ORIGINAL ARTICLE

Prevalence of acquired von Willebrand syndrome during essential thrombocythemia: a retrospective analysis of 170 consecutive patients

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KEY WORDS

bleeding disorders, coagulation, hemorrhage, von Willebrand factor

ABSTRACT

INTRODUCTION The identification of patients with essential thrombocythemia (ET) who are at increased risk of acquired von Willebrand syndrome (AVWS) would likely facilitate individualization of treatment and improve its outcomes.

OBJECTIVES The aim of the study was to determine the prevalence of AVWS in patients with ET and to verify whether individuals with and without this bleeding disorder differ in terms of their baseline clinical parameters.

PATIENTS AND METHODS The study included 170 consecutive patients with ET. AVWS was diagnosed on the basis of reduced levels of von Willebrand factor and abnormal results of other routine tests. Patients with and without concomitant AVWS were compared in terms of their demographic characteristics, past and current medical histories, and laboratory parameters.

RESULTS Concomitant AVWS was found in 34 patients (20%). Individuals with AVWS were diagnosed with ET at a significantly younger age than those without the syndrome. In addition, these patients significantly less often were in remission at the time of testing, had significantly higher erythrocyte and platelet counts, and showed abnormalities of the coagulation profile corresponding to defects of primary hemostasis as well as abnormal values of most parameters used in the routine diagnosis of AVWS.

CONCLUSIONS Even every fifth patient with ET may develop AVWS. Young age at diagnosis of ET and the lack of response to its previous treatment are potential risk factors for AVWS that should be considered during the management of the primary condition. All patients with ET and signs of a bleeding disorder, irrespective of the platelet count, should be tested for the presence of AVWS.

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Received: October 15, 2015.
Revision accepted: November 20, 2015.
Published online: December 10, 2015
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (12): 914-920

INTRODUCTION Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder with the spectrum of clinical and laboratory findings mimicking that of a hereditary form of von Willebrand disease. Principal factors distinguishing AVWS from the latter condition include the lack of previous bleeding disorders, diagnosis at an older age, and a negative family history.[1,2] AVWS develops secondarily to other conditions, in particular myeloproliferative and lymphoproliferative neoplasms.[3] Among myeloproliferative neoplasms, AVWS is most commonly observed in patients with essential thrombocythemia (ET).[4] This may have serious clinical implications, as one component of ET treatment is the prevention of thrombosis, which in turn may exacerbate the course of an undiagnosed bleeding disorder or even result in life-threatening hemorrhage. Therefore, the identification of patients with ET who are at increased risk of AVWS would likely facilitate individualization of treatment and improve its outcomes.

The aim of this study was to determine the prevalence of AVWS in patients with ET and to verify whether individuals with and without this bleeding disorder differ in terms of their baseline clinical parameters.

TABLE 1 Differences in age of patients with essential thrombocythemia with and without acquired von Willebrand syndrome

Parameter	AVWS (n = 34)	No AVWS (n = 136)	*P* value
	mean ±SD	mean ±SD	
age at diagnosis of ET, y	45.35 ±16.67	57.71 ±12.94	<0.001
age at the time of testing for AVWS, y	48.26 ±16.82	62.99 ±13.01	<0.001
time between ET diagnosis and AVWS testing, y	2.91 ±2.34	5.29 ±4.25	0.002

Abbreviations: AVWS, acquired von Willebrand syndrome; ET, essential thrombocythemia; SD, standard deviation

PATIENTS AND METHODS

The study included 170 consecutive patients with ET treated at the University Clinical Center, Medical University of Gdansk, Gdańsk, Poland, between 2004 and 2013. A mean age of the patients was 60 ±15 years (range, 22–86 years). The group included 110 women (64.7%) and 60 men (35.3%). The study protocol was approved by the Bioethics Committee at the Medical University of Gdansk, and written informed consent was obtained from all participants to use their clinical data for the research purposes.

