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ORIGINAL ARTICLE

Serum miRNA-210 Expression at Different Stages of Spontaneous Intracerebral Hemorrhage

Si-Yuan Chen, He Wang

Department of Neurosurgery, Affiliated Hospital of Beihua University, Jilin, China

SUMMARY

Background: **This study investigates the changes in serum miRNA-210 expression at different stages of spontaneous intracerebral hemorrhage (sICH) and their clinical significance.**
Methods: **Twenty patients with sICH and admitted to the Neurosurgery Department of the Affiliated Hospital of Beihua University between August 2022 and January 2023 were selected for this study. Venous blood samples were collected on Day 1 (within 12 hours) and Day 7 after disease onset. Serum miRNA-210 expression was quantified using quantitative reverse transcription polymerase chain reaction (qRT-PCR).**
Results: **Serum miRNA-210 levels on Day 7 (31.5775 ± 0.13242) were significantly lower than on Day 1 (31.6865 ± 0.1654) in patients with sICH. Results of a paired *t*-test analysis showed a *t* value of 2.268, p = 0.035 (p < 0.05).**
Conclusions: **In this study, differences in serum miRNA-210 expression at different stages of sICH were found to be significant. Changes in miRNA-210 levels may serve as potential biomarkers for disease progression, providing insights for clinical management.**
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Correspondence:
He Wang
Department of Neurosurgery
Affiliated Hospital of Beihua University
No. 12 of Jiefang Middle Road, Chuanying District
Jilin,132000
China
Phone: +86 15004323115
Email: kekeqiqi_125@126.com

KEYWORDS

biomarker, different stages, miRNA-210, quantitative reverse transcription polymerase chain reaction, serum, spontaneous intracerebral hemorrhage

LIST OF ABBREVIATIONS

PCR - Polymerase Chain Reaction
qRT-PCR - Quantitative real time polymerase chain reaction
VEGF - Vascular Endothelial Growth Factor
HIF - Hypoxia inducible factor
ROS - reactive oxygen species
sICH - spontaneous intracerebral hemorrhage

INTRODUCTION

Spontaneous intracerebral hemorrhage (sICH) is a condition characterized by cerebral vascular rupture and intracranial hemorrhage caused by non-traumatic factors, with hypertension and arteriosclerosis identified as the

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primary etiologies [1]. The incidence of sICH ranges from 12 to 15 per 100,000 person-years, making it the second most common subtype of stroke. In China, it accounts for approximately 18.8% to 47.6% of stroke cases [2]. Middle-aged and elderly patients with comorbid hypertension and arteriosclerosis are typically affected, with hemorrhages most commonly occurring in areas such as the basal ganglia and thalamus.

As a neurological emergency associated with rapid progression and deterioration in some cases, sICH can potentially lead to severe outcomes such as cerebral herniation and mortality. Additionally, as the condition progresses, patients may experience increased intracranial hematomas, persistent cerebral edema, and various complications, which may further exacerbate the condition and even lead to death. Given the dynamic nature of sICH, therapeutic strategies must be adjusted according to the specific disease stage. Therefore, identifying and thoroughly investigating potential biomarkers indicative of pathological changes are crucial for optimizing the management of sICH.

In recent years, microRNAs (miRNAs) have been extensively researched due to their regulatory roles in various physiological and pathological processes [3]. miRNAs constitute a class of small non-coding RNAs, approximately 22 nucleotides in length, that regulate gene expression post-transcriptionally by targeting messenger RNAs (mRNAs) [4]. It has been demonstrated in several studies that miRNA-210 is involved in the promotion of angiogenesis in ischemic cerebrovascular diseases [5,6], and its expression has been found to be significantly elevated in patients with spontaneous intracerebral hematomas and traumatic brain injury compared to those without such conditions [7]. miRNA-210 may hold clinical significance given its potential as an important biomarker; however, research on the changes in miRNA expression across different stages of sICH is limited. The present study was designed to address this gap.

STUDY PARTICIPANTS AND METHODS

Clinical data

Twenty patients with sICH (17 males and 3 females, mean age: 60.10 ± 7.594 years) admitted to the Neurosurgery Department of the Affiliated Hospital of Beihua University between August 2022 and January 2023 were selected for this study.

Inclusion criteria: All patients who fulfilled the diagnostic criteria outlined in the *Chinese Guidelines for the Diagnosis and Treatment of sICH* (2019); individuals who presented with a first-time onset of sICH; patients in whom sICH was confirmed based on cranial imaging, with symptom onset time within 12 hours prior to admission; and patients who were hospitalized for more than one week without surgical intervention.

Exclusion criteria: Patients who were excluded were as follows: those cases where the intracranial hemorrhage was caused by cranial trauma, intracranial tumors, cerebral vascular malformations, or use of anticoagulant medication; patients with coexisting severe primary diseases in other systems (e.g., heart, lung, liver, kidney, hematological, or endocrine system); those with malignancies in other organs; a history of acute cerebral infarction within the past six months; the presence of other systemic diseases; and those with progressive worsening of the condition or complications within seven days of admission.

