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RESEARCH ARTICLE

miRNAs as Valuable Diagnostic Biomarkers in Patients with Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is an autoimmune condition caused by chronic inflammation of central nervous system and demyelination of neurons. At present, microRNAs (miRNAs) are recognised as a diagnostic and prognostic indicator of the diseases. But they are also a new and innovative goal in gene therapy. Therefore, the aim of this study is to find a simple, non-invasive, and valuable biomarker for early detection and potential treatment of MS. In the present study, 30 serum samples of patients with recurrent MS (recurrecy dettermined with McDonald's criteria) were obtained along with the 30 healthy samples. The qRT-PCR method was performed to evaluate the expression level of miR-155a, miR-146a, miR-34a, miR-143a and miR-373a in both groups. The results revealed that miR-155a and miR-146a were significantly upregulated while miR-34a, miR-143a and miR-373a were significantly downregulated in the patient group in comparison with healthy subjects. These results candidate these microRNAs with altered levels as potential diagnostic and prognostic markers in patients with MS, which may be involved in the therapeutic schedule for MS like microRNA replacement therapy in the near future.

Introduction

Multiple Sclerosis (MS) is an autoimmune condition caused by chronic inflammatory demyelination of neurons in the Central Nervous System (CNS). This can lead to some neurological dysfunction that would disrupts persons activities [1-3]. Different phenotypes of clinical MS include Relapsing-Remitting MS (RRMS) and Progressive MS, which includes both Primary (PPMS) and Secondary (SPMS) types. RRMS is the most prevalent MS subgroup with 70% of cases being RRMS type. The phenotype status for many of the patients would change from RRMS to SPMS after approximately 10 to 15 years after the onset of MS, which does not respond to any of the known treatments [2,4,5].

Micro RNA (miRNA) is a class of small endogenous and non-coding RNA, which is only 22-25 nucleotide long. miRNA's main function is controlling the gene expression. They also play a role in many of the cellular functions, including homeostasis, organogenesis and cell cycle development. They apply their influence by binding to the 3'UTR region of the target gene, which cause miRNA degeneration and inhibit the translation [6-8]. It is said

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that dysregulated expression of miRNAs contributes to the onset of various immune and neurological diseases. In addition, miRNAs have been identified in different bodily fluids, such as serum, urine and saliva. Previous studies have indicated that different phycological conditions (e.g., pregnancy) or diseases can alter the miRNA expression levels in serum [7]. The source of these circulating miRNAs is not clear; nonetheless, they are easy to identify and can be obtained from patients via non-invasive measures, thus making them and ideal predictive marker for disease management and therapeutic strategies [9-11]. Previous researches indicated the involvement of miRNAs in the pathogenesis of MS. It has been proven that the expression levels of some miRNAs in serum of MS patients have been altered in comparison to a healthy person [10].

Nowadays, the most important challenge is identifying the biomarkers that can help to diagnose and to predict MS. Thus, the miRNAs may act as precious biomarkers because of their aberrant expression in diseases. Previous studies have shown that miR-146a and miR-155a upregulate in brains white matter lesion biopsies obtained from both MS patients and the mouse models [12]. In addition, miR-143 has been shown to be downregulated in the injured dorsal root ganglia [13]; suggesting that the expression of miRNAs may be involved in MS pathogenesis. Defining the role of the miRNAs involved in neuronal proliferation and apoptosis would be helpful in understanding the underlying mechanism of MS, which may act as a diagnostic and therapeutic factor in approaching to MS. For example, firstly, miR-373a induces the proliferation of primary human cells via targeting oncogenic RAS and the active type p53 [14]. Secondly, enforced expression of miR-34a leads to stimulated cell cycle arrest, apoptosis and suppression of epithelial-mesenchymal transition [15]. Consequently, evaluating the expression level of the mentioned miRNAs (miR-34a, miR-143a, miR-146a, miR-155a and miR-373a) in blood samples obtained from patients with MS can be used as a sensitive diagnostic and prognostic method in which their inhibition or stimulation might be hopeful therapeutic approach in the future.

