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Assessment of the relationship between platelet reactivity, vascular risk factors and gender in cerebral ischaemia patients

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ABSTRACT

Aim. Excessive activation and platelet aggregation play important roles in the aetiopathogenesis of cerebral ischaemia. The aim of this study was to assess the relationship between platelet reactivity, gender and vascular risk factors in cerebral ischaemia patients.

Clinical rationale for the study. The research is useful because we found high risk groups of inefficient aspirin treatment in cerebral ischaemia patients.

Material and methods. The study involved 101 patients, including 69 patients with ischaemic stroke and 32 patients with transient ischaemic attack. The assessment of platelet reactivity was made within 24 hours of the disease onset using two aggregometric methods: impedance and optical.

Results. Resistance to acetylsalicylic acid among people with cerebral ischaemia was estimated at 30.69% using impedance aggregometry and 9.2% using optical aggregometry. There were no differences in platelet reactivity or ASA resistance between the groups of patients with stroke and TIA in either method. In the whole group of patients ($p = 0.04$), and in the group of patients with stroke ($p = 0.0143$), higher reactivity of platelets was observed by impedance aggregometry in men than in women. In the whole group of patients ($p = 0.0229$), and in the subgroup with stroke ($p = 0.0123$), it was shown that aspirin resistance is significantly more common in the subgroup of men than in women. In patients suffering from nicotine addiction, significantly higher platelet reactivity was found in the whole group of patients ($p = 0.004$), as well as in the subgroup of patients with stroke ($p = 0.0135$).

Conclusions. There are no differences between platelet reactivity and the incidence of aspirin resistance in patients with stroke and TIA. Male gender and smoking are associated with greater reactivity of platelets and more frequent occurrence of acetylsalicylic acid resistance in patients with cerebral ischaemia.

Clinical implications. Dual antiplatelet therapy or clopidogrel treatment should be considered in smoking males with cerebral ischaemia due to the high risk of aspirin inefficiency.

Key words: platelet reactivity, stroke, aspirin resistance, gender, risk factors

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Introduction

Stroke is a crucial social and medical problem of the 21st century, and one of the main causes of morbidity and long-term disability. It is also the second most frequent cause of death in the world [1]. In 2013 the American Heart Association/American Stroke Association (AHA/ASA) proposed a new definition of ischaemic stroke as an episode of sudden neurological disorder caused by focal cerebral, spinal cord or retinal ischaemia persisting over 24 hours or corresponding to the morphological features of central nervous system ischaemia. Thus, due to such an updated definition, ischaemic stroke can also be diagnosed when clinical symptoms last less than 24 hours but where neuroimaging studies have demonstrated an ischaemic infarction, as well as in thrombolytic patients whose symptoms of focal deficit have undergone a rapid regression [2]. If the time and radiology criteria are not met, transient ischaemic attack (TIA) is diagnosed.

Platelet activation plays an important role in the pathomechanism of ischaemic stroke, especially in the thrombotic mechanism. Antiplatelet therapy, by inhibiting the activation and aggregation of platelets, is the current standard of pharmacological treatment, both in the treatment of the acute phase and in the prophylactic treatment of secondary ischaemic stroke [3]. Both European and American standards recommend several antiplatelet drugs with similar efficacy, but acetylsalicylic acid (ASA) is still the most commonly used. Unfortunately, a phenomenon that limits the effectiveness of ASA is the so-called resistance to acetylsalicylic acid [4]. In order to optimise antiplatelet therapy, tests evaluating platelet function-platelet reactivity are used, and these form the basis for the diagnosis of laboratory resistance. Obtaining high values of platelet reactivity indicates a weak therapeutic effect on the anti-aggregation drug [5].

Previous reports in the literature regarding the occurrence and importance of aspirin resistance in patients with cerebral ischaemia are scarce and have had inconclusive results. Therefore, the aim of this study was to assess the relationship between platelet reactivity, vascular risk factors and gender in patients with cerebral ischaemia.

Clinical rationale for the study

The results of this study will be clinically useful, because we found high risk groups of aspirin treatment inefficiency in patients with cerebral ischaemia and were able to offer them a different, more effective, prophylaxis.

