Expression Patterns of Micro-RNAs 146a, 181a, and 155 in Subacute Sclerosing Panencephalitis

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Abstract
Subacute sclerosing panencephalitis is caused by persistent brain infection of mutated virus, showing inflammation, neurodegeneration, and demyelination. Although many factors are emphasized in the pathogenesis of subacute sclerosing panencephalitis, the exact mechanism of neurodegeneration remains unknown. Micro-RNAs are small, noncoding RNAs that regulate gene expression at the posttranscriptional levels. Micro-RNAs are essential for normal immune system development; besides they are also implicated in the pathogenesis of many chronic inflammatory disorders. The aim of this study is to investigate the expression patterns of micro-RNAs 146a, 181a, and 155 in peripheral blood mononuclear cells of patients with subacute sclerosing panencephalitis. We enrolled 39 patients with subacute sclerosing panencephalitis and 41 healthy controls. Quantitative analysis of micro-RNAs 146a, 181a, and 155 were performed using specific stem-loop primers followed by real-time polymerase chain reaction. All of 3 micro-RNAs were upregulated in subacute sclerosing panencephalitis patients. In addition, the level of micro-RNA 155 expression was higher in stage 3 patients. But, micro-RNA 146a and 181a expression levels showed no association or correlation with clinically relevant data. Alteration of peripheral blood mononuclear cell micro-RNAs in subacute sclerosing panencephalitis may shed new light on the pathogenesis of disease and may contribute to the aberrant systemic rise in mRNA levels in subacute sclerosing panencephalitis.

Keywords
subacute sclerosing panencephalitis, micro-RNA 146a, micro-RNA 181a, micro-RNA 155

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Subacute sclerosing panencephalitis is persistent and chronic encephalitis secondary to measles virus infection that causes widespread demyelination.¹ The incidence of the disease is inversely related to measles vaccine coverage. The highest incidence of subacute sclerosing panencephalitis relative to the rate of measles is reported in the Middle East, where the rate is 360/100 000 in individuals infected before 1 year of age.² Current reported incidence rates are 21 cases per million population in India, 0.461 per million in Turkey, 11 per million in Japan, and 0.06 per million in Canada.³⁻⁵ The earlier the age at which an individual is exposed to the measles virus, the greater the likelihood of that developing subacute sclerosing panencephalitis because of immune system immaturity.⁶ The disease is pathologically characterized by brain atrophy, infiltrations of inflammatory cells, demyelination throughout the central nervous system, and frequent occurrence of neurofibrillary tangles.⁷

Impaired immune response to measles virus plays an important role in subacute sclerosing panencephalitis. Most patients with subacute sclerosing panencephalitis exhibit a decreased measles virus–specific T helper (Th) 1 cytokine and preserved Th2 cytokine synthesis.¹ Additionally, immunohistochemical studies revealed that the cytokines mediating inflammation are expressed in subacute sclerosing panencephalitis brain lesions. The presence of interleukins IL-1β, IL-2, and IL-6; tumor necrosis factor alpha; and interferon-gamma (IFN-γ) was

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demonstrated in these lesions.\textsuperscript{8,9} Polymorphisms affecting certain interleukins are also thought to take place in the pathogenesis of subacute sclerosing panencephalitis.\textsuperscript{10,11} Neuronal death in subacute sclerosing panencephalitis is also mediated by apoptotic mechanisms triggered by the inflammatory cascade or oxidative stress.\textsuperscript{12,13} Recently antiapoptotic drugs have also been suggested for subacute sclerosing panencephalitis.\textsuperscript{14,15} However, the exact mechanism of neurodegeneration remains still unknown.

