial cancer by the implementation of preventive measures.

The purpose of primary prophylaxis is to prevent the development of malignant tumours through an overall set of activities which aim at lowering the risk of getting cancer. Primary prophylaxis intends to reduce the mortality rate and development of malignant neoplasms by defining factors which impact the emergence of the disease, finding out about mechanisms related to how the disease progresses and promoting a pro-health lifestyle.

Apart from primary prophylaxis, an important role is played by secondary prophylaxis, which consists in screening. Screening makes it possible to detect precancerous conditions or early stages of cancer. The early detection of cancer affords a greater chance of a cure by using treatment methods which are less severe for the patient. It also reduces the risk of metastasis or relapse, which results in longer life and improved quality of life [1].

In order for screening tests for cervical and breast cancer to be successful, it is important to ensure that such tests are organized effectively and social awareness of the issue is augmented and maintained.

Aim

The aim of the paper was to assess women's awareness about prophylaxis and risk factors related to reproductive and breast cancers.

From the initial problem, it was hypothesized that women have a very good understanding of the factors and prevention of gynecological and breast cancer in women.

Materials and Method

The study was conducted between 17 March and 30 July 2015. The group subject to analysis comprised 154 women at the age from 17 to 70. The group included students, employees, disability benefit recipients and pensioners. The surveyed women varied in terms of age, place of residence, education, marital status and type of work pursued.

The research tool used in the survey was an independently prepared questionnaire consisting of 23 open – ended and close – ended questions. The questions were formulated in a way that made them comprehensible for a large group of people. The questionnaire contained questions concerning social and demographic data (age, marital status, place of residence), preventive medical examination and risk factors connected with female reproductive and breast cancers. Furthermore for each question were used criteria of points (0 – no, 5 – very good).

The results obtained were analyzed on the basis of Kruskal-Wallis test, Fisher-Freeman-Halton test and Mann-Whitney test. The p – value of < 0.05 was adopted as the level of statistical significance.

Results

Social and demographic data related to the surveyed women is found in **Table 1**. The most numerous group (48.70%) was made up of women at the age from 20 to 30. The study reveals that 68.83% of the respondents, that is 106 women, completed secondary education and 12.98% possessed vocational qualifications. The analysis of places of residence shows that 42.20% of the women were from cities of 51,000 to 100,000 inhab-

itants, and only 1.94% from large cities of over 500.000 inhabitants.

29.81% of the respondents reported breast and ovarian cancers to be present in their relatives in the first and second degree of consanguinity.

The results show that over 3/4 of the women (n = 106; 68.83%) regularly visit a gynecologist (p = 0,002297). Significant differences in the knowledge of screening were found concerning age. Unfortunately, only 25.97% ask a consultant to prescribe breast ultrasonography (p = 0,0002). Depending on age there was statistically significant difference in the knowledge about the test. 9.74% (15 women) asked a doctor to carry out a breast ultrasound. However, the examination was denied. Another worrying fact is that 20.77% of the respondents had never had cytology performed. In the case of 4.54% (7 women) cytology was performed 3 years before and in the case of 35.71% (55 women) one year before. In the current calendar year cytology was performed in 30 women (19.48%).

61.68% of the women perform a breast self-exam up to the 10th day of the cycle. The remaining numerical and percentage data is presented in **table 2**.

The assessment of knowledge about risk factors concerning breast and cervical cancers is presented in **figures 1** and **2**. A statistically significant difference (p = 0.0330) was observed resulting from the relation between the age of the respondents and the knowledge of risk factors concerning breast and cervical cancers.

As regards the most frequent symptom of breast cancer, the surveyed women pointed to changes in breast size and shape (88.96%) and changes in the look of the nipple (86.36%). The remaining symptoms of

Table 1. Social and demographic data of the surveyed women

Factors	N = 154	%
Age		
Below 20	19	12,33
20–30	75	48,70
31–40	14	9,09
41–50	24	15,58
51–60	14	9,09
61–70	8	5,19
Education		
Higher	28	18,18
Secondary	106	68,83
Vocational	20	12,98
Place of residence		
Up to 10,000 inhabitants	61	39,61
11,000–50,000 inhabitants	21	13,63
51,000–100,000 inhabitants	65	42,20
101,000–500,000 inhabitants	4	2,59
Over 500,000 inhabitants	3	1,94
Marital status		
Single	77	50
Married	46	29,87
Divorced	8	5,19
Widow	9	5,84
Domestic partnership	14	9,09

Table 2. Time of breast self-exam

Time	N = 154	%
Up to the 10th day of the cycle	95	61.68
Up to the 20th day of the cycle	24	15.58
Day of the cycle is not important	15	9.74
Do not know	20	12.98

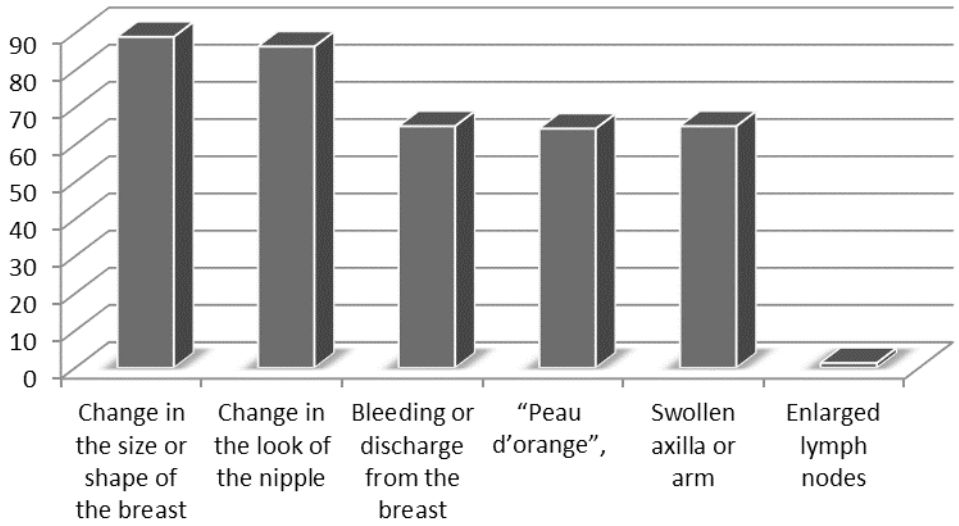

Figure 1. Assessment of knowledge about risk factors concerning breast and cervical cancers

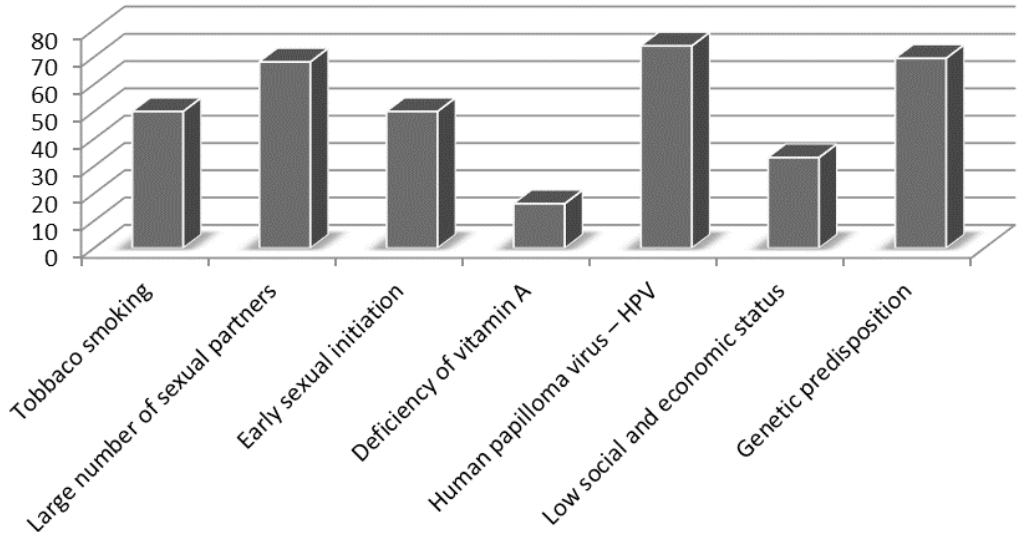

Figure 2. Assessment of women's knowledge about risk factors related to cervical cancer

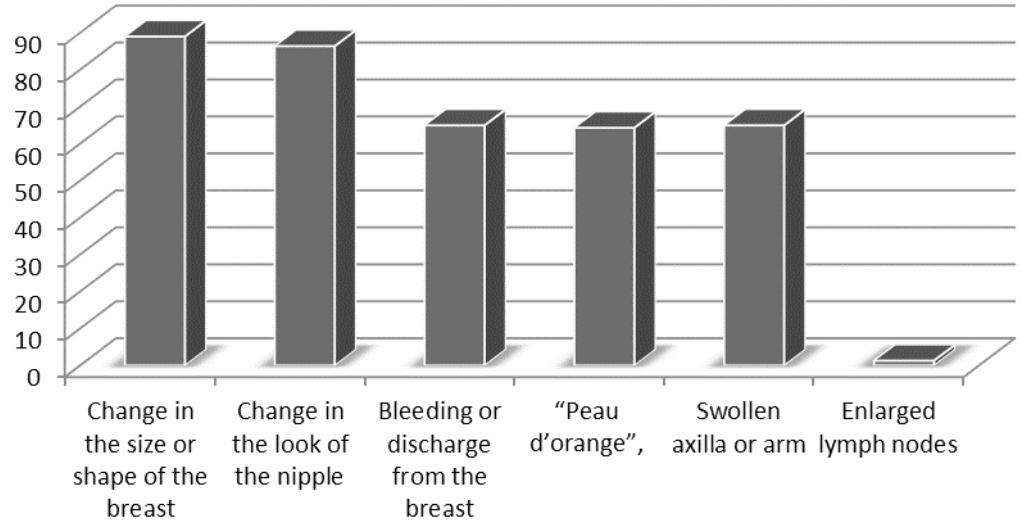

Figure 3. Symptoms of breast cancer

carcinogenesis are presented in **Figure 3**. The analysis showed no statistically significant differences between the knowledge of clinical symptoms of breast cancer and age.

The respondents used a variety of sources to find out about cancer. 73.37% obtained information from the Internet, 42.20% from TV and 31.16% from medical magazines. Only 13.63% (21 women) obtained information from mid-level medical personnel. The remaining numerical and percentage data is presented in **Table 3**.

The study also revealed that 92.85% of the respondents believe that screening tests for cancer should be obligatory. 66.23% know that mammography is a radiological examination of the breast and 88.96% know that cytology is a method of cervical screening consisting in collecting cells at the outer opening of the cervix. The remaining numerical and percentage values are presented in **Tables 4** and **5**.

Table 3.Sources of information used by the respondents

Internet	113	73.37
TV	65	42.20
Radio	16	10.38
Medical magazines	48	31.16
Conferences/Campaigns	36	23.37
Doctor	45	29.22
Midwife/Nurse	21	13.62

Table 4. What is mammography?

	N = 154	%
Radiological examination of the breast	102	66.23
Breast ultrasonography	45	29.22
Visual inspection of the breast	2	1.29
Palpation of the breast	3	1.94
Do not know	1	0.64

Table 5. What is cytology?

	N = 154	%
Collecting cells at the outer opening of the cervix	137	88.96
Ultrasonography	15	9.74
Cervical self-exam	0	0.00
Do not know	2	1.29

Discussion

Despite access to knowledge about factors precipitating the onset of carcinogenesis, reproductive and breast cancers still pose a major problem for modern oncological gynaecology.

The National Cancer Institute [12] puts the risk of developing breast cancer at the level of 12%. It is estimated that the risk in the case of 40-year-old, 50-year-old and 60-year-old females is 1 out 69, 1 out of 42 and 1 out 29 women respectively. One can also observe an increase in the occurrence of the condition among younger females. It is probably associated with a higher ratio of women subject to preventive screening. However, the biggest group of cancer-affected patients is made up of women between the age of 50 and 69, who are subject to screening tests performed as part of the National Breast Cancer Early Detection Programme [13].

Performing screening tests allows to diagnose cancer at the early stage of its clinical condition. It is currently recommended for women at the age 50–69 to have screening mammography performed once a year. Moreover, it was proven that an additional physical examination of the breast reduces the mortality rate ranging from 5% up to 20% [14].

The value of mammography in screening is high because women subject to this type of assessment have an opportunity to detect a lesser change than in the case of a breast self-exam or breast ultrasound. This study shows that 66.23% of the surveyed women know what mammography consists in and how significant it is in the prevention of cancer. Maybe this is related to the young age of women participating in the study. On the other hand, Najdyhor et al. [15] state that 97% of the respondents understand what mammography is about (37% women aged 41–50, 29% women aged 51–60 with secondary education) but only 52% have taken advantage of this test. Research by Przysada et al. [16] shows that 53% of women at the age between 51 and 60 have had a mammography done once in their life.

A basic measure used in the prevention of breast cancer is to perform a self-exam. This study shows that there are women who possess no knowledge about such a procedure. 12.98% of the women did not respond to the question posed and 9.74% of the women think it is has no significance when and how such a procedure should be performed. Research by Paździor et al. [17] reveals that women perform a breast self-exam, but in an irregular way. Only 36% of the women perform a self-exam once a month, while 42% do not pay attention to the right time of doing it. Similar results were obtained by Przestrzelska et al. [18] where, out of 77% of the women performing a self-exam, 12% do it regularly and 10.7% during the recommended time of the menstrual cycle.

An important element of prophylaxis is to perform a regular examination of the breast during an appointment with a gynecologist. This study shows that out of 68.83% of the women presenting to a gynecologist only 25.97% ask for a breast ultrasound. It is also worrying that 9.74% of the women did not have such a test done even if they asked for it. Research by Przysada et al. [16] shows that 60% of the women hardly ever have their breast examined during an appointment with a gynecologist. Only 21% of the women have a breast ultrasound done during each medical checkup, whereas 8% have never had such a test done.

Other elements of breast cancer diagnostics include medical history, physical examination and microscopic examination subject to individual recommendations.

A symptom of breast cancer is a tumour which is markedly different from neighbouring tissues. It is less seldom diagnosed as an ill-defined thickening or concentration of tissue. Advanced cancer-linked changes include skin dimpling, nipple retraction, erythema, swelling, peau d'orange and enlarged irregular veins. Additionally, the ulceration of skin, breast muscles and thoracic wall can be observed.

A rare symptom of breast cancer is a bloody or serous, sticky or watery discharge from the nipple. It must be underlined though that a possible discharge from the nipple should be differentiated from other

non-cancerous causes such as cysts, enlarged milk ducts, using contraceptives or problems with the body's hormones [19].

This analysis shows that in the case of 88.96% of the surveyed women a feature which may testify to breast cancer is a change in the size and shape of the breast and a change in the look of the nipple (86.36%). The lowest number (n = 2; 1.29%) pointed to enlarged lymph nodes as a symptom of breast cancer. Different results were obtained by Paździor et al. [17], where 73% of the respondents quoted the appearance of a lump in the breast, 40% pointed to a bloody discharge from the nipple and 35% to enlarged lymph nodes. Also different results were obtained by Zych et al. [20] from which it results that in the case of most women the primary symptom of breast cancer is the appearance of a lump (84.3%), enlarged lymph nodes (63.7%), discharge from the nipple (66%) and nipple pain (44.6%).

Cervical cancer is a condition closely related to a lifestyle. It is largely contingent on risk factors which include an inadequate amount of physical exercise, bad eating habits, taking stimulants or inappropriate sexual behaviour.

Observations carried out over the past few years have affirmed that sexual activity is a factor that determines the frequency of cervical cancer occurrence. It is particularly visible in female partners of men with a chronic HPV infection.

This analysis shows the main precipitating cause of cervical cancer quoted by the respondents was an HPV infection (74.02%), a large number of sexual partners (68.18%) and genetic predisposition (69.48%). It is confirmed by a study done by Cichocka et al. [21], in which 66% of the respondents point to an HPV infection as the main source of cervical cancer. A different result was obtained by Mędrela-Kuder [22], where as many as 90% of the women consider a chronic HPV infection as a risk factor of cervical cancer.

25–30% of deaths caused by cancer are related to smoking tabacco [23, 24]. In the case of cervical cancer, the probability of developing the condition is twice as high among smokers than non-smokers [24].

The impact which tobacco smoking has on the risk of developing cervical cancer is not fully recognized. Toxins present in tobacco smoke most likely affect the repair process in the DNA of the cervical epithelium cells. Prokopczyk et al. [25] showed a higher concentration of oncogenes in cervical mucosa in tobacco smokers. Additionally, a direct pro-carcinogenic influence of nicotine and conitine was confirmed.

50% of the women surveyed in our study declared tobacco smoking to be a significant factor contributing to the development of cervical cancer.

The basis of diagnostic tests for precancerous and cancerous processes in the cervix is a Pap smear. Kazimierczak et al. [26] conducted research which covered 200 females from the Silesia and Świętokrzyskie Provinces. They provided evidence that women do not have sufficient knowledge about prophylactic cytological investigation for cervical cancer. Only one in every three respondents performed a cytological test once a year, 30% perform it very seldom and 15% do not do it at all. In the group of women aged between 19 and 23, 41% of the respondents had their cytological test done for the first time and 10% of the women had never had cervical specimens collected from the ectocervix. This study revealed that 19.48% had their smear test performed in the current calendar year, 35.71% a year before, 12.98% two years before and 10 women (6.49%) 3 years before.

Health education, which comprises health-improvement activities, ways to prevent diseases and knowledge related to factors precipitating disease emergence, is an inseparable and complementary element of health promotion. A study by Najdyhor et al. [15] shows that a significant role is played by the media, including TV and the press. A much lesser role is played by healthcare workers. Hence, it is a small wonder that as many as 47% of the respondents found out about prophylaxis from TV, 30% from a consultant and only 7% from a nurse. Similar results were shown in this study, where 42.20% of the respondents obtained knowledge about cancer from TV and 31.16% from medical magazines. Only 13.63% (21 women) obtained relevant information from medical staff.

Conclusions

The present study and the analysis of the collected material allowed to get to the following conclusions:

1. Knowledge about reproductive and breast cancer prevention among women is not fully satisfactory and needs to be broadened.
2. Media (internet, television) were the most popular source of information on cancer prevention among the respondents.
3. Extensive social education plays a major role in cancer prevention. A significant responsibility for that rests on family doctors and midwives who, through their statutory activity, should take care of all women, in particular those representing an increased risk group.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-1-20
Acceptance for publication: 2017-03-27

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ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.128

Can a healthcare worker be a source of an infection of a patient – a risk of transmitting the chickenpox and shingles virus VZV by the staff of hospital wards – preliminary research findings

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ABSTRACT

Introduction. Chickenpox is a highly infectious disease, caused by the *Varicella-zoster* virus. An infection during pregnancy poses particular risk, as it may have serious consequences for both the pregnant woman and the fetus. The only effective and safe method of preventing chickenpox is protective vaccination.
Aim. This study aims to assess the risk of contracting the *Varicella-zoster* infection in a selected population of hospital workers, as well as the further transmission of the virus to newborns, mothers and older children.
Materials and Methods. A survey was conducted in September 2014 in three public hospitals in Poznań, among nurses and midwives working in paediatric, neonatal and maternity wards. 136 nurses and midwives participated in the survey.
Results. The analysis of the findings reveals that 114 staff members of the hospital wards, i.e. 83.82%, have had chickenpox in the past, 14 respondents (10.29%) have never had this illness, and 8 (5.88%) do not know if they have been ill, which means that 16% of the respondents could potentially contract chickenpox. For the majority of nurses and midwives (103) the infection had taken place before they started work. However, 11 respondents (8,08) were infected during employment.
Conclusions. 1) Nearly one out of 4 hospital staff members had no history of chickenpox contraction at the beginning of their employment. 2) Nearly 15% of the workers confirm that at the beginning of employment their immunity status was established on the basis of an interview. 3) The majority of employees negatively interviewed for chickenpox history have not been recommended to be vaccinated against this disease.

Keywords: chickenpox, healthcare staff, vaccinations

Introduction

Chickenpox is a highly infectious disease, caused by the *Varicella-zoster* virus (VZV), which belongs to the group of *Herpesviridae*. The infection is reactivated in the form of shingles.

Every year around 150–200 thousand people contract chickenpox, out of which 1,000 require hospitalisation, due to the severe course of the disease and complications. 208,276 cases of chickenpox were reported in 2012, whereas 1,364 persons were taken to hospital – which means that 1 in every 153 patients was hospitalised. In 2013 – 178,379 infections were reported [1].

As many as 90% of cases of chickenpox affect children and adolescents up to the age of 15 [2]. In many countries there are no precise statistics related to

this disease. However, data collected in the course of observational studies reveal a large scale of the problem of chickenpox infections and the resulting complications in the countries where mass preventive programmes through vaccinations are not run [3]. A large German study showed that the frequency of hospitalisation resulting from chickenpox and its complications before the introduction of the preventive vaccinations programme was 14.1 out of 100,000 children up to 16 and the rate for infants was 89.5 out of 100,000 [4].

The following groups of patients are particularly vulnerable to the severe course of chickenpox [2, 5]:

- persons with primary and secondary immunodeficiency,
- pregnant women,
- preterm newborns, born before the 28th week of pregnancy, regardless of the serological situation of the mother, as well as preterms born from seronegative mothers after the 28th week of pregnancy,
- newborns, particularly those whose mothers contracted chickenpox 5 days before or 2 days after birth,
- patients with chronic skin diseases (e.g. atopic dermatitis), or respiratory diseases.

Particular attention should be paid to the issue of the VZV infection during pregnancy, as it may have serious consequences for both the pregnant woman and the fetus [2]. Infection in the first 20 weeks of pregnancy carries a 2% risk of the innate chickenpox syndrome in the infant, with the hypoplasia of limbs, low birth weight, scars on the skin, microcephaly, chorioretinitis, cataracts and other organ lesions, as well as a 30% risk of death in the first months of life [6]. Chickenpox also poses a risk for the pregnant woman, particularly in the third trimester of pregnancy, as it causes a risk of pneumonia with the VZV etiology, which may lead to death in as many as 45% of cases [6].

