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ASPIRIN RESISTANCE IN PATIENTS WITH CEREBRAL ATHEROSCLEROSIS: POSSIBLE ROLE OF MICRORNAS

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Abstract

Introduction. *Cerebral atherosclerosis remains a major cause of ischemic cerebrovascular disease, and variability in response to antiplatelet therapy may contribute to persistent vascular risk. MicroRNAs have emerged as potential epigenetic regulators of platelet function and may help explain laboratory aspirin non-response. This study investigated the association between selected microRNAs and platelet reactivity in patients with cerebral atherosclerosis receiving acetylsalicylic acid.*

Methods. *This prospective single-center cross-sectional study included 54 patients with cerebral atherosclerosis treated with low-dose acetylsalicylic acid for primary or secondary stroke prevention. Platelet aggregation was measured in vitro by light transmission aggregometry using adrenaline and adenosine diphosphate. Patients were classified as responders or non-responders according to adrenaline-induced platelet aggregation, with values above 25% indicating non-response. Leukocyte expression of eight microRNAs was quantified. Correlation, linear regression, logistic regression, and receiver operating characteristic analyses were performed with adjustment for relevant clinical variables.*

Results. *Laboratory non-response to acetylsalicylic acid was observed in 64.8% of patients. Of the eight microRNAs analyzed, only microRNA-126-3p and microRNA-126-5p showed significant inverse associations with adrenaline-induced platelet aggregation after correction for multiple comparisons. In adjusted analyses, microRNA-126-3p remained independently associated with lower platelet aggregation (β = -0.3129; p = 0.0483) and with a lower probability of non-response (OR = 0.850; 95% CI 0.684–0.968; p = 0.0466). Its predictive value was moderate alone and improved when combined with clinical characteristics.*

Discussion. *MicroRNA-126-3p appears to be a promising epigenetic marker of variability in aspirin response in patients with cerebral atherosclerosis. These findings support further prospective validation of microRNA-126-3p as a tool for identifying patients at risk of inadequate platelet inhibition on aspirin.*

Keywords: cerebral atherosclerosis, aspirin resistance, platelet aggregation, epigenetics, microRNA

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Introduction

Cerebral atherosclerosis (CA) is a major cause of ischemic cerebrovascular disease worldwide, with the prevalence of carotid artery disease very common (up to 51.9%) among mid-to-older aged asymptomatic individuals [*Tattersall M. et al., 2025*]. The current mainstay of medical cerebral atherosclerosis treatment remains preventive overall: it involves long-term antiplatelet treatment in high-risk (e.g., >50% carotid stenosis) asymptomatic patients and in patients with transient ischemic attacks (TIA) and/or non-cardioembolic stroke; lipid-lowering drugs (e.g., statins); management of arterial hypertension and/or diabetes mellitus therapy in eligible patients [*Naylor R. et al., 2023*]. There remain certain nuances when considering the regimen of antiplatelet therapy in CA, but the majority of guidelines recommend low-dose acetylsalicylic acid (ASA, aspirin) single therapy for stroke prevention [*Kleindorfer D. et al., 2021; Bushnell C. et al., 2024*].

Stroke risk (first or recurrent) remains high in patients with cerebral atherosclerosis despite advances in optimal medical management: 15% to 50% of patients have recurrent stroke and major vascular events – one of the reasons for this may lie in individual variability to aspirin treatment, i.e. aspirin resistance (AR) [*Petty G. et al., 1998; Tanashyan M. et al., 2016*]. It is an umbrella term encompassing different mechanisms and possible causes, but a division may be made into clinical aspirin resistance (a transient ischemic attack /stroke happens despite aspirin) and laboratory aspirin resistance (high on-treatment platelet reactivity despite aspirin exposure) [*Cattaneo M., 2013*].

