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Expression of plasma microRNA-145-5p and its correlation with clinical features in patients with refractory epilepsy

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ABSTRACT

Purpose: The potential of microRNAs (miRNAs) as biomarkers has been explored in various brain diseases, including epilepsy. In this study, we are aiming to analyze the aberrant expression of miRNA-145-5p in patients with refractory epilepsy, and to further explore the correlation with clinical features.

Methods: The study cohort comprised 40 patients with refractory epilepsy and 42 healthy controls. MiRNA-145-5p expression levels in plasma were analyzed by quantitative real-time polymerase chain reaction (qRT-PCR). Data analysis was performed using IBM SPSS Statistics 22.0.

Results: Compared with healthy controls, the expression of miRNA-145-5p in plasma was downregulated significantly in the patients with refractory epilepsy (1.180 ± 1.036 vs. 1.541 ± 0.936, p = 0.033) and mesial temporal lobe epilepsy (MTLE) (0.517 ± 0.483 vs. 1.541 ± 0.936, p = 0.004). ROC analysis showed that the area under the curve (AUC) was 0.632 (95%CI: 0.508 − 0.755; P = 0.040) in refractory epilepsy and 0.829 (95%CI: 0.702 − 0.955; P = 0.001) in MTLE. Furthermore, the expression of miRNA-145-5p was positively correlated with earlier age at epilepsy onset, more frequent seizures and past history.

Conclusions: We suggested that decreased expression of miRNA-145-5p could be a potential non-invasive biomarker for early detection and clinical evaluation of refractory epilepsy. However, further studies are still required.

1. Introduction

Epilepsy is one of the most common neurological conditions, with more than 50 million people affected worldwide (Reynolds, 2002). Antiepileptic drugs (AEDs) merely provide symptomatic control of seizures, but a third of patients remain refractory to AEDs (Geerts et al., 2010). The pathogenic mechanisms underlying drug-resistant epilepsy remain unknown. The transporter hypothesis is one of the most widely accepted and investigated theory (Potschka, 2012), which is associated with polymorphic transporter proteins such as P-glycoprotein (P-gp, encoded by MDR1/ABCB1), breast cancer resistance protein (BCRP, encoded by ABCG2) and multi-drug resistance protein 2 (MRP2, encoded by ABCC2) (Aronica et al., 2004; Shen et al., 2016a,b).

In recent years, the role of microRNAs (miRNAs) in the pathogenesis of neurological diseases is a fast expanding area of research (Tiwari et al., 2018; Van Scheppingen et al., 2018). Alterations have been previously observed in the levels of miRNAs in patients with epilepsy, such as miRNA-134, miRNA-181a and miRNA-146a (Ma, 2018). As a family of single-stranded, small non-coding RNAs, miRNAs may decrease mRNA stability and translation to inhibit the expression of multiple proteins and could therefore provide a key regulatory mechanism and therapeutic target for epilepsy (Liu et al., 2018; Rodriguez et al., 2017). Ikemura et al. has revealed miRNA-145-5p post-transcriptionally regulates the expression and function of P-gp in intestinal epithelial cells through the direct action of 3'-UTR of MDR1 mRNA (Ikemura et al., 2013). There is also evidence that ABCG2 and ABCC2 were the direct targets of miRNA-145-5p proved by in vitro models and dual-luciferase reporter gene assay (Gao et al., 2016; Shi et al., 2014). Given that miRNA-145-5p may be involved in the pathogenesis of drug-resistant epilepsy by transporter proteins, we hypotheses it was deregulated in refractory epilepsy and could be used as a potential therapeutic target and biomarker for diagnosis and clinical evaluation. Therefore, we are aiming to investigate the differential expression of serum miRNA-145-5p in patients with refractory epilepsy and to further explore the correlation with clinical features.

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2. Materials and methods

2.1. Patients and study design

We recruited patients with epilepsy from December 2017 and May 2018. All patients were treated at the Epilepsy Center of the Second Affiliated hospital of Zhejiang University School. Inclusion criterias were as follows: (1) patients were diagnosed as refractory epilepsy by experienced clinicians according to the guidelines for the Classification and Diagnosis of Epilepsy of the International League Against Epilepsy (Berg et al., 2010), meaning that they had persistent seizures despite trials of 2 or 3 adequately tolerated and appropriate AEDs; (2) patients had no generalized convulsive seizures within two days when blood samples were taken (Surges et al., 2016); (3) patients had no severe organ diseases, mental disorders, or progressive nervous diseases; (4) patients suffered no epilepsy-related surgical treatments before. Informed consents were obtained from all the participants, and the study was approved by the Second Affiliated hospital of Zhejiang University School of Medicine Ethics Committee.

