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Is There a Relationship Between Aspirin Responsiveness and Clinical Aspects of Ischemic Stroke?*

Czy istnieje związek między odpowiedzią na aspirynę a klinicznymi aspektami udaru niedokrwiennego mózgu?

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Abstract

Background. The issue of aspirin responsiveness in ischemic stroke patients is still unresolved.
Objectives. The aim of the study was to determine whether aspirin responsiveness is related to the clinical status of stroke.
Material and Methods. Platelet response to acetylsalicylic acid (ASA) was assessed in 64 patients (41 men, mean age: 57.9 ± 10.4 years) with ischemic stroke or transient ischemic attack receiving the routine dose of 150 mg of ASA daily. Platelet reactivity was assessed using a platelet function analyzer (PFA-100) with collagen/epinephrine cartridges and by whole-blood platelet aggregometry with 0.5 mM arachidonic acid on the first day of acute stroke and after 10 days of ASA intake.
Results. Of the 64 patients, 23 (36%) were ASA unresponsive as assessed by the platelet reactivity tests. Based on the Rankin Scale (of 1–5), significantly worse neurological status was observed in the group of grade-3 ASA-unresponsive compared with grade-2 ASA-responsive patients 10 days after stroke occurrence ($p = 0.02$). In all the ASA-unresponsive patients, clinical worsening and/or computed tomography signs of progression before modification of the antiplatelet and/or antithrombotic treatment were observed.
Conclusions. These findings suggest that assessment of ASA response might be a predictive factor in stroke prognosis and therapy (**Adv Clin Exp Med 2009, 18, 5, 473–479**).

Key words: acetylsalicylic acid, antiplatelet therapy, aspirin responsiveness, ischemic stroke.

Streszczenie

Wprowadzenie. Problem odpowiedzi na aspirynę u pacjentów z niedokrwiennym udarem mózgu pozostaje przedmiotem dyskusji.
Cel pracy. Zbadanie, czy odpowiedź na aspirynę jest związana z klinicznym przebiegiem niedokrwiennego udaru mózgu.
Materiał i metody. Oceniano reakcję płytek krwi na kwas acetylosalicylowy (ASA) u 64 pacjentów (41 M, średnia wieku 57,9 ± 10,4 lat) z niedokrwiennym udarem mózgu lub przejściowym atakiem niedokrwiennym (TIA), otrzymujących rutynową dawkę ASA dziennie. Reaktywność płytek krwi oceniano za pomocą analizatora czynności płytek krwi (PFA-100™) z użyciem kartridży kolagen/epinefryna i na podstawie pomiaru agregacji we krwi pełnej z 0,5 mM kwasem arachidonowym w pierwszym dniu wystąpienia udaru i po 10 dniach przyjmowania 150 mg ASA.
Wyniki. Wśród 64 pacjentów – 23 (36%) nie wykazywało odpowiedzi na ASA na podstawie oceny reaktywności płytek. Zgodnie z oceną neurologiczną według skali Rankina, po 10 dniach trwania udaru obserwowano statystycznie istotny gorszy stan neurologiczny w grupie pacjentów nieodpowiadających na ASA 3 (1–5) w porównaniu z grupą pacjentów z prawidłową odpowiedzią na ASA 2 (1–5) (p = 0,02). U wszystkich pacjentów nieodpowiada-

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jących na ASA obserwowano kliniczne pogorszenie i/lub cechy progresji w badaniu tomografii komputerowej przed modyfikacją leczenia przeciwpłytkowego lub przeciwzakrzepowego.
Wnioski. Badania własne sugerują, że ocena odpowiedzi na ASA może być czynnikiem predykcyjnym w rokowaniu i leczeniu udaru mózgu **(Adv Clin Exp Med 2009, 18, 5, 473–479)**.

Słowa kluczowe: kwas acetylosalicylowy, leczenie przeciwpłytkowe, niedokrwienny udar mózgu, odpowiedź na aspirynę.

Aspirin, one of the most popular drugs and known for more than 100 years, has been assessed in many randomized trials as an effective antiplatelet drug for the primary and secondary prevention of cardiovascular events [1–3]. Among the various antiplatelet drugs, such as clopidogrel and thienopyridine, acetylsalicylic acid (ASA, aspirin) remains the drug of first choice because of its efficacy and low costs. However, clinical observations identified a subpopulation of patients who do not respond to therapeutic doses of ASA [4]. It is still not clear if patients who suffer from subsequent episodes of stroke despite ASA treatment are ASA unresponsive. Apart from the clinical effectiveness of ASA, laboratory measurements help to identify patients who, despite receiving the routine doses of ASA, have diminished or absent platelet response. However, the relationship between clinical and laboratory unresponsiveness/resistance is not fully elucidated [5–6]. This study was conducted to assess ASA unresponsiveness in stroke patients in relation to clinical aspects of stroke, i.e. neurological status and stroke subtype.