Estimations of the prevalence of aspirin resistance vary considerably due to different methodological approaches: a 2025 study using VerifyNow Aspirin test found 4% and 13% of patients demonstrating resistance to aspirin in the primary and recurrent stroke populations, respectively [*Cencer S. et al., 2025*]. Other publications offer a wider margin of aspirin resistance prevalence in patients with ischemic stroke and/or transient ischemic attack ranging from 5% to 65% [*Hankey G., Eikelboom J., 2006*].

Testing for aspirin resistance exists, but up to now there has been no 'gold standard': common assays include light transmission aggregometry, serum/urine thromboxane metabolites, VerifyNow, Platelet Function Analyzer-100/200, and thromboelastography/platelet mapping [*Khan H. et al., 2022*]. A reasonably effective test – light transmission aggregometry with agonists (specifically adrenaline and adenosinediphosphate (ADP]) – has been utilized in our center for determining aspirin resistance in patients with cerebrovascular disease using a >25-30% threshold.

Potential mechanisms of aspirin resistance include (but are not limited to): reduced bioavailability (e.g. age, poor compliance); inadequate dosing; concurrent administration with nonsteroidal anti-inflammatory drugs; metabolic comorbidity (e.g. diabetes mellitus, obesity); genetic polymorphisms (e.g. affecting COX-1 gene) [*Krishnan K. et al., 2023*]. Another promising novel but understudied in aspirin resistance potential mechanism is epigenetic regulation due to differential microRNA expression [*Krammer T. et al., 2020*].

MicroRNAs are small (~22 nucleotides) non-coding RNAs which are involved in posttranscriptional regulation of gene expression by (usually) inhibition of translation of messenger RNAs [*Guo H.* et al., 2010]. Most of the studies on platelet reactivity were done using platelet/circulating microRNAs in coronary/peripheral vascular cohorts, but data regarding cerebral atherosclerosis remains scarce. Previously, we have demonstrated differential patterns of microRNA expression in patients with CA, depending on stroke/severity status [*Raskurazhev A. et al., 2022b; Tanashyan M. et al., 2024; Ni P. et al., 2025*]. In this study we aim to identify possible microRNA s correlates of resistance to aspirin in the setting of cerebral atherosclerosis.

Material and methods

Object of study: patients with cerebral atherosclerosis (CA) (n = 54, 56% male) that have been prescribed low-dose aspirin for ischemic stroke prevention.

Methods of study: This was a prospective single-center non-randomized cross-sectional study which was conducted at our research facility (Research Center of Neurology and Neurosciences, Moscow, Russian Federation). We included patients with cerebral atherosclerosis (as defined by carotid ultrasound and/or magnetic resonance an-

giography), that were prescribed aspirin: either for primary stroke prevention (due to high/grade carotid stenosis) or secondary stroke prevention (due to transient ischemic attack /non-cardioembolic stroke > 6 months). Exclusion criteria included: any evidence of malignancies, current infectious diseases, decompensated somatic pathology (including severe renal/hepatic disease), autoimmune disorders. Patients were assessed clinically with a thorough neurological exam and sex, age, body mass index (BMI), history of stroke, coronary artery disease (CAD), diabetes mellitus (DM), and degree of carotid stenosis (internal carotid artery [ICA] maximal stenosis) were noted for further use in regression analyses.

Used reagents, kits and medication of the study: In vitro platelet aggregation (PA) was analyzed: platelet-rich plasma (PRP) was obtained by centrifugation of citrated blood at 800 *rpm* for 10 min, whereas platelet-poor plasma (PPP) was prepared by centrifugation at 3000 *rpm* for 10 min. The platelet aggregation recording time was 10 min. platelet aggregation was assessed according to the standard protocol using a Biola laser aggregometer by the turbidimetric method. platelet aggregation results (expressed as %) reflect the degree of plasma light transmission after addition of an aggregation inducer. PPP was taken as 100% and PRP as 0%. To assess baseline PA, an inducer - either adrenaline or ADP - was added to the measuring cuvette containing the sample to achieve final concentrations of 2.5 *μg/mL* (adrenaline-induced platelet aggregation) and 10^{-6} *M* (ADP-induced platelet aggregation), respectively. Measurements were performed at 37°C with continuous stirring using a magnetic stirrer at 900 *rpm*. We divided patients according to adrenaline-induced platelet aggregation into non-responders (>25%) and responders to aspirin.

