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Original article

The significance of microRNAs in the course of rDD

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ABSTRACT

Background: In recent years, special attention in genetic studies dedicated to the development of various diseases, including mental disorders, has been paid to micro ribonucleic acids (miRNA, microRNA). As an object of our analysis we have selected the miRNAs which – due to the profile of their activity – may be significant in the aetiology and course of recurrent depressive disorders, i.e. miRNA-370, miRNA-411, miRNA-433, miRNA-487b and miRNA-539.
Methods: The examined population included 138 patients suffering from depression and 95 individuals from the control group (CG). The subjects suffering from depression were divided into two sub-groups: ED-I group (46 patients), rDD group (92 patients).
Results: No significant statistical differences were observed between the ED-I and rDD group for all the variables included in the analysis. No significant interrelation was noticed between the number of depression episodes, the severity of depressive disorders and the expression of miRNA selected. Results of the analysis indicate statistically significant differences between the control subjects and the patients with symptoms of depression in terms of all the variables analysed.
Conclusions: 1. There is no significant difference in miRNAs expression between patients with recurrent depressive disorders and those in the first episode of depression. 2. The differences in terms of expression of the analysed variables between the subjects with symptoms of depression and healthy individuals were confirmed.

Introduction

Recurrent depressive disorder (rDD) is a disease of multifactorial aetiology. Its possible causes include neurotransmission disorders, stress, inflammatory factors and genetic factors [1,2]. In recent years, special attention in genetic studies dedicated to the development of various diseases, including mental disorders, has been paid to micro ribonucleic acids (microRNAs, miRNAs).

MicroRNAs are a family of single-stranded, approximately 20-nucleotide, untranslated, endogenous RNA molecules, which are produced from double-stranded precursors. They are present in plants, animals and human cells [3,4]. Their role, observed in nuclear organisms, is to reduce gene expression at the stage of genetic information translation by means of promoting messenger-RNA (mRNA) degradation or inhibiting translation [5]. A single miRNA molecule can simultaneously control expression of hundreds of target genes [6]. MiRNAs play a very important role in cell division, differentiation, apoptosis, angiogenesis, oncogenesis [7] as well as regulate inflammatory processes [8,9]. MicroRNAs are highly expressed in neurons, where they regulate brain development processes, including neurogenesis, neuronal proliferation, metabolism and apoptosis [10]. The last of the aforementioned functions of miRNAs may be significant from the perspective of the aetiology and course of depression.

As an object of our analysis we have selected the miRNAs which – due to the profile of their activity – may be significant in the aetiology and course of recurrent depressive disorders, i.e. miRNA-370, miRNA-411, miRNA-433, miRNA-487b, miRNA-539. The aim of our analysis was to evaluate expression of the selected miRNAs in depressed patients and healthy subjects, and to compare expression of the selected miRNAs between patients with a first episode of depression (ED-I) and recurrent depressive disorders (rDD).

miRNA-370 is a tumour suppressive factor which targets multiple critical oncogenic pathways [11]. Overexpression of miRNA-370 significantly inhibits cell proliferation and induces cell apoptosis by targeting tumour necrosis factor receptor-associated factor 4(TRAF4) [12]. In the case of miRNA-411, overexpression inhibits expression of metalloproteinases-13

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(MMP-13, participates in neuroprotection and neurorepair) [13], while overexpression of microRNA-539 suppresses expression of MMP-8 (released in places of inflammation and considered the main regulator of chemokine activity) [14]. MicroRNA-433 may be of importance in the aetiology of the Parkinson's disease (PD) [15]. Overexpression of microRNA-487b is observed in HIV carriers, in people suffering from malignant diseases [16] and in patients after an acute ictal episode [17]. Additionally, miR-487b plays a negative regulatory role in macrophages by controlling the levels of IL-33 transcript and protein to fine-tune innate immune host defense and proinflammatory responses of these cells [18]. The microRNAs selected by us may potentially be of significance in the processes of brain neuroplasticity, by regulating synaptic plasticity and neurotransmission processes, which mediate stress-related disorders, including depressive disorders [19,20]. Therefore, the miRNAs selected by us are associated with the factors that were examined many times in the context of depression occurrence, among others inflammatory factors [21,22].