Material and Methods

Sixty-four patients hospitalized at the Department of Neurology, Medical University of Lodz, Poland, with a diagnosis of ischemic stroke with symptoms lasting < 72 hours or a diagnosis of transient ischemic attack (TIA) who received the routine dose of ASA (150 mg daily) were included. The patients and control subjects entered the study after providing their informed consent according to the local ethics committee.

Neurological examination, laboratory parameters, and computed tomography and/or magnetic resonance imaging of all patients allowed establishing the diagnosis of stroke or TIA. The type of ischemic event (atherothrombotic, cardioembolic, lacunar, unclassified stroke, or TIA) was based on the criteria of the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke Ad Hoc Committee [7]. Neurological status was clinically assessed by neurologists after the first 10 days of acute stroke with the Rankin Disability Scale [8]. Only patients were enrolled for whom neurologists recommended the routine dose of ASA (150 mg daily) as an antiplatelet therapy. Patients with infections, cancer, hepatic or renal failure, known hemostatic disorders, or aspirin allergy were excluded. Anticoagulant, thrombolytic, or antiplatelet therapy, such as ASA, clopidogrel, thienopyridine, or nonsteroidal anti-inflammatory drugs (NSAIDs), at least 10 days before admission to the hospital was also classified as an exclusion criterion.

The control group consisted of 37 age- and sex-matched healthy volunteers (physicians and laboratory staff of this hospital) who received the same dose of acetylsalicylic acid (150 mg daily) for the same period as the studied group. Exclusion criteria for the control group additionally included a history of stroke, ischemic heart disease, diabetes mellitus, hyperlipoproteinemia, and hypertension. The clinical data of the studied groups are shown in Table 1.

Blood Collection

Blood was drawn in the fasting state (12 hours) by venipuncture from the stroke and TIA patients on the first or second day after admission to the hospital before receiving ASA and then after 10 days of therapy with 150 mg ASA daily. Tubes with buffered citrate were used for platelet reactivity. Whole blood was used within 1 hour after blood withdrawal for the platelet assessment. Platelet reactivity was assessed using two methods: a platelet function analyzer (PFA-100) with collagen/epinephrine and collagen/ADP cartridges to measure the aperture closure time (Dade Behring, Germany) and whole-blood platelet aggregometry with the agonists 20 μM ADP, 2 μg/ml collagen, and 0.5 mM arachidonic acid (Chrono-Log, USA). Aspirin unresponsiveness was defined as a lack of prolongation of the collagen/epinephrine closure time ≤ 150 sec. (PFA-100 method) and/or a lack of complete inhibition of arachidonic acid-induced whole-blood aggregation.

Statistical Analysis

Data are expressed as the mean ± standard deviation (*SD*) or the median and range (if the distribution was not normal). For comparisons of means between two groups, Student's *t* test or Mann-Whitney's *U* test (by non-normal distributions) was used and Fischer exact test or chi-squared test was performed for test-

Table 1. Clinical data of the patients and controls

Tabela 1. Charakterystyka kliniczna pacjentów i grupy kontrolnej

Characteristics (Charakterystyka)	Stroke patients (Pacjenci z udarem mózgu) n = 64	Controls (Grupa kontrolna) n = 37	*p*
Age, years (Wiek, lata)	57.9 ± 10.4	55 ± 14	n.s.
Sex, n, M/F (Płeć, n, M/K)	41/23	20/17	n.s.
BMI (kg/m^2)	26.6 (19.3–38.3)	25.8 (21.2–44.2)	n.s.
Smokers, current, n (%) (Palący papierosy obecnie) n (%) former, w przeszłości n (%)	24 (53.3) 21 (46.7) 10 (58.8)	7 (41.2)	n.s.
Hypertension (Nadciśnienie) n (%)	41 (64.1)****	0 (0)	
Ischemic heart disease (Choroba niedokrwienna serca) n (%)	24 (37.5)****	0 (0)	
Family history of stroke (Wywiad rodzinny w kierunku udaru mózgu) n (%)	42 (65.6)***	0 (0)	
Clinical subtypes of stroke (Kliniczne podtypy udaru mózgu)*: atherothrombotic (miażdżycowo-zakrzepowy) n (%) cardioembolic (sercowo-zatorowy) n (%) unclassified (niesklasyfikowany) n (%)	 45 (70.3)**** 6 (9.4)**** 4 (6.3)****	 0 (0) 0 (0) 0 (0)	
TIA** n (%)	9 (14)****	0 (0)	
Neurological status (Stan neurologiczny)*** grade 1(stopień 1) n (%) grade 2 (stopień 2) n (%) grade 3 (stopień 3) n (%) grade 4 (stopień 4) n (%) grade 5 (stopień 5) n (%)	 15 (23.4)**** 11 (17.3)**** 23 (35.9)*** 8 (12.5)*** 7 (10.9)****	 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)	

n – number, *p* – level of statistical significance, n.s. – not significant.
* according to the classification of stroke [7].
** TIA – transient ischemic attack.
*** according to the Rankin Disability Scale [8].
**** statistical testing was not performed because subjects with a history of prior vascular disease or family history of stroke were excluded from the control group.