We described microRNA extraction and quantification in detail previously [*Raskurazhev A.A.* et al., 2022a]. Extraction of microRNA was performed using Leukocyte RNA Purification Kit (NORGEN Biotec Corp., Thorold, ON, Canada) according to modified manufacturer protocol. The PCR was performed starting with the reverse transcription step.

The following reagents and equipment have been used: validated 20X primers for has-miR: miR-126-5p, miR-126-3p, miR-29-5p, miR-29-3p, miR-33a-5p, miR-33a-3p, miR-21-5p, miR-21-3p (ThermoFischerScientific, Waltham, MA, USA); Leukocyte RNA Purification Plus Kit (NORGEN Biotec Corp., Thorold, ON, Canada); TaqMan™ Advanced microRNA cDNA Synthesis Kit (Applied Biosystems™, Thermo Fisher Scientific, Waltham, MA, USA); Real-time CFX96 Touch amplifier (BioRaD, Hercules, CA, USA)

Method of statistical analysis: Statistical analysis was performed using the R programming language v. 4.4.1 in the RStudio software environment (v.2025.05.1) with the following packages: "tidyverse", "gtsummary", "corrplot", "ggplot2"; boxplot visualization was made in GraphPad Prism 10 (v. 10.4.0). Descriptive statistics were represented by medians, as well as upper and lower quartiles for continuous variables and frequencies for discrete variables. For comparisons between two independent groups, the Wilcoxon–Mann–Whitney test (for continuous variables) or Pearson's $\chi 2$ test (for discrete variables) was used. Associations between microRNA levels and platelet aggregation parameters were assessed using Spearman's rank correlation analysis. To account for multiple comparisons, false discovery rate (FDR) correction was applied using the Benjamini–Hochberg method. The relationship between individual microRNA s and adrenaline-induced platelet aggregation was further evaluated by univariable linear regression analysis, with regression coefficients (β), standard errors (SE), and p-values reported. To account for potential confounding, multivariable linear regression models were constructed with adjustment for clinical covariates, including gender, age, body mass index, history of stroke, coronary artery disease, diabetes mellitus, and degree of carotid stenosis. In addition, a reduced multivariable model adjusted only for age, sex, and body mass index was analyzed.

For subgroup analysis, patients were stratified into responders and non-responders according to the level of adrenaline-induced PA. The association between miR-126-3p expression and the probability of being in the non-responder group was assessed using multivariable logistic regression analysis, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs). The discriminatory performance of miR-126-3p and of the combined

(clinical + microRNA) model was evaluated by receiver operating characteristic (ROC) analysis with calculation of the area under the curve (AUC) and corresponding 95% CIs. The optimal cutoff value was determined using the Youden index, and sensitivity and specificity were calculated. All tests were two-sided, with alpha-level at 0.05.

Results

As the first stage of the analysis, we elucidated the relationship between the expression levels of several microRNAs and platelet aggregation (platelet aggregation) parameters via correlation analysis (Table 1).

The only microRNA s associated with platelet aggregation (adrenaline-induced) were both strands of miR-126: -3p (-0.381, pFDR = 0.0382) and -5p (-0.378, pFDR = 0.0382) – both also exhibited a negative relationship with platelet aggregation (meaning lower microRNA expression levels were associated with higher levels of platelet aggregation).

Table 1.

