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ASPIRIN RESISTANCE AND ISCHEMIC STROKE

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ABSTRACT

Objective: Acetylsalicylic acid (ASA) is the most widely used antiplatelet agent in treating ischemic strokes. ASA resistance varies between the populations, from 5% to 60%. We aimed to determine the prevalence of ASA resistance in our population, its association with demographic characteristics, risk factors, and the occurrence of recurrent ischemic stroke (IS). (IST).

Methods: One hundred consecutive patients with primary or recurrent IS were prospectively included. Strokes were diagnosed with computed tomography (CT) or magnetic resonance imaging (MRI). In all patients a detailed history of cardiovascular risk factors and fasting blood analyzes (blood count, glycemia, HbA1c, degradation products, lipid profile) were taken, and the ASA resistance was examined with the Innovance PFA 200 system. The ASA resistance was examined after a minimum of 1 month of regular use of ASA 100 mg per day.

Results: The prevalence of ASA resistance was 32%. ASA-resistant patients were statistically significantly older (69.9±7.5 vs, 61±1 y., $p<0.05$), and of male gender (75 vs, 45.6%, $p<0.05$). Previous cardiovascular diseases were statistically significantly more common in the ASA-resistant patients compared to the ASA-sensitive patients (46.8 vs 26.5%, $p<0.05$). The presence of recurrent stroke in the ASA-resistant versus ASA-sensitive patients was statistically significant (75% vs. 22.05%, $p<0.0001$). There was no statistically significant difference in the investigated laboratory parameters and the risk factors between the ASA-resistant and the ASA-sensitive patients.

Conclusion. The prevalence of ASA resistance in our population is high. According to our results, ASA resistance testing should be done in the older male individuals with a previous burden of cardiovascular diseases.

Keywords: ASA resistance, ischemic stroke, recurrent stroke

INTRODUCTION

Stroke is the second leading cause of death globally [1,2]. Today, the prevention of primary and secondary ischemic stroke of non-cardioembolic origin is done with the use of antiplatelet therapy, acetylsalicylic acid (ASA), as well as the strict control of the risk factors [3,4,5]. ASA achieves its antiplatelet effect through inhibition of platelet aggregation [6].

People with cerebrovascular and cardiac diseases can reduce the risk of new vascular occurrence to 25% by taking one ASA tablet daily [7]. However, certain patients show resistance to the ASA therapy. ASA resistance has been described in the medical literature by several authors and was confirmed by various platelet function laboratory tests [8,9,10,11,12,13,14]. The presence of ASA resistance in patients with ischemic stroke (IS) should be taken into account since it can be one of the reasons for failure in the therapy and the ischemic stroke recurrence. The reasons for ASA resistance are clinical and genetic, yet they have not been sufficiently clarified [15].

In our country, until now, there have been no published results on the prevalence of ASA resistance, as well as its association with demographic characteristics, risk factors, and the occurrence of recurrent IS.

MATERIALS AND METHODS

One hundred consecutive patients presented to the neurology department at the Clinical Hospital in Shtip with a diagnosed primary or recurrent IS between September 2022 and September 2023 were prospectively included. The patients were divided into two cohorts (one with primary and one with recurrent IS), and all were treated with regular therapy of ASA tablets, 100 mg once daily.

In all patients a detailed history was taken to assess the existing cardiovascular risk factors, such as cigarette smoking, arterial hypertension, dyslipidemia, alcohol consumption, diabetes mellitus, chronic kidney disease, and a previous cardiovascular event. Blood was taken in the morning on an empty stomach for blood count, glycemia, glycated hemoglobin (HbA1c), degradation products and lipid profile.

The ischemic stroke was diagnosed with CT or brain MRI. Silent strokes without clinical symptomatology that were noted on any of the neuroimaging techniques were also included in both groups. Patients with hemorrhagic stroke, severe anemia (hemoglobin ≤90 g/l), thrombocytopenia (platelets ≤150), acute infection, NSAID use, contraindication to ASA, anticoagulant therapy or dual antiplatelet therapy were not included in the study.