n – liczba, *p* – istotność statystyczna, n.s. – nieistotne statystycznie.
* zgodnie z klasyfikacją udaru mózgu [7].
** TIA – przejściowy atak niedokrwienny.
*** zgodnie ze skalą niesprawności Rankina [8].
**** testy statystyczne nie były wykonywane, ponieważ osoby z wywiadem w kierunku chorób naczyniowych lub udarem mózgu w rodzinie były wykluczone z grupy kontrolnej.

ing frequency distributions. To compare the means of three groups, one-way analysis of variance with the Tukey B test for multiple comparisons or the Kruskal--Wallis test (non-normal distributions) was used. Comparisons of means in the same group were assessed by Student's *t* test for dependent data or Wilcoxon's test (non-normal distributions). Correlation assessment was performed using Pearson's correlation coefficient or Spearman's rank correlation coefficient. $\alpha = 0.05$ was considered the significance level of the statistical tests.

Results

The clinical data of the patients and controls are shown in Table 1. ASA unresponsiveness was found in 23/64 (36%) stroke patients. In the control group, only 3 (8%) persons were ASA unresponsive. ASA unresponsiveness was confirmed by both methods (PFA-100 and lack of aggregation with arachidonic acid) in 7 of the 23 (30%) ASA-unresponsive stroke patients; in 15 of the 23 (65%), ASA unresponsiveness was confirmed only by the PFA-100 method and in 1 (4%) only by the lack of aggregation with arachidonic acid. In the control group, ASA unresponsiveness was confirmed by both methods in 1 of the 3 (33%) ASA-unresponsive subjects and in 2 (67%) only by the PFA-100 method.

Comparing the clinical data of the ASA--responsive and -unresponsive patients (Table 2), no differences were observed in the proportion of smokers, patients with hypertension, ischemic heart disease, or family history of stroke. The clin-

Table 2. Clinical data of the ASA (acetylsalicylic acid)-unresponsive and -responsive stroke patients

Tabela 2. Charakterystyka kliniczna pacjentów z udarem mózgu nieodpowiadających i odpowiadających na ASA (kwas acetylosalicylowy)

Characteristics (Charakterystyka)	ASA-unresponsive stroke patients (Pacjenci z udarem mózgu nie odpowiadający na ASA) n = 23	ASA-responsive stroke patients Pacjenci z udarem mózgu odpowiadający na ASA) n = 41	*p*
Age, years (Wiek, lata)	59.5 ± 9.9	57 ± 10.7	n.s.
Sex, n, M/F (Płeć, n, M/K)	18/5	23/18	n.s.
BMI (kg/m^2)	29.1 (20–35.2)	25.9 (19.3–38.3)	n.s.
Smokers current, n (%) (Palący papierosy obecnie) n (%) former (w przeszłości) n (%)	7 (41.2) 10 (58.8)	7 (41.2) 10 (58.8)	n.s.
Hypertension (Nadciśnienie) n (%)	16 (69.6)	25 (61)	n.s.
Ischemic heart disease (Choroba niedokrwienna serca) n (%)	8 (34.8)	16 (39)	n.s.
Family history of stroke	15 (65.2)	27 (65.9)	n.s.
(Wywiad rodzinny w kierunku udaru mózgu) n (%)			
Clinical subtypes of stroke* (Kliniczne podtypy udaru mózgu*): atherothrombotic (miażdżycowo-zakrzepowy) n (%) cardioembolic (sercowo-zatorowy) n (%) unclassified (niesklasyfikowany) n (%)	 18 (78.3) 2 (8.7) 1 (4.3)	 27 (65.8) 4 (9.8) 3 (7.3)	 n.s.
TIA**, n (%)	2 (8.7)	7 (17.1)	
Neurological status (Stan neurologiczny)*** Grade (Stopień)	 3 (1–5)	 2 (1–5) 0.02	

n – number, *p* – level of statistical significance, n.s. – not significant.
* according to the classification of stroke [7].
** TIA – transient ischemic attack.
*** according to the Rankin Disability Scale [8].

n – liczba, *p* – istotność statystyczna, n.s. – nieistotne statystycznie
* zgodnie z klasyfikacją udaru mózgu [7].
** TIA – przejściowy atak niedokrwienny.
*** zgodnie ze skalą niesprawności Rankina [8].

ical subtypes of stroke did not differ in the studied groups. Based on the Rankin Disability Scale clinically assessed by neurologists, significantly worse neurological status was observed in the ASA-unresponsive compared with the ASA-responsive patients 10 days after stroke occurrence (Table 2) [8]. In all the ASA-unresponsive patients, clinical worsening and/or progression of computed tomography signs were observed before modification of the antiplatelet and/or antithrombotic treatment. One patient in this ASA-unresponsive group (male, 57 years old, hypertension, diabetes mellitus, and obesity) died despite modified therapy.