Micro-RNAs constitute an abundant class of small noncoding RNAs of \textasciitilde 22 nt in size that act as posttranscriptional regulators of gene expression. A single micro-RNA can modulate the expression of dozens of mRNAs by regulating translational repression or degradation with targeting the 3′, 5′ untranslated regions or coding sequences of specific micro-RNAs.\textsuperscript{16} Alteration of micro-RNA expression and function is associated with a variety of human diseases, including cancer and many inflammatory diseases.\textsuperscript{17} Micro-RNAs are also very important for the development of the immune system and affect developmental outcomes in thymic T cell precursors, influence T regulatory cell development and affect the production of antibodies to thymic-dependent antigens.\textsuperscript{16} Micro-RNAs also control innate and adaptive immune responses. To date, micro-RNA 155 is the most mentioned micro-RNA in inflammation. Previous studies showed that micro-RNA 155 has regulatory functions in different immune cells, including T cells, B cells, and dendritic cells. It has been demonstrated that micro-RNA 146a is one of key molecules in toll-like receptor signaling. Micro-RNA 146 can be induced by proinflammatory stimuli such as lipopolysaccharide in human monocytes, and induced expression of micro-RNA 146a is nuclear factor \textsuperscript{B (NF-\textsuperscript{B}) dependent. Micro-RNA 181a was preferentially expressed in the B-lymphoid cells of mouse bone marrow, and the expression of micro-RNA 181 in hematopoietic stem/progenitor cells led to an increase in B-lineage cells and a decrease in CD\textsuperscript{B}+ T cells.\textsuperscript{16,18}

Several studies have observed changes in expression of micro-RNAs in inflammatory disorders. But the role of micro-RNAs in subacute sclerosing panencephalitis pathogenesis is unknown. In this study, we aimed to investigate expression patterns of micro-RNA 146a, 181a, and 155, which are important players in the regulation of normal immune function and inflammation.

Material and Methods

Study Subjects

Patients followed with a diagnosis of subacute sclerosing panencephalitis in the pediatric neurology divisions of Dokuz Eylül University, School of Medicine, İzmir, and Gaziantep Children’s Hospital, Gaziantep, Turkey, were included in the study. Subacute sclerosing panencephalitis was diagnosed by a pediatric neurologist according to the established diagnostic criteria, that is, clinical features, an increased measles virus antibody titer in the cerebrospinal fluid, and a typical electroencephalograph (EEG) showing periodic slow waves early in the disease. The disease was staged as: stage 1, mental and behavioral symptoms; stage 2, stereotypical jerks; stage 3, rigidity, extrapyramidal symptoms, diminished responses to stimuli; and stage 4, coma, vegetative state, autonomic failure, and akinetic mutism. Age, gender, clinical onset findings, latency period, history of measles vaccination, presence of seizures, current medication history, and brain magnetic resonance imaging (MRI) findings were evaluated. Control subjects were selected from age-matched healthy children. The study was approved by the Ethics Committee of Dokuz Eylül University, School of Medicine, İzmir, Turkey.

Peripheral Blood Mononuclear Cell Isolation

Blood samples of patients with subacute sclerosing panencephalitis who were followed in Gaziantep Children’s Hospital, Gaziantep, were transferred at 4°C to Dokuz Eylül University, İzmir, where the molecular studies were carried out. Peripheral blood mononuclear cells were isolated from patient and control cases by Ficoll separation. In this technique, 6 mL ethylenediaminetetraacetic acid–blood was diluted with phosphate-buffered saline, layered on 4 mL of Biocoll (Biochrom AG, Berlin, Germany) solution, and centrifuged at 830 \times g speed with no acceleration and deceleration. A peripheral blood mononuclear cells layer was obtained and washed twice with phosphate-buffered saline. Cell pellet was finally lysed in Qiazol (Qiagen, Hilden, Germany) and stored at \textasciitilde80°C until RNA isolation.

RNA Isolation

RNA isolation from patient and control samples were made using miRNeasy Mini Kit (Qiagen) following the manufacturer’s instructions. RNA concentration and quality were determined by using a Nanodrop spectrophotometer. \textasciitildeA\textsubscript{260}/\textasciitildeA\textsubscript{280} and \textasciitildeA\textsubscript{260}/\textasciitildeA\textsubscript{230} ratios were used to determine RNA quality.

Quantitative Polymerase Chain Reaction (PCR)

For first strand cDNA synthesis, miScript II RT Kit (Qiagen) was used according to manufacturer’s instruction. A total of 200 ng of RNA from samples were used for reverse transcription. The reverse transcription was performed in MyCycler thermal cycler system (Bio-Rad, Berkeley, CA) for 60 minutes at 37°C, followed by 5 minutes at 95°C. The cDNA was diluted 1:3 for the subsequent quantitative reverse transcription PCR.