Due to the high infectivity of chickenpox, the only effective and at the same time safe method of its prevention is protective vaccination.

Healthcare workers are a professional group which, on the one hand, is exposed to the risk of infection through contact with patients, or infected material and, on the other hand, may become a source of infection for patients. The latter aspect, often disregarded, imposes a moral obligation on the healthcare staff and personnel to protect themselves from infections, especially those which can be prevented through vaccination. In the first place this obligation refers to the staff and personnel members who have contact with patients from the risk groups of the severe course of the disease and complications, i.e. patients with chronic illnesses, newborns, infants, and pregnant women. The role of healthcare workers in transmitting infections of influenza and diphtheria has been described and documented. VZV infection also belongs to this group of diseases.

According to American standards only staff and personnel members with documented immunity to the VZV infection may have contact with patients with chickenpox, disseminated shingles, or uncovered skin lesion related to shingles. Nevertheless, it should be pointed out that a patient's infectivity starts 2 days before the appearance of the first symptoms, so it is difficult to conduct such a selection of workers from the beginning [7]. Therefore, it would be justified to introduce a mandatory test of the level of the IgG antibodies among staff and personnel of infectious diseases wards and vaccinate those who do not have the immunity against the VZV virus.

Aim

The research objective was to assess the risk of the chickenpox virus infection in the selected population of workers of hospital wards and the further transmission of the virus to newborns, mothers and older children.

Material and Methods

Diagnostic survey was used as a method. On the basis of literature and the authors' professional experience, an original questionnaire was formulated. It consisted of eight closed questions, related to the respondents' chickenpox history (two questions), their decision to get vaccinated against chickenpox (two questions), their contact with the VZV at work (one question), as well as the medical care provided by the occupational physician in terms of the chickenpox prevention (three questions). Along with the above mentioned questions, the respondents' demographic data were collected (gender, age, work experience, occupation, workplace, education).

The survey was conducted in September 2014 in three public hospitals in Poznań, among nurses and midwives employed in paediatric, neonatal and maternity units, as well as in delivery rooms and wards of pregnancy pathologies. The medical staff and personnel selected for the survey had contact with patients who run the highest risk of contracting chickenpox with a severe course and complications. 136 employees took part in the survey: 58 (42.65%) nurses and

Table 1. Characteristics of the surveyed group of health professionals

Total number of respondents	N = 136
Gender	women 97.8% (n = 133) / men 2.2% (n = 3)
Neonatal/maternity/other wards	neonatal ward – 63.24% (n = 86) paediatric ward – 18.38% (n = 25) maternity ward – 5.88% (n = 8) delivery room – 6.62% (n = 9) pregnancy pathologies ward – 5.88% (n = 8)
Age	20–30 – 22.8% (n = 31) 31–40 – 27.9% (n = 38) 41–50 – 40.5% (n = 55) > 50 – 8.8% (n = 12)
Work experience	< 10 – 36.8% (n = 50) 10–20 – 25.7% (n = 36) 21–30 – 32.4% (n = 44) > 30 – 5.1% (n = 7)

78 (57.35%) midwives. Data related to the group of respondents are presented in **table 1**.

The quantitative study was conducted by means of the JMP 4.0.2. statistical programme.

Results

The conducted analysis shows that 114 of the surveyed employees of hospital wards, i.e. 83.82%, have had chickenpox in the past, whereas 14 respondents (10.3%) have not had this disease, which means that more than 16% of the survey participants are potentially vulnerable to contracting chickenpox. The majority of the nurses and the midwives, i.e. 75.74% (103 respondents) were infected with the *varicella* virus in the pre-employment period. However, 11 respondents (8.08%) were infected during their employment. Thus, if a similar survey had been conducted for this population at the moment they were beginning their employment, the proportion of persons with the chickenpox history would have been 24.26% (33 persons). These data have been illustrated in **Figure 1**.

As many as 91 respondents (66.91%) have had contact with a patient with chickenpox or shingles at work. However, only 20 survey participants (14.70%) declare that the occupational physician asked them about their *varicella* history during the interview before employment. Nearly a third of the respondents i. e. 38 respondents (27.95%) did not hear such a question, whereas 78 persons (57.35%) do not remember if this issue was raised during the medical interview. In the population of healthcare workers with no history of *varicella*, only in 2 cases the occupational physician informed them about a possibility of getting vaccinated and only in one of these cases such vaccination would have been financed by the employer. Only two persons from the group of employees with negative *varicella* history got vaccinated, which accounts for only 9.09%. On the other hand, 50% of this group (11) would not decide to get vaccinated, even if the procedure were financed by the employer. As few as 8 respondents (36.36%) would take advantage of the procedure and 3 persons (13.65%) have no opinion in this matter (**Figure 2**).

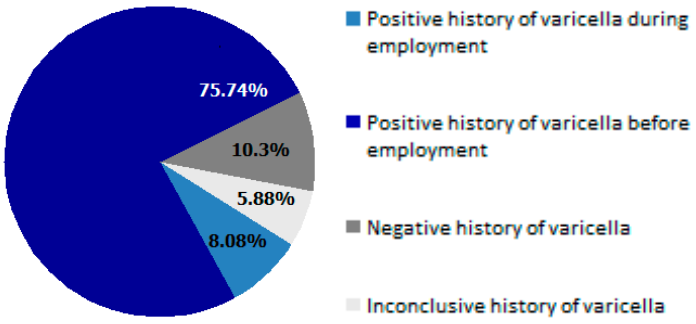

Figure 1. The percentage of respondents surveyed for *varicella* infection before the onset of work

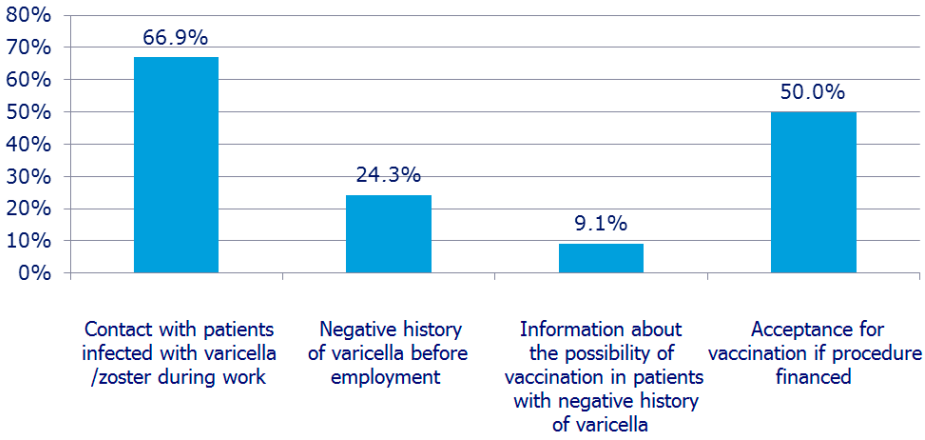

Figure 2. Selected aspects of prevention and treatment in the surveyed group of health care professionals

Discussion

Among the surveyed healthcare staff and personnel who have contact with patients from the groups of a high risk of a severe course of *varicella* infection, at the moment of the survey every sixth of them cannot be regarded as immune to the virus, on the basis of the interview. Almost 10% of the respondents were infected with *varicella* during their employment in the hospital. In other words, at the onset of employment in hospital wards every fifth person should be considered vulnerable to VZV infection in their first professional contact with a patient. Literature based on the results of serological tests for the VZV antibodies in the IgG class reveals that the proportion of staff vulnerable to infection is lower [8, 9]. A Spanish study showed 95% of seropositive healthcare employees, as opposed to 83% in our research [8]. In compliance with the guidelines of the Centre for Disease Control and Prevention (CDC), staff members who, until the moment of exposure, had not been vaccinated against chickenpox and who cannot be deemed immune on the basis of the generally accepted criteria (documentation, serological test, or two doses of vaccination), in the case of a contact with a patient with chickenpox, disseminated shingles, or uncovered shingles rush, should be removed from work between the 8th and the 21st day from the contact [7].

Only around 15% respondents declare that at the onset of their employment they were asked about their history of *varicella* infection, the majority of them do not remember this fact, whereas nearly every third respondent claims that such interview never took place. Among the employees without documented immunity, only two were informed about the indication for vaccination against chickenpox. Over 66% of respondents have had contact with patients infected with VZV in the course of their professional activity. As the research shows, the majority of employees participating in the survey are exposed to contact with patients infected with VZV. Lack of information and a failure to undertake preventive actions poses a risk for employees to be infected with the *varicella* virus and to further transmit it. Taking into account the fact that infectivity starts 2 days before the first symptoms of chickenpox, the procedure of removing a staff/personnel member from work upon the appearance of the first symptoms does not seem justifiable. Instead, the recommended by CDC principle of removing from work employees potentially vulnerable to infection would bring much better results. Unfortunately, in Poland there are no guidelines for collecting data related to employees' immunity, which substantially hampers effective protection of patients exposed to the risk of infection.

The presented findings definitely indicate a high proportion of healthcare workers who, on the one hand, are vulnerable to infection with the chickenpox and shingles virus, and on the other, are themselves a potential source of infection for patients. The most worrying facts are: the lack of knowledge about the state of immunity of workers, the lack of awareness of the necessity of taking a preventive action by means of protective vaccination among healthcare employees, as well as the lack of appropriate procedures for situations when an employee has had contact with a person infected with VZV. A case of chickenpox infection in the maternity ward in Częstochowa, described in *Medycyna Praktyczna* magazine, may serve as an example. The Director of the hospital underlines the fact that 3 members of the maternity ward workers were removed from work for 2 weeks. However, undertaking the proper action in this situation was difficult because of

the fact that no data about the employees' immunity against VZV had been collected before.

The findings related to the recommendations with respect to VZV vaccinations for employees who are not immune to the chickenpox virus are equally alarming. Only 9% (2 persons) of those who were not proven to have the immunity, were recommended to get vaccinated, and only one person was offered a vaccination at the employer's cost. Lack of such recommendations in Polish healthcare institutions, shown by this research, results from the absence of official guidelines for vaccinating medical staff against the chickenpox virus in Poland. It is worthwhile to mention the fact that the recommendations for vaccinating employees vulnerable to chickenpox, particularly those working in paediatric, gynaecological-maternity, oncological, and intensive care units, have been issued by the German Standing Committee on Vaccination at the Robert Koch Institute (STIKO), CDC, Immunization Action Coalition, Green Book and Royal College of Physicians in Great Britain and others [7, 11–14].

The recommending bodies stress the fact that the risk of a hospital infection with the *varicella* virus disrupts the organisation of hospital care and the necessary preventive measures are time-consuming and costly.

Taking into account the security of patients and the staff, functioning of healthcare institutions and the costs, it seems justified to expand the recommendations for protective vaccinations of the healthcare staff in Poland [15–17]. On the basis of literature, as well as the findings of the conducted research, it is reasonable to consider performing serological tests of medical staff with a negative history of chickenpox.

Another disquieting fact are the data revealing that only a half of the surveyed nurses and midwives would decide to get vaccinated against *varicella*, even if the procedure were financed by the employer.

The Society for Healthcare Epidemiology of America emphasises the fact that protective vaccinations of healthcare employees are safe and effective and serve the purpose of protecting both the staff and the patients. Moreover, the introduction of an educational programme for medical staff has substantially improved the proportion of vaccinated healthcare employees. The Society is of the opinion that if the percentage of the vaccinated employees remains low, the vaccinations should be made mandatory [18]. A further question that arises here is whether or not vaccinations against chickenpox should become a part of the Vaccination Calendar.

Conclusions

1. Nearly every fourth healthcare employee could not be regarded as immune to VZV at the onset of their employment, on the basis of the interview.
2. Less than 15% of workers confirm that at the beginning of their employment in a healthcare institution their immunity status was established by means of an interview.
3. The majority of employees with a negative *varicella* history were not recommended to get vaccinated against chickenpox.
4. It is worthwhile to consider routine testing of the staff of infectious diseases wards for the *varicella* antibodies and persons without the immunity should be obligatorily vaccinated.
5. It would be justified to introduce vaccinations against chickenpox into the Vaccination Calendar.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-1-20
Acceptance for publication: 2017-03-27

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ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.206

Quality of life of the elderly residents of nursing homes and patients of the Psychogeriatric Day Ward

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ABSTRACT

Introduction. Due to the prolonged average life span and constantly increasing number of the elderly, research of this population's quality of life (QoL) is being conducted to assess the spheres requiring improvement.
Aim. To assess and compare the life quality in different domains between residents of nursing homes (NH) and patients of the Psychogeriatric Day Ward (PDW).
Material and Methods. The study encompassed 68 PDW patients and 62 NH residents. The WHOQOL-BREF questionnaire and a structured interview concerning diseases, different forms of support and activities preferred were used.
Results. Women predominated among the subjects (83%). The elderly aged 75–90 constituted the majority (64.62%). The average assessment of QoL in the whole group amounted to 3.6 points. No significant differences in the assessment of QoL satisfaction and one's own health satisfaction were observed between PDW patients and NH residents. The participants of both groups assessed the highest QoL in the environment domain and the lowest in the social relationships domain. A relationship between higher QoL in the physical health domain and participation in social forms of spending free time was observed. Relationships between QoL in particular domains and age, marital status and length of stay in NH were found.
Conclusions. Elderly people's QoL, similarly to their satisfaction with health, were on an average level regardless of the institutional care. The QoL remains in a significant relationship with health. The changing needs of the elderly should be the basis for creating an individual plan of professional support.

Keywords: the elderly, quality of life, institutional care.

Introduction

According to the official forecasts the population of people aged 65 and over in the European Union will increase from 87.5 million in 2010 to 152.6 million in 2060. There are also predictions of the number of persons aged 80 and above growing from 23.7 million in 2010 to 62.4 million in 2060 [1]. Designing and implementing measures aimed at improving the quality of such extended life is one of the challenges facing medicine today.

Quality of life (QoL) is a multi-dimensional and interdisciplinary term. Various sciences make attempts to conceptualise this term – above all medicine and psychology, but also sociology, pedagogy and economics. Hence the multitude and variety of definitions highlighting different aspects of human functioning and their importance in the process of formulating a subjective assessment of one's own life. Assessment of the QoL of the elderly is very difficult because the elderly are not a homogenous social group [2], and old

age is a phase where the biggest personal differences occur. Experiencing the ageing process and old age is an individual matter. There is no universal way of living through and assessing this period of life.

Attempts to narrow down the semantic area of QoL has led in medicine to the formulation of the term health-related quality of life (HRQOL). According to Schipper at al. [3], HRQOL is the functional effect of a disease and its treatment perceived by the patient, and to put it more precisely, a subjective and multidimensional assessment of the impact of a disease and its treatment upon the physical condition and vocational functioning, psychological state, social interactions and somatic sensations. Research into the consequences of illnesses, i.e. extensive and usually adverse changes in all important walks of human life, is also of interest to psychology.

According to the definition of the World Health Organization (WHO), quality of life refers to "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [4]. The diversity of QoL definitions is reflected in the creation of many different research tools used for its global assessment, allowing measurement of generic or disease specific QoL [5]. The WHO definition was used as the point of departure in designing the WHOQOL–100 measurement tool, followed by the elaboration on its basis of the WHOQOL-BREF survey (used in the own research presented). WHOQOL allows to make an individual valuation and a subjective assessment of the following domains: physical health (pain and discomfort, energy and tiredness, sexual activity, sleep and rest, sensual sensations), psychological health (positive and negative feelings, cognitive processes, self-appraisal, image of one's own body and appearance), level of independence (ability to move, daily activities, dependence on medical and non-medical substances, ability to communicate and take up work), social relationships (personal ties, experiencing social support; conduct directed towards supporting others), environment (freedom, feeling of physical security, home environment, work satisfaction, financial resources, health and access to social care, possibility to gain new information and skills, recreation possibilities, physical environment, transport), spirituality/religion/personal beliefs [6]. Analysis of the usefulness of individual dimensions of the WHOQOL–100 and WHOQOL-BREF scales in studying the elderly has led to the creation of the WHOQOL-AGE scale, validated also for Polish senior citizens [7].

Aim

The objective of the study was to assess the QoL of elderly persons subjected to institutional care and to compare the life quality in different domains between residents of nursing homes (NH) and patients of the Psychogeriatric Day Ward (PDW).

Material and Methods

The study was carried out January 2015 to January 2016 and included a total of 130 persons. Among them were 62 residents of two NH in Poznań, and 68 patients of the PDW of the Regional Hospital for Neurotic and Psychiatric Patients in Gniezno. PDW patients spent 8 hours daily at the hospital ward for the eight consecutive weeks. The following study inclusion criteria were adopted: age 60 or above, ability to establish and maintain full logical contact, consent to participation in the study.

The researcher used the WHOQOL-BREF questionnaire and an own survey. The WHOQOL-BREF questionnaire is a research tool used for assessing the QoL of healthy and ill persons, both for cognitive and clinical purposes [8]. It contains 26 questions and allows assessing the QoL in four domains: physical health, psychological health, social relationships and environment. It also includes two questions subject to separate analysis: the first pertains to the general perception of the QoL, the second to an overall perception of one's health. Persons taking part in the study made the assessment on a five-point scale; the higher the score, the better the QoL. The researcher's own survey contained nine questions regarding duration of stay at the NH, illnesses and medications, ability to move unassisted, frequency of rehabilitation procedures and preferred forms of spending free time.

The study was approved by the Bioethics Committee at Poznań University of Medical Sciences (No 44/15).

Statistical analysis

The results were presented as mean values and a standard deviation (SD), providing the minimum and maximum ranges. In the case of category variables data were presented as figures and percentages. Comparison of two independent groups was conducted using the Mann-Whitney U test, and in the case of qualitative variables the Chi-square and a test for structure indi-

cator were used. Tests were considered statistically significant at $p < 0.05$.

Results

The demographic characteristic of the studied group is presented in **table 1**.

In the NH residents group, 40 persons (64.5%) remained at the facility for more than three years, 12 persons (19.3%) from two to three years, and 10 persons for no longer than one year.

In both groups of respondents, 103 persons (79.2%) reported no fall during the last two months preceding the study, with 27 persons (20.8%) experiencing a fall in that period. The most frequently indicated causes of falls included uneven surface or vertigo. The frequency of falls did not depend on the age of subjects ($p = 0.5$).

In both groups 83 persons (63.8%) used daily rehabilitation treatment, 20 persons (15.45%) several times a week, and 27 persons (20.8%) used no rehabilitation at all. The number of persons not using this form of professional support was significantly higher among the NH residents ($p = 0.002$).

Almost all subjects participating in the study (98.5% of the PDW patients and 100% of the NH residents) followed medical recommendations, 69.3% of NH residents and 53.7% of PDW patients took diet supplements.

Multiple chronic disorders were diagnosed in 103 persons (79.2%); at the same time no significant difference was found between age and the occurrence of three or more diseases ($p = 0.5$). The largest number of diagnosed disorders involved the skeletal-joint-muscle system and the cardio-vascular system. A dependence between heart diseases and age was observed ($p < 0.029$). Persons with heart diseases accounted for: 35.3% in the 60–75 group, 60.7% in the 75–90 group and 66.7% in the above 90 age group, respectively. The occurrence of multimorbidity was similar in two studied groups.

No significant statistical differences were found between both groups when it came to QoL satisfaction (WHOQOL-BREF1 $p = 0.64$) and satisfaction with one's health (WHOQOL-BREF2 $p < 0.07$). NH residents (WHOQOL-BREF1 points: 3.61± 0.75, range 1–5; WHOQOL-BREF2 points: 3.46 ± 0.82, range 2–5) and PDW patients (WHOQOL-BREF1 points: 3.62 ± 0.75, range 2–5; WHOQOL-BREF2 points: 3.13 ± 1.03, range 1–5) similarly assessed their level of satisfaction with regard to both these aspects. A statistically significant medium dependence was found between QoL assessment and health satisfaction assessment, both in the entire sample examined ($p < 0.05$) and in both sub-groups. PDW patients, just like NH residents gave the highest score to their QoL in the domain of environment, and the lowest in the social relationships domain. The results of the QoL assessment in the particular domains for the two studied groups, PDW and NH patients, are presented in **Table 2**.

Table 1. Demographic characteristics of the studied group

Characteristics	Total	NH	PDW	p-value
Number of patients	130	62	68	
Women n (%)	108 (83)	54 (87.10)	54 (79.41)	0.2431
Men n (%)	22 (17)	8 (12.90)	14 (20.59%)	
		Age (years)		
Mean ± SD Range	80.38 ± 8.26 (aged 60–98)	84.47 ± 6.94 (aged 66–98)	76.65 ± 7.62 (aged 60–94)	< 0.0001
		Age groups, n (%)		
60–75 years	34 (26.15)	6 (9.68)	28 (41.18)	< 0.0001
75–90 years	84 (64.62)	46 (74.19)	38 (55.88)	0.0292
> 90 years	12 (9.23)	10 (16.13)	2 (2.94)	0.0095
		Education, n (%)		
Primary	31 (23.85)	12 (19.35)	19 (27.94)	0.2512
Vocational	35 (26.92)	12 (19.35)	23 (33.82)	0.0632
Secondary	41 (31.54)	25 (40.32)	16 (23.53)	0.0396
Higher	23 (17.69)	13 (20.97)	10 (14.71)	0.3501
		Marital status, n (%)		
Single	22 (16.92)	18 (29.03)	4 (5.88)	0.0004
Married	25 (19.23)	2 (3.23)	23 (33.82)	< 0.0001
Widowed	83 (63.85)	42 (67.74)	41 (60.29)	0.3773

Table 2. Summary of the quality of life assessment values in particular domains in PDW and NH patients

Domain score in points	NH (n = 62)	PDW (n = 68)	p-value
Physical health			
Mean ± SD	55.27 ± 11.4	59.45 ± 10.19	0.0237
Range	19–81	19–81	
Psychological health			
Mean ± SD	56.25 ± 13.68	58.57 ± 9.87	0.3717
Range	19–81	31–81	
Social relationships			
Mean ± SD	30.53 ± 22.86	38.5 ± 23.93	0.0372
range	0–94	0–94	
Environment			
Mean ± SD	76.12 ± 10.73	75.73 ± 9.85	0.9008
Range	44–100	50–94	

A statistically significant difference was found in the assessment of the QoL in the physical health ($p < 0.02$) and social relationships ($p < 0.04$) domains; PDW patients assessed their QoL in both these domains higher than NH residents.