Materials and Methods

Sample collection and storage

Lab data from a group of 30 patients with RRMS and another group of 30 healthy people (control group) were chosen from the patients, who were referred to Alborz University of Medical Sciences, Karaj, Iran, were included in this study. Blood samples (5 ml) were obtained from both the patients and control groups without additives. Each sample was centrifuged at 2000 RPM for 15 minutes to isolate the serum. The serum was kept at -70˚C until the time for RNA extraction. Written informed consent was obtained from all individuals and demographic and clinical characteristics of the patients were summarized in table 1. The age and sex disrebution between both groups were similar. The study protocol was approved by the ethical committee of Alborz University of Medical Sciences, Iran.

RNA extraction, cDNA synthesis and quantitative Real Time-PCR (qRT-PCR) analysis

RNAs were extracted using the TRIzol® Reagent (Gene all, South Korea). Then, the extracted RNAs were converted to cDNA using a cDNA synthesis kit for microRNAs (Eurex, South Korea). Prepared cDNAs were stored at -20˚C until use. The primers sequences are presented in table 2. The qRT-PCR was utilized to identify the expression of purchased miRNAs (Eurex, South Korea). Normalization was performed using the mean expression of the miRNA-103 with the best stability index. miRNA expression levels were measured by the QIAGEN Real-Time PCR Detection System. Relative quantification of miRNA was performed using the $2^{-\Delta\Delta CT}$ method.

Statistical analysis

The data were analyzed by SPSS software version 23 and independent samples t-test was used to compare

Table 1: Demographic characteristics of patients with MS.

Variable	MS (mean ± SD) *n* = 30	Control (mean ± SD) *n* = 30
Age	41.18 ± 11.29	44.37 ± 9.47
Sex (men/women)	13 (43%)/17 (57%)	14 (46%)/16 (54%)
CRP, mg/L	6.14 ± 2.17	1.13 ± 0.69
ESR	20.02 ± 8.63	9.01 ± 5.72
CSF IgG positivity	23 (76%)	-
Onset age	30.07 ± 8.73	-
Duration of the disease	7.89 ± 3.95	-
EDSS	4.39 ± 1.06	-
MSSS	4.14 ± 0.67	-

*Data are presented as number and/or mean ± SD *vs.* Controls.
MS: Multiple Sclerosis; CRP: C-reactive Protein; ESR: Essential Sedimentation Rate; CSF: Cerebrospinal Fluid; IgG: Immunoglobulin G; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score

Table 2: The stem loop primers sequences for cDNA synthesis and qRT- PCR.

hsa-miR-146a-5p	Stem loop	5'GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACAACCCA3
	Forward	5'CACGCATGAGAACTGAATTCCA3'
hsa-miR-373a-5p	Stem loop	5'GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACGGAAAG3'
	Forward	5'CACGCAACTCAAAATGGGGGCG3'
hsa-miR-34a-3p	Stem loop	5'GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACAGGGCA3'
	Forward	5'CACGCACAATCAGCAAGTATAC3'
hsa-miR-143a-3p	Stem loop	5'GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACGAGCTA3'
	Forward	5'CACGCATGAGATGAAGCACTG3'
hsa-miR-155a-5p	Stem loop	5'GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACACCCCT3'
	Forward	5'CACGCATTAATGCTAATCGTGAT3'
hsa-miR-103a-3p	Stem loop	5'GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACTCATAG3'
	Forward	5'CACGCAAGCAGCATTGTACAGGG3'

both patient and control groups as verification. $p < 0.05$ was considered significant.

Results

Altered expression of miR-155a, miR-146a, miR-34a, miR-143a and miR-373a in MS patients

The expression levels of five miRNAs were evaluated in the serum of patients with MS and control groups. The results showed that miR-155a and miR-146a levels were increased in the blood samples obtained from the patients with MS compared to the control group ($p < 0.001$) (Figure 1). It was also revealed that miR-34a, miR-143a, miR-373a levels were decreased compared to the control group ($p < 0.5$) (Figure 2).