Table 1 presents a summary of current research studies regarding expression of selected miRNAs in mental disorders. A comprehensive search was performed in the PubMed/MEDLINE electronic databases from the very beginning until August 1, 2016. We looked for terms such as: miRNA-370, miRNA-411, miRNA-433, miRNA-487b, miRNA-539, depression and depressive disorders. Only the articles written and published in English were taken into consideration. Based on their overall quality of methodology, the articles were selected and included in our study. Moreover, we took into account relevant *meta*-analyses. There are only few publications dedicated to the role of miRNAs in the aetiology and course of mental disorders.

Materials and methods

Participants

The study was conducted on 233 individuals—138 patients suffering from depression and 95 individuals from the control group (CG). The subjects suffering from depression were divided into two sub-groups: ED-I group—46 patients, rDD group—92 patients.

The patients were selected on the basis of the inclusion criteria for ED and rDD specified in ICD-10 (F32.0–7.32.2, F33.0–F33.8) [30]. All the subjects were examined during their hospitalisation and no symptoms of concurrent somatic diseases or axis I and II disorders other than depressive episodes were diagnosed in them. Inflammatory or autoimmune disorders, central nervous system traumas and unwillingness to give informed consent were additional exclusion criteria. Patients with familial prevalence of mental disorders other than recurrent depressive disorders were excluded from the examined group. A case history was obtained from each patient using the standardised Composite International Diagnostic Interview (CIDI) [31] prior to the start of the experiment.

The patients from the ED-I group had been qualified for participation in the study before antidepressant pharmacological treatment started, while the patients from the rDD group were qualified for the study during the process of pharmacological therapy modification. The subjects from the latter group were treated with agents from the group of selective serotonin reuptake inhibitors (SSRI).

The CG comprised healthy subjects without any familial cases of mental disorders. The group of healthy controls was composed of community volunteers who were qualified for the study based on the criteria of the psychiatric CIDI interview [31]. Individual suffering from other psychiatric diseases, axis I and II disorders, neurological disorders, or diagnosed with substance abuse or dependence, were excluded from the experiment. Individuals with familial prevalence of any axis I or II mental disorders were excluded from the control group.

The control subjects or depressed patients were not treated with the use of the drugs known to influence lipid metabolism, immune responses or endocrine functions. The control subjects had not been taking any medications for at least 2 months prior to blood sampling.

The individuals taking part in the experiment were native Poles from central Poland (not related). They were chosen for the study group at random without replacement sampling. Participation in the study was voluntary. Before making a decision to participate in the study, the subjects were informed of the purpose, assured of the voluntary character of the experiment and guaranteed that their personal data would be kept in secret. Written informed consent was given in accordance with the study protocol, approved by the Bioethical Committee of the Medical University of Lodz (No. RNN/272/15/KE).

Methods

Depression severity was evaluated and classified using the 21-item Hamilton Depression Rating Scale (HDRS) [32,33]. Each patient was examined by the same psychiatrist. Peripheral blood was used as material in the genotype study (in volumes of 5 ml on EDTA).

Table 1
Research regarding the role of miRNA-370, miRNA-411, miRNA-433, miRNA-487b and miRNA-539 in mental disorders.

Schizophrenia		Bipolar affective disorders	
miRNA-370	Smalheiser et al. [23]	miRNA-370	Smalheiser et al. [23]
miRNA-411	–	miRNA-411	–
miRNA-433	Gardiner et al. [24]	miRNA-433	–
miRNA-487b	Gardiner et al. [24]	miRNA-487b	–
miRNA-539	–	miRNA-539	–
Depression		**Alzheimer's disease (AD)/Parkinson's disease (PD)**	
miRNA-370	Smalheiser et al. [23]	miRNA-370	Sheinerman et al. (AD) [26]
miRNA-411	–	miRNA-411	–
miRNA-433	Belzeaux et al. [25]	miRNA-433	Wang et al. (PD) [27] de Mena et al. (PD) [28] Haghnejad et al. (PD) [29]
miRNA-487b	–	miRNA-487b	–
miRNA-539	–	miRNA-539	–