For each eligible case, the following data were collected: patient demographics, age at seizure onset, seizure frequency, past history (i.e., head trauma, stroke, encephalitis), family history of epilepsy, febrile seizures (FS), EEG, MRI and PET findings before surgery. Postoperative pathology was recorded if patients had surgeries. Mesial temporal lobe epilepsy (MTLE) was classified by experienced clinicians according to clinical, EEG, MRI criteria and postoperative pathology. Controls were Chinese unrelated individuals from Physical Examination Center of the Second Affiliated hospital of Zhejiang University School, with no neurological disease, who voluntarily agreed to donate plasma samples to our study.

2.2. Blood collection and RNA isolation

Plasma samples from patients with refractory epilepsy and healthy age- and sex-matched controls were selected in the morning after overnight fasting. Blood samples were drawn into EDTA-containing tubes and the plasma was immediately separated using a centrifuge at room temperature. The supernatant was then transferred into RNase-free EP tubes and stored at −80 °C until use. Total RNA was extracted from 100 μL of plasma samples using TRIzol (Invitrogen) according to established protocols.

2.3. Reverse transcription and quantitative real-time PCR

The reverse transcription reaction was performed in a 20 μL reaction volume using TAKARA PrimeScript™ RT reagent Kit with gDNA Eraser (TAKARA, Japan) with miR-145-5p specific stem-loop primers, following the manufacturer instructions. The reaction mixtures were sequentially incubated at 37 °C for 15 min and 85 °C for 5 s. qRT-PCR was performed using an ABI Step-one Plus PCR System (Applied Biosystems) with the following conditions: 95 °C for 6 min, followed by 50 cycles of 95 °C for 10 s, 55 °C for 10 s and 72 °C for 30 s. The PCR primers for miR-145-5p were designed as follows: the stem-loop reverse transcription (RT) primer: GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAA TTGCACTGGATACGACAGGGATT; Forward primer: GTCCAGTTTTCCC AGGAAT; Reverse primer: TGCGTGTCGTGGAGTCG. U6 was chosen as the endogenous control for data normalization. All reactions were performed in triplicate. The relative quantification was calculated and normalized to U6 by the comparative ΔCt method and the equation $2^{-\Delta\Delta Ct}$.

2.4. Statistical analysis

Statistical analysis were performed using SPSS 20.0 software. Student's *t*-tests and chi-squared test were used to compare the results for clinical data between patients and controls. The expression levels of miRNA-145-5p were calculated with the $2^{-\Delta\Delta Ct}$ method and expressed with mean ± standard deviation (Mean ± SD). Since the levels of miRNA-145-5p were not normally distributed according to Shapiro-Wilk normality test, their group differences were analyzed by non-parametric method of Kruskal-Wallis test and Mann-Whitney U test. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic value by calculating the area under the curve (AUC), including sensitivity and specificity. A two-side P value less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the study population

A total of 40 patients with refractory epilepsy and 42 healthy controls were recruited. The mean age of patients was 28.5 ± 13.7 years old. 7 patients have positive past history, including head trauma and encephalitis. Among 40 enrolled patients, 11 were classified as MTLE. Each patient underwent a neurological exam, EEG and high resolution MRI with a specific epilepsy protocol. Of 40 patients with refractory epilepsy, 13 underwent PET scan and 12 had surgeries. The detailed demographic and clinical characteristics of individuals are listed in Table 1. There was no significant difference in age or gender ratio between the patient and control group ($P > 0.05$).

3.2. Differential expression of miRNA-145-5p in plasma between patients with refractory epilepsy and healthy controls

Compared with controls, miRNA-145-5p in plasma shows significant downregulation in patients with refractory epilepsy (1.180 ± 1.036 vs. 1.541 ± 0.936, p = 0.033; Fig. 1A). The accuracy for identifying patients with refractory epilepsy was AUC = 0.632 with a sensitivity of 65% and a specificity of 33% (95%CI: 0.508 − 0.755,

Table 1
Clinical and demographic data on enrolled patients and healthy controls.