Results of the correlation analysis between microRNA levels and platelet aggregation in patients with cerebral atherosclerosis receiving aspirin

microRNA	Platelet aggregation	Spearman coefficient	p	pFDR (adj.)
miR-126-5p	ADP-ind.	-0.248	0.071	0.379
miR-126-3p	ADP-ind.	-0.226	0.0997	0.399
miR-29-5p	ADP-ind.	-0.195	0.158	0.507
miR-21-5p	ADP-ind.	0.092	0.507	0.86
miR-33a-3p	ADP-ind.	-0.054	0.696	0.86
miR-29-3p	ADP-ind.	0.047	0.735	0.86
miR-33a-5p	ADP-ind.	-0.028	0.843	0.86
miR-21-3p	ADP-ind.	-0.025	0.86	0.86
miR-126-3p	Adr.-ind.	-0.381	**0.00446**	**0.0382**
miR-126-5p	Adr.-ind.	-0.378	**0.00477**	**0.0382**
miR-29-5p	Adr.-ind.	-0.158	0.255	0.681
miR-21-3p	Adr.-ind.	-0.13	0.35	0.801
miR-29-3p	Adr.-ind.	-0.071	0.612	0.86
miR-21-5p	Adr.-ind.	0.055	0.694	0.86
miR-33a-3p	Adr.-ind.	0.053	0.704	0.86
miR-33a-5p	Adr.-ind.	0.025	0.855	0.86

Note: ADP-ind. - ADP-induced platelet aggregation; Adr.-ind. - adrenaline-induced aggregation; pFDR - p-value adjusted for multiple comparisons (Benjamini–Hochberg method).

Table 2.

Results of the univariable linear regression analysis of the association between microRNAs and adrenaline-induced platelet aggregation

microRNA	β	SE	p
miR-126-3p	-0.3814	0.1521	**0.0153**
miR-126-5p	-0.3915	0.1678	**0.0236**
miR-29-5p	-0.2277	0.1855	0.2250
miR-29-3p	-0.0186	0.1833	0.9194
miR-33a-5p	0.0476	0.1621	0.7700
miR-33a-3p	0.0914	0.1605	0.5717
miR-21-5p	-0.1643	0.3229	0.6130
miR-21-3p	-0.2791	0.3836	0.4701

Table 3.

Multivariable linear regression analysis of the association between miR-126 and epinephrine-induced platelet aggregation

Parameter	Model 1: miR-126-3p, β	p	Model 2: miR-126-5p, β	p
miR-126	-0.2566	0.1461	-0.2792	0.1992
Male	-4.9300	0.0712	-5.0659	0.0647
Age	0.1241	0.5218	0.1597	0.4102
BMI	-0.3498	0.4645	-0.3682	0.4450
Stroke	0.7672	0.7998	1.5188	0.6254
CAD	3.3206	0.2858	3.1644	0.3134
DM	0.1114	0.9661	-0.2702	0.9178
Degree of ICA stenosis	0.0156	0.8180	-0.0017	0.9816

Note: *β - linear regression coefficient ICA - internal carotid artery, CAD – coronary artery disease, DM – diabetes mellitus SE — standard error*

At the next stage, univariable (Table 2) and multivariable (Table 3) linear regression analyses were carried out including clinical covariates (sex, age, body mass index, history of stroke, coronary artery disease, diabetes mellitus, and degree of carotid stenosis).

In the univariable models, miR-126-3p and miR-126-5p showed a statistically significant inverse association with the level of adrenaline-induced PA. However, after adjustment for clinical factors, these associations were no longer statistically significant: for miR-126-3p, the regression coefficient was β = -0.2566 at p = 0.1461, and for miR-126-5p, β = -0.2792 at p = 0.1992. Nevertheless, the direction of the association remained negative in both models.

In the reduced model (Table 4), adjusted for

TABLE 4.

Multivariable linear regression analysis of the association between miR-126 and adrenaline-induced platelet aggregation (reduced model)

Parameter	Model 1: miR-126-3p, β	p	Model 2: miR-126-5p, β	p
miR-126	-0.3129	**0.0483**	-0.3273	0.0592
Age	0.1999	0.2193	0.2135	0.1884
Male	-4.2541	0.0959	-4.3181	0.0921
BMI	-0.3567	0.4342	-0.4032	0.3805

NOTE: *β — linear regression coefficient*

age, sex, and BMI, the association between miR-126-3p and the level of adrenaline-induced platelet aggregation remained statistically significant (β = -0.3129; p = 0.0483). For miR-126-5p, a similarly directed association was observed; however, it was of borderline significance (β = -0.3273; p = 0.0592).