It was also noticed that a significantly higher QoL in the physical health domain was connected with the participation of the NH residents and the PDW patients in socialised forms of spending the free time, such as chess and/or card games; meetings with friends; looking after grandchildren; cinema outings; choir practice ($p < 0.005$).

Analysis of the results enabled us to observe statistically significant relations between the QoL in the physical health domain and the duration of stay at the NH ($p < 0.02$). The lowest QoL in the physical health domain was found in persons in their first year of stay at the NH and the highest in those who stayed there from two to three years. No statistically significant differences were found in other domains.

Taking into account the effect of the marital status on the QoL of NH residents it was observed that in the social relationships domain it was higher among widows/widowers compared with singles ($p < 0.0034$). QoL assessments in the physical health, environment and psychological health domains were similar in both groups (widowed-single). In the case of NH residents no statistically significant dependences were found between QoL assessment and education as well as QoL assessment and age.

A statistically significant difference in QoL was shown among PDW patients in the social relationships domain depending on the marital status ($p < 0.0002$). Married persons graded their QoL in this area much higher than widows/widowers.

There was also a statistically significant difference in the QoL results in the environment domain depending on the age of the PDW patients ($p < 0.0073$); subjects aged between 75–90 years scored higher than those aged 60–75.

Discussion

The overall assessment of QoL of the NH residents and the PDW patients in our study was average. Both groups also expressed similar satisfaction with their state of health. A medium strong dependence was found between QoL and satisfaction with one's health across the entire studied group, as well as in individual sub-groups. A significant correlation between satisfaction with one's state of health and a subjective assessment of QoL was observed by Waszkiewicz et al. [9]; in a study conducted using the WHOQOL-BREF survey more than half of the elderly assessed their life quality as being at least good, with 5.5% expressing a negative opinion. The differences in QoL assessment were related to gender with men scoring higher than women. Research into the impact of nutrition upon the QoL of the over-60 NH residents and the University of the Third Age (UTA) students showed that most people assessed their QoL positively [10]. The QoL in all areas was assessed better among the UTA students than among the NH residents. The NH residents most often complained about their state of health, unlike the UTA student group who mostly saw it in a positive light. In our study residents who remained in NH for no longer than one year were also unsatisfied with their health conditions. It is not surprising as the worsening of the health status is usually the reason of admission to welfare service institution. In the study conducted by Waszkiewicz et al. [9] just under 45% of respondents indicated satisfaction (at various levels) with their state of health, while 21% voiced strong dissatisfaction.

A significant correlation was also observed between satisfaction with the state of health and gender – men showed more satisfaction in this regard.

We noted significant ties between QoL assessment in individual areas and specific variables, such as: duration of stay at the facility, marital status, age. It was also established that QoL was highest in the environment domain, lower in the psychological health and physical health domains and lowest in the social relationships domain. In the study carried out by Waszkiewicz et al. [9] the highest QoL was observed in the area of social relationships, followed by the environment and the psychological domain with the lowest quality recorded in the physical health domain. In the study conducted by Kurowska and Kajut [11] the highest score was obtained in the environmental domain, followed by the physical health, social relationships and psychological domains. The lowest QoL in the psychological domain was also observed by Zboiny [12]. Kurowska and Kajut [11] did not find statistically significant correlations between QoL and age, which was in agreement with our results, but only with regard to NH residents. In this group of subjects the level of education did not influence the QoL. According to Kurowska and Simon [10] persons with higher education better assessed their own life quality and were more satisfied with their health.

Based on own research it was established that QoL in the physical health domain was higher among persons preferring social forms of spending their free time. The availability of support resulting from membership in social networks is conducive to maintaining high QoL [13]. Kurowska and Kajut [11] point to a correlation between higher QoL in the social area and maintaining contacts with the family or friends. In a Turkish study [14] conducted among the elderly living in their family homes and using institutional assistance QoL as well as satisfaction with the state of health was similar in both groups. Persons living with their family better assessed their QoL in the area of social relationships and the environment. As determined by Garcia et al. [15], deficits in contacts with the family and friends are significantly correlated with a reduction of QoL of the elderly. The study by Xavier et al. [16] indicates that the overall state of health is a significant factor reducing the QoL of elderly patients; a positive role is played by factors such as: physical activity, financial security and participation in family and social life. The impact of exercise upon functional abilities and the QoL of the elderly was also confirmed by others [17].

The majority of respondents in our study presented multiple morbidity, mainly cardio-vascular diseases and skeletomuscular system disorders. The prevalence of multiple chronic conditions among older persons is increasing worldwide and is associated with poor health status [18, 19]. The occurrence of more than four chronic diseases in one NH patient aged above 60 [20] as well as the multiple morbidity in persons above the age of 90 [21, 22] were documented. Four or more chronic diseases predisposes to cognitive disorders or depression [23]. Depression may lead to functional limitations [24], increase the risk of all types of dementia [25] and as a consequence significantly impact the QoL [26] and self-care motivation [27]. Our study revealed that elderly hospitalized at the daily ward presented similar number of diseases as nursing home residents but assessed the physical health domain of their QoL better. They were also more satisfied with their social life. The limitation of our study is a small number of participants but on the other hand up to our best knowledge the comparison of different areas of QoL between PDW patients and NH residents was not conducted before.

Conclusions

The overall QoL of the elderly under the institutional care, both the NH residents and the PDW patients, is at an average level. There exists a significant connection between the QoL assessment and the level of satisfaction with one's state of health. QoL assessment with the use of WHOQOL-BREF differs between individual domains of functioning of the elderly. The study of the QoL results in the elderly population may be used in the process of drawing up individual care and support plans taking into account the deficits and resources of the elderly in specific areas.

Acknowledgements

We wish to offer our sincere thanks to nursing home residents and patients who helped with the development of this work.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

Informed consent and ethical approval
Informed consent was obtained from all subjects included in the study. The study design was positively evaluated and approved by the Bioethics Committee at Poznan University of Medical Sciences.

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Acceptance for editing: 2016-1-20
Acceptance for publication: 2017-03-27

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BRIEF REPORT

DOI: https://doi.org/10.20883/jms.2017.122

Harmful results of improper fitted wheelchair – case study

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ABSTRACT

Wheelchair is perceived basic orthopaedic equipment, both for permanent and temporary use. Proper wheelchair fitting, and correct education of both medical staff, patients, and their families/caregivers may influence increased awareness of threats, limitations, and results of incorrect patient's positioning in wheelchair. Basic knowledge and experience may significantly reduce consequences in aformentioned area, and influence to shorter and more effective therapeutic process. Aim of this paper is to discuss possible problems resulting from improper wheelchair fitting on the basis of presented case study, explore the relationship between improper wheelchair fitting and limitations of wheelchair users independence, mobility, and life quality based on own experience and propose solutiopna and direstions of further research.

Keywords: rehabilitation; disabled people; elderly people; wheelchair users; wheelchair fitting; wheelchair safety.

Introduction

Wheelchair is perceived basic orthopaedic equipment, both for permanent use (usually in disabled people) and temporary use (in weakened patients during recovery or in elderly patient for increased mobility purposes). Moreover temporary wheelchair use may be useful in patients with fractures, amputations, or neurological diseases, where neurorehabilitation may provide further recovery and possibility of increased mobility without wheelchair. Particular area of wheelchair application are perceived disorders of central nervous system (CNS), where may be observed movement/mobility limitations associated with disturbed sensation. Thus there is need to pay particular attention to a proper wheelchair fitting in patients with neurological deficits. The topic of the wheelchair fitting has been studied in the scientific literature (Steenbekkers & Molenbroek, 1990; Chih-Chin Hsieh et al., 2011).

No doubt proper wheelchair fit is essential to promote community participation, and to prevent harm. Improper wheelchair fitting (including basic dimensions and features of the wheelchair) may cause significant harmful secondary changes. Basic patological secondary changes are perceived bedsores, resulting mainly from too narrow seat (bedsores in the area of great trochanters of lower limbs) or too short footrests (particularly with association of too big seat angle – what provide increased pressure, and even bedsores, in the area of sacral bone). Too wide seat may cause spine defirmities, spine pain and hips pain. Moreover too wide seat associated with too long footrests may cause improper (inclined) position of lower limbs, and scoliosis. Rare cases are shortening of the Achilles tendon resulting from too long footrests and associated improper feet position. Thus improper wheelchair

Table 1. The most common results of the improperly fitted wheelchairs

Source	Observed changes in user's health status	Remarks
Mikołajewska [1]	various patologic changes depends on problem in wheelchair fitting	results for Poland – there were observed: unproper seat width in 62.5% of cases, unproper seat depth in 62.5% of cases, unproper footrest lenght in 87.5% of casus
Amos & Winter 2006 [2]	bedsores	results for Tanzania
Park & Jang 2011 [3]	bedsores	buttock pressure depends on backrest inclination in patients with spine cord injuries (SCI)
Giesbrecht et al. 2012 [4]	discomfort, poor positioning and mobility, bedsores	prevalence rate of inappropriate seating in elderly patients was 58.6% (ranging from 30.4 to 81.8%)
Bourbonniere et al. [5]	decreased mobility	prevalence rate of inappropriate seating in elderly patients was 22%

fitting may be perceived the global problem and need for common approaches to resolve it.

Wheelchairs need to be fitted with the consideration of the current user's health status, size, age, goals of the therapy, functional limitations, requirements, and possiblities (including style of living), among other factors. Despite efforts both medical staff and engineers improper wheelchair fitting still happens both in disabled (Mikołajewska, 2012; Park & Jang, 2011; Amos & Winter, 2006) and elderly people (Giesbrecht et al., 2012). It may result in harmful changes in users health status (**Table 1**). Unfortunately there is lack of studies including bigger amount of patients providing more reliable data.

Aim of this paper is to discuss possible problems resulting from improper wheelchair fitting on the basis of presented case study, explore the relationship between improper wheelchair fitting and limitations of wheelchair users independence, mobility, and life quality based on own experience and propose solutiopna and direstions of further research.

Case report

Patient

The patient was a 21-years-old male, one year after road accident, at first with tetraplegia. This patient was admitted to the neurological rehabilitation ward during the subsequent stage of the therapy with diagnosis: tetraparesis with predominance of left side hemiparesis. Clinical status of the patient is summarized in **Table 2**.

Unfortunately patient was unable to participate in gait re-learning therapy as a result of improper wheelchair fitting. Despite neurorehabilitation succesful recovery of the patient with primary dignosis tetraplegia was restrained. The patient obtained possibility of gait, but main limitation during further therapy (including gait re-education) was fixed deformity in the area of ankle (i.e. improper foot positioning). Both standing and walking was painful, non-functional, and further therapy remained impossible. The patient observation and assessment provided evidence of long-term wheelchair sitting in a pathological position. Problems was increased by previous improper fitting of the wheelchair dimensions: too short seat, to narrow seat, too short footrests. Rest of the wheelchair features and accesories was perceived properly fitted, but previous training of the patients and his family was barely existent, so their consciousness of possible harmful results of improper whelchair fitting and use was rather poor. Aforementioned discomfort caused footrests non-use, and changing position into another with stright lower limbs. Long-term use of the new position, with pato-

Table 2. Clinical status of the patient

Criteria	Score / result
diagnosis	tetraparesis with predominance of left side hemiparesis
general health status	patient after treatment regained muscle strength and active movements within lower limbs allowing for introduction of gait reeducation
Ashworth Scale for grading spasticity results: left lower limb right lower limb	 4 3 diagnosed tension in left lower limb resulted in improper feet position (at a 40-degree angle) without possibility of the therapy towards physiological position
other	diagnosed fixed contractures in the areas of muscles and Achilles tendon, bender of big toe, and muscle tibialis posterior of the both lower limbs

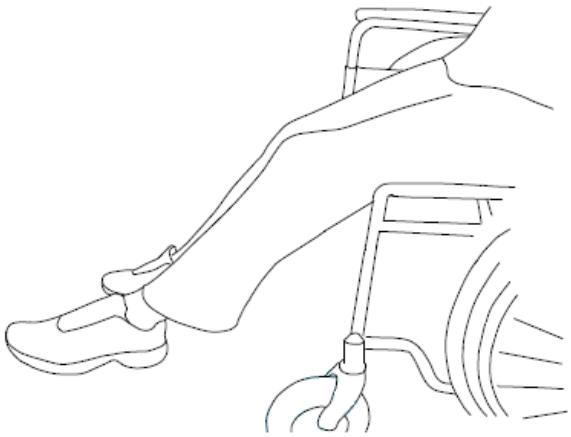
logical muscle tone, caused patological feet positioning and limitations of further gait re-education.

Therapy

There was introduced eight-week therapeutic approach aiming at decreasing of pathologic muscle tension for physiological feet positioning purposes and increasing of range of movement within ankle. Basic components of aforementioned therapy were as follows:

1. hydrotherapy of the lower limbs – six times a week,
2. massage – five times a week,
3. parafango wrap – six times a week,
4. redression – six times a week,
5. passive exercises of ankles – five times a week,
6. orthopaedic equipment: shoe with enlarged opening (to improve the shoe wearing), gimp with metal insert (to avoiding the show deformation) – there was lack of acceptance to use orthopaedic shoes due to psychological issues (**Figure 1**),
7. botunlinum toxin type A injestions into: muscle plantaris, bender of big toe, muscle triceps surae, and muscle tibialis posterior.

a)



b)

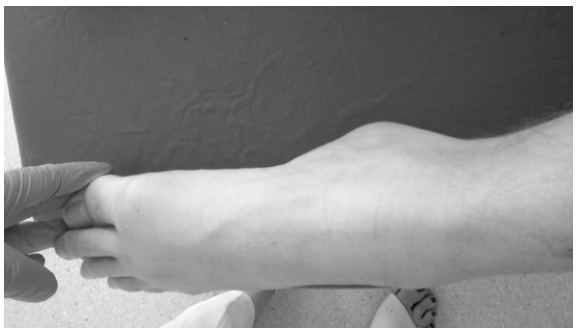


Figure 1. Patient's foot deformation: a) improper wheelchair use influencing increased pathology, b) pathologic foot deformation as a result of improper wheelchair use

Results

Aforementioned therapy, despite efforts of the patient and interdisciplinary therapeutic team, resulted in a lack of recovery. Supplementary diagnosis provided suggestion of surgical intervention for deformation correction purposes, which next proved effective. But this way whole therapy of the patient was significantly prolonged.

Discussion

Wheelchair use may significantly influence activity and participation both disabled, severely ill, and elderly people (Mortenson et al., 2008). Although at least several studies reported 40–80% of nursing home residents (wheelchair users) who need for some type of seating intervention for increased mobility purposes. Moreover further research indicate that use of wheelchairs and seating systems do not fitting the individual needs, a lot of problems can become evident: pressure ulcers, difficulty in propulsion, discomfort, dysphagia, falls, and decreased quality of life (Gavin-Dreschnack et al., 2005). Thus described therapy resulting from improper wheelchair fitting may be additional limitation, decreasing of patients quality of life, and cost generated by improper wheelchair fitting. It needs for additional research, especially due to limited evidences. Role of aforementioned research, particularly in long-term rehabilitation and care, may be hard to overestimate, influencing both independence, mobility, quality of life, and even, as a consequences, mortality and cost of the therapy in disable people and elderly people. Newest tools, including Seating Identification Tool (SIT), Resident Ergonomic Assessment Profile for Seating, and Wheelchair Seating Discomfort Assessment Tool, help to assess selected possible risks in a quick, easy to use, reliable and valid way (Gavin-Dreschnack et al., 2005; Miller et al., 2004; Crane et al., 2005). But no doubt outcomes of clinical trials should be involved into strategic planning for both the home therapy and care, and institutionalized therapy and care.

Apart of described foot deformation as harmful results of improper fitted wheelchair there is need for paying particular attention to subsequent possible negative result of the improper position in wheelchair: increased lumbar lordosis and risk of pain in lumbar-sacral spine. Due to importance of this issue future patiet's assessment needs to be supplemented by more detailed questions concerning previous his-

tory of spine pain and influence of the angle between the thighs and trunk.

Due to poor scientific evidence it should be noted, that clinical picture of the different types of aforementioned harmful results of improper fitted wheelchair may be caused by more than one mechanism, making possible whole spectrum of disorders. Thus presented way of the therapy needs further investigation. Moreover clinical picture of disorders resulting from improper wheelchair fitting may change depends on the clinical status of the patient, place of lesion, functional possibilities, life style, age, etc. No doubt there is need to explore more varieties of treating for other cases (Mikołajewska & Mikołajewski, 2010; Gaal et al., 1997; Cooper et al., 2006). Contemporary approach in presented area may be insufficient. Knowledge in the area of basic wheelchair fitting should be common within multidisciplinary therapeutic team, to avoid mistakes and misunderstandings. Training of the patient and his/her family/caregivers shoul cover these issues, including response to observed changes (possibly harmful). This may require additional effort within system of medical staff education, with emphasizing the role of supervision form local medical authorities. This approach may result e.g. in significant decrease of the secondary complications. Presented case report pays particular attention both to proper diagnosis, early beginning of the rehabilitation, and moreover proper wheelchair fitting and with further control (and modification, if necessary). Well fitted wheelchair may decrease possible threats, and allow to avoid secondary complications described above. If not it may be true, that presented therapy of harmful results of improper wheelchair fitting may be useful and effective therapeutic approach, but should be as quick as possible, patient-oriented and patient-tailored.

Conclusions

Aformentioned case study shows importance of proper wheelchair fitting, and correct education of both medical staff, patients, and their families/caregivers. Increaed awareness of threats, limitations, and results of incorrect patient's positioning in wheelchair resulting from improper fitting of wheelchair dimensions and features may influence decreasing harmful results as described. It seems basic knowledge and experience may significantly reduce consequences in aformentioned area, and influence to shorter and more effective therapeutic process. There is need for common effective prevention policy in the area of wheelchair fitting.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-1-20
Acceptance for publication: 2017-03-27

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REVIEW PAPER

DOI: https://doi.org/10.20883/jms.2017.143

Products of plant origin – benefits and the potential risk for the consumer

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ABSTRACT

Phytochemical compounds are widely used in traditional medicine in the treatment of many ailments. In recent years, an increasing interest is observed in the use of new natural bioactive substances and whole standardized extracts in the prevention and therapy of diseases. Some of these are the components of the diet, diet supplements or at higher doses are used as herbal medicines. Many phytochemicals have documented a beneficial effect on health, but they must be used properly. Therefore, it is important to inform about differentiating between herbal medicine and dietary supplement. Further, the possibility of interactions with synthetic drugs and the mechanisms of these effects is necessary to describe for the safety of phytotherapy. The goal of our paper is to show high prophylactic and medicinal potential of natural active compounds of plant origin. We also want to draw attention to the safety of their use by the consumer. Therefore, we present some studies on the benefical properties of natural active compounds, mainly in the prevention and treatment of cancers and neurodegenerative diseases. The results of the described studies are extensively discussed and their suitability for further testing *in vivo* and in clinical trials is examined. At the same time we show selected interaction of common medicinal plants or their raw materials with synthetic drugs.

Keywords: herbal products, pro-health effect, chemoprevention, herb-drug interaction.

Introduction

Wide properties of phytochemical compounds and their multidirectional action caused that they are used in the treatment of many diseases as herbal medicines and as foods components or dietary supplements. The pharmacological action in many of them is supported by well documented studies *in vitro*, *in vivo* and in some cases tested in clinical research. Overall, awareness of the benefits from the use of herbal products is very high in society. It is worth noting that currently there is an increasing interest in the screening for natural bioactive substances and whole standardized extracts for use in new applications, especially in the treatment of cancer, neurodegenerative diseases, metabolic disorders and chronic inflammation. Beside the well-known components with numerous *in vitro* and *in vivo* studies (green tea plyphenols, quercetin, genistein from soybean and allicin from garlic), there are still new scientific evidences with promising results.

It can be also noted that consumers often believe that natural products are considered safe but this is oversimplification. Admittedly, the safety and efficacy of herbal raw materials is usually confirmed by experience during many years of use in traditional medicine

in the treatment of many common ailments or diseases. However, due to the multi-activity of products with herbal origin, the studies on their safety are needed. This is important in view of the fact that for some consumers, such as pregnant women, nursing women and children, insufficient number of well-documented research or no research supporting the safety of most herbal products is observed. Further problem is the difficulty in differentiating between a dietary supplement and herbal remedy for the treatment of a specific disease [1].

There has been a lack of sufficient knowledge of patients about the potential risks of consumption of herbal products with standard drug therapy and other adverse consequences of their abuse. The risk is particularly high in consumers with advanced and very young age, in patients with hepatic impairment and/or kidney disease, in patients dehydrated, in cases with metabolic diseases and endocrine system disorders. The consequence of the interaction may be a change in half-life synthetic drug, modification of their actions as well as other negative effects on the body. Interaction between the drug and herbal product may occur at various stages of the pharmacological processes including changes in pharmacokinetics at the absorption step, binding proteins, membrane transport, distribution, metabolism and excretion. Interactions may also occur at the stage of the biotransformation by cytochrome P450 enzymes.