Characteristics	Epilepsy	Control
No.	40	42
Age (years)	28.5 ± 13.7	33.3 ± 10.8
Sex		
Male	21	25
Female	19	17
Age at epilepsy onset	19.6 ± 13.1	NA
Duration of epilepsy	8.9 ± 7.3	NA
Past history		
Head trauma	5	NA
Encephalitis	2	NA
Negative	33	NA
MRI findings		
Hippocampal sclerosis	9	NA
Focal cortical dysplasia	3	NA
Glioneuronal tumors[a]	3	NA
Others[b]	14	NA
Negative	11	NA
PET findings		
Abnormal	12	NA
Normal	1	NA
NA	27	NA
Pathology		
Hippocampal sclerosis	3	NA
Focal cortical dysplasia	2	NA
Glioneuronal tumors (GG and DNET)	3	NA
Others (trauma, hemanigoma, et al)	4	NA
NA	28	NA

Age, age at epilepsy onset and duration of epilepsy were presented as mean ± standard deviation, rest of data were presented as amount.

[a] Glioneuronal tumors were defined as ganglioglomas (GG) and dysembryoplastic neuroepithelial tumors (DNET).

[b] Others: Hemangioma, Gray matter heterotopia, Encephalomalacia, et al.

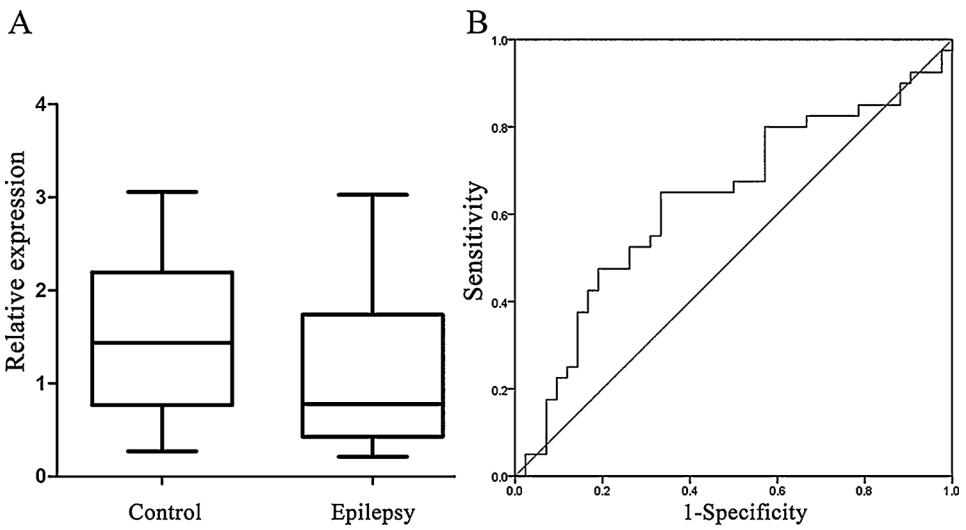

Fig. 1. (A) The relative expression levels of miRNA-145-5p in plasma from patients with refractory epilepsy and healthy controls. The box plots were represented with median (10–90 percentile), and the data was statistically significant between groups with Kruskal-Wallis test ($P < 0.05$). (B) ROC curves for miRNA-145-5p expression in plasma (AUC = 0.632, 95%CI: 0.508 − 0.755; p = 0.040).

p = 0.040; Fig. 1B).

We also found that the expression of miRNA-145-5p was significantly downregulated in the plasma of patients with MTLE, when compared with healthy controls (0.517 ± 0.483 vs. 1.541 ± 0.936, p = 0.001; Fig. 2A) and patients without MTLE (0.517 ± 0.483 vs. 1.431 ± 1.083, p = 0.003). The accuracy for identifying patients with MTLE from controls was AUC = 0.829 (95%CI: 0.702 − 0.955, p = 0.001; Fig. 2B).

3.3. Relationship between plasma levels of miRNA-145-5p and clinical features

The expression of miRNA-145-5p was significantly correlated with earlier age at onset (P = 0.024), more frequent seizures (P = 0.020) and past history including head trauma and encephalitis (P = 0.014) (Table 2). However, there is no significant associations between plasma levels of miRNA-145-5p in patients with refractory epilepsy and sex, duration of epilepsy, family history, febrile seizures and MRI findings ($P > 0.05$).