ET was diagnosed on the basis of the 2008 World Health Organization criteria,[5] while AVWS—on the basis of abnormal levels of von Willebrand factor (VWF) to VWF ristocetin cofactor (Rco) activity (VWF:Rco, reference range: 60%–170%), von Willebrand antigen (VWF:Ag, reference range: 50%–160%), and VWF collagen-binding activity (VWF:CB, reference range: 40%–250%). Furthermore, VWF:Rco/VWF:Ag and VWF:CB/VWF:Ag ratios (reference range ≥0.6) were determined. AVWS was distinguished from the hereditary form of von Willebrand disease on the basis of the lack of personal and family histories of bleeding disorders.

Patients with and without concomitant AVWS were compared in terms of their demographic characteristics (sex distribution, age at diagnosis of ET, and age at the time of testing for AVWS) and past medical histories. Moreover, we compared their characteristics at the time of testing for AVWS: clinical activity of ET, prevalence of typical clinical symptoms (including signs of a bleeding disorder), the medications used, and laboratory parameters (complete blood count, coagulation profile, C-reactive protein levels, activity of lactate dehydrogenase, prevalence of *JAK2* mutations, and results of specific tests for AVWS: activity of VWF, factor VIII and factor IX, level of VWF:Ag, VWF/VWF:Ag ratio, and VWF:CB).

Statistical analysis

Normal distributions of continuous variables were verified with the Kolmogorov–Smirnov test, and the results were presented as arithmetic means, standard deviations, and medians and ranges. Statistical characteristics of discrete variables were presented as numbers and percentages. The *t* test or Mann–Whitney test was used for intergroup comparisons of continuous variables, and distributions of discrete variables were compared with the Pearson χ^2 test or Fisher exact test. Power and direction of relationships between the presence of AVWS and demographic and clinical characteristics of patients with ET were determined on the basis of odds ratios (ORs) and their 95% confidence intervals (CIs) calculated using a logistic regression analysis. All calculations were performed with the Statistica 10 package (StatSoft, United States), with the threshold of statistical significance set at a *P* value of 0.05 or lower.

RESULTS

Demographic characteristics

The group of 170 patients with ET included 34 individuals (20%) who were diagnosed with AVWS. Patients with and without AVWS did not differ in terms of sex distribution (women: 22/34 [64.7%] vs 88/136 [64.7%], respectively; men: 12/34 [35.3%] vs 48/136 [35.3%], respectively; *P* = 0.575).

Individuals with concomitant AVWS were diagnosed with ET at a significantly younger age than the remaining patients. Moreover, positive results of the test for AVWS were obtained in significantly younger subjects than the negative results (TABLE 1). A total of 5 subjects (14.7%) were diagnosed with AVWS simultaneously with ET, whereas 13 (38.2%), 9 (26.4%), 3 (8.8%), and 4 patients (11.8%)—within 2, 4, 6, and 8 years from the primary diagnosis.

A median age at diagnosis of ET and a median age at the time of testing for AVWS for the whole study group were 56 and 61 years, respectively. AVWS was detected significantly more often in individuals who were diagnosed with ET at the age of 56 years or younger than in those in whom ET was diagnosed at the age of more than 56 years (30/88 [34.1%] vs 4/82 [4.9%], *P* <0.001; OR, 10.09, 95% CI, 3.34–30.46, *P* <0.001), as well as in patients who were tested for ET at the age of 61 years or younger in comparison with those tested at the age of more than 61 years (30/86 [34.9%] vs 4/84 [4.8%], *P* <0.001; OR, 10.71; 95% CI, 3.55–32.37; *P* <0.001).

Past and current medication history

At the time of testing, individuals with AVWS received a hematological treatment (OR, 3.88, 95% CI, 1.72–8.72, *P* = 0.001), and specifically hydroxyurea (OR, 3.17, 95% CI, 1.40–7.16, *P* = 0.005), significantly less often than the remaining patients. Furthermore, subjects with AVWS less often presented with a history of previous hematological treatment (OR, 4.75, 95% CI, 1.06–21.23, *P* = 0.040; TABLE 2).