All patients were tested for ASA resistance. In patients with primary IS the testing was done after a minimum of 1 month from the start of therapy with ASA 100 mg daily. They were evaluated in the first 72 cases after taking the ASA tablet. The evaluation was done immediately before taking a regular daily dose of ASA with the PFA 200 System, which enables a rapid assessment of the ASA-induced platelet dysfunction. In 5-8 minutes the system measures the platelet clot formation in 800 microliters of citrated whole venous blood, and reports on the closure time using disposable cartridges that simulate injured blood vessels. All blood passes through a small opening made of collagen and epinephrine or collagen and ADP (adenosine diphosphate). Collagen/epinephrine cassettes are capable of detecting qualitative platelet defects including the ASA-induced platelet dysfunction. Collagen ADP cassettes are relatively ineffective in detecting an inhibitory effect of ASA. The activated platelets aggregate to form a platelet plug. The time required to close the opening is called a closure time and it is a parameter used to assess the platelet function. We used a COL/EPI cassette. There is no agreed-upon unified closure time defining the ASA resistance in the literature. In our laboratory the normal values are from 80-150 seconds. ASA resistance was defined as a closure time <150 sec. despite the regular ASA intakes. Unlike other analyzers that measure only the inhibition of the platelet aggregation, PFA 200 also measures the ability of ASA to prevent platelet aggregation. The patients response to ASA and the antiplatelet effect of the drug are evaluated. The test has 95% sensitivity in patients with normal platelet function after ASA intake. It clearly delimits responders from non-responders based on a pre-defined and validated reference value. This test is not specific for ASA and correlates well with the light transmission aggregometry.

All data were processed with SPSS 20.0 for the Windows program. The results are presented as mean ± SD and percentages. The normal dis-

tribution of the variables was proven using the Kruskal–Wallis test. T-test for quantitative, x2 test for qualitative variables, and Pearson correlation were used. P<0.005 was considered statistically significant.

RESULTS

Out of a total of 100 analyzed patients, 55 were men and 45 were women, with an average age of 61 ± 9 years, and an average body mass index (BMI) of 27.71 ± 4.21 kg/m2. According to the presence of the cardiovascular risk factors, 13% consumed alcohol regularly, 44% were smokers, 48% were diagnosed with diabetes mellitus, 93% with arterial hypertension, 85% with dyslipidemia, 6% with chronic kidney disease, 33% with a previous cardiovascular event and 40% had recurrent IS (Table 1).

Table 1. *Demographic and clinical characteristics of the analyzed population*

	Number of patients (N=100)
Age (mean±SD)	61±9 years
Gender (m:f)	45:55
BMI (kg/m2)	27.71±4.21
Cardiovascular risk factors:	
Alcohol consumption	13 (13%)
Smoking	44 (44%)
Diabetes mellitus	48 (48%)
Arterial hypertension	93 (93%)
Dyslipidaemia	85 (85%)
Chronic kidney disease	6 (6%)
Previous CVD	33 (33%)
Recurrent IS	40 (40%)

Abbreviations: SD= standard deviation, BMI= body mass index, CVD= cardiovascular disease, IST=ischemic stroke.

In this study ASA resistance was found in 32 out of 100 patients (32%). 43.6% (24/55) were male and 17.8% (8/45) were female. In the group of 32 resistant ASA patients, males dominated with a representation of 75% (24/32), and the remaining 25% were females. The mean age of the ASA-resistant patients was 69.9 ± 7.5 years. Of them 43.7% were cigarette smokers, 15.6% consumed alcohol, 46.8% had type 2 diabetes mellitus, 96.8% arterial hypertension, 90.6% dyslipidemia, 12.5% had chronic kidney disease, 46.8% had a history of previous cardio-vascular event, and 43.7% had a recurrent IS.

When comparing the patients with IS with or without ASA resistance, there was a statistically significant difference in age and gender. The patients with ASA resistance were older and predominantly male (p<0.05) (Table 2). There was a statistically significant difference in the prevalence of a previous cardiovascular event; they were more frequent in the patients with ASA resistance (p<0.05). There was no statistically significant difference in the representation of the risk factors such as the number of platelets, haemoglobin, hematocrit, HBA1C, fasting glycemia, creatinine, urea, smoking habit, consumption of alcohol, persons with type 2 diabetes, arterial hypertension, dyslipidemia and chronic kidney failure (Table 2).