4. Discussion

Our study indicated a significant downregulation of miRNA-145-5p in plasma of patients with refractory epilepsy and MTLE, suggesting it could be served as a potential biomarker in epilepsy. Furthermore, we demonstrated the lower expression of miRNA-145-5p was associated with earlier age at epilepsy onset, more frequent seizures and past history.

An ultimate diagnosis of refractory epilepsy usually requires a long-term treatment cycle of several years, during which time, repeated seizures may not only aggravate patients' cerebral function but also lead to delays in terms of the optimal opportunity for comprehensive treatment, including surgery. Besides, refractory epilepsy poses a significant threat to patients' family and even society, whether economically, physically, or psychologically. Thus, researchers are always aimed to identify a noninvasive, rapid, broadly accessible, and economical method for the early recognition of refractory epilepsy (Shen et al., 2016a,b; Labate et al., 2016; Kuzmanovski et al., 2016). Nervous system cells can secrete miRNAs into the peripheral blood and miRNAs have been shown to be stable in plasma, which makes miRNAs potential candidates as noninvasive biomarkers for early detection and clinical evaluation of refractory epilepsy. Studies on refractory epilepsy have offered the exciting possibility of miRNAs acting as potential biomarkers for epilepsy diagnosis, such as miRNA-134, miRNA-129-2-3p and miRNA-935 in plasma with a high sensitivity and specificity (Avansini et al., 2017; Sun et al., 2016). MiRNA expression profiles in human brain tissue have also indicated aberrant expression of some miRNAs (miR-21, miR-129-2-3p, miR-142-5p et al.) in patients with refractory epilepsy (Bencurova et al., 2017; Prabowo et al., 2016). In addition, Raoof et al. has found the levels of miR-19b-3p, miR-21-5p and miR-451a were differentially expressed in CSF samples from TLE and/or SE patients that can support differential diagnosis of temporal

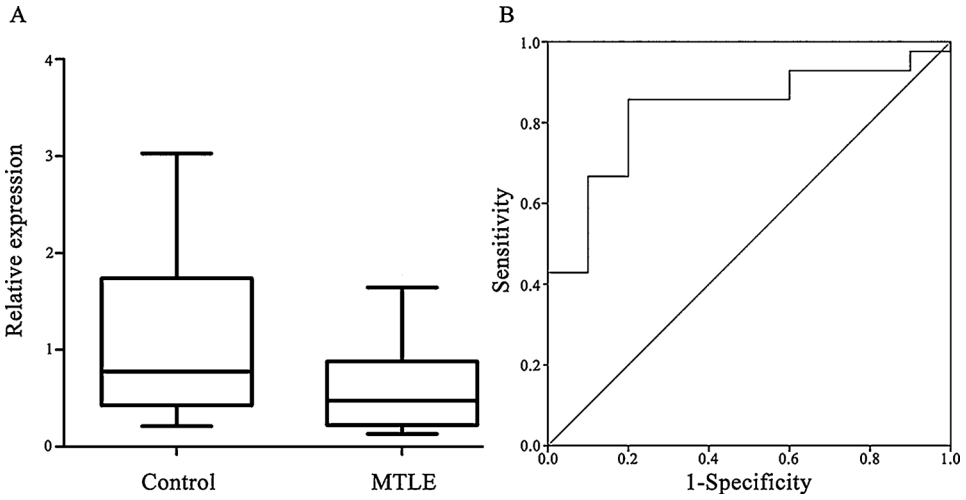

Fig. 2. (A) The relative expression levels of miRNA-145-5p in plasma from patients with MTLE and healthy controls. The box plots were represented with median (10–90 percentile), and the data was statistically significant between groups with Kruskal-Wallis test ($P < 0.001$). (B) ROC curves for miRNA-145-5p expression in plasma (AUC = 0.632, 95%CI: 0.508 − 0.755; p = 0.001).

Table 2
Relationship between plasma levels of miRNA-145-5p and clinical characteristics in patients with refractory epilepsy.

