American Journal of Clinical and Experimental Medicine
2026, Vol. 14, No. 5, pp. 112–118
https://doi.org/10.11648/j.ajcem.20261405.12

Research Article

Laboratory Resistance to Antiplatelet Therapy as Part of Secondary Prevention of Ischemic Stroke in a Young Patient (Clinical Case)

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Abstract

In recent years, the incidence of ischemic strokes in young people worldwide has been increasing, leading to early disability, loss of work capacity, and reduced quality of life. Platelets play an active role in the pathogenesis of ischemic stroke. The main drugs for secondary prevention of ischemic stroke are acetylsalicylic acid (ASA) and clopidogrel (CL). ASA inhibits cyclooxygenase-1 (COX-1), which prevents the production of thromboxane A2 (TXA2), thereby inhibiting platelets, while CL acts by inhibiting ADP, which binds to two protein receptors on platelets (P2Y1 and P2Y12) and leads to platelet aggregation. Effective antiplatelet therapy can significantly reduce the risk of recurrent ischemic stroke. *Aim*. To identify clinical and genetic factors contributing to the development of laboratory resistance to antiplatelet agents in a patient with a previous ischemic stroke. *Materials and methods*. The medical history of a patient who had a previous ischemic stroke of unknown origin was studied In Sverdlovsk Regional Clinical Hospital No 1 (SOKB 1). To identify laboratory resistance, we used the optical aggregometry method and a set of genes (*ABCB1, CYP2C19*2, CYP2C19*3, CYP2C19*17, ITGA2, ITGB3, PAI-1*) that affect the development of high residual platelet reactivity. *Results*. For the first time, the patient was examined 3 months after the development of an ischemic stroke, against the background of regular ASA intake. Laboratory resistance to this antiplatelet agent was detected using optical aggregometry. Subsequently, against the background of ASA correction, the introduction of clopidogrel (CL) was repeatedly revealed ineffective disaggregation. When analyzing anamnestic data, it was revealed that the development of high residual platelet reactivity could be influenced by the presence of obesity, hypertension, which are present in this patient. Genetic studies have identified mutations in two genes (ABCB1, CYP2C19*2) that may also contribute to the development of laboratory resistance. *Conclusions*. Conclusions. Effective disaggregation against the background of ASA and CL intake is an important factor in the secondary prevention of ischemic stroke. The study and identification of clinical and genetic risk factors that may affect the development of high residual platelet reactivity remains an important clinical task that requires further study.

Keywords

Antiplatelet Therapy, Laboratory Resistance, Ischemic Stroke, Secondary Prevention

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Received: 8 July 2026; **Accepted:** 25 August 2026; **Published:** 4 September 2026

1. Introduction

Stroke is the fifth leading cause of death among people aged 15 to 59, according to the World Health Organization's Global Burden of Disease study [1].

In recent years, the incidence of ischemic strokes among young people worldwide has been increasing, leading to disability, loss of work capacity, and reduced quality of life [2].

Platelets play a crucial role in the formation of an occlusive thrombus in the cerebral artery and the development of ischemic stroke [3].

To achieve effective secondary prevention after a vascular event, it is necessary to reduce platelet activity, which requires the use of antiplatelet therapy. Effective antiplatelet therapy is crucial for preventing recurrent cardiovascular events in individuals with a history of ischemic stroke [4].

The main antiplatelet drugs for secondary prevention of ischemic stroke are ASA and CL [5].

ASA leads to effective platelet inhibition due to non-selective and irreversible inhibition of COX-1 and prevention of thromboxane A2 production. [6]. According to the literature, regular intake of ASA can reduce the risk of recurrent vascular events by up to 75% [7].

CL is a prodrug that is metabolized into its active form by the hepatic cytochrome P450 system (CYP). This pharmacokinetic profile of CL differs from other antiplatelet agents, as it is active from the outset and does not require transformation [8]. The active form of CL acts by inhibiting ADP, which binds to two protein receptors on platelets (P2Y1 and P2Y12) and leads to platelet aggregation. It should be noted that the pharmacokinetics of this antiplatelet agent do not affect the metabolic pathways of arachidonic acid [4, 8, 9].