The aim of this paper is to present selected new lines of research on the use of plant compounds for health purposes. On the other hand, we want to underline the possibility of occurrence of interaction between the herbal medicine and synthetic drug.

The current state of knowledge on new applications of selected natural active compounds in the prevention and therapy

It is known that plants extracts and parts of plants or their preparations have been used in traditional medicine for several thousand years. They were used mainly by the taste properties and especially the therapeutic effect. Recently, the herbal medicines and diet supplements are commonly used in developed countries. In this paper, we have elucidated the possible pro-health effects of few natural substances of plant origin, including their potential in the prevention of diseases and treatment.

Chemoprevention and cancer treatment

Chemoprevention of cancer focuses on the factors affecting the early stages of cell transformation. Naturally occurring phytochemicals have a wide range of cellular effects including carcinogens protection and the detoxification of reactive molecules. Moreover, they may enhance innate immune surveillance and improve the elimination of transformed cells. Further, phytochemicals have several impacts on the mechanisms of DNA repair and can cause the inhibition of cell proliferation pathways [2]. Numerous reports, including clinical studies suggest the beneficial effects of medicinal herbs and their active compounds in combination with conventional therapeutics on the survival, immune modulation and quality of life of cancer patients. Scientists examine the possibility of using the herbal materials mainly in the chemotherapy resistance and in the reduction of side effects. Moreover, among the new applications of active compounds with plant origin is treatment of diseases, the blood-brain barrier modulation and as a chemotherapeutic agent sensitizers.

Based on preclinical studies it can be assumed that curcumin, a polyphenol derived from the roots of *Curcuma longa* plant, may be useful for the prevention and/or treatment of several diseases, such as colorectal cancer, cystic fibrosis, inflammatory diseases and Alzheimer's disease [3]. Curcumin seems to have anti-tumor properties by inducing cell cycle arrest and apoptosis most importantly through pleiotropic modulation on nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), STAT-3 and cyclin D1 in *in vitro* models [2, 4–7]. Further, several phase I clinical trials confirmed safety of curcumin in patients (up to 8 g/day, p.o.) [2, 3, 8]. However, excessive use of curcumin can damage the intestinal microflora, disrupt the normal physiology and immune response [9]. The bioavailability of curcumin after oral administration is relatively low and mainly metabolites are detected in plasma [3, 10]. On the other hand, measurable biological effects have been demonstrated in patients with different types of malignancies including pancreatic cancer, multiple myeloma and advanced colorectal cancer resistant to standard chemotherapy [11–13].

Another known active compound is quercetin found in a wide variety of foods including capers, apples, onions, berries, green and black tea, and red wine [14]. This flavonoid showing antioxidant properties acts

mainly by scavenging reactive oxygen species. In addition, anticancer, antiviral, anti-inflammatory, and anti-amyloidogenic activities of quercetin have been extensively analyzed [15, 16]. Rivera et al [17] showed that combination of polyphenols (resveratrol, quercetin and catechin) reduces breast cancer growth and metastasis in mice. Further, quercetin (15mM) caused the inhibition of proliferation similar to the combination of all three of polyphenols. In mice with very severe immunodeficiency (SCID) a reduction of tumor growth by about 70% was observed after administration of quercetin (15 mg/ kg body weight). In conclusion, quercetin appears to be a promising polyphenol for future development as therapeutic preparation for breast cancer. It has been reported that quercetin (doses up to 1 g/day) had no adverse effects on blood parameters, liver and kidney function, hematology, or serum electrolytes in human [3, 14]. But the elimination of quercetin metabolites from plasma is quite slow (half-lives ranging from 11 to 28 h), which means the accumulation of this compound in the body in daily uptake [3, 18].

Epigenetic changes in neoplastic cells are frequently observed in carcinogenesis. Therefore, new therapies could restore the correct pattern of methylation of oncogenes and tumor suppressor genes. Recent reports indicate that resveratrol in breast cancer restore the hypomethylated and hypermethylated status of key tumor suppressor genes and oncogenes, respectively. The authors showed that the corresponding changes were also noted in mRNA expression [19]. It is known that resveratrol is the most common phytoalexin tested in modern health care. It is a polyphenolic compound belonging to the stilbenes and is produced in a several plant after exposure to stress, injury, fungal infection, or UV radiation [3]. Resveratrol shows antioxidant, neuro- and cardio- protective properties and may also act as a factor retarding the aging process, antifungal, antibacterial, antiviral, anti-inflammatory and a chemoprevention agent. Moreover, resveratrol can inhibit tumor growth at the initiation, promotion and progression step. Early studies identified that resveratrol can induce cancer cell apoptosis by affecting signaling pathways in transformed cells [2, 20, 21]. Recently it was described that resveratrol may repress collagen deposition in the vasculature, heart, lung, kidney, liver, and esophagus in animal models. Some data suggest that lung fibroblasts and prostate fibroblast to myofibroblast phenoconversion can be both repressed and reversed by resveratrol *in vitro* treatment [22]. This may indicate that the antifibrotic therapeutics might be efficacious for the treatment of lower urinary tract dysfunction (LUTD). However, the low bioavailability (2%) and a rapid biotransformation to less active metabolites limit the possibilities of resveratrol use in medicine. Therefore, researchers are working on resveratrol derivatives whose biological properties have proved to be higher as compared to their natural precursor [23]. Clinical trials have also defined the safety, pharmacokinetics and metabolism of resveratrol and showed that adverse effects, including abdominal pain, diarrhea, and nausea occur at doses above one gram daily [24]. On the other hand, it was demonstrated that a dose of 1 gram per day for four weeks significantly inhibit the plasma cytochrome P450 and induces CYP1A2 in healthy volunteers. Thus, resveratrol perhaps may affect the metabolism of drugs, and raises concerns about the combined use with pharmaceuticals [2, 25].

The fact that diet is important for health confirms another report indicating that the 1.5% polymeric black tea polyphenols (PBPs) have chemopreventive effect through inhibition of cellular proliferation, inflammation and induction of apoptosis. This effect was observed after 28 weeks of treatment in mice with induced lung cancer. The histopathological evaluation of lung showed decrease in tumor multiplicity which was also correlated with different molecular markers such as reduced Cox-2 expression. Moreover, PBPs down-regulated the cell proliferation induced earlier by tobacco carcinogens [26].

Epidemiologic data indicate that Asian diets containing high amounts of soy products, reduce a women's risk of breast cancer. On the other hand, it has been difficult to dissociate the benefits of soy from others environmental and lifestyle factors. Moreover, soybean isoflavones are phytoestrogens that reduce menopausal symptoms and decrease the risk of certain chronic diseases, such as cancer and cardiovascular diseases. Despite the widespread use of soybean isoflavones as functional food and dietary supplements, data regarding the safety as well as herb-drug interactions, remain scarce. Daidzein, genistein, glycitine and equol are major food-derived phytoestrogens. They bind weakly to estrogen receptors. Therefore, it has been proposed that soy isoflavones can reduce breast cancer risk by interfering with the binding of endogenous estrogens to estrogen receptors [27]. Animal and population studies have indicated that soy intake may also reduce the risk of lung cancer [28, 29]. It seems that dietary isoflavones, may protect against several cancer types, without exerting toxic effects on

normal cells [30]. Especially, genistein showed ability to increase the anti-neoplastic activity of certain chemotherapy drugs in multiple tumor types. On the other hand, some researchers say that dietary soy isoflavones increase metastases to lungs in a model of breast cancer and significantly increased cell proliferation in breast cancer patients who used soy supplementation [31, 32].

So far, it is known that soy isoflavones sensitize non-small cell lung carcinoma cancer cells (NSCLC) to radiation both *in vitro* and *in vivo* studies [33]. On the other hand, radioprotection was demonstrated of normal lung tissues in the lung tumor model [34]. Furthermore, it was shown that soy can protect against radiation-induced injury to normal lung tissue [34]. It is postulated that the use of soy isoflavones as radioprotectors is attractive because they were proven to be safe in controlled human clinical trials [35, 36]. Therefore, in non-randomized, open label clinical trial no NCT01958372 the soy isoflavones may promote radiation therapy, cisplatin, pemetrexed sodium, and etoposide work better by making tumor cells more sensitive to the drug. Soy isoflavones may also protect normal cells from the side effects of radiation therapy and chemotherapy in patients with stage IIIA-IIIB NSCLC. It was also described that combination of genistein and low concentrations of cisplatin induced significantly greater growth inhibition and increased apoptosis in lung cancer cells compared with either agent alone. In addition, the use of both substances together suppress tumor growth *in vivo* compared with either agent alone [30]. A similar synergistic effect of genistein and cisplatin was observed in hepatocellular carcinoma [37]. Moreover, genistein may sensitize estrogen receptor-positive breast cancer cells to tamoxifen treatment [38].

Impact of plant-derived substances on neurodegenerative diseases

The pathologies of the central nervous system (CNS) may be caused by toxic agents, traumatic injury, or may be the result of neuronal degeneration associated with degenerative disease or aging. Currently available drugs make it possible to alleviate the symptoms of Parkinson's disease (PD). While the search for new substances to achieve therapeutic benefit in patients with PD and Alzheimer's disease (AD), including plant origin is the subject of many recent investigations, it has been shown that a diet rich in flavonoids reduces the risk of neurodegenerative diseases in humans, induced the neuroprotective effects in rodents and increased the cognitive function in an animal model. Flavonoids induce large effect on neurons and glial cells in culture and in a model for neurodegenerative diseases *in vitro*. In this regard they can be considered as potential neuroprotectors agents and neuroimmunomodulators *in vivo*. Flavonoids also induced neuronal differentiation of mouse embryonic stem cells and human pluripotent stem cells [39].

Polyphenolic compounds (flavonoids, phenolic acids, stilbenes, and lignanes) and terpenes have established effects against Parkinson's disease. The mechanisms of action of the active compounds are various. Parkinson's disease is a neurodegenerative disease associated with loss of dopaminergic neurons in the substantia nigra and with accumulation of aggregated α-synuclein in specific central nervous system (CNS) regions [40]. The complex of flavonolignans obtained from the seeds of *Silybum marianum* and known as silymarin is widely used as an antioxidant and tissue regenerative agent, especially in the treatment of hepatic disorders induced by alcohol, viral hepatitis and the toxin. Besides, it was recently demonstrated that silymarin probably posesses neuroprotective properties against many neurological diseases, including Alzheimer's and Parkinson's diseases, and cerebral ischemia. It was shown that 100 mg / kg of silymarin administered over five days intraperitoneally diminished the number of apoptotic cells and preserved dopaminergic neurons in the substantia nigra in PD model in mice [41].

The flavonoid silibinin is the major active constituent of silymarin. Some authors suggest that silibinin protects mitochondria in PD models and that it offers a starting point for the development of treatments that ameliorate the symptoms of PD. Silibinin pretreatment alleviates motor disorders and loss of dopaminergic neurons. *In vitro* studies showed that silibinin may be considered for use as a potential method for treating PD and other disorders related to neuroinflammation [42]. Pretreatment with silymarin, dose-dependently (1–10μg / kg, i.v.) reduces cerebral ischemic / reperfusion brain infarction by 16–40% and improved neurological deficits in rats with a stroke. Elevated biomarkers for induced brain injury, including lipid peroxidation, protein nitrosylation, and oxidative stress, were all reduced after the application of silymarin. Moreover, expression of inflammation-associated proteins including inducible nitric oxide synthase, cyclooxygenase-2 and myeloperoxidase, and transcriptional factors (nuclear factor (NF)-kappa B and signal transducer and

activator of transcription (STAT-1), as well as proinflammatory cytokine level (interleukin-1β and tumor necrosis factor-α) was significantly prevented by silymarin. Consequently, it seems that silymarin displays beneficial effects of preventing inflammation-related neurodegenerative disease, stroke including but needs further investigation and clinical evidences [43].

Alzheimer's disease (AD) is the one of the most common neurodegenerative disorder with reduced therapeutic or prophylactic treatment. AD histopathologically is manifested by the presence of β-amyloid (Aβ) deposits and formation of neurofibrillary tangles [3]. Medicinal plants are firstly important source of protective compounds against AD and further using the structure of active substances with plant origin as templates for synthetic drugs provides a wide variety of potential neuroprotective compounds. *In vitro* and *in vi*vo studies suggest that the neurobiological effects of active compounds of plant origin may contribute to the clinical benefit in a model of Alzheimer's disease.

One of neuroprotective natural substances is bilobalide (BB), the main terpenoid of *Ginkgo biloba* leaves. This compound has the protective effects on neurons and Schwann cells. However, it should be noted that this sesquiterpene trilactone induces some xenobiotics metabolizing enzymes (CYP3A1 and CYP1A2) in liver which may be associated with interactions between *G. biloba* and pharmaceutical drugs or other herbal medicines [3]. Bilobalide in the range of concentrations *in vitro* (25–100 mM) blocked reactive oxygen species (ROS)-induced apoptosis in early stages and decreased the elevated levels of *apoptotic* factors. In addition, some authors suggest that bilobalide can inhibit the β-amyloid production [44]. However, it suggested that excessive dose of BB can cause adverse reactions [45].

Furthermore a beneficial effect on AD seems to have quercetin (QCT). To improve the penetration of the compound across the blood brain barrier the solid lipid nanoparticles (SLNs) of quercetin were prepared. Behavioral studies confirmed a better neuroprotective effect of this formulation [46]. *In vitro* study showed that QCT (10 μM) can exert anti-amyloidogenic effects by inhibiting the formation of Aβ fibrils [47] or at lower doses (5–20 μM) significantly attenuated apoptosis in hippocampal cultures. At the same time, quercetin may induce cytotoxicity at high doses (40 μM) [48]. QCT combination with BB could significantly enhance the level of brain-derived neurotrophic factor (BDNF) which plays important role in neurogenesis, neuronal survival, neuronal differentiation, and synaptic plasticity in mice brain [49].

Epigallocatechin gallate (EGCG) is the most abundant catechin from *Camellia sinensis* leaves. As a flavonoid it has antioxidant properties and has been the subject of many studies in cancer, atherosclerosis, and neurodegenerative diseases. The elimination half-life of EGCG is about 3 h [50]. Orally administered EGCG at a dose of 10 mg / kg could reduce acetylcholinesterase activity, glutathione peroxidase activity, nitric oxide metabolites and ROS content in model of dementia [51]. In other study, EGCG (3 mg/kg in water) enhanced memory formation and α-secretase activity, and suppressed γ-secretase activity in AD mice [52]. At higher doses the EGCG improved the cognitive abilities of mice. EGCG also prevented lipopolysaccharide -induced memory impairment and apoptosis, astrocytes activation and inflammatory factors. Moreover, *in vitro* and *in vivo* studies described by Dragicevic et al [53] showed that EGCG and luteolin were the main two mitochondrial restoration compounds among 25 tested flavonoids.

Rosmarinic acid (RA) is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid which is the main phenolic compound in *Lamiaceae* family used commonly as culinary herbs, such as lemon balm (*Melissa officinalis*), rosemary (*Rosmarinus officinalis*), oregano (*Origanum vulgare*), sage (*Salvia officinalis*), thyme and peppermint. Rosmarinic acid possesses many biological activities including antiviral, antibacterial, antioxidant, anti-inflammatory, anticancer, and neuroprotective effects. Several human studies investigated the potential beneficial effects of RA on cognitive function [54]. Based on a review of literature it may be noted that the RA (0.25–4 mg / kg, i.p.) significantly prevented β-amyloid -induced memory impairments, mainly by NF-κB and TNF-α. In other study RA (1–10 μM) could inhibit apoptotic pathways by decrease of ROS formation, caspase-3 activation, and DNA fragmentation. Generally, no severe side effect has been described for RA application [55–57].

Natural products of plant origin can be considered as pharmaceuticals or future therapy complementary to conventional therapeutic approaches to mitigate adverse effects and improve the effectiveness in the treatment of neurodegenerative diseases. Previously well-designed clinical trials are needed to assess the safety and therapeutic benefits of phytochemicals for the patient. Despite the fact that some neuroprotective compounds derived from natural sources are attractive in the treatment of neurodegenerative dis-

ease, the poor bioavailability and low clinical efficacy are the serious problems. Possibly, the advanced pharmaceutical technologies and medicinal chemistry will use the opportunity to prepare novel formulations or design new compounds based on natural templates.

Herb-drug interaction as a potential risk for the consumer

It is known that some components of the herbal products can modulate xenobiotic metabolism and transport systems which play an important role in the absorption and disposition of drugs. Interaction between the drug and herbal remedies may occur on the various stages including pharmacokinetic: absorption, binding proteins, membrane transport, distribution, metabolism and excretion. Studies have shown that interactions are often caused by the modification of the cytochrome P450 (CYP-450) isoenzymes in phase I biotransformation of drugs. CYP isoforms carry out conversion of the lipophilic compounds, including drugs to the hydrophilic metabolites to facilitate its excretion in the urine or bile. Cytochrome P-450 isoenzymes are expressed at the highest level in the liver. Inhibition of the CYP450 isoform activity leads an increased drug concentration in plasma and intensifying its action and toxicity. The induction of the enzyme causes the opposite effect, the decline in plasma concentrations and reduced the effectiveness of therapy. It is recognized that approximately 70–80% of all currently prescribed drugs are metabolized by the CYP system. Briefly, the CYPs most active in drug metabolism are CYP2C, CYP2D and CYP3A subfamilies. It has been shown that CYP3A4 isoforms involved in the metabolism of nearly 50% of clinically used drugs. While the CYP1A, CYP2A and CYP2E subfamilies metabolize, besides drugs, also many protoxins and procarcinogens. Therefore, modifications of their activities by phytochemicals can have clinical relevance.

The multidrug resistance protein (P-glycoprotein) is ATP-dependent protein in the apical membrane of intestinal epithelium, hepatocytes, kidney proximal tubule epithelium, and brain capillary endothelium. In these structures P-gp pumps a variety range of xenobiotics into the intestinal lumen, bile duct, renal tubule, and brain capillary, respectively. In this regard it plays an important role in the intestinal absorption, distribution in the central nervous system and excretion of drugs. Thus, inhibition or induction of CYP enzymes and/or P-gp by administration of prescribed drugs with some herbs can cause pharmacokinetic interactions potentially leading to failure of therapeutic agents [58]. In this paper we draw attention only to some of the commonly used medicinal or dietary herbs as factors causing drug interactions.

Extracts and preparations of the leaves of *Ginkgo biloba* are used for the treatment of cerebrovascular dysfunctions, dementia, memory impairment (120–240 mg/day), and peripheral vascular disorders [58, 59]. *G. biloba* has anti-platelet activities and among the interactions mentioned the possibility of bleeding during the use of the extract with other anti-platelet agents (warfarin, aspirin) or herbal remedies possessing similar anti-platelet activities (garlic or ginseng) are worth noting [60]. Data from *in vitro* studies suggest the existence of interaction of *G. biloba* on the stage of biotransformation of xenobiotics by changes in the activity of cytochrome P450 isoforms [61]. It is possible that terpenoid fraction of *G. biloba* extract (EGb 761) inhibited CYP2C9 while flavonoids decrease the activity of CYP2C9, CYP1A2, CYP2E1 and CYP3A4 [62]. Generally, it has been shown that the level of CYP2B1 / 2 and 3A1/2 are induced in the rats under the influence of *G. biloba* while CYP1A1/2, 2C11, 2E1 and 4A1 do not change significantly. In the human CYP3A4 and CYP1A2 grows, but CYP2C9 and CYP2E1 falls under the influence of *G. biloba* extract. It is believed that the induction of CYP3A4 may be due to the interaction of ginkgolide A via pregnane X receptor. Further, the activity of human P-gp was significantly reduced by *G. biloba* extract in the *in vitro* or *in vivo* studies [58]. On the other hand, Li et al. showed that ginkgolide A and B induce hepatic P-gp while flavonoids and bilobalide do not influence P-gp activity [63]. Long-term use of extract in rats decrease bioavailability of cyclosporine which may affect the modulation of P-gp activity [64].

Allium sativum (garlic) is widely used as a medicinal and dietary product, which has a wide pharmacological activity such as antimicrobial, hypolipidemic, antihypertensive, procirculatory, antidiabetic, and anti-immunoenhancing efficacy [58]. Chemopreventive properties of garlic are not fully understood, but it is suggested that that this may be an inhibiting effect on CYP2E1 and induction of phase II metabolism of xenobiotics. Among the active compounds include alliin, allicin, diallyl disulfide, and diallyl sulfide. There are studies indicating that uncontrolled dosage *A. sativum* is not always safe, and necrotic changes in the histopathological study of the liver and kidney in rats after administration of high doses of garlic [1000 mg / kg] for 30 days have been observed [66]. There-

fore, according to some authors, the recommended daily dose of fresh garlic is about 4 g or 600–900 mg garlic powder standardized to 1.3% of the alliin [58, 59]. Some studies suggest that garlic can modify the pharmacokinetics of paracetamol and cause hypoglycemia together with the chlorpropamide dosage [67]. Well described interaction is the impact of garlic with a CYP2C9 substrate warfarin, which is probably due to antiplatelet activity of garlic [68]. Therefore, garlic should not be taken with anticoagulants due to the increasing risk of bleeding. Administration of the enteric coated 2g/dose x twice a day for two weeks garlic does not alter the pharmacokinetics of warfarin and its effects in healthy males but the chronic (above 21 days) consumption of garlic powder increases clearance saquinavir, CYP3A4 and P-glycoprotein substrate [69–71]. In general, garlic extract inhibited *in vitro* CYP2C9 * 1, 2C19, 3A4, 3A5 and 3A7 activity, but does not alter the CYP2D6, and increased CYP2C9 * 2 activity in recombinant human CYP isozyme system. Administration of the garlic oil causes an induction of rat CYP2B1 activity in mice. Moreover, the clinical studies show the lack of connection between the intake of garlic extract and CYP2D6 and CYP3A4, but there have been reports concerning the induction of CYP3A4 [65]. In addition, diallyl disulfide induced *in vivo* CYP2B1 / 2 activity in rats and *in vitro* inhibited CYP2E1 activity in rat and human recombinant CYP isozyme system. Allicin also inhibited CYP1A2 activity in recombinant human CYP isozyme system. The effect on P-gp is not clear [58].