Next, we divided the entire cohort of patients into two groups according to the level of adrenaline-induced platelet aggregation achieved during aspirin therapy: non-responders (adr.-ind. PA > 25%; aspirin resistant) and responders (Table 5). In our patient population we observed a relatively high proportion of aspirin resistance – 64.8%.

Both subgroups were comparable by most clinical factors (including gender and age), though coronary artery disease was more prevalent in the

TABLE 5.

Clinical characteristics of the cerebral atherosclerosis group by aspirin resistance status

Parameter	Responders, n = 19	Non-responders, n = 35	p
Men, n (%)	14 (73.7%)	16 (45.7%)	0.084
Age, years (median [Q1; Q3])	62 [61.5; 66]	66 [61; 71]	0.136
BMI, (kg/m^2) (median [Q1; Q3])	26.8 [25.1; 27.7]	27.3 [26.1; 29.6]	0.215
Carotid stenosis, % (median [Q1; Q3])	45 [35; 57.5]	60 [45; 75]	0.055
Smoking, n (%)	6 (31.6%)	11 (31.4%)	1
History of stroke, n (%)	6 (31.6%)	14 (40%)	0.572
Hypertension, n (%)	12 (63.2%)	19 (54.3%)	0.555
CAD, n (%)	3 (15.8%)	16 (45.7%)	**0.038**
MI, n (%)	3 (15.8%)	9 (25.7%)	0.506
DM, n (%)	8 (42.1%)	17 (48.6%)	0.777

NOTE: *OR - odds ratio; 95% CI - 95% confidence interval, CAD – coronary artery disease, DM – diabetes mellitus, MI - myocardial infarction*

TABLE 6.

Results of the multivariable logistic regression analysis of the association between miR-126-3p and aspirin resistance

Parameter	OR	95% CI	p
miR-126-3p	0.850	0.684–0.968	**0.0466**
Male sex	0.136	0.018–0.696	**0.0269**
Age	0.994	0.871–1.119	0.9211
BMI	1.036	0.798–1.346	0.7852
Stroke	5.433	0.827–52.582	0.1009
CAD	6.344	0.932–67.826	0.0824
DM	1.466	0.299–7.779	0.6375
Degree of stenosis	0.995	0.951–1.038	0.8052

NOTE: *The multivariable model included miR-126-3p, sex, age, BMI, stroke, coronary artery disease, diabetes mellitus, and the degree of carotid stenosis. The optimal cut-off was determined using the Youden index. CAD – coronary artery disease, DM – diabetes mellitus*

aspirin resistant group (45.7% vs 15.8% in non-responders and responders, respectively). Borderline significant (p = 0.055) was also the difference between carotid stenosis, the median of which was higher in non-responders (60% vs 45%) – so overall, the non-responder group may have had higher atherosclerotic burden than patients without aspirin resistance.

In the extended multivariable logistic regression model (Table 6), which included sex, age, BMI, stroke, coronary artery disease, diabetes mellitus, and the degree of carotid stenosis, miR-126-3p retained a statistically significant inverse association with the probability of non-responding to aspirin (OR = 0.850; 95% CI 0.684–0.968; p = 0.0466). Of note, a statistically significant gender association was also observed: men with cerebral atherosclerosis were less likely to belong to the aspirin non-responder group in our cohort (OR = 0.136; 95% CI 0.018–0.696; p = 0.0269).

A comparison of the expression of the studied microRNAs between patients with moderate-to-high residual platelet activity during aspirin therapy is shown in Figure 1.