Discussion

MicroRNAs, as one of the main molecules burdened with an important role in regulation of various biological processes, may have different effects by inhabiting multiple target genes. These effects being either beneficial of harmful would depend on the targeted gen. Thus, if the targeted gene is a tumor-suppressor, Then the microRNA is classified as an oncogenic microRNA. In contrast, if the targeted gene has an oncogenic role and by inhibiting it can prevent carcinogenesis, Then the microRNA is known as a tumor-suppressor microRNA. Therefore, aberrant expression of microRNAs could be considered as potential diagnostic biomarkers for diseases. In some studies, the dysregulation of miRNAs in autoimmune diseases, including MS, have been proven [16-19]. After thorough consideration of said results, we have decided to investigate the alteration in expression levels of five important miRNAs; which, their dysregulation may serve as a possible diagnostic tools in MS.

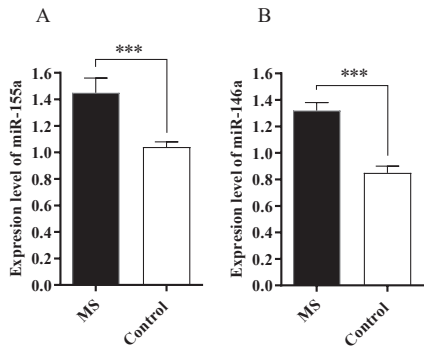

Figure 1 Relative expression of serum levels of miR-155a and miR-146a and using qRT- PCR in MS patients (n = 30) versus control groups (n = 30). This figure demonstrates that miR-155a and miR-146a have an elevated expression level in MS patients in comparison with controls. $^{***}p < 0.001$ *vs.* control group.

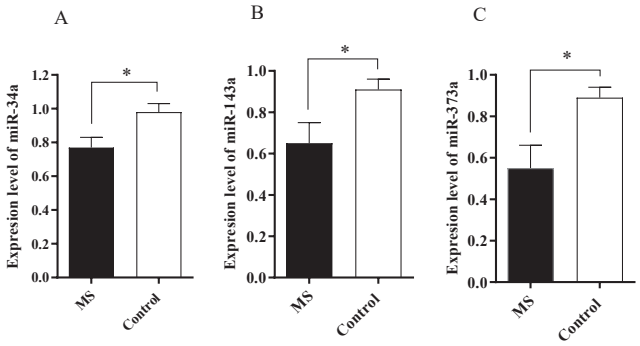

Figure 2 Relative expression of serum levels of miR-34a, miR-143a and miR-373a using qRT- PCR in MS patients (n = 30) versus control groups (n = 30). This figure illustrates that miR-34a, miR-143a and miR-373a showed lower expression levels in comparison with control groups. $^{*}p < 0.5$ *vs.* control group.

This study showed that miRNA-146a and 155a levels were upregulated in the serum of MS patients during the relapsing-remitting phase. As a confirmed role of miR-146a, it can target the 3′-UTR of different mRNAs involved in immune-related signaling

pathways; which shows the major role of it in the innate immune and inflammatory response.

In addition, miR-155a has an important role in adaptive and innate immunity. The involvement of miRNA-155 has been reported in the immunopathology of MS [20]. miR-155a exerts its effects via targeting 3′-UTR of CD47, which leads to the downregulation of CD47 on brain-resident immune cells, and macrophage-mediated phagocytosis of myelin [21]. Rajasekhar M, et al. [22] showed that elevated levels of miR-155a in monocytes leads them to be resistant to apoptosis, which can cause autoimmune disease. Furthermore, monocytes, derived from patients with rheumatoid arthritis, showed increased resistance to apoptosis. The result of another study showed that miR-155a destabilizes caspase-3 in macrophages and leads to apoptosis repression [23]. To sum up the results of mentioned studies, it can be concluded that miR-155a has an anti-apoptotic effect and be one of the factors that can cause autoimmune disease like MS. In line with our study, the elevated levels of miR-155a may have a correlation with apoptosis resistance in autoreactive macrophages in MS. Moreover, it has been revealed that in mice lacking miR-155, the severity of EAE (Experimental autoimmune encephalomyelitis) and CNS inflammation has been decreased; which is consistent with our findings [24].