Patients who experience cardiovascular events, such as acute ischemic stroke, while taking adequate doses of ASA and CL, are considered to be "resistant" to these antiplatelet drugs [9].

There are two types of resistance: laboratory and clinical. "Clinical resistance" is the occurrence of an ischemic stroke in the background of regular intake of any antiplatelet. Laboratory resistance is the detection of reference values of indicators, such as ADP and adrenaline, used to diagnose the effectiveness of disaggregation [4].

According to the literature, the prevalence of laboratory resistance to ASA and CL in patients with MI ranges from 3% to 65% and from 17% to 44%, respectively [10, 11]. The presence of laboratory resistance to ASA and (or) CL increases the comparative risk of recurrent cardiovascular events up to 4 times during 18 months of follow-up, compared to a group of individuals without signs of resistance [12].

Various factors can influence the formation of high residual reactivity to these antiplatelet agents. These factors can be divided into exogenous and endogenous. Smoking, low adherence to therapy, and concomitant therapy (such as proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), and calcium channel blockers) are examples of exogenous factors. According to literature, interactions between different medications can lead to a reduced antiplatelet effect. Thus, NSAIDs and ASA compete for similar receptors, which can lead to high residual reactivity [11].

Diabetes mellitus, accompanied by chronic inflammation of the vascular wall, endothelial dysfunction, and platelet damage due to chronic hyperglycemia, increases the risk of developing drug resistance when taking these antiplatelet drugs [4].

Genetic predisposition (mutations in *the ABCB1, CYP2C19*2, CYP2C19*3, CYP2C19*17, ITGA2, ITGB3, and PAI-1* genes), gender, age, obesity or metabolic syndrome, diabetes mellitus, hypercholesterolemia, hypertension, and chronic kidney disease are endogenous factors [11, 13-16].

The importance of timely assessment of platelet reactivity in the context of antiplatelet therapy has recently been widely studied. Despite the relevance of this issue, there is currently no gold standard for identifying resistance to acetylsalicylic acid [13].

One of the methods for determining the effectiveness of disaggregation is optical aggregometry. The essence of the method is for the reagents (ADP and adrenaline) to interact with platelet-rich plasma. With effective disaggregation against the background of ASA intake, adrenaline will interact more strongly than ADP, according to the pharmacodynamic laws of this antiplatelet agent [17, 18]. Conversely, ADP interacts more strongly with ADP than with adrenaline [19]. Figure 1 shows a graph of effective platelet inhibition in the presence of ASA.

2. Aim

To identify clinical and genetic factors that could affect the development of laboratory resistance in a patient with a previous ischemic stroke, taking ASA and CL as part of secondary stroke prevention.

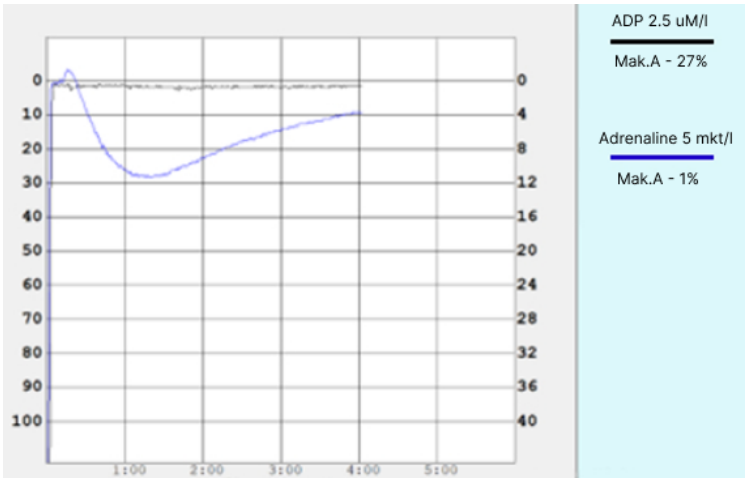

Figure 1. *Graph of effective platelet inhibition in the presence of ASA.*

3. Materials and Methods

To write the article, a search of literature data was carried out in PubMed, eLibrary.ru, RusMed, Cochrane Library, Trip. Keywords used in the search: "antiplatelet agents", "laboratory resistance", "ischemic stroke".