Clinical symptoms at the time of testing

At the time of testing for AVWS, individuals who were diagnosed with this condition were in remission significantly less often than those without AVWS (6/34 [17.6%] vs 49/136 [36.0%], *P* = 0.029; OR, 2.63, 95% CI, 1.01–6.83, *P* = 0.046). No significant intergroup differences were observed with regards to the prevalence of splenomegaly

TABLE 2 Past and current medication history in patients with essential thrombocythemia with and without acquired von Willebrand syndrome

Medication	AVWS (n = 34)		No AVWS (n = 136)		*P* value
	n	%	n	%	
current history					
any treatment	12	35.3	93	69.9	0.001
hydroxyurea	11	32.4	83	62.5	0.004
busulfan	1	2.9	5	3.7	0.671
other	0	0.0	4	2.9	0.418
past history					
any treatment	2	5.9	32	24.3	0.017
hydroxyurea	2	5.9	23	17.6	0.092
busulfan	0	0.0	11	8.1	0.086
other	0	0.0	2	1.5	0.649

Abbreviations: see TABLE 1

TABLE 3 Complete blood count in patients with essential thrombocythemia with and without acquired von Willebrand syndrome

Parameter	AVWS (n = 34)	No AVWS (n = 136)	*P* value
	mean ±SD	mean ±SD	
erythrocytes, T/l	4.78 ±0.77	4.16 ±0.87	<0.001
hemoglobin, g/dl	14.50 ±1.58	13.68 ±1.56	0.007
hematocrit, %	43.29 ±4.68	41.16 ±4.68	0.019
MCV, fl	91.69 ±8.74	100.50 ±12.10	<0.001
MCH, pg	30.99 ±3.53	33.68 ±5.03	0.004
MCHC, g/dl	33.46 ±1.13	33.30 ±1.12	0.457
leukocytes, G/l	8.71 ±2.83	7.64 ±3.95	0.141
neutrophils, G/l	5.80 ±2.53	4.79 ±3.34	0.100
neutrophils, %	64.66 ±11.92	60.76 ±10.90	0.069
eosinophils, G/l	0.25 ±0.22	0.22 ±0.50	0.695
eosinophils, %	2.70 ±2.06	2.28 ±1.72	0.223
basophils, G/l	0.07 ±0.06	0.05 ±0.05	0.083
basophils, %	0.74 ±0.55	0.64 ±0.63	0.394
lymphocytes, G/l	1.97 ±0.49	2.33 ±4.61	0.653
lymphocytes, %	24.36 ±8.26	26.98 ±9.65	0.147
monocytes, G/l	3.57 ±17.22	0.61 ±0.28	0.045
monocytes, %	7.38 ±5.69	8.54 ±3.63	0.142
platelets, G/l	700.91 ±243.02	472.36 ±187.20	<0.001

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; others, see TABLE 1

(1/34 [2.9%] vs 8/136 [5.9%], *P* = 0.461), hepatomegaly (1/34 [2.9%] vs 7/136 [5.1%], *P* = 0.529), and thrombosis (1/34 [2.9%] vs 2/136 [1.5%], *P* = 0.479). The only intergroup difference in the prevalence of clinical symptoms that was at a threshold of statistical significance pertained to the signs of bleeding disorders (eg, skin manifestations, epistaxis, prolonged bleeding after an injury), which were more frequent in individuals diagnosed with AVWS (15/34 [44.1%] vs 38/136 [27.9%], *P* = 0.053).

Laboratory parameters at the time of testing for acquired von Willebrand syndrome **Complete blood count** Patients who were diagnosed with AVWS presented with significantly higher erythrocyte, monocyte, and platelet counts, as well as with significantly higher hemoglobin and hematocrit levels than individuals without AVWS. Moreover, they showed significantly lower values of mean corpuscular volume and mean corpuscular hemoglobin (TABLE 3). Importantly, only 3 patients (8.8%) with concomitant AVWS had platelet counts exceeding 1000 G/l; 26 subjects (76.5%) from this subset had platelet counts between 451 and 1000 G/l; and 5 patients (14.7%) presented with normal platelet levels (≤450 G/l).

Coagulation profile Patients with concomitant AVWS were characterized by significantly higher values of thrombin time, epinephrine and adenosine diphosphate closure times, as well as by higher (at a threshold of statistical significance) value of activated partial thromboplastin time. Furthermore, they showed significantly lower values of the prothrombin index and significantly lower fibrinogen concentrations than individuals without AVWS (TABLE 4).