Camellia sinensis is used worldwide as a medicinal and dietetic herbs and typically contains catechins as the principal pharmacologically active phytochemicals, including EGCG. Among the interactions is mentioned lowering the absorption of alkaloids such as morphine, antidepressants and neuroleptics as a result of the impact of tannin tea [72]. There is also a risk of modulation of cytochrome P450 activity. Green tea extract may increase CYP1A, 2B and 3A activity in rats, while in humans reduces CYP2C9, 2D6, and 3A4 in human liver microsomes [73]. Our results suggest that green tea extract may decrease mainly the expression of CYP2C6 in rat liver (homologue to human CYP2C9) and may participate in clinically significant interactions with drugs metabolized by these enzymes [74]. In addition, EGCG may inhibit CYP1A2 and CYP3A4 in human cells [75]. Green tea polyphenols including EGCG also appears to inhibit the activity of P-gp [58].

Rosemary extract increased the protein expression of hepatic CYP2B1 / 2, but did not change hepatic CYP1A1 /2 in rats [76]. Further, rosmarinic acid induced the *in vitro* activity of CYP1A, 2B and 3A in both human and rat hepatoma cells but inhibits human recombinant CYP3A4 activity, not CYP2C9 and 2D6 [77]. In addition, rosemary extract inhibited P-gp-mediated efflux of doxorubicin and vinblastine in P-gp-overexpressing human breast cancer cells [78], mRNA and protein expression of P-gp and efflux of doxorubicin and rhodamine 123 used as a dye in human gastric cancer cells resistant to Adriamycin [58, 79].

The protein expression of intestinal CYP3A and P-gp was significantly reduced by treatment with curcumin (60 mg / kg / day) for 4 days [80]. Curcumin decreases the expression of MDR1 gene (P-gp) leading to increase the sensibility of resistant human gastric cancer cells on the vincristine action [64, 81]. In addition, curcumin inhibited the activity of CYP1A1, 1A2, and 2B1 in rat liver microsomes [58].

Numerous authors claim that *Panax ginseng* may interact with oral anticoagulants, hypoglycemic agents, corticosteroids and antiplatelet agents [60, 82]. The interaction was observed of ginseng with monoamine oxidase inhibitor- of phenelzine. In addition, ginseng may increase the effect of warfarin, heparin, aspirin and other anticoagulants. In animals, ginseng induces alcohol and aldehyde dehydrogenases activity increasing the clearance of alcohol. Ginseng taken with stimulants can cause tachycardia or hypertension. The suggested daily dose is 80-350 mg of the extract or 1–2 grams of powdered raw material [72]. Studies have shown that interactions are the result, among others, of changes in the activity of drug metabolizing enzymes. Ginseng extract inhibited the *in vitro* activity of CYP1A1 / 2, 1B1, and 2E1 in rat liver microsomes [83], while it did not modify the mRNA expression of rat hepatic CYP1A2, 2B1, and 3A23 [84]. It was also shown that ginseng extract inhibited CYP1A1, 1A2, 1B1 and activities in recombinant human CYP isozyme system [58].

Products containing *Echinacea purpurea* are commonly used in phytotherapy of colds, coughs, bronchitis, influenza, inflammation of the mouth and throat. It is one of the most commonly used therapeutic agents in adults and children and its application declare for 10–20% of herbs consumers. Although *E. purpurea* appear to be tolerated in short (8–10 days) and long-term (2 months), uncontrolled consumption can generate a multiple drug interaction [85]. Therefore, *E. purpurea* should not be administered with drugs that affect liver function: anabolic steroids, amiodarone, methotrexate, and ketoconazole as well as with immu-

nosuppressive drugs such as cyclosporin. Prolonged stimulation of the immune system can lead to immunosuppression. There are also studies *in vivo* indicating the possibility of interaction between *E. purpurea* and other therapeutic agents including antibiotics, and substrates of CYP enzymes such as anticoagulants, benzodiazepines and calcium channel blockers [86].

Alcoholic extracts of valerian root are used as a sedative in nervous tension, anxiety, sleep disorders and vegetative neurosis. It has been shown that isolated valepotriates, as used in the treatment of geriatric have affinity for benzodiazepine receptors in the brain, which explains their sedative and little anxiolytic effect. Valerian should not be used with benzodiazepines and alcohol. Based on presented studies, it is claimed that valepotriates may prolong the action of barbiturates whereas intraperitoneal administration of valerenic acid may cause an increase of the anesthetic effect of pentobarbital [72]. Many studies indicated that *V. officinalis* with drugs can lead to the potential herb-drug interactions, mainly by CYP3A4, CYP2C9 and CYP2C19 enzymes modification. Our results suggest that standardized *V. officinalis* extract can decrease the CYP3A4 activity *in vivo* and may participate in clinically significant interactions with drugs metabolized by this enzyme. Inhibition of the CYP3A4 enzyme causes a decrease of drug metabolism leading to an undesirable pharmacological effect and the appearance of toxic symptoms of overdose [87].

It is known that the active substances of alcoholic extract of *Hypericum perforatum* are hyperforin and hypercin which inhibit the reuptake of neurotransmitters such as serotonin and noradrenaline. Moreover, many studies confirmed the effect of St. John's wort on the expression level of P-gp and CYP3A4 [64]. Clinical studies indicate that St. John's wort (SJW) may interact with antidepressants, antiepileptics, immunosuppressants (cyclosporine, tacrolimus), oral contraceptives, anticoagulant (warfarin), calcium blockers (nifedipine, verapamil), digoxin, anti-HIV, anticonvulsants, anesthetics, drugs used in addicted patients (e.g., methadone), muscle relaxing agents, drugs acting on the respiratory system, hypoglycemic, antimicrobic, and antimigraine medicines as well as cytostatics [88]. Most of these interactions are the result of induction of CYP3A4 and P-glycoprotein (P-gp) by St. John's wort extract. For example SJW can reduce the serum concentration of selected antineoplastic agents such as imatinib, irinotecan and docetaxel and reduce the clinical efficacy of these drugs [89]. Furthermore, the clinical studies shown that extract of St. John's wort induces CYP2E1 and CYP2C19 but not CYP1A2, CYP2D6, or CYP2C9 [88].

The study highlighted only the selected aspects of the herb-drug interaction. This subject is inexhaustible and the underlying mechanisms of interaction are still the topic of many research. Due to the possible occurrence of herb-drug interactions, safely is to consult the use of herbal products in high doses. In addition, consumers/patients should describe the use of herbal remedies or supplements in medical interviews.

Acknowledgements

Author's contributions:
Monika Karasiewicz – author of the concept of publication, review of the literature manuscript preparation.
Anna Bogacz – review of the literature, co-author of the text.
Jana Krzysztoszek – review of the literature, proofreading.
Daniel Pędziwiatr – proofreading.
Bogusław Czerny – critical revision and acceptance of the manuscript.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-12-10
Acceptance for publication: 2017-03-27

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REVIEW PAPER

DOI: https://doi.org/10.20883/jms.2017.167

Cognitive functioning of women in pregnancy and early postpartum

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ABSTRACT

Pregnancy and early postpartum is an extremely stressful time in a woman's life. Emotional and cognitive functioning are mutually interconnected. The psyche also influences the physical health on the functional and physical basis. The physiological hormonal changes adapt woman to the development and labour of a child and reflect in the central nervous system functioning. In the presented manuscript, the basic psychological problems accompanying women in this period, as well as mutual relationships between the hormonal and central nervous systems during pregnancy and early postpartum have been presented.

Keywords: pregnancy, postpartum, cognitive functioning.

Introduction

The functioning of the human consciousness and the interrelations between the mind and the brain have been subject to analysis of numerous scientists representing various branches of science. From Antiquity until the modern times it has been an issue not only philosophical in nature, but also psychological and medical. Despite the centuries of research and the search for more and more precise research tools dealing even with molecular structures and for theories trying to find explanations basing on quantum physics (Hameroff, Penrose), the knowledge of the functioning of human consciousness still remains to a greater extent a secret closely guarded by Nature. In medical practice, the aspect of cognitive and emotional functioning is of extreme importance, yet, quite often not widely acknowledged.

Pregnancy is an exceptional time in a woman's life, as well as in the lives of those closest to her. It is not only a medical situation, but also a psychological and social one. The physiological changes which take place in an expectant mother are accompanied by a number of psychological ones. Two spheres of expectations arise from of such changes: one – of a medically healthy child, and the other – of the woman becoming a mature and responsible mother, the person most important to her offspring, at least for the time in which she devotes herself to their upbringing and care. Since pregnancy involves so numerous changes within the body and the psyche of the woman in pregnancy, as well as influences her relations with the world, it is a disruption of the biopsychosocial balance requiring readjustment, and, as such, it is a highly stressful time.

Pregnancy (physiological) is defined as "the period and the range of changes taking place in a woman with a foetus developing in her uterus. It is a physiological condition, yet it is very demanding to the woman's body and, as such, it can easily become a pathological state, detrimental to the woman's organism, as well as the child's" [1]. The maternal pregnancy changes involve main body organs and systems and are present within the whole gestation period [2, 3].

Since pregnancy is considered a physiological condition, it does not require a considerable change in one's lifestyle. The processes taking place in the pregnant woman, however, require a different approach to such matters as nutrition, physical activity, addictions or hygiene. Thus, it can be stated that although it is a natural condition, it is also an additional burden for the expectant mother [4]. Whereas the whole strain on the body, as well as the changes in it, are a source of physical stressors and may become a source of physiological stress. This immense mobilisation of the body influences, in turn, the psychological well-being of the mother-to-be [5].

Morphological and functional changes influence the alterations in the pregnant woman's psyche. The whole gestation period and labour, in turn, are extremely relevant to her emotional state [6]. From the psychological point of view, even a healthy pregnancy is an extremely challenging time. In order to prepare emotionally and practically for the new child, the woman in pregnancy and her partner have several tasks to complete. These are as follows:

- accepting the reality of the pregnancy;
- facing the consequences of being pregnant;
- coping with physical changes;
- coping with uncertainty and unpredictability;
- coping with changes in role and relationships;
- managing unexpected and untoward events and minor pregnancy complications [7].

The experiences and emotional processes of the expectant mother (and more precisely their character, proportions and intensification) vary in each of the trimesters. A considerable portion of the maternal changes can be analysed with respect to the three aspects of the mother's functioning: perception of her own body, perception of herself and changes in social contacts (the physio-psycho-social "I" changes) [8].

Learning about certain elements of the human cognition of "be" may turn out not only to be the matter of discovering new realms of interest, but also translating this into medical practice.

This manuscript presents the character and the role of changes in cognitive functioning in pregnancy and early postpartum.

Cognitive dysfunction during pregnancy

'I swear, I lose brain cells with each pregnancy and I never get them back.'

The above words were written by a woman on an Internet forum. Is there any truth in them? Let us have a closer look at the results of experimental research on animals providing the basis for further clinical analyses.

Animal research showed an increase in dendritic tree density, a higher concentration of the Brain-Derived Neurotropic Factor (BDNF), E2 estrogen receptor density (neuroprotection) and NMDA (Long-Term Potentiation processes improving memory), a decrease in the astroglial reactivity, a decrease in apoptosis and an increase in synaptophysin (synaptic vesicle protein, takes part in neurotransmitter release) in the CA1 region of the hippocampus. A decreased activity of the c-Fos gene and a lower density of dendrites was noticed within the amygdala (responsible for experiencing fear, among others). Simultaneously the volume of those cells increases. Hypothalamus is also subject to changes: there is a change in the immunoreactivity of GFAP (Glial Fibrillary Acidic Protein – intermediate filament protein, found in glial cells, such as, for instance, astrocytes).

Care over children stimulates neurogenesis and the incorporation of new cells into the existent neural networks. New neural connections are formed and provide the basis for development and faster learning. The above changes are accompanied by the changes in the hypothalamic-pituitary axis and opioid receptor sensitivity The plasticity of sensory cortex increases. The above anatomical changes are reflected in a change in behaviour, with a visible improvement in memory, increased speed, decreased fear and they were persistent throughout the whole life of the animal. What is more, the number of amyloid deposits (responsible for aging of the central nervous system and the development of dementia) is lower in multiparous animals as compared to nonparous ones.

Thus, assuming that cognitive dysfunction in pregnancy in fact occurs, one can notice a paradox between the problem reported by women in pregnancy and the experimental data from animal research (Rodent-human paradox). Obviously, as in any case of an attempt to relate animal research results to humans, one should take into account the enormous differences in physiology of the subjects and methods applied in tests; yet this problem seems to be extremely interesting [9].

Among the many factors which could influence the homeostasis of the central nervous system, the influence of the hormonal changes in pregnant women should be analysed. The changes in hormone concentrations are considerable, and literature shows numerous interconnections between the functioning of the central nervous system and the endocrine system in physiology and pathology.

Hormones: neuroprotection and damage

1. Estrogens

Basic science has outlined the role of estrogens as neurotrophic and neuroprotective substances. The preventive role of estrogens for the CNS is stressed, as observational research points to the procognitive effect in women in a good initial neurological condition, undergoing a replacement therapy. Administering estrogens to women with pre-existent neurological damage aggravated the hitherto prevailing bad neurological condition. Details on the above issue are presented by the authors of the WHIMS study (Women's Health Initiative Memory Study) [10]. What is the underlying aspect of estrogen neuroprotection? Complicated relations on the subcellular level include calcium homeostasis, enhanced ATP production in neuronal cells, whereas the common link between those mechanism is the mitochondrion, in which estrogens, through their influence on the expression of several dozen proteins, induce changes in cellular energetics, functioning of oxygen radicals, stress response and cell survival.

2. Androgens

In laboratory and clinical research the neuroprotective role of androgens is quite well-known. On the one hand, it is known that androgens are endogenous negative regulators of beta-amyloid accumulation and that they alter neuronal sensitivity to pathological deposits, on the other, that they play a role in transferring signals inhibiting apoptosis. Brain is an organ strongly reactive to androgens, while mood disorders, cognitive dysfunction and libido disorders constitute a neurological representation of their deficiency. CNS aging processes and the development of neurodegenerative changes are closely related to androgen deficiency. Androgens are neuroprotective thanks to the inhibitory activity of 5α-androstane-3α,17β-diol metabolite, which activates GABA-A receptors (in the same manner as benzodiazepine anticonvulsants). There are other possible mechanisms responsible for the protection of the CNS. These are: the aromatisation of androgens to estrogens (which role has already been mentioned), the induction of Hsp-70 heat shock proteins production and increased catalase activity (antioxidating function) [12].

3. Progesterone

This hormone has numerous functions in the CNS which are not related to procreation and is responsible for regulating the CNS in many of its aspects. There are progesterone receptors in virtually every cell of the central nervous system. There is an especially high amount of them in the hypothalamus, but they are also present in the hippocampus and the frontal cortex – structures of key importance to human cognitive functioning (diminishing inflammation and the activity of nitric oxide syntase, decrease in the brain barrier permeability, glia activation). Progesterone receptors can be also found in other locations, such as the posterodorsal nucleus of the amygdala (a structure responsible for emotions), brain stem structures, the cerebellum or even the spinal cord (stimulation of Brain-Derived Neurotrophic Factor (BDNF) production, enhanced acetylcholinesterase activity). The basic mechanisms of progesterone activity are as follows: regulating gene expression, modulating neural transmission systems and activating signalling cascades. Certain locations of receptors are related to the anti-apoptotic function (the hypothalamus and the spinal cord). Progesterone and its 5α-reduced derivatives (dihydroprogesterone and tetrahydroprogesterone) stimulate Schwann cells proliferation and activate them to produce myelin. Other functions: stimulation of aerobic metabolism, decreasing the production of oxygen free radicals and lipoperoxidation. It stimulates mitosis of neural progenitor cells and their proliferation. These positive effects of progesterone are currently reflected in the trials consisting in the application of this hormone in experimental models of CNS trauma and inflammation. As it turns out, however, the relationship between estrogens and progesterone may be antagonistic in nature and reduce the neuroprotective influence of estrogens. On the clinical level, a progesterone metabolite – allopregnanolone – has anticonvulsant and tranquilising properties (stimulation of GABA-A receptors). Clinical research on Premenstrual Dysphoric Disorder (PMDD) showed that negative mood changes in the luteal phase are at least partly related to the high level of progesterone. Single doses of progesterone administered orally to young women impair face perception [13].

4. Corticosteroids

The influence of a high level of corticosteroids on lower memory word retrieval results, but not on working memory or recognition in pregnant women was presented by Laura Glynn. It should be remembered that for the optimum functioning of the CNS the optimum level of corticoids is indispensable. Both, their too low and too high level disrupt mental processes [14]. The hippocampus (memory) and the frontal lobes (work-

ing memory) are CNS structures susceptible to the fluctuation of steroid levels, and cognitive dysfunctions have been widely described among patients with Cushing's and Addison's diseases [15]. Steroid therapy may cause dysfunctions of the declarative or verbal memory and may occur even after 4–5 days of dexamethasone or prednisone therapy. The dysfunction occurrence is dose-dependent, and the dysfunctions resolve once the therapy is terminated. Patients undergoing steroid therapy present psychiatric symptoms early in its course. The symptoms which include manic episodes (short term therapy), depression (longer therapy) or mixed states. 1/6 of patients treated with steroids experience acute psychotic disorders in the form of delirium. It should be stressed that women are minimally, yet statistically significantly, more prone to psychiatric side effects of the steroid therapy [16].

5. Oxytocin

In mammals oxytocin is responsible for complex emotional and social behaviours: it increases group attachment, social recognition and lowers aggression. What is more, it also lowers anxiety and has effect on the level of fear. In the human being oxytocin administration enhances trust, which suggests that the target of its effect is the amygdala. In Kirsch's study involving the use of the functional magnetic resonance imaging with BOLD technology, the administration of 27 IU of oxytocin nasally to men resulted in the lack of reaction of the amygdala to the presented image of an angry or fearful face as compared to placebo (especially on the left) [17].

Changes in the CNS occurring during pregnancy

1. Quantitative changes.

Oatrige et al. conducted MRI brain volume measurements in 9 healthy women and 5 women with pregnancy induced hypertension (PIH). As a result it was stated that both groups of women were characterised by the decrease in brain volume, which was the highest at the peripartum period, and regained its normal volume within 52 weeks after labour. A statistically significant difference was also recorded referring to a greater decrease in brain volume in women with the PIH. Simultaneously, no discrepancies regarding the volumes of brain ventricles were noted. The probable aetiology of the aforementioned changes may be hormonal, vascular and metabolic changes. The authors suggest the role of high levels of corticosteroids, which are known to cause neuronal atrophy during exogenous administration. The biochemical changes in the cerebrospinal fluid resulting in a decrease in density in the peripartum period may constitute the cause for the change in the metabolic state and the size of the CNS cells. The increase in triglycerides, LDL and HDL cholesterol may be answerable for the changes in the volume of cell membranes. The authors suggest that the changes in cell membranes may occur as a result of the foetus drawing the necessary fatty acids, contributing with that to the occurrence of the aforementioned cell membrane changes. A greater brain volume decrease in women with the PIH may be related to the typical to this condition intravascular hypovolemia aggravated by second-line diuretin therapy, endothelial dysfunction resulting from oxidative stress, anomalous vessel reactivity with vasoconstriction and higher vessel permeability [18].

2. Cognitive changes

One of the most important cognitive functions is memory. Many authors have dealt with the problem of the potential occurrence of memory dysfunctions. Many of them agreed that the problem exists in reality (Condon et al. 1991, Sharp et al. 1993, Keenan et al. 1998, Buckwalter et al. 1999, Shetty, Pathak 2002, de Groot, Horstra et al. 2003, Lurie et al. 2005, de Groot, Vuurman 2006, Rendell, Henry 2008, Glynn 2010). On the other hand, there are a number of researchers questioning such a possibility (Casey et al. 1999, Christansen 1999, McDowall, Moriarty 2000, Crawley 2003, Christensen 2010). The issue is difficult to settle.

Where can such dysfunctions originate? It seems that if they occur they are stimulated by metabolic conditions related to hormonal changes or the changes in CNS neurotransmitters. Cultural stereotypes and lifestyle-related factors are also relevant. Let us have a closer look at the hormonal changes. As early as in 1998 Buckwalter et al. examined 19 women in the final 2 months prior labour and after labour. They were evaluating the relations between various hormones (cortisol, DHEA, estradiol, progesterone, testosterone) and cognitive tests results (21 tests assessing various functions). It turned out that in their statistical analysis no uniform pattern of the dependence between the levels of the said hormones and changes in cognitive functions was found [19]. Studies analysing various levels of plasma neurotransmitters and memory tests in healthy women in pregnancy were carried out by Shetty and Pathak in 2002. The researchers evaluated the levels of epinephrine, norepinephrine, serotonin and dopamine

and stated a significant decrease in the levels of epinephrine, serotonin and dopamine in each of the trimesters as compared to healthy not pregnant women. Additionally, a statistically significant increase in the level of norepinephrine in pregnant women was noted. Psychometric studies confirmed a significant ($p < 0.001$) memory loss. In their final conclusions the authors suggest interrelations among the measured parameters [20].