Comparisons were performed between aspirin responders and non-responders within each miRNA subgroup. Only statistically significant intergroup differences are shown; miR-126-3p and miR-126-5p expression levels differed significantly between aspirin responders and non-responders

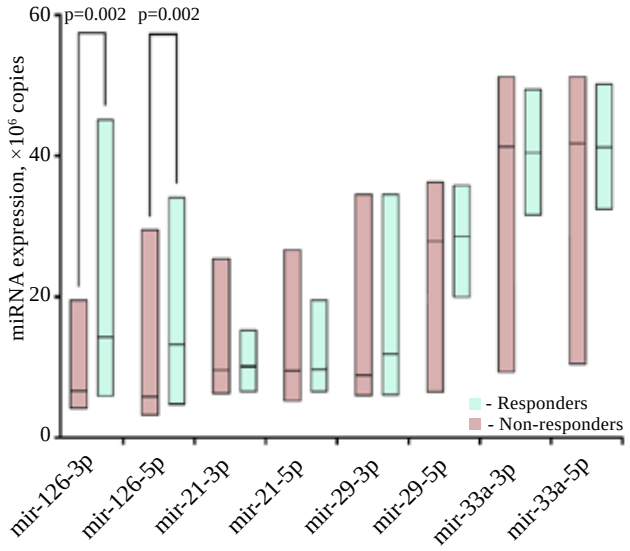

***FIGURE 1**. miRNA expression in patients with cerebral atherosclerosis according to aspirin (ASA) response.*

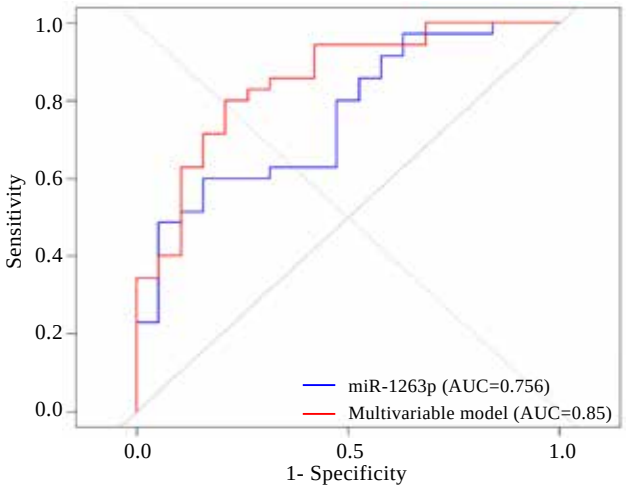

***FIGURE 2.** Comparison of the discriminative ability of miR-126-3p and the multivariable (clinical + microRNA) model for identifying* aspirin resistance. *The dashed line corresponds to the line of random classification.*

(p = 0.002 for both comparisons), whereas no statistically significant differences were observed for the other analyzed miRNAs.

In the ROC analysis (Table 7), miR-126-3p demonstrated a moderately good ability to discriminate patients with AR: the AUC was 0.756 (95% CI 0.624–0.889). The optimal cut-off based on the Youden index was 6.91, at which sensitivity was 60.0% and specificity was 84.2%.

For the extended multivariable model, which included miR-126-3p and clinical parameters (sex, age, BMI, stroke, coronary artery diseas (CAD), diabetes mellitus, degree of stenosis), the predictive performance was higher: area under the curve (AUC) was 0.850 (95% CI 0.742–0.958), with a sensitivity of 80.0% and a specificity of 78.9% (Figure 2).

TABLE 7.
Receiver operating characteristic (ROC) analysis of the predictive value of miR-126-3p and the multivariable model for identifying aspirin resistance

Parameters	Model	
	miR-126-3p	Multivariable model
AUC	0.756	0.850
95% CI	0.624–0.889	0.742–0.958
Cut-off	6.91	0.687
Sensitivity, %	60.0	80.0
Specificity, %	84.2	78.9

DISCUSSION

Aspirin resistance (AR) is not infrequent in patients with cerebral atherosclerosis (CA) – in our cohort 64.8% were non-responders according to laboratory tests (adrenaline-induced platelet aggregation (PA)). Epigenetic markers (e.g., microRNAs) may play a role in the development of AR: out of 8 studied microRNA s, two (namely miR-126-3p/-5p) proved to be inversely correlated with PA, and one (miR-126-3p) was independently associated with aspirin -responder status.