Other laboratory parameters Individuals with concomitant AVWS did not differ significantly from the remaining patients in terms of C-reactive protein levels (2.21 ±3.00 mg/l vs 3.21 ±4.73 mg/l, *P* = 0.424), lactate dehydrogenase activity (198.25 ±58.17 units/l vs 225.93 ±111.48 units/l, *P* = 0.176), and prevalence of *JAK2* mutations (25/34 [73.5%] vs 96/136 [70.6%], *P* = 0.489).

Specific tests for acquired von Willebrand syndrome Compared with other patients, individuals who were diagnosed with AVWS presented with significantly lower values of most parameters used in the diagnosis of this condition, namely VWF:Rco, factor VIII, VWF:Ag, VWF:Rco/VWF:Ag ratio, and VWF:CB (TABLE 5).

DISCUSSION

Although the occurrence of AVWS in patients with ET is a well-established phenomenon, the available data on the simultaneous prevalence of these 2 conditions are still inconclusive. According to the literature, from 5% to 30% of patients with ET may develop bleeding disorders of various types.[6] However, most data on the prevalence of AVWS among individuals with ET originate from single case reports or relatively small patient series.[4] Our findings, based on the data of a total of 170 patients, suggest that AVWS may develop even in every fifth patient with ET.

Having a relatively large data set of patients with these 2 conditions (n = 34), we tried to identify potential etiological mechanisms and risk factors for the development of AVWS during the course of ET. According to current knowledge, at least 3 mechanisms may be involved in the pathogenesis of AVWS. In most cases of AVWS, the synthesis and release of VWF are normal,

TABLE 4 Coagulation profile in patients with essential thrombocythemia with and without acquired von Willebrand syndrome

Parameter	AVWS (n = 34)	No AVWS (n = 136)	*P* value
	mean ±SD	mean ±SD	
activated partial thromboplastin time, s	35.90 ±3.45	33.86 ±5.57	0.053
prothrombin time, s	12 (12–13)[a]	12 (11–13)[a]	0.353
prothrombin index, %	95.81 ±7.18	99.42 ±8.76	0.035
thrombin time, s	19.91 ±1.60	18.47 ±2.36	0.007
fibrinogen, g/l	2.70 ±0.65	3.39 ±0.80	<0.001
D-dimer, μg/l	328.33 ±159.37	469.65 ±385.70	0.095
EPI closure time, s	221.19 ±71.84	178.47 ±66.99	0.004
ADP closure time, s	201.95 ±71.44	137.83 ±61.44	<0.001

a median (interquartile range)

Reference ranges: activated partial thromboplastin time, 26–37 s; prothrombin time, 10–15 s; prothrombin index, 80%–120%; thrombin time, 16–21 s; fibrinogen, 1.8–3.5 g/l; D-dimer <500 μg/l; EPI closure time, 84–160 s; ADP closure time, 68–121 s

Abbreviations: ADP, adenosine diphosphate; EPI, epinephrine; others, see **TABLE 1**

TABLE 5 Parameters used in the diagnosis of acquired von Willebrand syndrome (AVWS) in patients with essential thrombocythemia with and without AVWS

Parameter	AVWS		No AVWS		*P* value
	n	mean ±SD	n	mean ±SD	
VWF:Rco, %	34	57.00 ±33.82	136	122.45 ±44.83	<0.001
factor VIII, %	29	94.14 ±27.78	127	127.37 ±45.07	<0.001
factor IX, %	10	99.50 ±16.69	74	119.26 ±32.82	0.066
VWF:Ag, %	32	92.69 ±38.06	128	143.48 ±44.54	<0.001
VWF:Rco/VWF:Ag ratio	32	0.62 ±0.16	128	0.86 ±0.18	<0.001
collagen-binding assay (VWF:CB), %	6	67.83 ±16.24	10	139.90 ±42.67	0.002
VWF:CB/VWF:Ag ratio	6	0.93 ±0.23	10	1.03 ±0.26	0.447