It may be a relevant question to pose whether cognitive dysfunctions are more common in the case of multiparous or primiparous pregnant women. Parsons et al. analysing pregnancy histories and comparing them to the results of psychometric measurements of verbal functions believe that the highest risk of dysfunction occurrence is borne by the woman in her first pregnancy [21]. Brindle et al., in turn, stress the finding that memory dysfunctions are more common in multiparous women [22]. Moriarty and McDowall challenged the results of these studies, as they found no discrepancies in the declarative and non-declarative memory tests carried out on women [23]. The pregnancy trimester may constitute a different issue. Brindle et al. suggested the relevance of the second trimester of pregnancy as the time most susceptible to the occurrence of dysfunctions [22]. Keenan et al. do not concur, as according to their findings it is the third trimester that bears the greatest risk of dysfunction occurrence [24]. De Groot et al. seem to have assumed a mediative role in this dispute. Cognitive dysfunctions are characteristic to the whole duration of pregnancy [25]. Bearing in mind the lack of a joint stance and so many, often exclusive, conclusions, it is important to note the scientific work carried out by Helen Christiansen et al. In The Personality and Total Health (PATH) Through Life Project the subjects were 2404 women aged 20–24. Within 8 years of observing the cohort group 188 women were pregnant and became mothers. The authors evaluated cognitive functions in 4 domains: cognitive speed, working memory, as well as short-term and long-term memory. The final conclusion of such a large study as it was, was the rejection of the hypothesis that pregnancy and maternity are related to the impairment of mental functions [26].

3. Interpretation problems.

It seems that when analysing data and studies on as complicated a field as cognitive psychology in pregnancy one should take into account a manner of additional factors. These may include:

- sleep disorders,
- depression,
- anxiety and fear,
- aspect of social perception,
- research conditions.

Sub a) Sleep disorders.

The REM cycle is shortened as a result of high concentrations of estrogens, whereas progesterone causes the non-REM phase to lengthen. Frequent urination, coexistent gastroesophaegeal reflux and breathing difficulties contribute to the poorer quality of sleep. The clinical symptoms are insomnia, parasomnia, restless leg syndrome, snoring, sleep apnea syndrome, excessive daytime somnolence [27].

Sub b) Depression.

Even up to 10% of pregnant women comply with the major depression criteria, whereas in 18% of cases it is possible to notice symptoms characteristic for depression. In the first 6 weeks after the labour 10–15% of women suffer from depression, and if they experienced depression episodes prior to labour the percentage is higher – even up to 25–50% of cases. The occurrence of depression during pregnancy and in postpartum results in: a higher percentage of peripartum complications, aversion to breastfeeding, infants' sleep disorders, a poorer relationship between the mother and the child, inappropriate affective control, and even poorer results in children's psychological tests [28]. Sleep disorders and depression are linked and the correlation between them was proven by Okun et al., who showed, basing on a study involving 56 women with a prior history of depression, that bad sleep quality in the first 17 weeks after labour increases the risk of depression relapse [29].

Sub c) Anxiety.

It is a common phenomenon. Multiparous women are exposed to a higher level of anxiety as compared to the primiparous, in whose case the level of anxiety grows gradually [30]. Analysing the degree of anxiety intensity and depressive symptoms in pregnancy one can notice a specific pattern of their occurrence. Anxiety has the pattern resembling the letter 'U', whereas the aggravation of depression has a tendency for gradual decline [31]. The influence of mother's anxiety is not neutral to the child – Beijers et al. conducted a study among 174 mothers and their children which showed that stress and anxiety in the prenatal period may have an influence on the increased incidence of infections in infants (increase by 9.3% in the number of respiratory tract infections, by 10.7 in systemic infections and

by 8.9% in skin infections) and the need to administer antibiotics (7.6%), even after taking into account many external factors. There were no indication of the influence of prenatal anxiety on the development of digestive system dysfunctions [32].

Sub d) Aspect of social perception.

It should be also taken into consideration that a large part of society expects, or even imposes, the coexistence of mental dysfunctions in pregnant women. In a simulation research on workplace conflicts the behaviour of subordinate men or women towards the female team manager was studied. Each of the participants in the study took part in two 10-minute interactive sessions with two managers, one of who pretended to be pregnant. The meetings were recorded and the emotional responses of the participants were recorded basing on an appropriate questionnaire. The research showed that the participants had more negative emotional responses and a lower level of satisfaction following the interaction with the 'pregnant' manager. The subjects expected the pregnant manager to be more passive, nicer and prone to suggestions and were astonished at her authoritarian behaviour [33]. Such results constitute an example of the dominance of our expectations over objective judgement.

Sub e) Research conditions.

What is evaluated in laboratories does not have to correspond to the real life situation. The short duration of research in laboratories may be misleading. Rendell and Henry ran a comparative study on 20 women in pregnancy and 20 not pregnant women to evaluate their prospective memory. And, while in laboratory no dysfunctions were noted, the home part of the study, involving longer memory tasks showed the existence of memory dysfunctions. The above results provide a new research perspective and party explains the discrepancies among various studies [34].

Summary

Although professional experience and observations quite clearly suggest the occurrence of CNS dysfunctions in pregnancy and early postpartum, studies have not yet been able to provide a clear-cut basis to diagnose them. Perhaps the new suggestions of a different research methodology shall constitute a basis for more decisive tests.

The functioning of the human brain maintains largely a 'terra incognita'. Despite the incredible progress in cognitive science, many problems are, and most certainly will remain, unsolved for a long time. The presented results of various studies show how many contradictions and newer and newer questions are yet to be tackled.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-12-10
Acceptance for publication: 2017-01-15

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REVIEW PAPER

DOI: https://doi.org/10.20883/jms.2017.210

Auto-aggressive behavior in dental patients

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ABSTRACT

Auto-aggression can be defined as all actions that aim to inflict mental or physical harm to oneself. It can be caused by a dysfunction of the self-preservation instinct, which can manifest in life-threatening self-mutilation tendencies. Auto-aggression can also be one of the symptoms of psychiatric or emotional dysfunctions such as borderline personality disorder, psychopathy or schizophrenia. Dental practitioners can recognize some abnormal lesions or changes of anatomical structures in the oral cavity which may show tendency to auto-aggressive behaviors manifesting in patient's mouth. On the other hand dental appointment being usually a source of great stress can also induce auto-aggressive behaviors.

Keywords: auto-aggression, behavior, dentistry.

A growing tendency for auto-destructive behavior has recently been observed among children and young adults who try (in this way) to relieve tension caused by often exaggerated parental expectations, an inability to adapt to school or conflicts in their peer groups [1].

Some researchers have noted that the tendency for self-mutilation can be linked to the level of a neurotransmitter called beta-endorphin [2, 3]. Beta-endorphin is an endogenous substance similar to opiates in the brain and self-mutilation may cause an increased production and/or release of this endorphins [4]. This in turn causes a person to experience effects similar to those caused by anesthesia and not feel pain. In addition, the release of beta-endorphins may induce a state that mimics euphoria. The occurrence of those processes has been confirmed by studies in which opioid receptor antagonists such as naltrexone and naloxone have been successfully used to minimize self-mutilation [4].

There are several types of auto-aggression: direct – where we can observe self-mutilation, physical abuse, self-incrimination, and indirect – where the subject forces, provokes and subjects to the aggression of others [5]. A condition concurrent to indirect auto-aggression has also been observed. It can be described as a mentally conditioned tendency to suffer accidents, where the affected persons unconsciously cause life- and health-threatening situations, even seek out circumstances in which the risk of an accident occurring is high. Auto-aggression may also be defined as verbal – where it manifests in self-criticism or lowering ones self-esteem, and non-verbal i.e. self-mutilation, bodily harm [5, 6].

Self-mutilation can manifest in the form of inflicting superficial or deep cuts, plunging sharp objects into the body or swallowing them, dousing in acid, burning, breaking bones, damaging or cutting out fragments of flesh [1]. Those behaviors can be classified as apparent self-mutilation. But the term auto-destructive behavior also covers eating disorders (bulimia, anorexia, obesity), addictions, compulsive biting and picking of nails and cuticles, compulsive skin picking (scratching, reopening wounds, biting lips) and compulsive hair pulling and eating (from eyebrows, eyelashes and head). Feigning symptoms of a physiological or mental disease is typical in hidden auto-aggression [5, 7].

A tendency for self-mutilation is one of the most destructive behaviors of people of all ages that suffer from developmental disorders [3]. There are many possible reasons for those tendencies to occur – from bio-

chemical (lack of endorphins) to environmental (lack of attention). The theoretical and behavioral analyses of factitial injury support the hypothesis that the mutilating activities are learned and are related functionally or instrumentally to the presentation or withdrawal of various reinforcers such as affection or attention [6].

A visit to the dentist can have a dual outcome. It can be a factor that induces auto-destructive behavior due to a high level of psycho-emotional tension and stress usually accompanying such a visit, but on the other hand – a detailed dental examination can help discover early signs of self-mutilation of the masticatory system [2, 7]. Auto-destructive behavior within the oral cavity usually manifests in ulceration caused by chronic biting of the buccal and labial mucosa and tongue and in gingival recession, dehiscence or even auto-extraction of teeth [8].

When analyzing the type of lesions observed in the patient's oral cavity it is worth taking into account the criteria of diagnosing/suspecting lesions in the periodontium that point to auto-destruction as proposed by Stewart and Kernohan:

- lesions do not correspond with clinical picture of known periodontal diseases
- abnormal configuration of periodontal tissue with sharp borders/edges
- rarely observed location/arrangement of lesions
- lesions present in locations that are easily accessible to the patient
- pathological lesions are more likely to occur individually [6].

Some authors emphasize that diagnostic evaluation in case of observed self-mutilation of the oral cavity is a difficult task, as the concern and attention of the doctor and the family may strengthen the auto-destructive tendencies of the patient due to a strong need for attracting attention in people suffering from those disorders [7].

The therapeutic process should include behavior modification with a system of rewards for the renunciation of self-destructive behavior. After the successful modification of a patient's behavior, the restoration and maintenance of the tissues of the oral cavity can be achieved without any clinical difficulties [4, 8].

Situations in which a mental disorder may influence the clinical process in dentistry include: coercion of unnecessary dental procedures, self-mutilation of the oral cavity, abandonment of treatment of the oral cavity and development of conditions due to psychological degradation caused by mental disorders and damage to the viscerocranium caused by psychomotor agitation [7, 9].

An important group of patients at risk of auto-destructive behaviors are people suffering from psychotic disorders from the group of schizophrenic disorders i.e. schizophrenia, schizotypal disorders, persistent delusional disorders [3]. Those people are prone to experiencing delusions (i.e. false beliefs immune to persuasion) that they suffer from disorders of the oral cavity [8]. Sometimes these are accompanied by hallucinations of internal sensations, mostly in the form of pain, paresthesia or other somatic sensations located in the oral cavity. Such patients will consequently try to coerce unnecessary procedures or even self-mutilate [7].

Self-mutilation can also occur during relatively brief psychotic episodes, usually presenting during somatic disorders i.a. infectious or metabolic diseases, addiction to psychoactive substances, brain damage. In those patients, psychomotor agitation may cause, among others, fractures of the viscerocranium or knocked out teeth [3]. The cause can be agitation itself or the fact that the perception of the surroundings has been altered by the disease. Damage to the oral cavity can also occur during attempts at securing the patient. Some people with profound mental disorders are constantly agitated (described as erethism) [6]. They may suffer from numerous injuries and self-inflicted injuries such as damage to the viscerocranium due to frequent head banging [7, 9].

Cases of self-mutilation of the periodontium in autistic patients have also been observed [7]. It presented with persistent scratching and pressing the nail against the tissues of the periodontium which in turn caused stomatitis with post-inflammatory gingival enlargement and gingival recession. Autistic patients have also been observed to auto-extract their teeth, puncture their tongues due to chronic biting or suffer from gingival dehiscence [6, 9].

Rhombencephalosynapsis is a rare malformation of the cerebellum which has been observed to sometimes present with auto-extraction of teeth that were persistently and compulsively touched, pressed and loosened. Patients removed all their permanent teeth one by one in this manner [4].

HSAN (Hereditary Sensory and Autonomic Neuropathy) type IV is a rare disease in which the manifestation of the first symptoms in the oral cavity very often leads to a diagnosis [3]. A frequent problem which occurs at the stage of eruption of deciduous teeth is self-mutilation of the tongue and lower lip caused by that eruption. The source of auto-destructive behavior in HSAN Type IV patients is the congenital insensitivity to pain which causes a functional lack of response

to stimuli. Typical changes in the oral cavity of HSAN IV patients are ulcerations in the inferior surface of the tongue caused by the tongue touching the incisal edges of teeth during sucking or feeding [4]. Similar symptoms in the oral cavity can be observed in patients with Riga-Fede syndrome, here however the injuries are caused by natal or baby teeth characteristic of this disease. As the teeth erupt, the ulcerations of the tongue are joined by other symptoms i.e. biting of the lips and tongue [8]. Persistent and involuntary biting of the tongue is one of the most important diagnostic criteria of HSAN IV, causing the tissues to rip and bleed profusely, recurrent episodes of fever, infections and eating disorders. Children with this disorder have been observed to auto-extract teeth due to increased bruxism or as a reaction to the discomfort that accompanies the eruption of teeth [10, 11].

The behavior of young adults manifesting in increased tendency for drinking alcohol, attempting suicide, auto-aggressive behavior and instrumental aggression points to a serious and progressing problem with coping with the difficult situations experienced in life [12]. Adapting to the realities of life surpasses the possibilities of many young people. They turn to auto-destructive behaviors hurting themselves and the people around them [13, 14].

According to the Protection of Mental Health Act (art. 21 § 1), the examination of a person with a mental disorder without that persons consent can only be carried out if the person's behavior indicates that he or she may pose a direct threat to his or her life or the life and health of others or if that person is not able to fulfill his or her basic human needs [10].

Patients who coerce unnecessary dental procedures, who due to mental disorders refuse treatment or self-mutilate in a non-life-threatening manner cannot even be examined psychiatrically, not to mention treating them without their consent [13, 14]. Even after a psychiatric exam, patients who have been diagnosed with non-psychotic disorders (neurosis, eating disorders, personality disorders, some forms of depression) will be legally deemed fit to decide about their treatment even if their behavior is life-threatening [10, 12].

In light of the above, it is crucial for every doctor, including the dentist, to have basic knowledge in the field of psychiatry. Due to legal constraints, when the patient refuses a psychiatric consultation, the doctor must often rely solely on his or her knowledge.

If a patient attempts to coerce an unnecessary procedure, the doctor should refuse to perform it. Observations have shown however, that this is not always the case [10].

From a legal standpoint the cases of self-mutilation and neglect are slightly more complicated. In such cases one should assess if there is a real and direct threat to the life of the patient such as e.g. the possibility of a suppurative process spreading to the skull cavity. In such a case, according to the Protection of Mental Health Act, the patient shall undergo an involuntary psychiatric evaluation and if diagnosed with a mental disorder – an involuntary commitment. In urgent situations, in which the life of the patient is in immediate danger, action can be taken based on the Medical Profession Act – without analyzing the mental status of the patient [10].

People who suffer from mental disorders or intellectual disabilities and behave in an aggressive or agitated manner can be subjected to involuntary medical treatment [10].

Dental appointment, being usually a source of great stress, can induce certain auto-aggressive behaviors as a way to attract attention or relieve psycho-emotional tension, but it is also an invaluable diagnostic tool not only in regards to lesions that may manifest in the oral cavity but also for other aggression-related behaviors that may endanger the patient's health or life.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2017-02-28
Acceptance for publication: 2017-03-27

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THOUSAND WORDS ABOUT...

DOI: https://doi.org/10.20883/jms.2017.145

Selected issues of GABA metabolism and its potential role in neuropsychiatric disorders

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ABSTRACT

This mini review is limited to chosen problems about GABA metabolism mainly in aspect of associated disorders. GABA primarily identified as inhibitory neurotransmitter plays also excitatory function. Abundant investigations concern the role of GABA in forming and development of neuronal structures in the brain. Resolving of this basic questions will allow to understand the etiology of related neuropsychiatric disorders.

Keywords: *ABAT*, GABA, interneurons, autism, bipolar disorder, schizophrenia.

Introduction

Gamma (γ)-amino-butyric acid (GABA) is the primary inhibitory neurotransmitter in adult human brain. During early development stages GABA plays both inhibitory and excitatory roles. GABA is created by decarboxylation of glutamic acid, a main excitatory neurotransmitter. There is evidence that GABA level is elevated in bipolar disorder (BP) [1] and impairment of genes involved in GABA metabolism has been linked to neuropsychiatric disorders such as epilepsy, autism and schizophrenia (SZ).

GABA interneurons

GABA producing (GABAergic) interneurons are the only source of GABA and the main source of inhibition in the mammalian central nervous system. GABAergic interneurons control the activity of pyramidal neurons and are responsible for the balance between excitation and inhibition signals in the brain. Depending on the brain region, they constitute 10–25% of the total number of cortical neurons. At least 20 different cortical subtypes and 21 hippocampal subtypes of GABAergic interneurons have been identified [2–4]. GABAergic neurons of the hippocampus are arising before the glutamatergic neurons [5]. They may play a role in the development of the hippocampus in a manner analogous to Cajal-Retzius cells [6]. There is evidence that differentiation of the GABAergic phenotype depends on activity of Dlx genes (*Dlx1/2*). Loss of *Dlx* function eliminates hippocampal GABAergic neurons [7].

Genes involved in GABA metabolism (synthesis, transport and decay)

GABA synthesis is controlled by two glutamic acid decarboxylases (GADs) – GAD67/65 encoded by *GAD1/2*, respectively. The two genes produce a number of alternative transcripts. As GADs are not expressed in the astrocytes these cells cannot synthesize GABA from glutamic acid. This process is possible after transforming glutamate into glutamine (in reaction catalysed by glutamine synthetase) which is then transferred by specific transporter to presynaptic terminal containing GADs [8]. Diminished level of GADs was observed in cortex of autistic persons [9]. GABA loaded into synaptic vesicles by the vesicular GABA transporter (encoded by *SLC32A1*) is secreted by exocytosis into the synaptic cleft. GABA inactivation is performed by reuptake into presynaptic membrane or into astrocyte controlled by GABA transporters: GAT-

1,GAT-2, GAT-3 and BGT-1, depended on Na^+/Cl^- ions. In human cortex GAT-1 and GAT-3 transporters are expressed. Decomposition of GABA depends on activity of GABA transaminase.

The GABA receptors

GABAergic neurotransmission is mediated by GABA receptors. There are fast receptors: $GABA_A$ and $GABA_C$ which are ionotropic Cl^- channels and slow ones – metabotropic $GABA_B$ G protein-coupled receptor. $GABA_A$ is the only GABA receptor whose subunit (α3) pre-mRNA is edited by adenosine deaminase [10]. This modification diminishes Cl^- current through the receptor [11]. $GABA_B$ plays a role of autoreceptor which inhibits neurotransmitter release through inhibition of calcium channels. Postsynaptically located $GABA_B$ produces slow inhibitory potentials through G protein–coupled inward rectifying potassium channels. GABA receptors are involved in the pathogenesis of absence and temporal lobe epilepsies, autism and SZ [12, 13].

The GABA transaminase

GABA transaminase (GABA-T) acts as a dimer protein in the mitochondrial matrix (monomer contains 500 amino acids). GABA-T catalyses amino group transfer from GABA to alpha-ketoglutarate using pyridoxal phosphate as a cofactor. This process generates glutamate and succinic semialdehyde which after converting to succinic acid is utilized by Krebs cycle. GABA-T locates to the 4-aminobutyrate aminotransferase gene -*ABAT* at chromosome 16p13.2. Genetic disorder associated with *ABAT* is GABA-T deficiency. This is unique recessive disorder (only three cases described) whose symptoms (severe early infantile epileptic encephalopathy and growth acceleration) are evoked by cerebral accumulation of GABA [14]. The diagnosis based on measuring of cerebral GABA concentrations may be performed non-invasively by magnetic resonance spectroscopy [15]. Recent findings reveal that GABA-T is also involved in the conversion of dNDP to dNTP within mitochondria and every case of GABA-T deficiency is associated with mitochondrial DNA depletion syndrome [16].

The role of GABA – inhibition and excitation

Primary role of GABA is the inhibitory neurotransmition in adult human brain. GABA acts postsynaptically by increasing membrane conductance to chloride ions. It results in inhibition of the generation of an action potential in postsynaptic cell. During early development stages GABA plays both inhibitory and excitatory roles. Excitatory actions of GABA are important for proliferation, migration, synaptogenesis, neuronal differentiation and neuronal network stability [2]. One of the conditions for excitatory GABAergic transmission is the negativity of the resting membrane potential (V_m) relative to the chloride equilibrium potential (E_{Cl}). This excitatory action of GABA in embrional neurons is enabled by the expression of sodium-potassium chloride cotransporter (NKCC1). NKCC1 uses the inward Na^+ gradient maintained by the Na^+ pump to transport Cl^- into the cell. The increase of intracellular Cl^- results in E_{Cl} that is more positive than V_m. Activation of $GABA_A$ receptor produces Cl^- efflux, resulting in membrane depolarization (excitation). During neuronal maturation GABA converts its action from excitatory to inhibitory due to the expression of the K^+/Cl^- cotransporter KCC2. This protein produces active chloride efflux reducing intracellular Cl^- concentrations. As a result E_{Cl} is more negative than V_m and activation of $GABA_A$ receptor produces Cl^- influx leading to membrane hyperpolarization (inhibition) [2]. GABA mediates excitatory actions in immature neurons, adult dorsal root ganglion, and the adult pyramidal cells of cornu ammonis 1 hippocampal subfield – a region critically involved in the pathophysiology of SZ [17, 18].