Apart from categorization into clinical and laboratory, antiplatelet (including aspirin) resistance can also be divided into primary and secondary: the former representing inherited genetic polymorphisms of drug-metabolizing enzymes or target receptor variations [*Hou X., 2024*]; the latter - triggered by acquired factors. Interestingly, epigenetic regulation may be attributed to both primary (as non-coding RNAs are a part of genome) and secondary aspirin resistance (e.g., microRNA expression depends heavily on existing diseases/drug interactions/lifestyle/etc.). Several studies corroborate the view that microRNAs are involved in regulating platelet function and reactivity, as well as in the mechanisms of antiplatelet drug resistance.

Stojkovic S. et al. review the role of platelet-derived microRNAs (among them niR-126) in antiplatelet resistance in coronary artery disease patients [*Stojkovic S. et al., 2019*]. Another study by

Singh et al. found lower miR-19b-1-5p expression to be associated with sustained platelet aggregation on aspirin and a higher risk of major cardiovascular events in patient with acute coronary syndrome [*Singh S. et al., 2021*]. In our study cohort of cerebral atherosclerosis we found that only miR-126 expression was associated with aspirin resistance – independently of major clinical confounders.

miR-126 is an endothelial-specific microRNA, that has been shown to be consistently down-regulated in atherosclerosis [*Van Solingen C. et al., 2009*]. de Boer H. et al. show that platelets are also a major source of circulating miR-126, and the administration of aspirin in patients with diabetes mellitus results both in platelet inhibition and concomitantly reduced circulating levels of platelet-derived microRNAs including miR-126 [*De Boer H. et al., 201*3]. In healthy volunteers more potent platelet inhibition resulted in a reduction of miR-126, as reported by Willeit P. et al (2013). Kaudewitz et al. reported that inhibition of miR-126 reduced platelet aggregation and that miR-126 directly or indirectly influenced ADAM9 and P2Y12-related pathways, providing a plausible biological basis for its association with variability in antiplatelet response [*Kaudewitz D. et al., 2016*].

In our study we found up-regulation of miR-126-3p in patients-responders relative to aspirin resistance patients – though it may seem contradictory to the studies mentioned before, most of the data regarding antiplatelet resistance come from platelet-derived circulating miR-126, while we measured specifically leukocyte miR-126 expression. These compartments are biologically distinct and may reflect different aspects of the response to aspirin therapy. Platelet-derived miR-126 is likely to be more directly related to platelet activation and inhibition, whereas leukocyte miR-126 may capture broader inflammatory or vascular regulatory processes that also contribute to residual platelet reactivity in cerebral atherosclerosis. Thus, our findings do not necessarily contradict the existing literature but rather suggest that the association of miR-126 with aspirin response may be pathogenetically dualistic.

Overall, our data support the concept that miR-126-3p may serve as a potential epigenetic marker of aspirin response variability in patients with cerebral atherosclerosis. Given the relatively small sample size and the laboratory-based definition of aspirin resistance used in this study, these findings should be interpreted with caution. Nevertheless, they provide a rationale for further investigations aimed at clarifying the role of miR-126 and determining whether miR-126 signatures may have value for identifying patients at increased risk of inadequate antiplatelet response.

CONCLUSION

miR-126-3p expression consistently demonstrated an association with the level of platelet aggregation in patients with cerebral atherosclerosis, which allows it to be considered a potential epigenetic marker of variability in response to antiplatelet therapy. These data suggest that the level of miR-126-3p may reflect individual features of residual platelet reactivity during aspirin therapy and, consequently, may be associated with the effectiveness of its therapeutic action in patients with cerebral atherosclerosis.

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