The study was approved by the ethics committee of the medical institution.

Methods

miRNA-210 Detection: Venous blood samples (10 mL) were collected at the time of admission (within 12 hours of symptom onset) and again on Day 7 of conservative treatment. Within two hours of collection, the samples were centrifuged at 3,000 r/minute for 10 minutes, and the supernatant was collected and aliquoted into RNase- and DNase-free cryovials. The samples were stored at -80°C until all samples were collected for analysis.

Details of the primer design and synthesis for experimental detection are presented in Table 1. RNA extraction was performed using a miRNA extraction reagent (Monzol™ Reagent Pro), followed by reverse transcription (MonScript™ miRNA First Strand cDNA Synthesis Kit) and polymerase chain reaction (PCR). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was conducted using a fluorescence real-time quantitative PCR system to measure the cycle threshold (Ct) values of the samples, following established RNA detection protocols.

Statistical analysis

All data were processed and analyzed using SPSS 22.0. Measurement data were expressed as the mean ± standard deviation (SD). A paired *t*-test was used to compare differences between groups, and a p-value < 0.05 was considered statistically significant.

RESULTS

The serum miRNA-210 levels in patients with sICH on Day 1 were (31.6865 ± 0.1654) and (31.5775 ± 0.13242) on Day 7. The results of the paired *t*-test analysis were as follows: $t = 2.268$, $p = 0.035$ ($p < 0.05$), indicating a significant decrease in miRNA-210 expression on Day 7 compared to Day 1 (Figure 1 and Table 2).

DISCUSSION

sICH is a severe neurological disorder associated with high rates of disability and mortality, posing significant threats to patient health and imposing substantial burdens on families and society. Following the onset of in-

Table 1. Primer design and synthesis.

Gene name	Upstream/downstream	Gene sequence	NCBI gene ID
U6	U6-F	TATACTAAAATTGGAACGATACAG	26827
	U6-R	AATATGGAACGCTTCACGA	
miRNA210	210-F	CCTGCCCACCGCACAC	406992
	210-R	CCAGGCACAGATCAGCCG	

Table 2. Results of statistical analysis.

Paired differences					*t*	df	Sig. (2-tailed)
Mean	Std. deviation	Std. error mean	95% Confidence interval of the difference				
			Lower	Upper			
0.10900	0.21494	0.04806	0.00841	0.20959	2.268	19	0.035