Epigenetic regulation of GABAergic genes

Recent study in SZ and BP point to a downregulation in the expression of several genes in GABAergic interneurons very probably caused by gene promoter hypermethylation mediated by overexpression of DNA methyltransferases (DNMTs) in these cells. DNMTs catalyze the transfer of a methyl group from the methyl donor S-adenosylmethionine (SAM) to the carbon 5' of cytosines embedded in cytosine phosphodiester guanine (CpG) islands of many gene promoters. SZ and BP disorder could be associated with the epigenetic downregulation of genes expressed in GABAergic neurons: GAD67and reelin – an extracellular large (400 kDa) matrix protein that regulates neuronal migration and positioning in the developing brain. Aberrant epigenetic mechanisms in the pathogenesis of SZ and BP are supported by observations that downregulated expression of GAD67 or reelin in GABAergic neurons

of the patients is associated with an overexpression of zNMTs (DNMT1 and DNMT3a). Valproic acid – an antipsychotic drug that enhances GABAergic transmission can reverse promoter hypermethylation [19].

Other genetic disturbances of GABA metabolism as the cause of neuropsychiatric disorders

Alternate transcripts from neuron-specific K^+/Cl^- cotransporter KCC2 gene (*SLC12A5*) may participate in the abnormal GABA signaling in SZ [20]. Succinic semialdehyde dehydrogenase (SSADH) is an enzyme catalyzing oxidation of succinic semialdehyde (generated in reaction catalysed by GABA-T) to succinic acid. SSADH locates to the aldehyde dehydrogenase 5 family, member A1 gene (*ALDH5A1*) at chromosome 6p22.3. The *ALDH5A1* associated disorder – SSADH deficiency identified in hundreds of persons worldwide is much more common than GABA-T deficiency. In the absence of SSADH succinic semialdehyde is reduced by 4-hydroxybutyrate dehydrogenase to gamma hydroxybutyric acid which is a potential neurotoxic agent. SSADH deficiency symptoms are: early hypotonia and developmental delays, later expressive language impairment and obsessive-compulsive disorder, nonprogressive ataxia, hyporeflexia, and epilepsy [14]. The mutations of MECP2 protein (that binds to methylated DNA during transcriptional silencing) are cause of Rett syndrome – an X-linked disorder associated with motor impairment and autism-like symptoms. MeCP2 deficiency in GABAergic neurons is associated with reduced GAD67/65 (*GAD1/2*) levels leading to reduction in presynaptic GABA release. This suggests that impairment of GABA synthesis may be responsible for neuropsychiatric symptoms in Rett syndrome [21].

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-12-11
Acceptance for publication: 2017-03-27

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THOUSAND WORDS ABOUT...

DOI: https://doi.org/10.20883/jms.2017.150

Endoleaks after endovascular abdominal aortic aneurysm repair

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ABSTRACT

Traditional surgical repair and endovascular repair (EVAR) are the treatment options for abdominal aortic aneurysm repair. EVAR as less invasive becomes a significant and widely accepted way of treatment aortic aneurysms with expanding number of procedures. This technique has a lover short-term mortality and a shorter hospital stay but is not free from complications. The most common complication after EVAR are endoleaks. For the first time summarised and assessed in 1997. Although it is often asymptomatic but may cause aneurysm expanding and rupture. Endoleak is defined as persistent blood flow into the aneurysm sac. It can be revealed intra-operatively or during the follow up – CT; arteriography, angio-MRI enables endoleak diagnosis. Usage of duplex sonography is questionable. In this mini-review we summarise endolek diagnostic, classification and treatment options.

Keywords: Endoleak, EVAR, Abdominal Aortic Aneurysm (AAA).

Traditional surgical repair and endovascular repair (EVAR) are the treatment options for abdominal aortic aneurysm repair [1]. EVAR as less invasive becomes a significant and widely accepted way of treatment aortic aneurysms with expanding number of procedures [2]. This technique has a lover short-term mortality and a shorter hospital stay but is not free from complications. The most common complication after EVAR are endoleaks [3]. For the first time summarised and assessed in 1997 [4]. Although it is often asymptomatic but may cause aneurysm expanding and rupture.

Endoleak is defined as persistent blood flow into the aneurysm sac. It can be revealed intra-operatively or during the follow up – CT; arteriography, angio-MRI enables endoleak diagnosis [4]. Usage of duplex sonography is questionable [5].

In this mini-review we summarise endolek diagnostic, classification and treatment options.

Classification

Due to their etiology, endoleaks are divided into five groups [5–7] (**Table 1, Figure 1**).

Type I endoleak results from incompetent seal at the proximal or distal end of the endograft. Blood enters the aneurysm sac through the leakiness between the graft and aortic mural. Causes of type I endoleaks are usually inadequate selection of patients (tortuosity, neck length and diameter), improper graft size, graft migration or improper placement of the graft due to incorrect imaging techniques parallax. This kind of endoleaks are often revealed intra-operatively, enabling immediate repair. Intervention should be prompt especially when sac enlargement is observed, because aneurysm rupture is probable. Type I endoleaks appears in up to 10% after EVAR procedures [5].

Type II endoleak develops as a result of retrograde blood flow into the aneurysm sac, through a patent lumbar arteries, inferior mesenteric artery or internal iliac artery (hypogastric artery). It is the most common complication after EVAR – in 25% of cases [5]. It often disappears as the vessel thromboses, self-limiting. When no sac enlargement is detected, observation is recommended.

Type III endoleak occurs due to fracture, hole, defect of the graft fabric, separation or mismatch of

Table 1. Classification of endoleaks

Type I (incompetent seal)	Type II (patent branches)	Type III (graft defect)	Type IV	Type V
Ia – proximal	IIa – 1 vessel	IIIa – graft components separation	leakage through grafts fabric porosity	sac diameter increasing with no endoleak detected
Ib – distal	IIb – 2 or more vessels	IIIb – grafts holes / fractures	–	–
Ic – iliac occluder	–	–	–	–

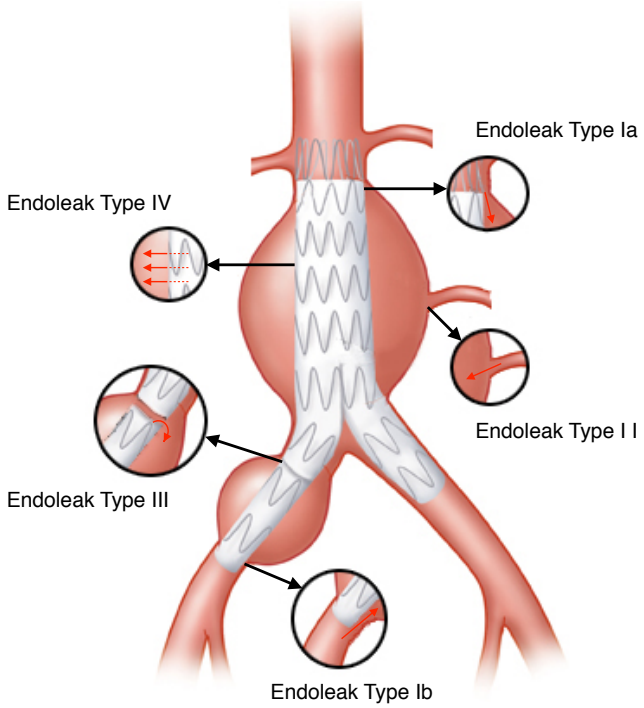

Figure 1. Classification of endoleaks

the graft components. It is as severe condition as type I endoleak, and also in this case repair is mandatory.

Type IV endoleak is an outcome of endografts fabric porosity. Osmotic pressure creates a exudation of molecules through a grafts wall into the aneurysm sac. It usually resolves spontaneously, and require no treatment.

Type V endoleak is also referred as the endotention which is defined as aneurysm sac pressure raising with no evidence of endoleak. The etiology of endotension is uncertain. Some authors suggest transmission of the systemic pressure through the graft wall and the aneurysm sac to the aneurysm wall.

Folllow up and modality [5, 6]

Contrast enhenced CT angiography (CTA) is a gold standard for aneurysm sac diameter measurement [6]. CTA is the best modality for endoleak detection and its sensitivity exceedes duplex ultrasonography [5, 6]. CTA also allows to reveal stent migration or fracture.

MRI/MRI angiography are comparable to CTA. Pros of MRI is avoidance of nefrotxicity and ionising radiation, whereas cons are high price of procedure and contraindications for patients with cardiac peacemakers and metal artefacts.

Plain radiographs, (A-P and lateral projections) enables detection of sent fracture or migration.

Contrast-enhanced duplex ultrasonography (CDU) is supposed to be a safe tool for endoleak detection [8]. Important benefit from usage of this modality is blood flow exposure.

Sac pressure measurement – It is an invasive technique and does not indicate for AAA and endoleak evaluation, thus its value is not clear [5–7].

According to ESVS guidelines [6], follow-up schedule is as follows:

- CTA and plain abdominal radiographs, conducted 30 days postoperatively.
- Endoleak / < 1 stent component / poor overlap – CTA and plain radiographs at 6 and 12 months postoperatively.

- No endoleak and good overlap – CTA and plain radiographs at 12 months postoperatively.
- If there is no endoleak evidence at 12 months, DU and palin radiographs are recommended. Any endoleak or sac diameter increase should be confirmed with CTA.
- DU / non-contrast CT / plain radiographs – might be a sollution for patients with renal failure.

Treatment [5, 6, 9, 10]

Type I endoleaks – discovered intra-operatively, re-ballooning of the landing sites is the method of choice [6]. When this procedure fails or endoleak is detected during the follow up, recommended treatment is usage of additional stent-grafts which seals the leaking end and exclude the aneurysm sac from the circulation. In some cases coil embolisation of a leak is feasible. If endovascular methods of treatment are insufficient, or endoleak is detected intra-operatively, conversion to the open method might be needed [10].

Type II endoleaks – as mentioned before a significant part of type II endoleaks resolves spontaneously [5, 6]. It is questionable weather management of type II endoleaks with no remarkable diameter changes is an appropriate way of treatment [5, 6]. In this case increased observation is suggested [6].

When 10 mm/year or bigger sac diameter enlargement is observed, coil embolization of patent branches is a possible solution whereas translumbar embolization is feasible and gives good early and long term results [5]. Third way of treatment is laparoscopic cessation of retrograde blood flow [5]. When excluded aneurysm sac is filled through a hypogastrisc artery at the level of common iliac artery, its unilateral ligation is justified [5]. In this particular case, administration of extra cuffs or endovascular embolization are also possible ways of treatment

Type III endoleaks – due to a threat of sac rupture this kind of leaks are treated immediately after detection, usually by placement an additional stent-grafts [6, 9]. If treatment is refractory for endovascular methods open surgery should be considered.

Type IV endoleaks – usually resolve spontaneously and require no intervention [6].

Type V endoleaks (endotension) – Asymptomatic cases management is controversial [5, 6]. When aneurysm sac enlargement is observed, additional stent-grafts insertion is advocated.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-12-10
Acceptance for publication: 2017-03-27

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THOUSAND WORDS ABOUT...

DOI: https://doi.org/10.20883/jms.2017.151

Intracrinology and gastric cancer

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ABSTRACT

Overall incidence of gastric cancer (GC) in most populations is approximately two times higher in men than women. Therefore, steroid hormones are suspect to play a role in gastric carcinogenesis. Large amounts of steroid hormones in postmenopausal women and older men are synthesized in peripheral tissues through enzymatic conversion of blood derived precursors into active estrogens and androgens in so called, intracrine mechanism. Moreover, abnormal expression of genes encoding steroidogenic enzymes was shown in numerous malignant tumors including GC. These abnormalities can be associated with deregulated production of steroid hormones in gastric tissue and thus affect the risk of GC. For that reason this short review aims to summarize the current knowledge about the expression of genes involved in metabolism of steroid hormones in normal and malignant gastric mucosa and thus, estimate the potential of these tissues to intracrine synthesis of steroid hormones. This findings could be useful in understanding the role of above mechanism in GC and could help to find therapeutic approaches in future.

Keywords: steroidogenesis; intracrinology; gastric cancer.

Introduction

Gastric cancer (GC) is one of the most common cause of cancer deaths worldwide diagnosed more often in men than women. The increased incidence of this tumor in men cannot be explained by any of known gender differences or environmental factors, therefore the growth of GC may be regulated by sex steroid hormones [1]. In fact, several studies demonstrated the protective role of estrogens, especially 17β-estradiol (E2) in the etiology of GC and furthermore, the presence of both, estrogen and androgen receptors has been detected in normal and cancerous gastric mucosa [1]. Findings focused on sex steroid biology revealed that large amounts of estrogens and androgens are produced locally in various peripheral tissues in postmenopausal women and older men [2]. Since synthesis of estrogens and androgens has been demonstrated in rat parietal cells it was suggested that the certain amounts of steroid hormones can be also synthesized in gastric mucosa [3, 4]. Relevant evidence confirming this statement came from studies concerned the expression of genes encoding steroidogenic enzymes in gastric tissues, which were responsible for *in situ* conversion of biologically inactive precursors into active steroids. Their deregulated expression has been shown in various neoplasm including GC [5–12]. These abnormalities can be associated with the formation of abnormal amounts of steroid hormones and thus, affect gastric carcinogenesis [9, 13].

Intracrinology

Close to 100% of active steroids in postmenopausal women and approximately 50% of androgens in adult men are produced locally in peripheral tissues [2]. However, in contrary to classical endocrine manner, the large amount of estrogens and androgens synthesized in peripheral tissues are not release into the general circulation but act locally, in the same cell where synthesis took place. To describe this local action of steroid hormones, in 1988 Labrie et al. coined new term – "intracrinology" [14]. In this process, circulating dehydroepiandrosterone (DHEA) and estrone (E1)

are metabolized to active steroid hormones by specific steroidogenic enzymes in peripheral tissues. Both, DHEA and E1, are mainly present in the blood as biologically inactive DHEA-sulfate (DHEA-S) and E1-sulphate (E1-S). DHEA-S and E1-S exhibit a long half-life, what makes them the most important reservoir of steroid precursors in the intracrine mechanism of steroid synthesis. In target tissues DHEA-S and E1-S are desulfated and then are involved in further steps of steroidogenesis [2, 5], detailed in **Figure 1**.

Expression of genes encoding steroidogenic enzymes in nontumoral and tumoral gastric mucosa

To date, the presence of mRNA and protein of numerous genes involved in steroidogenesis was found in nontumoral and tumoral gastric mucosa. Simultaneously, expression of some of these genes was altered in GC mucosa as compared with normal counterparts (**Table 1**). It was shown that the expression of steroid sulfatase (*STS*) at mRNA level was decreased in tumoral gastric tissues as compared with adjacent nontumoral mucosa [12]. Previous studies suggested that STS contributes to the *in situ* activation of E1 from E1-S in breast cancer and to mild androgen deficiency, with significantly lower circulating concentrations of DHEA and testosterone in patients with STS deficiency syndrome [15, 16]. Thus, decreased expression of *STS* in GC can be associated with an inhibited synthesis of estrogens and androgens due to depletion of available E1 and DHEA. Among 17β-hydroxysteroid dehydrogenases (HSD17Bs) family, mRNA of *HSD17B7* as well as mRNA and protein of HSD17B1 were detected in gastric mucosa; however, there was no difference

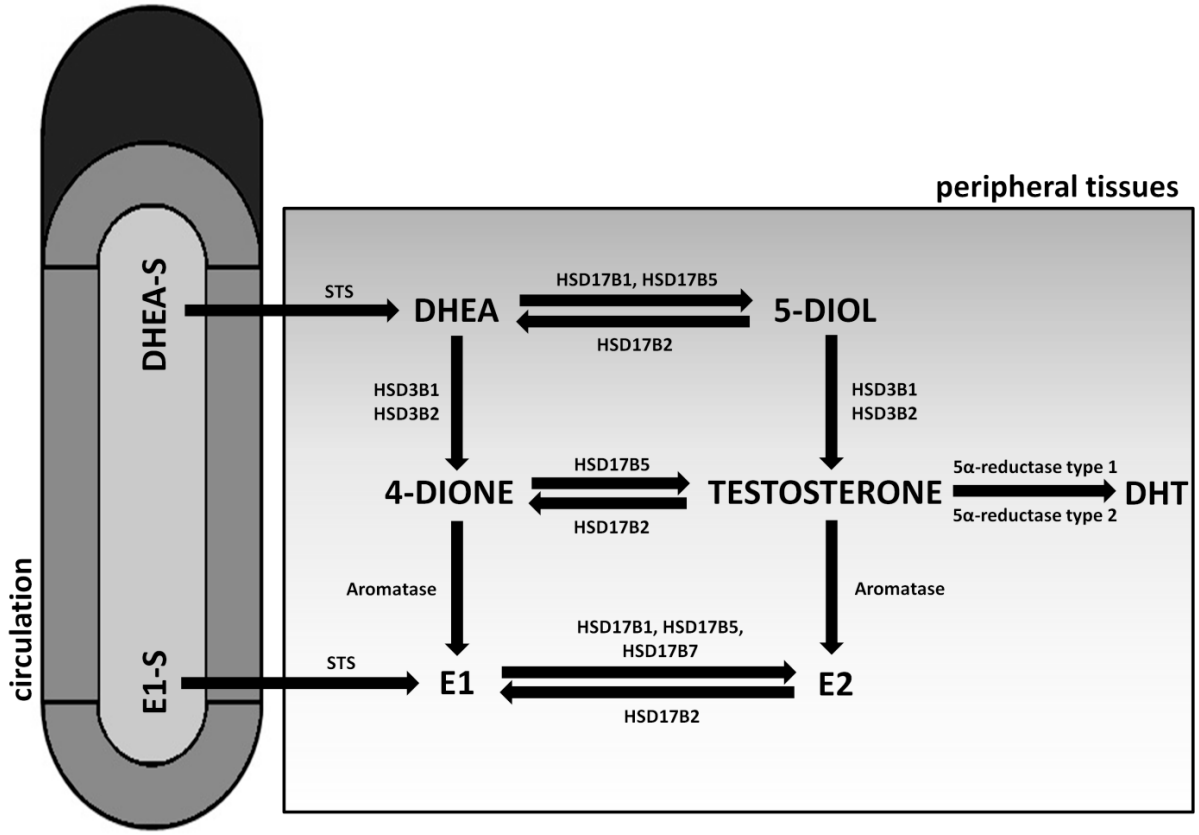

Figure 1. Steroidogenesis in peripheral tissues. Circulating dehydroepiandrosterone sulfate (DHEA-S) and estrone sulfate (E1-S), are taken up into the cell of peripheral tissues. Then, after the removal of sulfate by steroid sulfatse (STS), DHEA can be converted to 4-androstenedione (4-dione) by 3β-hydroxysteroid dehydrogenase/Δ5–4 isomerases (HSD3Bs) type 1 and 2 or to androst-5-ene-3β,17β-diol (5-diol) by the members of the family of 17β-hydroxysteroid dehydrogenases (HSD17Bs), mainly by HSD17B1 and HSD17B5. The both 4-dione and 5-diol can serve as a substrate to testosterone synthesis. Conversion of 4-dione to testosterone is catalyzed mainly by HSD17B5 whereas HSD3B1 and HSD3B2 mediate in metabolism of 5-diol. The most potent androgen, dihydrotestosterone (DHT) is produced from testosterone due to activity of 5α-reductases type 1 and 2. Estrogens are synthesized in so called "sulfatase pathway" and an "aromatase pathway". In the sulfatase pathway E1 is reduced to E2 due to the activity of HSD17B1, HSD17B5 and HSD17B7. In the aromatase pathway, E1 and E2 are synthesized by aromatase from 4-dione and testosterone respectively. Less active forms of androgens and estrogens are mainly produced by HSD17B2

Table 1. Expression of genes involved in steroidogenesis examined in gastric

Gene	Enzyme	Expression in gastric	Method	References
STS	steroid sulfatase	Decreased mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa (60 paired samples)	*Quantitative Real-Time PCR*	[12]
HSD3B1	3β-hydroxysteroid dehydrogenase/ Δ5–4 isomerase type 1	Decreased mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa, although very low mRNA level was observed in both type of tissues (60 paired samples)	*Quantitative Real-Time PCR*	[12]
HSD17B1	17β-hydroxysteroid dehydrogenase type 1	No difference in mRNA and protein expression between tumoral tissues and adjacent nontumoral mucosa (21 paired samples)	*Quantitative Real-Time PCR and Western Blot*	[17]
		mRNA expression was not observed in any examined histological types of mucosa (81 gastric and duodenal specimens containing normal, inflamed and neoplastic mucosa)	Hybridisation *in situ*	[19]
HSD17B2	17β-hydroxysteroid dehydrogenase type 2	Decreased mRNA and protein expression in tumoral tissues as compared with adjacent nontumoral mucosa (34 paired samples)	*Quantitative Real-Time PCR and Western Blot*	[10]
		Decreased mRNA expression in most cases of malignancy as compared with nontumoral mucosa (81 gastric and duodenal specimens containing normal, inflamed and neoplastic mucosa)	Hybridisation *in situ*	[19]
AKR1C3	17β-hydroxysteroid dehydrogenase type 5	Decreased mRNA and non-significantly decreased protein expression in tumoral tissues as compared with adjacent nontumoral mucosa (55 paired samples)	*Quantitative Real-Time PCR and Western Blot*	[11]
		Immunoreactivity detected in GC tissues and in the nontumoral mucosa (117 gastric cancer samples)	*Immunohistochemistry*	[9]
HSD17B7	17β-hydroxysteroid dehydrogenase type 7	No difference in mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa (60 paired samples)	*Quantitative Real-Time PCR*	[12]
CYP19	aromatase	Increased mRNA expression in tumoral gastric tissues as compared with adjacent nontumoral mucosa, although very low mRNA level was observed in both type of tissues (60 paired samples)	*Quantitative Real-Time PCR*	[12]
		Immunoreactivity observed in 23 among 30 cases of gastric cancer and no mmunoreactivity was observed in normal mucosa	*Immunohistochemistry*	[21]
		Protein presence in gastric cancer (30 gastric cancer samples)	*Western Blot*	[21]
		mRNA and protein presence in tumoral tissues and adjacent nontumoral mucosa (19 paired samples)	*Quantitative Real-Time PCR and Immunohistochemistry*	[25]
SRD5A1	steroid 5α-reductase type 1	Immunoreactivity in 69 of 117 cases of tumoral mucosa and no observed immunoreactivity in normal mucosa	*Immunohistochemistry*	[9]
SRD5A2	steroid 5α-reductase type 2	Immunoreactivity in 57 of 117 cases of tumoral mucosa and no observed immunoreactivity in normal mucosa	*Immunohistochemistry*	[9]

in the expression level of those genes among cancerous and histopathologically unchanged gastric tissues [12, 17]. On the other hand, the synthesis of E2 from E1 through HSD17B1 activity was demonstrated in GC cell lines therefore this enzyme can play a role in E2 synthesis during gastric carcinogenesis [17]. Other studies, detected an immunoreactivity of HSD17B5 in tumoral and nontumoral gastric specimens [9]. More importantly, the mRNA level of HSD17B5 (*AKR1C3*) was decreased in GC as compared with adjacent normal tissue [11]. Since *AKR1C3* participates in the conversion of both, 4-androstenedione to testosterone and

E1 to E2, its down-regulation can result in the reduction of intratissue concentration of biologically potent steroids [18]. Furthermore, the presence of *HSD17B2* mRNA was confirmed in different histological types of gastric mucosa. Its decreased expression at both mRNA and protein level has been observed in tumoral gastric specimens as compared with nontumoral counterparts [10, 19]. The role of androgens in GC is unclear; however, some studies suggest that testosterone can induce gastric cancerogenesis [20]. Therefore, down-regulation of HSD17B2 can be associated with increased intracellular concentration of E2 which can be protective, but also with an increased level of testosterone which can be noxious. In fact, an immunoreactivity of 5α-reductases type 1 and 2, which are responsible for the synthesis of DHT, the most biologically potent form of androgens, was reported in gastric carcinoma but not in the non-neoplastic gastric epithelium [9].