Recurrent stroke was registered in 42 patients (42%). Of the 68 ASA-sensitive patients, 15 (22.05%) had recurrent stroke. Of the 32 ASA-resistant patients, 24 (75%) had recurrent IS. The chi-square test showed a statistically significant difference in stroke recurrence between the ASA-sensitive and ASA-resistant patients (x2 =23.55; p<0.00001). Statistically significant IS occurred more often in ASA-resistant patients.

DISCUSSION

According to our results ASA resistance in our population is high compared to others. ASA resistance predominantly occurs in the adult male population with a previous cardiovascular event. Recurring IS is more frequent in the ASA-resistant patients.

ASA therapy is the gold standard in the prevention of secondary cardiovascular events and is the most commonly prescribed antiplatelet drug. The antiplatelet effect of ASA is attributed to the unique characteristics of the pharmacokinetics and pharmacodynamics of ASA in the inhibition of platelet function. [16,17].

Table 2. *Comparison of ischemic stroke patients with and without aspirin resistance*

	ASA sensitive (N=68)	ASA resistant (N=32)	P value T test
Age (mean±SD)	61±10	69.9±7.5	**0.036**
Gender (male)	31:37 (45.6%)	24:8 (75%)	**0.009**
BMI (kg/m2)	27.8±4.2	27.5±4.2	0.686
Platelets ($x10^9$)	248±65	232±55	0.216
Hemoglobin (mg/L)	138.1±16.3	137.5±15.6	0.859
Hematocrit (	40.1±3.9	39.9±4.0	0.859
HbA1C (%)	6.7±1.9	6.3±1.3	0.342
Glucose (mmol/L)	7.3±3.0	6.8±2.7	0.438
Triglycerides (mmol/L)	1.9±1.3	1.7±0.7	0.316
Total Cholesterol (mmol/L)	4.9±1.3	4.5±1.1	0.124
Urea (mmol/L)	5.8±1.9	6.5±1.8	0.097
Creatinine (μmol/L)	76.9±24.8	85.3±24.3	0.117
Alcohol	8 (11.7%)	5 (15.6%)	HC
Smoking	30 (44.1%)	14 (43.7%)	HC
Diabetes mellitus	33 (48.5%)	15 (46.8%)	HC
Arterial hypertension	62 (91.2%)	31 (96.8%)	HC
Dyslipidemia	56 (82.3%)	29 (90.6%)	0.43
Chronic kidney disease	2 (2.9%)	4 (12.5%)	0.15
CVD history	18 (26.5%)	15 (46.8%)	**0.047**
Recurent IS	15 (22.05%)	24 (75%)	**<0.0001**

Abbreviations: BMI= body mass index, CVD= cardiovascular disease, IS=ischemic stroke.

The prevalence of ASA resistance in patients with stroke is variable among studies [18]. The prevalence of ASA resistance depends on the test used, so ASA resistance ranges from 5-67%. When using the PFA-100 test, ASA resistance ranges from 9.5 to 35%. When the RPFA-ASA test is used, the prevalence is from 7 to 27%. If the optical aggregometry, a gold standard is used, the prevalence is much lower from 0.4 to 9% [19]. We used the Innovancea PFA 200 system for testing.

In our study, the prevalence of ASA resistance in IS patients was 32%. Similar results were

obtained by Bennett and his colleagues. Their study conducted on Australian patients showed the presence of ASA resistance in 30% of subjects [8]. A study in China found ASA resistance to be 20.4%, and diabetes and high LDL levels increased ASA resistance [20]. In a study in Colombia there was resistance to ASA of 7.4% [21]. In a study in Japan 27% of the examined patients with cardiovascular disease (CVD) showed ASA resistance [22]. In Turkish patients with a stroke in a study by EDA DERLE, 32.2% of the patients had ASA resistance, and it was the highest in the enteric-coated tablets (39.3%) [23]. These differences are mostly due to the use of different methods for the assessment of the ASA resistance, different definitions of the ASA resistance, the dose of ASA, and the differences in the analyzed population. The tests for the detection of ASA resistance have inconsistencies, such as poor standardization. Newer technologies are needed that will be cheap and accurate, and can be used for personalized anti-aggregation therapy [24].The higher prevalence in our study may be due to the higher representation of comorbid conditions such as diabetes, CVD, and previous cardiovascular events. Other studies have also found increased ASA resistance in patients with acute coronary syndrome, chronic kidney disease, and diabetes on insulin. Also, genetic factors that we did not investigate increase the ASA resistance.