Material and methods

Research population

The study was conducted between February and December 2016 in the Department of Neurology at the University Hospital No. 1 in Bydgoszcz. The prospective study included 69 patients who met the criteria for the diagnosis of ischaemic stroke and 32 patents with TIA. On admission oral treatment with acetylsalicylic acid (ASA) at a dose of 150 mg was commenced in all patients. The following exclusion criteria were used: lack of patient consent to participate in the study, or inability to express it consciously (e.g. stroke with aphasia or quantitative disturbances of consciousness), patients with embolic cerebral ischaemia (with documented atrial fibrillation, thrombus in the heart cavities or dilated cardiomyopathy), patients with oncological history, patients who had taken ASA before admission, patients with chronic inflammatory processes that may affect the objective assessment of platelet function, e.g. with chronic venous thrombosis of the lower limbs or chronic lower limb ischaemia, patients who had had a stroke or TIA during the previous two years, patients with significant bleeding in the last two years, e.g. gastrointestinal bleeding, thrombocytopenia < 100,000/ul, level of haemoglobin <9 g/dL, value of haematocrit < 35%. The general characteristics of the studied population and a comparison between the group of patients with stroke and those with TIA are set out in Table 1. The study protocol was approved by the Bioethics Committee of Nicolaus Copernicus University in Torun at Collegium Medicum of Ludwik Rydygier in Bydgoszcz (KB number 73/2016). This study included only patients who, having read the study protocol, signed informed consent to participate in the study.

Platelet reactivity research

The study of platelet reactivity was performed by optical aggregometry and impedance aggregometry in the Laboratory of Biotechnology of the Chair of Pharmacology and Therapy at Collegium Medicum in Bydgoszcz of UMK in Torun. Patients' blood tests to assess platelet reactivity were performed at a similar time of day (10am–12noon) within 24 hours of stroke symptoms onset. The optical aggregometry (LTA, light transmission aggregometry) test was performed using a Chrono-Log aggregometer (Havertown, PA, USA). Arachidonic acid was used as the agonist. The aggregometer analysed changes in transmitted light in percentages, with 0% being the maximum optical density of platelet rich plasma and 100% a complete lack of plasma optical density. Then, the signal was automatically converted to area under the curve (AUC) units — as the final result of the determination. An average increase in absorbance of more than 20% (or AUC > 115) was considered to be resistance to ASA that is equivalent to that of 'high' on aspirin treatment platelet reactivity induced by arachidonic acid. The test was performed according to the standard protocol [6]. The evaluation of optical aggregometry was performed in 65 of the 101 subjects, due to an aggregometer failure that could not be repaired during the study.

The study of platelet function by impedance aggregometry was performed using a Multiplate- Dynabyte multi-channel platelet function analyser (Roche Diagnostics, France). The study used the so-called ASPI test, i.e. aggregation dependent on

Table 1. Comparison of selected risk factors, anthropometric and biochemical parameters obtained in patients with stroke and TIA

Parameter	Stroke N = 69	TIA N = 32	P-values
Age median (range)*	67 (40–89)	70 (49–90)	0.1556
Male N, (%)**	35 (50.7%)	13 (40.6%)	0.3444
Hypertension N, (%)**	61 (88.4%)	26 (81.25%)	0.3628
Diabetes N, (%)**	25 (36.3%)	11 (34.3%)	1.0
Hyperlipidemia N, (%)**	28 (40.6%)	17 (53.12%)	0.2846
Smoking N, (%)**	24 (34.8%)	6 (18.75%)	0.1593
Ischaemic heart disease N, (%)**	9 (13.0%)	4 (12.5%)	1.0
Obesity N, (%)**	48 (69.5%)	22 (68.75%)	0.7675
CRP [mg/L] Median (range)*	4.79 (0.36–30.45)	1.835 (0.21–15.2)	0.5157
HBA1c [%] Median, (range)*	318 (59–590)	292.5 (168–469)	0.1864
Homocystein [µmol/L] Median (range)*	5,7 (5–10.04)	5.8 (4.2–7.5)	0.2713
Fibrinogen [mg/dL] Median (range)*	10.78 (3.52–48.6)	9.75 (5.88–18)	0.3524

*Mann-Whitney U-test; ** Chi^2 calculation

cyclooxygenase — using arachidonic acid as a platelet activator. Aggregation results were obtained after another 6 minutes for each test as an average of two measurements in the form of a curve, on the basis of which the area under the curve (AUC) was determined. The AUC parameter was reported as the final result of the determination. Those patients with results above 40 AUC were considered to be ASA resistant, that is equivalent to 'high' on aspirin treatment platelet reactivity induced by arachidonic acid. Patients with AUC values under 30 were treated as sensitive to ASA, and those measured as being from 30 to 40 as mildly sensitive to ASA. The test was performed according to the standard protocol [7]. The evaluation of impedance aggregometry was performed in all 101 subjects.