The expression of hsa-miR-146a, hsa-miR-155, and hsa-miR-181a was determined using miScript SYBR Green PCR kit (Qiagen). Twenty-microliter reaction samples were prepared using 10 \textmu L QuantiTect SYBR Green PCR Mastermix, 2 \textmu L micro-RNA-specific primer, 2 \textmu L universal primer, 3 \textmu L cDNA, and 3 \textmu L H\textsubscript{2}O. Micro-RNA amplification was performed on LightCycler 480 II (Roche, Penzberg, Germany) using manufacturer-recommended cycling conditions and to test specificity of PCR product, melting curve analysis from 65°C to 95°C was done. Mammalian RNU6 was used for the housekeeping gene. After cycling, threshold cycler values were calculated for each sample and the relative expression of each micro-RNA was calculated by the 2\textsuperscript{ΔΔCT} method.\textsuperscript{19}

Statistical Analysis

SPSS statistics (Version 15 for Windows) was used for statistical analysis. Data are presented as mean \pm standard deviation. Groups were compared by Student \textit{t} test. For analysis of nonparametric data, which included fewer than 30 cases, Kruskal-Wallis and Mann-Whitney \textit{U} tests were used. \textit{P} values less than .05 were considered statistically significant.
Results

Clinical Features of Subacute Sclerosing Panencephalitis Patients

Thirty-nine subacute sclerosing panencephalitis patients (25 boys, 14 girls, mean age 13.8 years) and 41 healthy controls (22 girls, 19 boys, mean age 13.5 years) were included in the study. All patients had increased anti-measles antibody titers with typical electroencephalograph showing periodic slow-wave complexes and clinical features as progressive cognitive decline and stereotypic myoclonus and fulfilled the criteria for subacute sclerosing panencephalitis. The mean age at diagnosis was 9.1 years. Twenty-nine (74%) patients had a history of measles infection, and the mean age of measles infection was 1.4 years. Seven patients (18%) were not vaccinated. Mean latency period was 12.5 years, and mean duration of the illness was 4.7 years. Three patients (8%) were in stage 1, 6 patients (15%) patients were in stage 2, and 30 patients (77%) were in stage 3. The most common complaint was drop attacks (n = 18, 46%), followed by mental and behavioral symptoms (n = 15, 38%), generalized seizures (n = 4, 10%), and cranial neuropathies (n = 2, 6%). Thirty-three patients (85%) had epilepsy and were using an antiepileptic drug. Twenty-seven patients (70%) were using Isoprinosine as an immunomodulatory agent. Nine patients (23%) had abnormal brain MRI findings. Clinical features of the patients are summarized in Table 1.

Table 1. Clinical and Radiologic Features of the Subacute Sclerosing Panencephalitis Patients.

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<th>Age at diagnosis (y)</th>
<th>Age of measles infection (y)</th>
<th>Measles vaccination</th>
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Abbreviations: F, female; M, male; MRI, magnetic resonance imaging; N/A, information not available; SSPE, subacute sclerosing panencephalitis; +, present; –, absent.
Table 2. Micro-RNA 146a, 155, and 181a Expression Changes in Subacute Sclerosing Panencephalitis.

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<tr>
<td>155</td>
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<tr>
<td>181a</td>
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Expression Analysis of Micro-RNA 146a, 181a, and 155 in Subacute Sclerosing Panencephalitis Patients and Controls

Micro-RNA expression analysis revealed an alteration in subacute sclerosing panencephalitis patients as compared with controls. The expression levels of micro-RNAs 146a, 181a, and 155 were significantly increased in subacute sclerosing panencephalitis patients as compared to controls (3.13 ± 6.61 vs 0.30 ± 0.26, \( P = .0001 \); 1.80 ± 2.53 vs 0.47 ± 0.29, \( P = .0001 \); 2.05 ± 3.54 vs 0.67 ± 0.59, \( P = .003 \)). Micro-RNA fold change was also significantly higher in the subacute sclerosing panencephalitis group (Table 2). In addition, micro-RNA 155 expression was significantly higher in stage 3 patients as compared to stage 1 patients (2.44 ± 3.94 vs 0.37 ± 0.18, \( P = .009 \)). Although micro-RNA 155 expression was also higher in stage 3 when compared to stage 2, this was not statistically significant (2.44 ± 3.94 vs 0.99 ± 1.39, \( P = .062 \)). No differences were found considering micro-RNA 146a and 181a expression between different stages of subacute sclerosing panencephalitis patients. No correlation was found between micro-RNA expression levels and duration of illness, latency period, brain MRI findings, presence of seizures, and current antiepileptic and immunomodulatory treatment.