The clinical case is described based on outpatient observation by a neurologist and laboratory examination at the regional outpatient clinic of the State Budgetary Institution of the Samara Region "SOKB No. 1". The patient's informed consent was obtained. The effectiveness of the antiplatelet effect of ASA and CL was evaluated in platelet-rich plasma using optical aggregometry with measurement of maximum light transmission as a percentage using the Born method with the use of inducers: 2.5 μmol/L (μM) ADP (reference range – 55–75%) and 5 μmol/L (μM) adrenaline (reference range – 65–85%). Using the polymerase chain reaction method in real time, using standardized reagent kits produced by NPO DNA-technology, genodiagnostics was carried out. Peripheral blood was used as the material for the study.

All data was obtained as part of routine clinical practice in compliance with ethical standards and patient rights.

4. Results

Clinical case

43-year-old woman on 02.04.2024 suffered an ischemic stroke of unknown genesis in the right middle cerebral artery. 3 months later, at a routine examination in the neurological status were revealed: left-sided hemiparesis 4 points.

According to the 2024 clinical guidelines for ischemic stroke in the Russian Federation, it was decided to prescribe ASA 150 mg per day for secondary prevention in collaboration with a hematologist. At the time of the secondary stroke prevention consultation, the patient was regularly taking ASA 100 mg in the evening, atorvastatin 20 mg per day, and enalapril 10 mg per day. She avoided taking NSAIDs and PPIs and did not use SSRIs or TCAs. The patient had grade 1 obesity, did not smoke, and did not suffer from diabetes mellitus or severe kidney disease. Optical aggregometry was performed to assess the effectiveness of platelet inhibition (Figure 2).

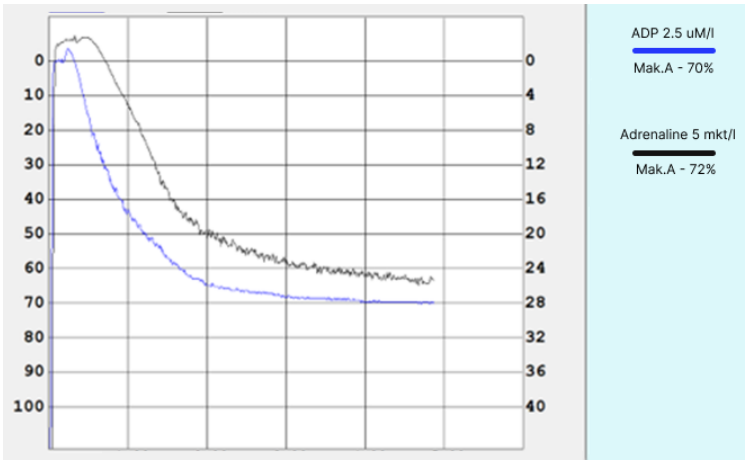

Figure 2. *The result of optical aggregometry in the background of ASA 100 mg per day.*

According to the results of optical aggregometry, the values of ADP 2.5 μM and adrenaline 5 μM are within the reference values: 70% and 72%, respectively, which corresponds to a high residual platelet reactivity in the presence of ASA.

The following changes were identified in the assessment of genetic mutations: *ABCB1* TT (CC), *CYP2C19*2* GA (GG), *CYP2C19*3* GG (GG), *CYP2C19*17* CC (CC), *ITGA2* CT (CC), *ITGB3* TT (TT), *PAI-1* 4G4G (5G5G), indicating an increased risk of a low aggregation response to ASA.

One week later, optical aggregometry revealed high residual platelet reactivity (Figure 3).