Statistical evaluation methods

The statistical analysis of collected data was performed with the help of STATISTICA statistical program — version 13.1, Dell. Compatibility with normal distribution was tested with the Shapiro-Wilk test and homogeneity of variance with the Levene test. Due to the incompatibility of the distribution of features with the normal distribution and the lack of homogeneity of variance in the analysis, non-parametric tests were used — U Mann–Whitney test (assessment of the relation between binary and continuous variables), Spearman's rank correlation test (evaluation of the relations between variables), and chi-square independence test (evaluation of relations between categorised variables). A significance level of $p < 0.05$ was considered statistically significant.

Results

Assessment of platelet reactivity

The assessment of platelet reactivity with LTA was performed in 65 patients: in the group of 43 stroke patients, the median was 8.8 AUC (min. 0 AUC, max. 208.6 AUC), while in 22 TIA patients the median was 8.25 AUC (min. 0.2 AUC, max. 278 AUC). There was no statistically significant difference in platelet reactivity between the study group of stroke patients and the TIA group ($p = 0.9558$). The incidence of aspirin resistance in all patients was 9.2%.

Evaluation of platelet reactivity with the Multiplate system was performed in 101 patients. The median of platelet reactivity in the whole group was 27 AUC (min. 6 AUC, max. 108 AUC). In the group of stroke patients, the median was 29 AUC (min. 6 AUC, max. 108 AUC), while in the TIA group the median was 24 AUC (min. 7 AUC, max. 108 AUC). There were no statistically significant differences in platelet reactivity between the study group of stroke patients and the TIA group ($p = 0.8667$). Using the criterion of ASA resistance to the ASA-resistant group (AUC > 40), 31 patients were included, 16 patients were included into the group with medium ASA-sensitivity ($30 \leq AUC \leq 40$), and 54 to the ASA-sensitive group (AUC < 30). The distribution of the occurrence of aspirin resistance in patients with stroke and TIA did not differ in a statistically significant way (Chi^2 NW = 0.17; $p = 0.9185$) (Fig. 1). The incidence of resistance to ASA in the Multiplate study was 30.69% in all patients with ischaemia of the brain; in the subgroup of patients with stroke it was 31.9%, and in the subgroup with TIA it was 28.1%.

Platelet reactivity and anthropometric parameters

There was no significant correlation between the age of the patients and platelet reactivity assessed with the Multiplate or the LTA method ($R = -0.1499$, $p = 0.3451$ for Multiplate and $R = 0.05$ and $p = 0.6585$ for LTA). In the whole group of subjects, statistically higher platelet reactivity was assessed by means of the Multiplate test in men than in women (median, respectively: 34.5 vs 23 AUC; $p = 0.04$) (Fig. 2). A similar difference was also found in the subgroup of patients with stroke

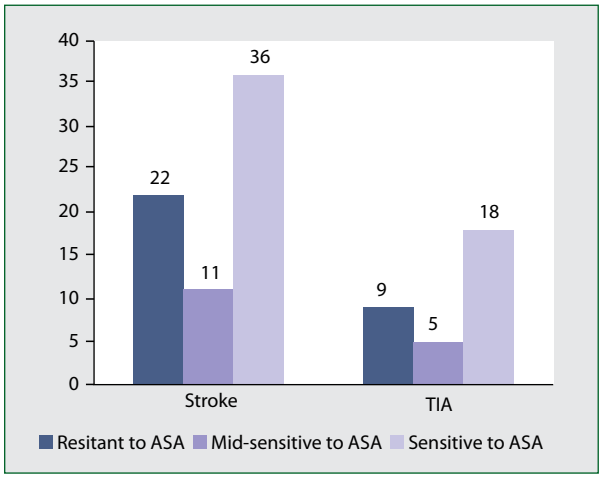

Figure 1. Distribution of the occurrence of aspirin resistance in patients with stroke and TIA