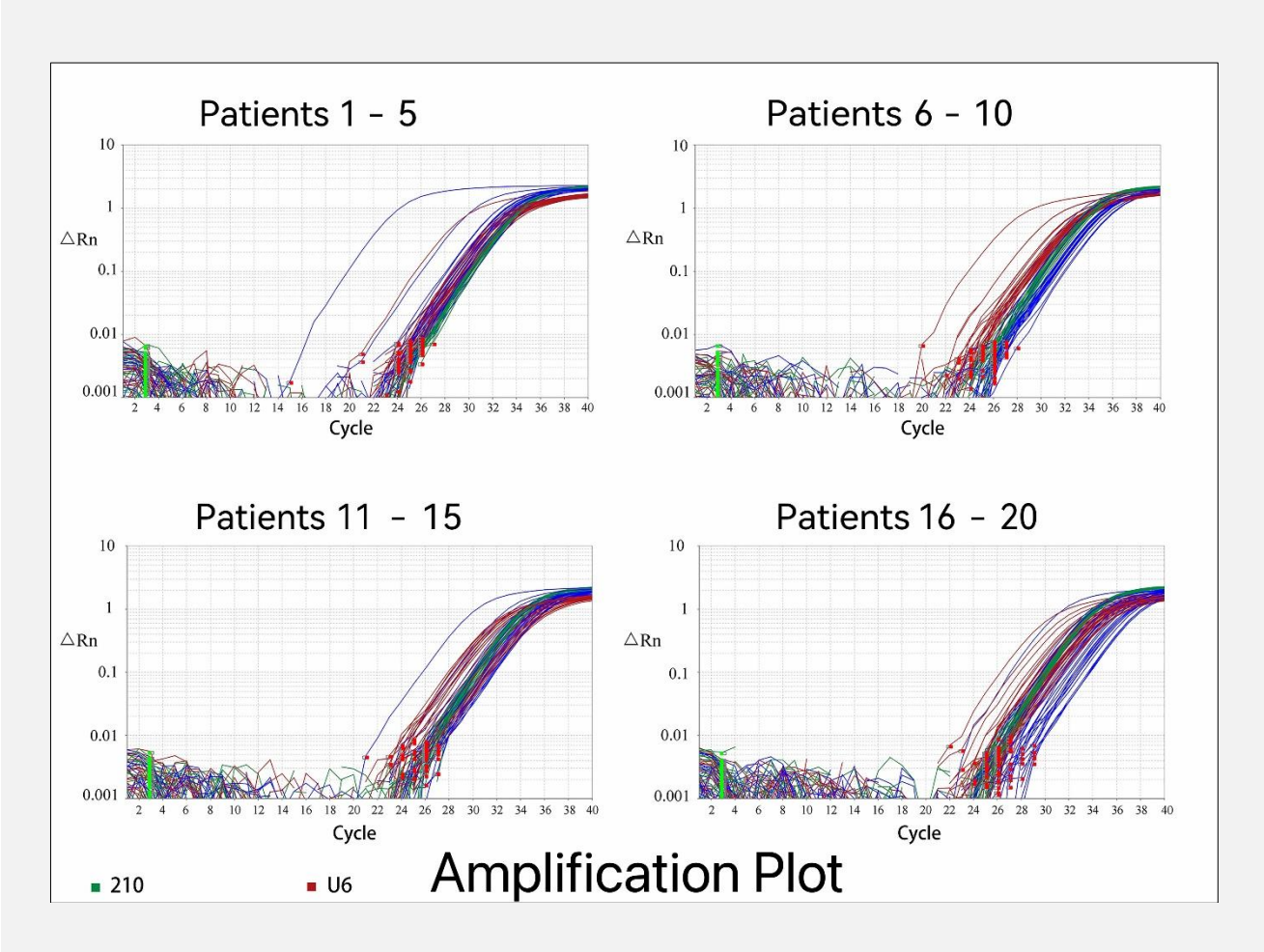

Figure 1. miRNA-210.

tracerebral hemorrhage, the disruption of cerebral tissue, breakdown of the blood-brain barrier, and development of cerebral edema contribute to ischemia, hypoxia, and neuronal death.

miRNA-210 has been identified as an ischemia- and hypoxia-related factor that is intricately involved in the pathophysiological mechanisms of various neurological disorders [3]. The unique composition and stability of miRNAs when encapsulated within exosomes render them suitable as biomarkers for monitoring disease progression [8]. Certain miRNAs have been reported to mitigate the disruption of the blood-brain barrier, reduce cell apoptosis, diminish reactive oxygen species (ROS) generation following intracranial hematoma formation, and facilitate neuronal repair by inhibiting neuroinflammation and immune activation, thereby promoting angiogenesis and restoring cerebral microcirculation [9, 10]. Furthermore, miRNAs derived from brain tissues and present in the bloodstream may serve as indicators of the extent of brain injury as well as blood-brain barrier damage and the prognosis of neurological recovery [11].

miRNA-210, a hypoxia-specific miRNA, has been identified as playing a pivotal role in post-ischemic angiogenesis [12], contributing to enhanced endothelial function [13] and providing neuroprotection against acute ischemia-induced apoptosis and oxidative stress [14]. In patients with acute cerebral infarction, reduced levels of miR-210 have been reported, with significantly lower survival rates in patients with downregulated miR-210 compared to those with miR-210 overexpression. The expression of miRNA-210 in the serum of patients with sICH or traumatic intracranial hematomas has also been found to be significantly elevated in comparison to healthy individuals [6].

In sICH, localized cerebral tissue within the intracerebral hematoma region undergoes structural damage. As cerebral edema progresses, it leads to ischemia, hypoxia, and neuronal death in adjacent brain tissue, increasing the production of vascular endothelial growth factor (VEGF) and activating hypoxia-inducible factor (HIF) [15]. Zaccagnini et al. demonstrated that miRNA-210 plays a pivotal role in the VEGF-mediated and HIF-activated signaling pathways [16], thereby influencing angiogenesis. However, the incomplete functionality of newly formed blood vessels renders them susceptible to rupture, hemorrhage, and increased blood-brain barrier permeability. These vascular changes contribute to a series of related reactions, such as extravasation of blood components, which may further exacerbate cerebral edema [17,18].

CONCLUSION

In summary, elevated miRNA-210 levels in the serum of patients with sICH is associated with post-hemorrhage tissue necrosis and localized cerebral ischemic-hypoxic conditions. The subsequent decline in miRNA-210 levels that was observed in this study within one week after hemorrhage may be attributed to feedback inhibition following cerebral angiogenesis and the progression of cerebral edema post-intracerebral hemorrhage. The dynamic expression of miRNA-210 may serve as a temporal indicator of disease progression. Gareev et al. proposed a systematic examination and analysis of miRNAs in the body, which have been recognized as valuable for the diagnosis and treatment of sICH. This approach may aid in the early assessment of the extent of damage to the cerebrovascular wall and the risk of rupture, thereby enabling the early diagnosis and prevention of spontaneous intracerebral hematoma [19]. miRNA-210 has been identified as a potential biomarker for the occurrence and development of sICH. However, the limited sample size and inadequate data in the current study necessitate further research to investigate the temporal variations of miRNA-210, optimize detection methodologies, and uncover the underlying biological mechanisms.

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Ethics Approval and Consent to Participate:
The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the Affiliated Hospital of Beihua University (No. 2023-67). Written informed consent was obtained from all participants.

Availability of Data and Material:
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declaration of Interest:
The authors declare that they have no competing interests.

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