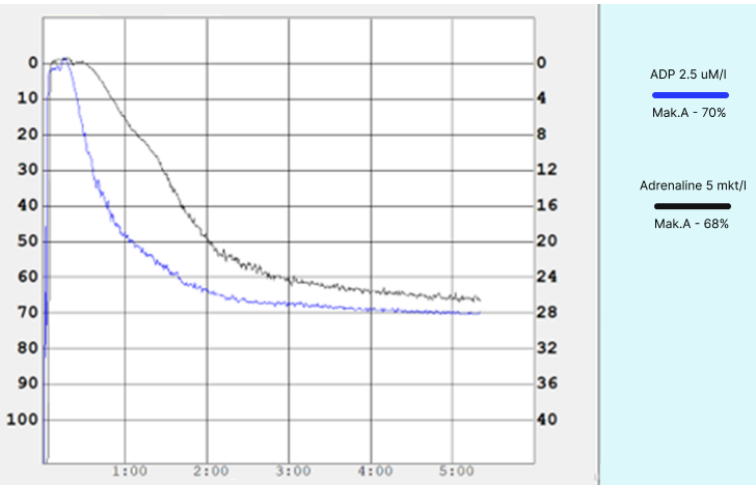

Figure 3. *The result of optical aggregometry against the background of ASA 150 mg per day.*

Addition of dipyridamole to ASA, according to the clinical recommendations on ischemic stroke, revealed intolerance to this drug. Dipyridamole was canceled.

In order to achieve effective disaggregation, it was decided to change the therapy to CL and discontinue ASA. After 7 days, low disaggregation was detected using aggregometry (Figure 4).

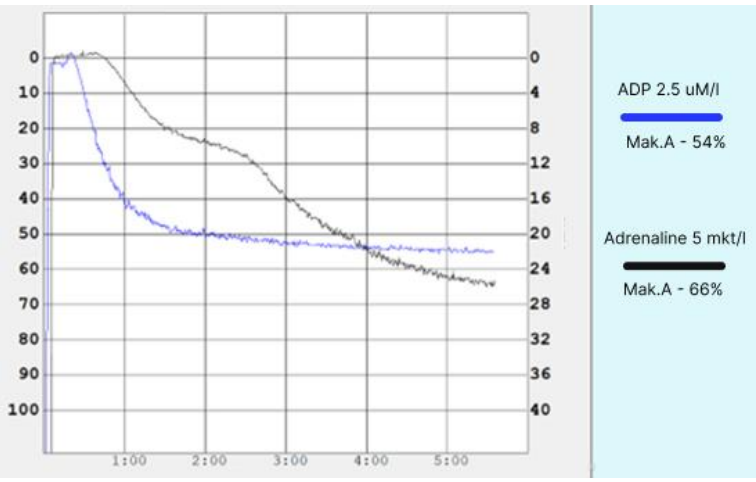

Figure 4. *The result of optical aggregometry in the background of taking CL at a dose of 75 mg per day.*

With these results of aggregometry, she was referred for consultation to a hemostasiolo, as a result, ASA 75 and clopidogrel 75 were prescribed. Since the end of 2024, the patient has not been observed by a neurologist or hemostasiolo for 1 year, and aggregometry has not been performed.

At the end of 2025, the patient was admitted to the neurological department of the First Regional Clinical Hospital with complaints of increasing left-sided hemiparesis, mainly in the leg. At the time of admission, the patient was taking ASA 75 and CL 75. No hemorrhagic complications were observed during the entire period.

In order to exclude a recurrent ischemic stroke, a magnetic resonance brain tomography was performed (no ischemic foci were detected), examined by a neurologist of the vascular department – a recurrent vascular event was excluded.

Optical aggregometry against the background of dual antiplatelet therapy revealed high residual platelet reactivity (Figure 5).