Discussion

The definition of aspirin unresponsiveness/resistance and its role in cardiovascular diseases based on clinical observations and laboratory assessment is still controversial [4–6]. The mechanisms responsible for this phenomenon are not clear and may include clinical factors, such as noncompliance with prescribed therapy, altered platelet activation, increased platelet sensitivity to collagen [9], tobacco use [10], interaction with NSAIDS [11], inappropriate ASA dose [12], the role of platelet interaction with erythrocytes [13], the effect of isoprostanes on platelets, similar to that of thromboxane A_2 [14], genetic mutations and polymorphisms involving COX-1 gene [15], glycoprotein Ia [16], and glycoprotein IIb/IIIa [17]. However, recent studies did not show any association between aspirin responsiveness and haplotypes of the seven gene candidates for integrins alpha2beta1 and alphaIIbbeta3 (ITGA2, ITGA2B, and ITGB3), platelet glycoproteins Ibalpha and VI (GPIBA and GP6), the purinergic

receptor P2Y1 (P2RY1), and prostaglandin H synthase 1 (PTGS1=COX1) with documented roles in platelet function [18].

In this study, ASA unresponsiveness was found in 36% of the stroke patients. The prevalence of ASA unresponsiveness in stroke patients varies in publications, for example 7% as primary and 4% as secondary unresponsiveness [19], 13% in the Uchiyama study [20], 25% at a dosage of 325 and 8.2% at 1300 mg aspirin per day [21], and 34% after 100 mg aspirin daily according to Grundmann et al. [22]. ASA unresponsiveness might be different in the early and late phase after ischemic stroke or TIA (60% vs. 43%, respectively, aspirin-resistant patients) [23]. The clinical consequences of ASA unresponsiveness were studied by Eikelboom in the Heart Outcome Prevention Evaluation (HOPE), who found a twofold increased risk of myocardial infarction and a 3.5-fold increased risk of death corresponding with increasing quartile of urinary thromboxane TXB_2 level [24].

Interestingly, in the present study, ASA unresponsive patients showed significantly worse neurological status than ASA-responsive as assessed by the Rankin Disability Scale and required modification of the antiplatelet or antithrombotic therapy [8]. In all the ASA-unresponsive patients, clinical worsening was the basic reason for changing the antiplatelet or antithrombotic therapy. After the modification of treatment, improvement in clinical status was observed.

The proportions of the clinical subtypes of stroke did not differ in the groups of ASA-responsive and -unresponsive patients. In the study by Englyst, patients with stroke and aspirin resistance had a higher Rankin score than in the present study (4.0 vs. 2.0, $p = 0.013$), but the subtype of stroke was also associated with aspirin resistance (lacunar more common than embolic strokes) [25].

Despite many studies, the clinical relevance of ASA is still open to discussion. Dual antiplatelet therapy (aspirin plus clopidogrel) in the secondary prevention of stroke was evaluated in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial without any benefit compared with aspirin alone [26]. Snoep et al. found in their review and meta-analysis a relationship between laboratory aspirin resistance and "clinical resistance", which was associated with a higher risk of recurrent cardiovascular events in a group of aspirin-resistant patients [27]. A recent meta-analysis published by Krasopoulus et al. concerning aspirin resistance and cardiovascular morbidity in 2930 patients with cardiovascular diseases from 20 studies showed aspirin resistance in 28% of patients, which correlated with greater risk of clinically important cardiovascular morbidity [28].

The primary and secondary prevention of stroke with antiplatelet therapy requires further study. The expected results of an ongoing prospective randomized trial, the ASpirin non-responsiveness and Clopidogrel Endpoint Trial (ASCET), should contribute to elucidating ASA resistance in patients with vascular events [29]. However, aspirin remains the drug of choice in antiplatelet therapy [30].

The authors concluded that aspirin unresponsiveness was found in 23/64 (36%) of all studied stroke patients and was associated with significantly worse neurological status according to the Rankin Scale. Individually modified antiplatelet or antithrombotic treatment in all ASA-unresponsive stroke patients was necessary. The findings suggest that assessment of ASA response might be a predictive factor in stroke prognosis and therapy.

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