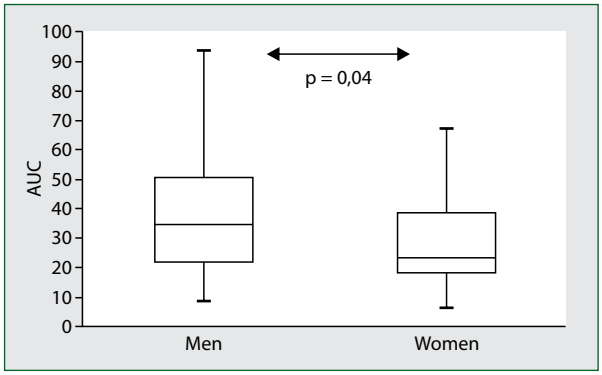

Figure 2. Comparison of platelet reactivity by impedance aggregometry (in AUC-units) in men and women with cerebral ischaemia

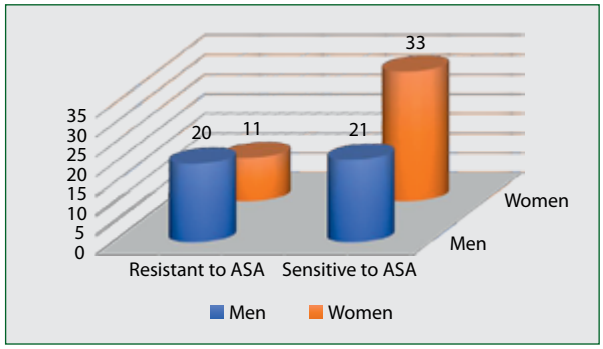

Figure 3. Occurrence of ASA resistance in men and women with cerebral ischaemia

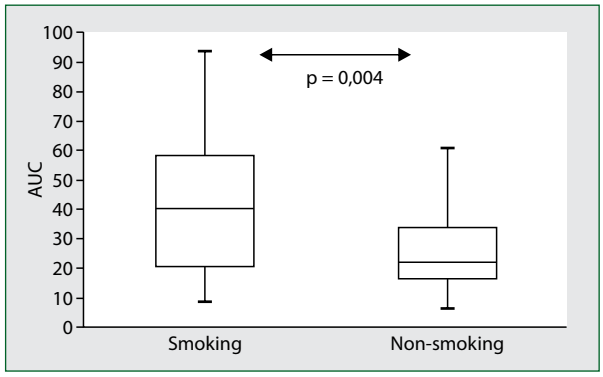

Figure 4. Comparison of platelet reactivity by impedance aggregometry (in AUC-units) in smoking and non-smoking patients with cerebral ischaemia

(median, respectively: 40 vs 23.5 AUC, p = 0.0143). In the subgroup of patients with TIA, similar relationships were not demonstrated (p = 0.7443). There was no relationship between platelet reactivity assessed by the LTA test and patient gender (in the whole group p = 0.6841, in the subgroup with stroke p = 0.6270, in the subgroup with TIA p = 0.8030). In the whole group of patients, it was demonstrated that aspirin resistance was significantly more common in the subgroup of men than in women (Chi^2 NW = 5.18; p = 0.0229) (Fig. 3). A similar relationship, statistically significant, was noted in the subgroup of patients with stroke (Chi^2 NW = 6.26; p=0.0123). In the subgroup of patients with TIA, there were no such relationships (Chi^2 NW = 0.08; p = 0.78).

Platelet reactivity and risk factors for vascular disease

In patients suffering from nicotine addiction, significantly higher platelet reactivity was found, assessed by the Multiplate method, both in stroke and TIA patients (p = 0.004) (Fig. 4), as well as in the subgroup of patients with stroke (p = 0.0135) There was no effect of smoking on the platelet reactivity assessed by LTA. Other risk factors for vascular disease did not have a significant impact on platelet reactivity, as assessed by the Multiplate method (Tab. 2) and the LTA method. In the group of patients with ischaemic stroke burdened with nicotine addiction, there was a significantly higher proportion of ASA-resistant patients compared to non-smokers (Chi^2 NW = 10.1592; p = 0.0014) (Fig. 5).