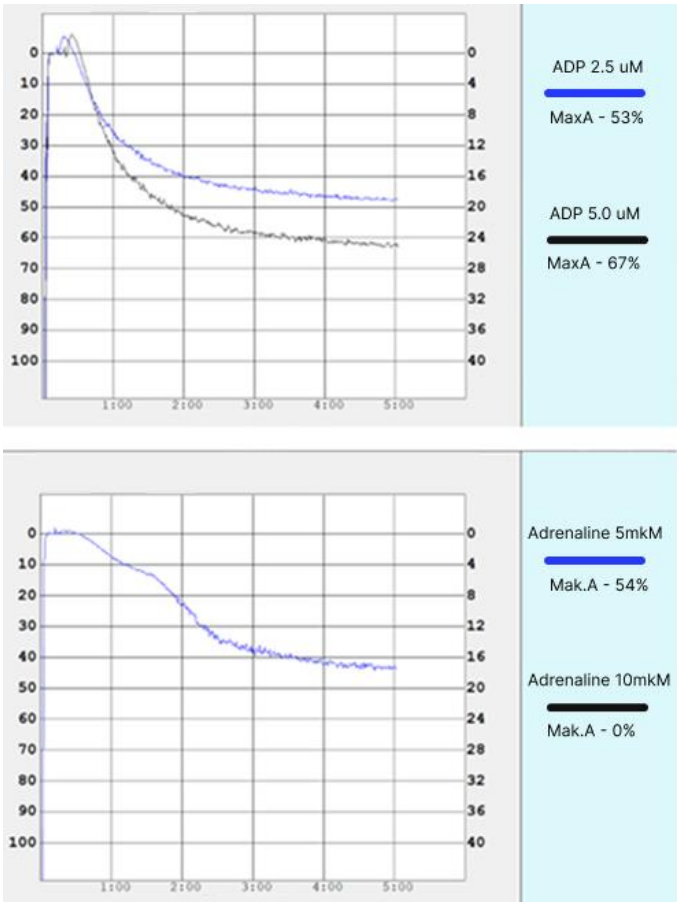

Figure 5. *The result of optical aggregometry against the background of taking CL 75 mg per day and ASA 75 mg per day.*

The patient is referred to a hemostasioloog for the selection of antiplatelet agents.

5. Discussion

Effective antiplatelet therapy after an ischemic stroke plays a key role in preventing a second vascular event. Early detection of laboratory resistance helps to improve the effectiveness of secondary stroke prevention. The presented clinical example demonstrates laboratory resistance to monotherapy and combined ASA and CL use in a young patient, which may have contributed to the worsening of neurological deficits.

The development of high residual platelet reactivity may be associated with the presence of exogenous factors. The patient did not take any medications that could have influenced the formation of laboratory resistance.

An elevated level of leptin, which is present in individuals with obesity, may lead to a low aggregation response in the presence of ASA. Increased lipid peroxidation leads to platelet activation in processes that bypass the classical pathway associated with COX-1 acetylation, which may contribute to high residual reactivity [20, 21].

The patient had arterial hypertension, for which she was taking antihypertensive therapy. High blood pressure (above 140/90 mmHg) can contribute to the development of laboratory resistance in patients taking these antiplatelet agents. Endothelial dysfunction and increased arterial wall tone, which develop in hypertensive disease, can affect the development of this condition [22].

The development of laboratory resistance to ASA and CL is influenced not only by clinical factors, but also by genetic factors. The CYP2C19 gene plays an important role in the metabolism of arachidonic acid and especially CL [23]. According to the literature, carriers of mutations such as CYP2C19*2 and *3 are candidates for high residual reactivity when taking an antiplatelet agent [24, 25]. The patient was found to have a mutation in the CYP2C19*2 allele, which may be an endogenous cause of laboratory resistance to these antiplatelet agents.

The ABCB1 gene is responsible for the absorption of these antiplatelet agents in the intestines [14]. According to the literature, individuals with the TC genotype in this gene have a higher risk of developing high residual reactivity compared to those with the TT genotype [11, 26]. The presence of a mutation in the ABCB1 gene may have contributed to the low antiplatelet effect in this patient.

6. Conclusions

Currently, effective disaggregation is one of the important criteria for the success of secondary prevention of ischemic stroke. In the presented clinical case, laboratory resistance to two antiplatelet agents was detected in a young patient using the optical aggregation method.

Among the concomitant and background diseases, the development of resistance may have been caused by arterial hypertension and obesity. However, genetic factors likely played a key role in the development of laboratory resistance in this case.

Further research is needed to investigate the role of various factors that may lead to the development of laboratory resistance in patients with ischemic stroke who are taking these antiplatelet drugs, in order to improve the effectiveness of secondary stroke prevention measures.

Author Contributions

Batenkova Tatiana Yurevna: Conceptualization, Resources, Data curation, Writing – original draft

Volkova Larisa Ivanovna: Project administration, Writing – review & editing

Funding

This work is not supported by any external funding.

Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript

Conflicts of Interest

The authors declare no conflicts of interest.

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