Variable	Patients (n = 40)	MiRNA-145-5p expression (Mean ± SD)	P value
Sex			
Male	21	1.097 ± 1.031	
Female	19	1.270 ± 1.061	0.715
Age at onset (years)			
≥20	25	0.917 ± 0.920	
< 20	15	1.618 ± 1.098	0.024*
Duration of epilepsy (years)			
≥10	18	1.157 ± 1.186	
< 10	22	1.198 ± 0.924	0.568
Seizure frequency (times/month)			
≥4	13	0.590 ± 0.361	
< 4	27	1.463 ± 1.136	0.020*
Past history			
Positive	7	0.428 ± 0.315	
Negative	33	1.339 ± 1.067	0.014*
Family history			
Positive	1	1.170 ± 0.000	
Negative	39	1.205 ± 1.036	0.129
Febrile seizures			
Positive	5	1.916 ± 1.646	
Negative	35	1.074 ± 0.906	0.357
MRI findings			
Abnormal	26	1.147 ± 1.021	
Normal	12	1.210 ± 1.159	
NA	2	–	0.851

* P < 0.05.

lobe epilepsy and status epilepticus from other neurological and non-neurological diseases (Raoof et al., 2017). To our knowledge, this result provides the first evidence of a role for miRNA-145-5p in refractory epilepsy and its potential diagnostic value, particularly in MTLE. Although our results were considered of statistical significant, it is more realistic to assume that no single biomarker will attain 100% sensitivity of specificity and that a combination of different biomarkers together with clinical information is more likely to be used in clinical practice.

Except acting as a biomarker, miRNAs decrease mRNA stability and translation to inhibit the expression of multiple proteins and could therefore provide clues to disease etiology and potential therapeutic target for the treatment of epilepsy (Tiwari et al., 2018; Pitkänen and Lukasiuk, 2011). Recent study has identified miRNA-145-5p in retinal endothelial cells as a novel regulator of apoptosis, oxidative stress and inflammatory cytokines secretion, which were also thought to be involved in epilepsy (Hui and Yin, 2018). Similarly, Liu et al. has suggested that miRNA-145-5p is involved in mitophagy activity and subsequently affect neuroblastoma celll survival in the context of TNFα-mediated inflammation injury (Liu et al., 2019). Our study revealed that plasma miRNA-145-5p levels in patients with refractory epilepsy was significantly reduced, this alteration may reflect the pathophysiological processes related to the neurobiology in epilepsy, like an abnormal quantity or functioning of miRNA-145-5p associated genes or proteins along with the process of apoptosis, cytokines and unknown mechanisms. Besides, as described above, studies have indicated that miRNA-145-5p post-transcriptionally regulated the expression and function of ABCB1, ABCG2 and ABCC2 (Ikemura et al., 2013; Gao et al., 2016; Shi et al., 2014), which suggested miRNA-145-5p may exert an effect on the pathogenesis of refractory epilepsy by targeting multidrug transporter proteins thereby inhibiting the transport of AEDs across the blood-brain barrier. However, the hypothesis requires confirmation from further animal experiments. Most previous studies have revealed patients with earlier age at seizure onset and more frequent seizures have poorer outcomes and higher chances of becoming refractory at long-term follow-up, with unknown mechanism (Labate et al., 2016). Another finding of our study was the positive correlation between the downregulated expression of miRNA-145-5p and the earlier onset, frequent seizures or past history, suggesting that the reduction of miRNA-145-5p in circulation may be accompanied by the progression of epileptic seizures and promote drug-resistant epilepsy.

The current study has several limitations. First, it is uncertain whether other possible factors can affect miRNA levels in plasma, which were not identified in our study and may in turn alter the plasma miRNA levels in refractory epilepsy. A particular concern was AEDs taken by each patient. Wang et al's study have shown plasma miRNA-134 levels in new-onset epilepsy patients were up-regulated when compared with that in healthy controls, and then considerably down-regulated after oral intake of valproic acid medication (Wang et al., 2017). Secondly, the miRNA-145-5p alterations in patients with newly diagnosed epilepsy and drug-responsive epilepsy are not analyzed. It would be better to include those patients to evaluate the role of miRNA-145-5p in differentiating between newly diagnosed epilepsy, drug-responsive epilepsy and drug-resistant epilepsy. As well, brain tissues from patients with refractory epilepsy are needed. Thirdly, we have a limited number of patients that underwent surgery to evaluate the effect of miRNA-145-5p on postoperative outcomes, further studies are still required in a larger sample. Finally, only miRNA-145-5p was analyzed in our study, larger panels including at least 5 miRNAs should be conducted in future.

These observations demonstrated that miRNA-145-5p could be a potential biomarker for refractory epilepsy, particularly MTLE. However, it remains unknown how miRNAs function as a biomarker in the circulation of blood and exert an effect on the development of refractory epilepsy, both in vivo studies and in vitro studies are required in future.

Financial disclosure/conflict of interest

No special explanation.

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