Some studies have reported that the prevalence of ASA resistance is higher in women and increases with age. In Chen's study, there was a higher percentage of ASA resistance in women, 30% compared to 16% in men, the subjects were older, they had higher cholesterol and low-density lipoproteins, lower hematocrit and higher platelet compared to the subjects sensitive to ASA [25]. In our study, the patients with ASA resistance were predominantly male (43.6%). Cardiovascular events were predominantly present in male patients, so maybe that's why we got these results. However, in the literature, there are similar results, Karsoopolous et al. in a meta-analysis of 20 studies found a higher ASA resistance in male patients and in patients with kidney damage [26]. In ADAM Wisniewski's study in patients with IST, the ASA resistance was 30% , and it was more predominant in males and in smokers [27].

In our study 75% of the ASA-resistant patients had recurrent IS, as in the study by Alexandro Roman González et al., where ASA resistance occurs in similar percentages of patients [21]. Also, in that study it was concluded that the ASA resistance is more frequent in patients with previous CV events ($p < 0.05$) which is in agreement with our results. In the study of Masume Sadegi et al. on the Iranian population, it was proven that as many as 75.3% of the examined patients with coronary artery disease were ASA resistant, but ASA resistance was more common in women [28]. Similar is the data from the study by Liu XF et al., which found a significant number of elderly patients with CVD to be resistant to ASA, and that the level of fasting blood glucose in these patients was closely related to the ASA resistance [29]. Our study does not demonstrate the association of fasting glycemia with ASA resistance, but the findings of CV diseases and older age of patients were consistent with the ASA resistance. Atherosclerosis and coronary events were significantly more common in the ASA-resistant patients in Kahraman's research. They concluded that a higher dose of the drug is recommended for these patients [30]. We also found greater resistance to ASA in patients with CVD.

Fong J et al. in their study, concluded that patients with heart failure and high haemoglobin values had a greater chance of not responding to the ASA therapy [31]. It is believed that the interaction between platelets and erythrocytes can increase the resistance to ASA by creating the prothrombotic effect. In our study, we didn't find this kind of correlation.

Meade TW et al found that the usage of ASA is less effective in patients with systolic blood pressure >145 mmHg. On the other hand, men with higher blood pressure could be exposed to a greater risk of bleeding, and not benefit from ASA in the prevention of CVD and IST [32]. In our study, there was no relation between hypertension and ASA resistance, yet the prevalence of hypertension in our population is at a very high level.

Similarly, in Gum's study, the resistance of ASA increased with age, as in our case. In this study, there was no difference in the ASA resistance among patients with platelet count, DM, diabetes, kidney disease, or liver disease [33].

Regarding other risk factors such as the number of platelets, hemoglobin, glycemia, HBA1C, urea, creatinine, smoking, alcohol, people with diabetes, hypertension, dyslipidemia, and chronic renal failure, in the study of Anil B et al. there was no statistical significant difference between the ASA resistant and ASA sensitive patients [34] as it was the case in our study. Regarding the diabetes

in Tasdemir E et al. research, no difference in the ASA resistance was observed between patients with diabetes and without diabetes, i.e. 41.9% of the patients with diabetes had ASA resistance and 43.2% of non-diabetics had resistance to ASA. Only hypercholesterolemia was an independent predictor of ASA resistance in the patients with diabetes [35]. Regarding diabetes, our findings were similar. Vardhan G's findings from a comprehensive meta-analysis suggest that none of the lipid parameters are significantly associated with ASA resistance, which was also the case in our study [36]. On the other hand, Di Chiara et al. in their research showed that ASA resistance is higher in patients with diabetes and CVD than in patients who did not have diabetes. The increased dose of ASA in these patients may partially overcome platelet reactivity [37]. Fateh Moghadam et al. proved that ASA resistance appears in patients with CVB and is related to a poor clinical prognosis. In the study, 21.5% of the patients were resistant to ASA, 16.9% were semi-resistant to ASA and 61.6% were ASA sensitive. According to this study a conclusion was drawn that a significant number of diabetic patients are ASA resistant [38].