Discussion

The evaluation of the impact of recognised risk factors for vascular disease on platelet reactivity has been the subject of many studies and publications. Independent authors have not shown, in their studies, a relationship between the occurrence of hypertension, diabetes, hyperlipidaemia or ischaemic heart disease and the level of platelet reactivity, using various methods of assessing platelet function [8–12]. Only El-Mitwalli et al. [13] reported that hyperlipidaemia is more common in an ASA-resistant group. In this study, a significant relationship between platelet reactivity and hypertension, coronary artery

Table 2. Comparison of platelet reactivity assessed by the Multiplate method (in AUC-units) in subgroups of patients with stroke with and without current given risk factor

Risk factor	Multiplate		P-values
	Risk factor present Median (range)	Risk factor absent Median (range)	
Hypertension	24.5 (6–87) AUC	29 (9–108) AUC	0.7800
Diabetes	29 (6–108) AUC	27 (9–79) AUC	0.6521
Hyperlipidemia	28 (6–87) AUC	30.5 (9–108) AUC	0.7848
Ischaemic heart disease	30 (6–108) AUC	17 (6–69) AUC	0.1077
Smoking	24 (6–108) AUC	40.5 (10–87) AUC	**0.0135**
Obesity	40 (6–87) AUC	27 (9–108) AUC	0.2420

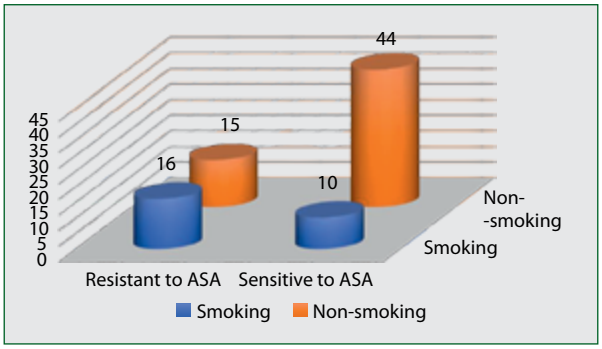

Figure 5. Occurrence of ASA resistance in subgroups of patients with cerebral ischaemia withand without nicotine addiction

disease, diabetes and hyperlipidaemia was also not shown, which coincides with the observations of most authors.

The risk factor that significantly differentiated the reactivity of platelets in this study was nicotine addiction. Active tobacco smokers were characterised by a higher median platelet reactivity than non-smokers. In addition, the incidence of nicotine addiction in the group of patients with cerebral ischaemia in the ASA-resistant group was significantly higher than in the ASA-sensitive group. Zheng et al. [12] also showed in their study that nicotine addiction is more common in patients with stroke in the ASA-resistant patients than those sensitive to ASA ($p = 0.02$); similar relationships were noted by El-Mitwalli et al. Other authors have not found a relationship between nicotine addiction and platelet reactivity or ASA resistance in patients with ischaemic stroke [8–11,14]. Smoking affects the functions of platelets in a multifactorial manner. Nicotine addiction intensifies platelet aggregation, and also reduces their sensitivity to exogenous NO (nitric oxide), thereby increasing their adhesion and activation [15]. Smoking three cigarettes quickly in a row increases the ADP-dependent platelet aggregation *in vitro*. Smoking also activates the expression of P-selectin on the surface of platelets and its serum level, which stimulates platelet activation. In addition, regardless of the mechanisms leading to the modification of platelet function, smoking cigarettes increases blood viscosity, the activity of coagulation processes, fibrinogen levels and blood pressure, and reduces cerebral blood flow through vasospasm. Nicotine addiction raises the risk of stroke on average by 1.5–3 times [16]. All patients after stroke or TIA are advised to stop smoking, including avoiding passive smoking. With regard to the results of this work, this recommendation proves to be a necessary requirement to obtain effective antiplatelet therapy. The American and European guidelines do not give information about the routine determination of platelet reactivity which points to a lack of antiplatelet therapy modifications in smokers. It is worth mentioning the work of Blache et al. [17] who showed that the increased reactivity of platelets is reduced to optimal limits only by a dose of 650 mg ASA. It is also worth noting the results of the work of Rollini et al. [18] who assessed platelet reactivity in patients with advanced atherosclerosis, who were taking ASA, and who were additionally given clopidogrel at a dose of 75 mg for 7–10 days, who then repeated platelet reactivity assessment. In the group of the greatest smokers, a significant decrease in platelet reactivity was achieved.