Regarding miR-146a, it has been upregulated in the samples obtained from patients with MS. Its pro-inflammatory function may be due to decreasing the complement factor H expression, a negative regulator of inflammation in brain [25]. Fenoglio C, et al. [26] indicated that miR-146a significantly upregulated in whole PBMCs (peripheral blood mononuclear cells) obtained from patients with RRMS. Additionaly, miR-146a functioned as a regulator of autoreactive Th17 cell differentiation which causes organ-specific autoimmune diseases [27,28]. Li Z, et al. [29] indicated that the upregulation of miR-146a leads to increased proliferation and decreased apoptosis of T cells.

TaqMan array studies showed that miR-34a was downregulated in $CD4^+$ T cells derived from PBMCs of patients with RRMS [30]. It has also been revealed that the expression of miR-34a in neurons has a crucial role in controlling neuronal cell cycle. miR-34a's upregulation leads to reversed cell cycle-related neuronal apoptosis [31]. These results revealed that miR-34a might be expressed differently at different stages of RRMS; which describe the complexity of the mechanism involved in the pathogenesis of MS.

No related studies on the evaluation of miR-373a and 143a in MS patients were found based on the author's knowledge.

It was reported that miR-143 expression levels were higher in I-B4 positive neurons, while it was downregulated in the inflammatory diseases [32]. The decreased levels of miR-143a in this study may be related to the chronic CNS inflammation that occurs in the MS patients [32]. Additionally, a recent survey has shown that miR-143 acts as a negative regulator of DNA methyltransferase 3A expression in the injured dorsal root ganglia [13].

Several in-vitro studies on cancers have revealed that miR-143 is downregulated; subsequently, its restoration could suppress cancer cell growth and promote apoptosis [33]. It has been reported that the upregulation of miR-373 could induce cancer cell proliferation, migration, and invasion by directly targeting EGFR (Epidermal growth factor receptor). Therefore, miRNA-143 is mainly recognize as a tumor-suppressor microRNA [34]. Since cellular sources of miR-143 are likely different than some miRNAs by mainly being expressed in lymphocytes, while others are specific to other cells; it could be proposed that regulation of miRNA relies on both the timing of expression and the cellular source [16]. There was no related study on the association of expression of miR-373a and 143a with MS. However, this study revealed that both miR-373a and 143a were downregulated in MS patients.

Conclusion

It can be gathered from this study that miR-146a and miR-155a are upregulated, while miR-34a, miR-143a, and miR-373a are downregulated in the serum samples obtained from patients with the relapsing-remitting phase of MS. These microRNAs are potentially related to MS; thus, their aberrant expression may serve an important role in the pathogenesis of MS. Furthermore, they may act as potential diagnostic and prognostic candidates for MS. This also could help to detect the target genes affected by these miRNAs. Moreover, their restoration or inhibition may be a possible therapeutic approach for MS patients. As a final remark, further studies are needed to confirm the exact role of miRNAs in the pathogenesis of MS. This would help to expand the knowledge associated with the microRNAs and MS in order to manage the patients more efficiantly.

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Authors' Contribution

Study concept and design: Nasim Niki Saeidi and Mahdi Goudarzvand. Acquisition of data: Nasim Niki Saeidi and Arezou Dabiri. Analysis and interpretation of data: Nasim Niki Saeidi, Mahdi Goudarzvand. Drafting of the manuscript: Nasim Niki Saeidi and Alireza Moumivand. Critical revision of the manuscript for important intellectual content: Reza Mansouri. Statistical analysis: Reza Mansouri, Mahdi Goudarzvand. Administrative, technical, and material support: Arezou Dabiri and Alireza Moumivand. Study supervision: Mahdi Goudarzvand.

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