Synthesis of androgens in peripheral tissues is also controlled by 3β-hydroxysteroid dehydrogenase/Δ5–4isomerase type 1 (HSD3B1). Surprisingly, studies has shown lower mRNA level of *HSD3B1* in gastric cancerous mucosa than in normal adjacent mucosa; however, overall mRNA content of this gene was low in both types of gastric tissues [12]. Importantly, androgens can be subsequently aromatized to estrogens by aromatase (CYP19) [2]. It was revealed that *CYP19* mRNA level was increased in GC as compared with nontumoral specimens, but similarly to *HSD3B1*, mRNA content of *CYP19* was found to be low in both types of examined tissues [12]. In the other studies, positive immunoreactivity for CYP19 was demonstrated in GC, whereas all nontumoral gastric mucosa specimens were negative for this enzyme [21]. Nevertheless, rat models demonstrated the capability of parietal cells to convert circulating androgens into estrogens with the simultaneous expression of CYP19 mRNA and protein [22–24]. Moreover, the synthesis of E2 through aromatization of exogenous testosterone was demonstrated in GC cell lines [25]. Thus, expression of CYP19 seems to play some role in estrogen synthesis from androgens in gastric mucosa.

Conclusion

Several studies confirmed that genes involved in local steroidogenesis are expressed in normal and cancerous gastric mucosa. Therefore, some amounts of steroid hormones can be synthesized in these tissues. Because the majority of examined genes were found to be down-regulated in GC as compared with nontumoral gastric mucosa, gastric cancerogenesis can be associated with reduced production of steroid hormones *in situ*. However, the exact role of estrogens and androgens in GC development and progression needs to by further clarified. At that time, above findings could be helpful in therapeutic approaches.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-12-22
Acceptance for publication: 2016-03-27

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CASE STUDY

DOI: https://doi.org/10.20883/jms.2017.120

A case report of a patient with blue rubber bleb nevus syndrome presenting with severe gastrointestinal bleeding

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ABSTRACT

Blue rubber bleb nevus syndrome (BRBNS) is an uncommon condition presenting with multiple cutaneous and visceral vascular malformations, predominantly in the gastrointestinal (GI) tract. Typical skin lesion consists of a blue, soft tumor of a rubber like cohesiveness, that is easily compressible and refills slowly on release of pressure. The GI lesions are more clinically relevant, as they may induce chronic bleeding or even life threatening massive hemorrhages. This report presents a case of BRBNS diagnosed in a 52-year-old male with signs of lower gastrointestinal bleeding. The patient presented with melena, fatigue and severe anemia, which were treated by numerous blood transfusions and iron supplementation. Multiple vascular changes were visualized in the small intestine. A typical skin lesion was also present in the skin. Additionally, this report describes the clinical aspects of the syndrome, diagnostic preferences, as well as possible critical complications.

Keywords: blue rubber bleb nevus syndrome, gastrointestinal bleeding, anemia.

Introduction

Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular disorder characterized by multifocal venous malformations. Numerous changes of variable size and structure are most prominent in the skin and gastrointestinal (GI) tract, but can frequently be observed in other locations such as central nervous system (CNS) [1].

The entity was originally described by Gascoyen in 1860, who first noted the association of cutaneous and GI lesions with bleeding [2]. Almost a century later, in 1958, Wiliam Bean further investigated and characterized these vascular anomalies, thereby giving rise to the eponym Bean's syndrome [3].

Here we report a patient with multiple intestinal lesions presenting with episodes of severe GI bleeding and iron deficiency anemia.

Case Report

A 52-year-old male patient was admitted to the Department of Gastroenterology, Medical University of Lodz, in April 2014. Patient's main complaint was disturbing melena observed for five days preceding the admission accompanied by dizziness, excessive fatigue and stenocardial pain on exertion. Hematomesis or recurrent epistaxis were denied. The patient had a medical history of non-steroid anti-inflammatory drugs (NSAIDs) intake, administered for upper respiratory tract infection a month prior to hospitalization. Additionally, the use of other NSAIDs due to persistent back pain was ascertained.

Existing concomitant disorders, being hypertension and benign prostate hypergrowth were determined. For each, relevant treatment had been introduced, including antiplatelet aminosalicylic acid therapy.

Past medical history was otherwise unremarkable. Family history was negative for similar GI disorders episodes. However, the existence of a skin hemangioma in patient's daughter was confirmed.

At the physical examination patient appeared pale with anemic mucosa, tachycardia and presented a bluish, soft, single nodule in the area of left scapula (**Figure 1**). The abdomen examined palpably emerged as soft and non-tender, without liver or spleen enlargement. Performed per rectum examination confirmed melena. Rest of the physical examination did not reveal any abnormalities.

According to laboratory data, performed routine blood analysis showed a significant decrease in hemoglobin (Hgb) concentration, lowered hematocrit (Hct), mean cell volume (MCV) and serum iron level. Moreover, blood cell counts revealed decreased level of red (RBC) and white (WBC) cells. In response to those values indicating severe anemia, blood transfusion of packed red blood cells and iron replacement therapy were administered. Applied medication resulted in significant improvement in blood parameters controlled at hospital discharge. During hospitalization patient underwent both upper and lower GI endoscopy. None of those imaging studies however, revealed abnormalities. Clinical evidence of GI bleeding required locating the exact source of bleeding. Therefore, the patient was scheduled for capsule endoscopy. The study showed multiple nodules with intensified vascular pattern in the wall of small intestine, which were referred to as varices of jejunum (**Figure 2**).

Complex diagnosis required additional examination of other potential locations affected with venous malformations. For this reason, successive actions involved extending diagnostics with further imaging studies including spine nuclear magnetic resonance (NMR) of the abdomen and head computed tomography with angiography (CTA)

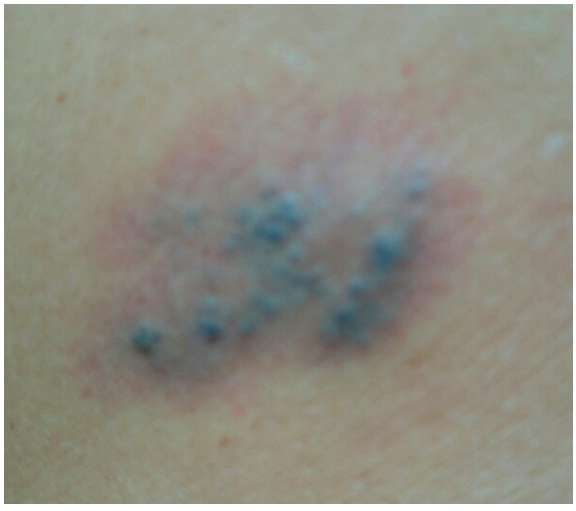

Figure 1. Skin hemangioma in the area of left scapula

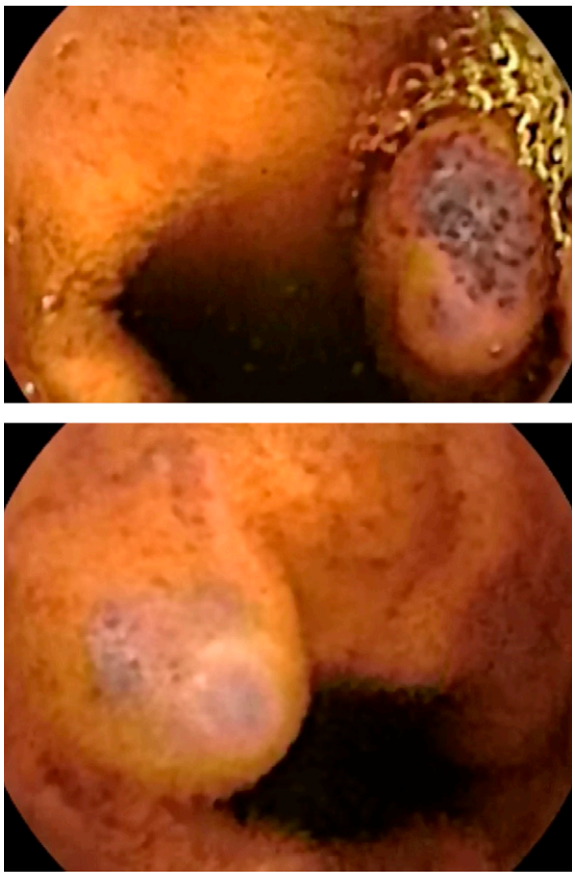

Figure 2. Capsule endoscospy image- intestinal nodules with intensified vascular pattern

Performed in the first instance spine NMR revealed a hemangioma in the body of L1 vertebra, partially explaining the origin of the persistent lower back pain reported by the patient.

The head CTA with a normal image did not confirm the suspicions of probable malformations presence. Oppositely, the abdomen scan revealed multiple, varying in size nodules, not associated with vessels in the mesentery (**Figure 3**). The unclear image of internal structures, orientated diagnosis towards lymphoma which consequently ended with laparoscopic mesenteric lymph node harvesting. In the laparoscopic surgery access enlarged mesenteric lymph nodes, grouped and surrounded by thick crown of vascular plexuses of cyanotic color were observed. The harvested tissue was microscopically analyzed. Regardless of the fragmentary material, elements of adipose tissue with venous malformation were identified. Continuing with the broadened diagnosis, the patient underwent another lymph node biopsy procedure. The investi-

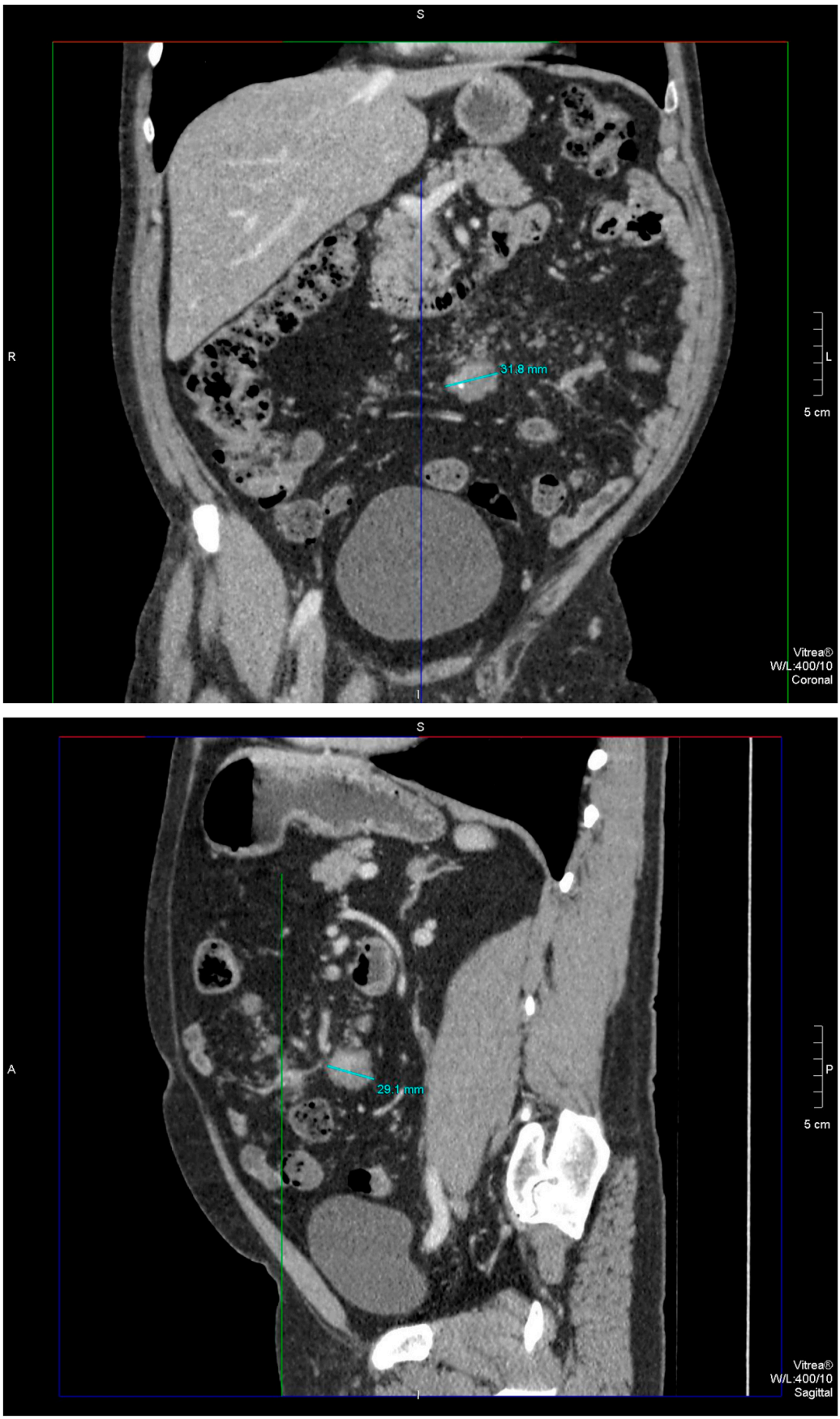

Figure 3. Abdominal angiotomography image – nodules not associated with vessels in the mesentery

gated right groin lymph node image was described as consistent with a reactive state structure.

All of the performed actions proved BRBNS to be the origin of the multifocal malformations. Having received essential treatment, the patient was discharged and educated for observation of early signs of GI bleeding and asked to attend outpatient follow up regularly.

Discussion

The initial report of the disease dates back to 1860, when Gascoyen reported the correlation of skin lesions and GI bleeding [4]. The description did not receive much clinical attention until 1958, when William Bean in detail described a condition with similar presentation and coined the term BRBNS, giving an adequate image of the typical blue, rubbery, bleb like vascular lesions [5].

Bean's description of the findings present in the disease might be in fact considered as inaccurate regarding their true nature. Although, both the original author and multiple contemporary scientists continue to inappropriately classify those as hemangiomas [6], in fact histologically they are considered venous malformations. According to a proposed biologic classification system, vascular anomalies are divided into hemangiomas representing neoplastic lesions with endothelial hyperplasia and vascular malformations, which are congenital lesions with normal epithelial turnover [7].

Cumulating evidence suggest that the lesions found in BRBNS then, should not be referred to as typical hemangiomas, but rather venous malformations [3]. Such changes can be found on any cutaneous surface but are most predominant in the trunk and upper extremities [8]. Altogether, 3 types of such malformations have been described [9]. Type I is a large disfiguring venous malformation that may increase in size and obstruct vital tissues. Type II, the most common finding, is a nontender soft nodule of bluish color which when compressed refills with blood rapidly (blue rubber nipple). Type III is an irregular blue-black macule or papule [10]. These lesions may be punctate, merge with adjacent pigmented nevi and rarely blanch on pressure [11].

Cutaneous malformations do not have a tendency to bleed spontaneously [6]. With the diameters ranging between few millimeters and several centimeters, they can number from several to more than a hundred with a tendency to escalate in size and quantity with age.

In general, venous malformations in the skin are usually first noticed at neonatal period or infancy, but can sometimes be latent until adulthood [12]. The latter mechanism corresponded with the described patient, who observed the presence of a skin hemangioma since early childhood. The presence of cutaneous lesions typical of BRBNS should alert the clinician for potential internal vascular malformations [13]. Analogous venous anomalies, to those in the skin, may be located throughout the GI tract. Although, possible to observe in any position from oral cavity to anus they are most prevalent in small intestine and distal colon [14]. In contrast to skin lesions, intestinal malformations are more susceptible to bleeding often resulting in iron deficiency anemia, which may require supplementation and blood transfusions [15]. Occasionally patients develop severe complications such as rupture, intestinal torsion, and intussusceptions [16]. GI tract appears as the second most involved organ in the disorder following the skin. However, case reports have demonstrated other tissues and organs involved in the pathology including the central nervous system, thyroid, parotid, eyes, oral cavity, musculoskeletal system, lungs, kidney, liver spleen and bladder, all of which being a potential cause of severe complications [17]. The presented patient showed no involvement of other internal organs except small intestine. There was also a spinal involvement and later on a vascular malformation in head magnetic resonance imaging (MRI) was found.Although most cases of BRBNS develop sporadically, a genetic model of inheritance has been proposed. Evidence suggest the disorder to have autosomal dominant transmission associated with gene located on chromosome 9 [18]. Furthermore, within the structure of the same gene, a locus associated with familiar venous malformations was identified, thus suggesting categorizing BRBNS in the category of familiar venous malformations [19]. In relationship to a typical BRBNS skin lesion present in patient's daughter, this model seems worth considering.Diagnosis of BRBNS can be often made by visual inspection of the skin lesions, and therefore biopsy is not routinely necessary [20]. Nevertheless, basic evaluation includes a complete history and physical exam, blood count and fecal occult blood (FOB) test to detect blood loss from GI lesions. Positive test result combined with anemia obligate to a full investigation of the GI tract to locate bleeding sites. This evaluation can be accomplished through various methods. Barium contrast studies are considered useful diagnostic tool, showing filling defects if a GI lesion is present. Also computed tomography (CT) and MRI are described to be highly specific diagnostic tools. The latter has proven to be a useful method for screening asymptomatic family members [6].

Compared with these techniques, GI endoscopy emerges as a superior modality as it provides the possibility of curing the lesions. At the other side of the spectrum, it is considered to be an invasive technique and its use within small intestine is limited [21]. To overcome these negative aspects, while keeping the high of the study a new, noninvasive tool - capsule endoscopy, is highly recommended [22]. In fact, capsule endoscopy was the technique to fully confirm BRNNS in our patient, with both upper and lower GI endoscopy showing no abnormalities. BRBNS should be differentiated from other clinical entities including hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), Klippel-Trenaunay syndrome, and Maffucci syndrome all characterized by different vascular malformations [23]. Osler-Weber-Rendu syndrome is described as episodes of recurrent epistaxis and gastrointestinal, punctiform lesions, morphologically and histologically different from those observed in BRBNS. Additionally, it is known to have positive family history [24]. Klippel-Trenaunay syndrome presents a characteristic triad of varicosities, port-wine stains and soft tissue and bone deformities generally located in just one of the extremities [25]. Lastly, Maffucci syndrome manifested by diffuse lesions in the skin and soft tissues accompanied by bone malformations and chondrodysplasias [26].

The management of cutaneous lesions includes laser ablation or cryotherapy. Surgical removal is usually not necessary and often limited to cosmetic indications [27]. Treatment for patients with visceral involvement largely comprises symptomatic treatment of iron deficiency anemia [15].

Although with results based only on case reports, the use of several medical agents for treating BRBNS have been documented. Such therapies were performed with the use of octreotide, interferon-α2a or sirolismus [29, 30].

Specialist suggest endoscopic sclerosis and laser photocoagulation of symptomatic lesions or segmental resection of the involved area as a prophylactic action against bleeding [31, 32]. Operative management however, should not underestimate the risk of significant hemorrhage and possible life-threatening complications. Still, in the event of massive hemorrhage radical steps involving partial resection should be taken [33].

Our patient showed significant involvement of small ileum and jejunum. Preventive surgical resection was not considered as a treatment option due to possible development of short bowel syndrome. The actions were limited to regular outpatient visits, blood and FOB tests, with mandatory imaging studies in an event of laboratory or clinical symptoms of internal bleeding. Furthermore, to minimize the influence on the hemostasis, instructions for avoiding use of any NSAID were implemented.

Conclusions

The presentation of this case demonstrates the invaluable role of an integrated approach to a patient. Thorough physical examination combined with patients medical history provide an opportunity for early diagnosis, management and complications prevention.

The role of used medication, established to influence the hemostasis, should also not be diminished. The report represents possible correlation between the GI lesions bleeding and using substantial amounts of NSAIDs. Vital in arriving at the diagnosis is the extensive search for the exact origin of the symptoms, which in the presented case required the use of 4 different imaging studies (conventional and capsule endoscopy, abdominal and head CT scans with angiography and MRI).

Several disorders involving vascular anomalies, all varying in medical approach to a patient, should be differentiated with BRBNS. Therefore, early recognition of typical cutaneous vascular lesions may bring rational benefits in patient treatment and preventing possible life threatening complications.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2016-12-20
Acceptance for publication: 2017-03-27

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