The presented results may suggest the necessity to adjust the doses of antiplatelet drugs in patients with nicotine addiction, the replacement of ASA with clopidogrel in patients with recurrent stroke, and even the consideration of dual antiplatelet therapy in smokers.

The results of the study showed higher platelet reactivity and a higher incidence of aspirin resistance in men compared to the whole group of subjects and compared to patients with stroke. Similar conclusions were drawn by Jaremo et al. [19], who in a population of men with ischaemic stroke had higher platelet activation assessed by the method of flow cytometry. However, the relation between platelet reactivity and gender remains debatable due to the fact that most other researchers have not shown any relationship between platelet reactivity and aspirin resistance in populations of patients with stroke [8, 9, 12, 20, 21].

In the analysis presented in this study, the groups of patients with stroke and TIA did not differ in terms of gender or platelet reactivity. Considering the abovementioned fact, the demonstration of a significant dependence of platelet

reactivity on gender in the whole group, and especially the significant gender relationship in the subgroup of patients with stroke, emphasises that male gender is an independent platelet activating factor in stroke patients. The explanation of the dependence of platelet activity on gender may be the hormonal basis, as it has been shown that testosterone increases platelet aggregation, while oestrogens and progesterone inhibit platelet aggregation [22, 23]. Greater platelet reactivity in the male gender may also partly explain why the incidence of stroke is lower in women and why stroke occurs in women at a later age [24, 25]. On the other hand, taking into account the greater aspirin resistance in the group of men noted in this study, women are also better beneficiaries of antiplatelet therapy than men, in whom greater resistance to ASA may result in a less effective anti-aggregatory effect of the drug. Similar observations were made by Becker et al. [26] who in their study showed that small doses of ASA (81 mg) more effectively inhibit platelet aggregation in women than in men, which corresponds to lower platelet reactivity found in women in the LTA and PFA (Platelet Function Assay) method — 100 after the ASA therapy. Although in the above study only healthy volunteers from a group at increased risk of cardiovascular incidents were evaluated, not a population of patients with stroke, its results may indirectly confirm the relationship between aspiring resistance and gender indicated in this study.

The current study has its limitations. The number of the studied population is moderate, but proved to be sufficient to formulate conclusions. Most conclusions were based only on the results of platelet reactivity by impedance aggregometry (Multiplate). The conclusions based only on one, poorly standardised, method, with agreed resistance criteria, should be approached with caution [27].

However, the authors consider the one-time assessment of platelet function to be the greatest limitation of their analysis, which was performed at different times after the onset of stroke symptoms within the first 24 hours and at different times from taking the dose of acetylsalicylic acid. It seems that an assessment of platelet function only in a single measurement may be insufficient to properly assess the effect of ASA resistance. Taking into account the data from the literature, the authors are of the opinion that only the sequential determination of platelet reactivity on successive days of stroke seems to be most optimal for the characterisation of aspirin resistance phenomenon [9, 21, 28]. Another limitation is the fact that laboratory resistance does not always correlate with clinical resistance [29, 30].

Conclusions

1. The prevalence of aspirin resistance in the group of patients with cerebral ischaemia is estimated at 30.69% in impedance aggregometry and 9.2% in optical aggregometry.
2. There are no differences between platelet reactivity and the incidence of aspirin resistance in patients with stroke and TIA.
3. Male gender and smoking are associated with greater reactivity of platelets, and more frequent occurrence of aspirin resistance, in patients with cerebral ischaemia.

Clinical implications

On the basis of this study it could be considered optional treatment in smoking males with cerebral ischaemia because of the high risk of aspirin inefficiency. A higher dose of aspirin, dual antiplatelet therapy, or clopidogrel treatment could be taken for this purpose, while bearing in mind the increased risk of bleeding complications. In smoking males, routine determination of platelet reactivity for evaluation of aspirin resistance should be considered, although this is still not available in many countries. Further studies on this subject are needed to confirm our observations.

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