Abbreviations: VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:CB, VWF collagen-binding activity; VWF:Rco, VWF ristocetin cofactor

and its functional deficiency results from: 1) inactivation with specific and nonspecific autoantibodies[7-11]; 2) absorption of VWF on the surface of platelets or malignant cells[12-16]; and 3) loss of high-molecular-weight multimers of VWF due to their exposure to high shear stress and proteolysis.[17-19] Our results and the available evidence regarding the pathophysiology of ET imply that it is the latter mechanism that is likely involved in the pathogenesis of AVWS in patients with ET. The loss of large VWF multimers, resulting from their enhanced proteolysis by the ADAMTS13 cleaving protease, has been previously demonstrated in individuals with ET, and the intensity of this process has been shown to depend on platelet count.[20-24] Importantly, our subset of patients with ET and AVWS included a significantly smaller proportion of individuals in remission or with a past or currrent history of hematological treatment. This implies that long-term remission of ET (which can be achieved with an appropriate treatment) and a resultant decrease in the number of circulating platelets may protect against AVWS. This hypothesis is also supported by the fact that participants with concomitant AVWS presented with significantly higher platelet counts than the remaining patients. Importantly, individuals with concomitant AVWS were also characterized by higher erythrocyte counts than the remaining subjects, which suggests the potential involvement of increased shear stress in the etiopathogenesis of this bleeding disorder. Also some ET-specific etiopathogenetic mechanisms of AVWS, such as in vivo platelet activation,[25] should be considered.

Apart from an insight into the etiopathogenesis of AVWS, our study provided several clinically important observations. Firstly, it implied that younger age at the diagnosis of ET may predispose to the development of AVWS, as patients with concomitant AVWS were diagnosed with ET approximately 10 years earlier than the remaining subjects. Importantly, in nearly 80% of the cases (n = 27), clinical and laboratory evidence of AVWS was found within 4 years from diagnosis, and in 5 subjects (14.7%), these 2 conditions were diagnosed simultaneously. Furthermore, as mentioned previously, AVWS was diagnosed significantly less often in patients with a history of past or current hematological treatment or remission of ET (or both). Although the majority of individuals with concomitant AVWS presented with elevated platelet counts, our series included only a small proportion of subjects with ultra-high platelet count (>1000 G/l), as well as a small subset of patients who developed this bleeding disorder despite normal platelet count. This is consistent with literature data showing that clinically-relevant AVWS may develop even if the platelet count is much below 1000 G/l.[26] Consequently, preventive measures that should be undertaken in patients with ET, especially those diagnosed with this condition at a relatively younger age, should include: 1) testing for AVWS whenever there is clinical evidence for a bleeding abnormality (irrespective of platelet count); 2) appropriate control of the primary condition; and 3) aiming at stable remission.

In line with the current guidelines,[27] the use of aspirin in ET requires caution, especially if platelet count exceeds 1000 G/l. It is noteworthy that all patients with ET included in this study received aspirin therapy before the diagnosis of AVWS, but only about 45% of them presented with typical signs of a bleeding disorder. Furthermore, we showed that such signs do not necessarily point to the presence of AVWS, as similar symptoms were also observed in approximately 30% of patients with ET and without AVWS. The signs of a bleeding disorder present in patients with ET without concomitant AVWS might reflect impaired

platelet function, which typically manifests as a prolonged closure time. Therefore, a platelet aggregation assay is another test that should be considered whenever a patient with a bleeding disorder tests negative for AVWS.

Not surprisingly, coagulation tests confirmed that all our patients with AVWS presented with defects of primary hemostasis.[28] In addition, the results of specific tests for AVWS were similar to those typically reported in individuals with this condition,[29] and the values of the most analyzed parameters differed significantly from those recorded in the remaining patients with ET. However, according to the literature, determination of VWF:Ag and FVIII levels alone may be insufficient in some cases,[20,30] and some functional assays (eg, VWF:Rco) should be also performed.[31-33] Importantly, we have conducted all coagulation tests at least 7 days after discontinuation of platelet aggregation inhibitors to exclude false-positive results, which should be a standard of evaluation for AVWS.[34]