Discussion

Subacute sclerosing panencephalitis is a slowly progressive central nervous system complication of measles. Patients with subacute sclerosing panencephalitis exhibit a decreased measles virus–specific Th1 cytokine and preserved Th2 cytokine synthesis. Most patients with subacute sclerosing panencephalitis also had a defect in measles virus specific production of interferon-gamma. Micro-RNAs are important regulators of immune cell development and as well as immune response. Micro-RNA 155 has powerful regulatory functions in a wide variety of immune cells and it is also one of the highly implicated micro-RNAs in autoimmunity. Downregulation of micro-RNA 155 leads to enhanced levels of Th2 cells and related cytokines. On the other hand, overexpression of micro-RNA 155 in activated CD4+ T cells promotes Th1 differentiation and, consistently, the frequency of interferon-gamma–positive cells significantly increase. In our study, micro-RNA 155 expression was significantly higher in patients with subacute sclerosing panencephalitis as compared to controls. Because patients with subacute sclerosing panencephalitis have a dominant Th2 response to measles virus, increased micro-RNA 155 expression in subacute sclerosing panencephalitis patients may be a compensatory mechanism to suppress Th2 responses and activate Th1 cells. Increased micro-RNA 155 expression in subacute sclerosing panencephalitis is also compatible with the results of Aydin et al., who found decreased levels of IL-4 along with peripheral Th1 activation. Micro-RNA 155 expression was significantly higher in patients with stage 3 when compared to stage 1 and 2 patients. On the other hand, no correlation was found between micro-RNA 155 expression levels and duration of illness, latency period, brain MRI findings, presence of seizures, and current antiepileptic and immunomodulatory treatment. These findings suggest that micro-RNA 155 may be used as an independent marker in clinical staging of subacute sclerosing panencephalitis.

Micro-RNA 181a also has important functions in modulation of the immune system and is also a marker of apoptosis. Overexpression of micro-RNA 181a in mature T-cell lymphocytes augments T-cell receptor sensitivity. Increased expression of micro-RNA 181a in patients with subacute sclerosing panencephalitis may be due to reactivation of measles virus, and increased T-cell receptor sensitivity may be needed to eliminate virus by T cells. On the other hand, apoptosis of various cell types contributes to the neuropathogenesis of measles virus infection in the human central nervous system, either as a direct effect of viral infection or cytokine-mediated responses. Lipid peroxidation and oxidative stress are also well-known causes of neurodegeneration in subacute sclerosing panencephalitis. Thus, increased expression of micro-RNA 181a in patients may also be a sign of apoptosis and increased oxidative stress.

It has been reported that micro-RNA 146a is predominantly expressed in T regulatory cells and its expression is very critical for their suppressor function. The deficiency of micro-RNA 146a results in a failure for controlling T regulatory cell–mediated regulation of Th1 responses. On the other hand, micro-RNA 146a is also a negative-feedback regulator of the astrocyte mediated inflammatory response. Increased expression of micro-RNA 146a in patients with subacute sclerosing panencephalitis may be a compensatory rise to suppress measles virus reactivation and uncontrolled inflammation.

Our study also has some limitations. The only control group in our study was healthy controls. Upregulation of micro-RNAs may also be due to epileptic seizures, anticonvulsant medications, or immune dysfunction in general. Further studies including epilepsy and autoimmune disease control groups should make the findings more interpretable and valuable.

In conclusion, micro-RNAs 146a, 181a, and 155 may be involved in subacute sclerosing panencephalitis pathogenesis that is characterized by abnormal immune response. Altered micro-RNA expression levels may be an adaptive response by the immune system, and the changed micro-RNA
expression levels may be an effect of the disease rather than a cause. Because micro-RNAs have the potential to become novel drug targets in virally induced infections, the roles of micro-RNAs in subacute sclerosing panencephalitis pathogenesis must be studied in detail.

Author Contributions

UY reviewed the patient’s medical charts and wrote the first draft of the manuscript. UKT and ŞG made microRNA measurements. KBÇ, YT, and EB collected data and modified subsequent drafts. SHK supervised and provided mentorship for completion of the manuscript.

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Ethical Approval

The study received internal ethical approval from Dokuz Eylül University School of Medicine, Izmir, Turkey (ethical approval number 2012/10-13).

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