In the research conducted by Schwartz et al. the patients with ASA resistance have an increased probability of subsequent vascular events. Detection and treatment of ASA resistance would be facilitated by the development of a bedside assay that uses whole blood count, which is technically simple, inexpensive, sensitive, specific, reproducible, and provides results within minutes. Future research in patients with inadequate response to ASA should also focus on mechanisms to improve compliance, which should reduce the risk of future vascular events [39].

Kasotakis G. et al. found that routine laboratory monitoring of platelet function in all chronic ASA users is not cost-effective, but should be performed in all individuals with clinical ASA insufficiency after compliance has been confirmed. For individuals identified as ASA resistant, the importance of compliance must be emphasized, suggesting smoking cessation, avoiding medications that inhibit ASA effectiveness (i.e., NSAIDs), and adding other antiplatelet drugs [40]. In our study, ASA-resistant patients had statistical significant previous CVD events. Helgason et al. found that some patients changed from complete to partial platelet inhibition during a constant dose of ASA over 6 months [41]. Andersen et al. found that 10% of the patients converted from aspirin responder to non-responder over a 5 months follow-up [42]. So, variability in response varies, depending on the time of the ASA resistance measurement. There is evidence of the larger effect of aspirin at 2 h post dose compared to 12 h and 24 h [43]. We did not precise the testing time after dose loading and this may be one of the reasons for higher ASA resistance in our population.

From the European region, developing countries have not provided research related to ASA resistance like other regions [44]. This is the first study of the Macedonian population, but it is still on a small sample. Large prospective studies including patients with and without ASA-resistance comparing adverse clinical outcomes are needed.

CONCLUSION

Patients who have ASA resistance have a higher chance of developing recurrent IS. The ASA resistance detection and treatment should be done after ensuring compliance with the therapy of the patients. In our research, according to the results, the examination should be with rapid, unified and standardized inexpensive laboratory tests in those patients who are older, mostly male, and who previously had CVD.

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Резиме

РЕЗИСТЕНЦИЈА НА АСПИРИН И ИСХЕМИЧЕН МОЗОЧЕН УДАР

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Цел: Студијата имаше цел да ја утврди преваленцијата на отпорност на ацетилсалицилна киселина (АСА) кај пациенти со исхемичен мозочен удар (ИМУ) и нејзината поврзаност со демографските карактеристики, факторите на ризик и појавата на повторливи мозочни удари.

Методи: Во студијата беа вклучени 100 пациенти со примарен или повторлив ИМУ. Мозочните удари беа потврдени преку КТ или МРИ. Собирањето податоци вклучуваше детални историјати на кардиоваскуларните ризици, анализи на крвта на празен стомак и тестирање на отпорност на АСА со користење на системот Innovance PFA 200. Отпорноста на АСА беше тестирана по најмалку еден месец од дневно користење на 100 мг АСА.

Резултати: Преваленцијата на отпорност на АСА беше утврдена на 32 % кај пациентите. Пациентите со отпорност на АСА беа генерално постари, со просечна возраст од 69,9 години во споредба со 61 година кај пациентите чувствителни на АСА. Исто така, постоеше поголема преваленција на мажи во групата отпорна на АСА (75 %) во споредба со групата чувствителна на АСА (45,6 %). Кардиоваскуларната историја беше почеста кај пациентите со отпорност на АСА (46,8 % наспроти 26,5 %), а појавата на повторливи мозочни удари беше значително повисока кај пациентите со отпорност на АСА (75 % наспроти 22,05 %). Не беа најдени значителни разлики во лабораториските параметри меѓу пациентите отпорни и чувствителни на АСА.

Заклучок: Студијата откри висока преваленција на отпорност на АСА, сугерирајќи дека тестирањето на отпорност на АСА треба да се разгледа за постари мажи со историја на кардиоваскуларни заболувања.

Клучни зборови: резистенција на аспирин, исхемичен мозочен удар, повторен мозочен удар