While interpreting our findings, potential methodological limitations of the study should be considered, which are primarily related to its retrospective design. Some patients with ET were referred to our center with an already established diagnosis of this condition or due to signs of bleeding disorder, and therefore their past medical histories might have been incomplete. Moreover, it cannot be excluded that because of the potential selection bias related to the fact that we analyzed solely the patients treated at the tertiary center, our findings (especially the data on the prevalence of simultaneous AVWS and ET) cannot be generalized onto the whole population of patients with this myeloproliferative disorder. Owing to the retrospective design, we were also unable to conclude on the cause and effect relationship between the tested associations. Another limitation of our study is that we did not perform a VWF multimer analysis. According to Tiede et al,[35] the sensitivity of routine tests for von Willebrand disease that have been used in our study is relatively low and can be strengthened with the multimer analysis. Consequently, the high incidence of AVWS in our study might still be underestimated. However, even these potential limitations do not diminish the fact that, to the best of our knowledge, the current analysis is the largest study on the simultaneous prevalence of AVWS and ET published to date.[36]

To summarize, this study showed that even every fifth patient with ET may develop AVWS. The principal etiopathogenetic mechanism behind AVWS in patients with ET seems to be the proteolytic loss of high-molecular-weight multimers of VWF. However, also a role of increased high shear stress cannot be excluded as a potential predisposing factor. Young age at diagnosis of the primary condition and the lack of its appropriate control constitute potential risk factors for AVWS that should be considered during the management of patients with ET. Individuals with ET and concomitant signs of bleeding disorders may present with AVWS and should be tested for this condition irrespective of their platelet count.

Contribution statement AM conceived the idea for the study. AM and AH contributed to the design of the research. All authors were involved in data collection. AM, WP, and MB analyzed the data. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Występowanie nabytego zespołu von Willebranda w przebiegu nadpłytkowości samoistnej – retrospektywna analiza 170 kolejnych chorych

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SŁOWA KLUCZOWE

czynnik von Willebranda, koagulologia, krwotok, zaburzenia krzepnięcia

STRESZCZENIE

WPROWADZENIE Identyfikacja chorych na nadpłytkowość samoistną (*essential thrombocythemia* – ET) zagrożonych wystąpieniem nabytego zespołu von Willebranda (*acquired von Willebrand syndrome* – AVWS) niewątpliwie ułatwiłaby indywidualizację leczenia i zaowocowała poprawą jego wyników.

CELE Celem badania było określenie częstości występowania AVWS u chorych na ET oraz wyjaśnienie, czy pacjenci z tym defektem krzepnięcia różnią się od pozostałych chorych pod względem wyjściowych parametrów klinicznych.

PACJENCI I METODY Badaniem objęto 170 kolejnych pacjentów z ET. AVWS rozpoznawano w oparciu o obniżony poziom czynnika von Willebranda oraz nieprawidłowe wyniki innych rutynowo wykonywanych testów. Chorych z AVWS i pozostałych pacjentów porównywano pod względem ich cech demograficznych, stosowanego leczenia (aktualnie i w przeszłości) oraz wyników badań laboratoryjnych.

WYNIKI Współistniejący AVWS wykryto u 34 pacjentów (20%). U osób z AVWS rozpoznanie ET stawiano w znamiennie młodszym wieku niż u pacjentów bez AVWS. Ponadto chorzy z tej grupy istotnie rzadziej znajdowali się w remisji w momencie badania, wykazywali znamiennie większą liczbę krwinek czerwonych i płytek krwi, nieprawidłowości profilu krzepnięcia odpowiadające zaburzeniom pierwotnej hemostazy oraz nieprawidłowe wartości większości parametrów oznaczanych rutynowo w diagnostyce AVWS.

WNIOSKI Do rozwoju AVWS może dojść nawet u co piątego chorego na ET. Potencjalne czynniki ryzyka AVWS, które należy uwzględnić w trakcie leczenia choroby podstawowej, to młody wiek w momencie rozpoznania ET oraz brak odpowiedzi na wcześniejsze leczenie. U wszystkich pacjentów z ET i objawami skazy krwotocznej, niezależnie od liczby płytek krwi, należy wykonać badania w kierunku AVWS.

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Praca wpłynęła: 15.10.2015.
Przyjęta do druku: 20.11.2015.
Publikacja *online*: 10.12.2015.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2015; 125 (12): 914-920