Journal of Psychiatric Research 115 (2019) 158–164

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Altered microRNA 5692b and microRNA let-7d expression levels in children and adolescents with attention deficit hyperactivity disorder

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ARTICLE INFO

Keywords:
Attention deficit hyperactivity disorder
Micro RNA
Children
Adolescent
Genetics
Psychiatry

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder. Its etiology is not clearly understood yet, but neurobiological, genetic and environmental factors are shown to play a role. The relationship between ADHD and miRNAs has been studied quite recently, and few studies have been conducted up to now. In this study, peripheral blood expression levels of miR-5692b, miR-let-7d, miR-124-3p, miR-4447 and miR-107 of 30 children and adolescents with combined type ADHD were compared to 30 healthy controls to understand the roles of these miRNAs in the ADHD etiopathogenesis. Compared to controls, levels of miR-5692b ($p = 0.006$) were found higher and levels of miR-let-7d ($p = 0.017$) were found lower in the ADHD group. There was no significant difference in terms of miR-124-3p, miR-4447, and miR-107 levels between the groups. In conclusion, our findings support other studies suggesting the importance of miRNAs in the pathogenesis of ADHD. Regarding the regulatory role of miRNAs in gene regulation, their contribution to etiopathogenesis and heterogeneity of ADHD should be investigated further.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), which is characterized by inattention, hyperactivity, and impulsivity, inappropriate with the age and development, is a complex and multi-factorial disorder (American Psychiatric Association, 2013). ADHD is the most common neurodevelopmental disorder in childhood (Leung and Hon, 2016) with a prevalence of 5.9%–7.1% (Willcutt, 2012) in children and adolescents. It is more common in boys than in girls (3–10:1 respectively) (Biederman, 2005). ADHD is considered to be one of the most inherited psychiatric disorders with a 76% heritability (Faraone et al., 2005). However, no single genetic risk factor has been identified yet; and thus, it is noted that ADHD develops as a result of multiple genetic risk variants' interaction (Thapar et al., 2013).

The genes suggested in the ADHD etiology are related to heterogenic neural modulation processes (Cristino et al., 2014; Gao et al., 2014; Zayats et al., 2015) which are probably affected by an interplay between genetic and environmental factors (Srivastav et al., 2017). In developmental and psychiatric processes, this has critical importance because small changes in both genetic and environmental factors may lead to psychiatric disorders (Dudley et al., 2011). Therefore many common phenotypic alterations are the results of gene regulatory element variations (Mostafavi-Abdolmaleky et al., 2011; Stranger et al., 2007). The interference of non-coding microRNAs (miRNA or miR) is one of the major epigenetic regulatory mechanisms involved in psychiatric disorders (Mostafavi-Abdolmaleky et al., 2011). In this context, miRNAs have emerged as potential agents and a significant number of miRNA dysregulations have been demonstrated to be associated with neuropsychiatric disorders (Abdolmaleky, 2014; Alural et al., 2017; Geaghan and Cairns, 2015; Maffioletti et al., 2014; Sun and Shi, 2015).

The impact of miRNA's in the etiology of ADHD has been a topic of interest in the past few years. A recent review of ADHD and miRNA studies have reported a significant difference in miRNA levels between the ADHD and control groups in both human and animal studies, and implicated miRNAs' role in ADHD etiopathogenesis. It was also noted in the review that a meta-analysis was not possible, due to the limited number of studies and the absence of overlap between them (Srivastav et al., 2017). Besides, two miRNA related findings attracted attention

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https://doi.org/10.1016/j.jpsychires.2019.05.021
Received 28 January 2019; Received in revised form 19 April 2019; Accepted 20 May 2019

among the conducted studies' results. One was a decrease in miR-107 levels (miR-107 was believed to be related to minimal brain change in ADHD) which was also suggested as a candidate biomarker (Kandemir et al., 2014) and the other was an increase in miR-let-7d levels (miR-let-7d was believed to have a role in neuronal adaptations) (Wu et al., 2015) in ADHD patients.

In this study, we wanted to demonstrate the expression differences of miR 124-3p, miR 4447, and miR 5692b between combined type ADHD patients and a healthy control group, along with the two other miRNAs which were previously reported to be related with ADHD (miR-107 and miR let-7d) (Kandemir et al., 2014; Wu et al., 2015) to uncover the potential roles of these miRNAs in the etiology of combined type ADHD. miR-107 and miR-let7d were chosen for the study with the aim to replicate the previously shown association (Kandemir et al., 2014; Wu et al., 2015). The other three miRNAs were selected in light of the literature data about the ADHD neurobiology. miRNA database (mirbase.org) was used to find out the related miRNAs targeting the determined proteins or receptors. To say in a more detailed way; firstly, we investigated miR-5692b levels, because one of its targets is Homer1a (Dweep and Gretz, 2015; Wong and Wang, 2015). Homer 1a is an important scaffolding protein in Homer family (Qiu et al., 2010) and has been found to be involved in dopamine, norepinephrine, and glutamate signaling pathways (De Bartolomeis and Tomasetti, 2012; Iasevoli et al., 2009). The possible role of Homer1a in ADHD was demonstrated in rats with artificial Homer1a specific miRNA (Yang et al., 2013). Secondly, miR-124-3p is included due to targeting the Dopamine D4 receptor (*DRD4*) gene (Dweep and Gretz, 2015). DRD4 has been widely observed in frontal-subcortical networks that play a role in the pathophysiology of ADHD (Faraone and Biederman, 1998). Thirdly, Dopamine transporter (*DAT1*) gene is a target of miR-4447 (Wong and Wang, 2015). Stimulants in ADHD treatment blocks dopamine transporter; this makes DAT1 a candidate gene for ADHD (Spencer et al., 2000). *DAT1* and *DRD4* genes are commonly studied in the researches investigating the etiopathogenesis of ADHD (Faraone et al., 2005). Meta-analyses pointed to an association between these genes and ADHD (Faraone et al., 2001; Li et al., 2006; Purper-Ouakil et al., 2005; Yang et al., 2007). To the best of our knowledge, this is the first study to evaluate the associations between combined type ADHD and miR 124-3p, miR 4447, and miR 5692b to date. The list of miRNAs included in the study and the rationale to include them are shown in Table 1.

2. Materials and methods

2.1. Patients and controls

The case group included 30 children and adolescents (6–17 years) who were assessed at Pamukkale University Child and Adolescent Psychiatry Clinic. All the children were diagnosed with combined type ADHD according to DSM-5 (American Psychiatric Association, 2013) diagnostic criteria, and they were all medication naïve. ADHD diagnosis was confirmed by using the ADHD Child Evaluation (ACE) semi-structured interview (Young, 2015). Teacher and parent forms of "Turgay DSM-IV based Child and Adolescent Behavior Disorders Screening and Rating Scale" (T-DSM-IV-S) (Turgay, 1994) were also filled to screen the ADHD symptoms. The control group consisted of 30 healthy volunteer children and adolescents. The participants who were asked to participate in the study to consist the control group were selected among the new outpatient referrals who admitted with mild issues such as developmental stage-specific difficulties and had not diagnosed with any psychiatric disorder or any chronic medical condition. The volunteers were invited to the DSM-5 based clinical interview to confirm the absence of any psychiatric diagnosis to be included in the control group. All participants underwent clinical evaluations according to DSM 5 in the child and adolescent psychiatry outpatient clinic by one consistent interviewer, and their socio-demographic data, diagnoses, medication histories, and accompanying psychiatric and physical disorders were noted. For both ADHD and control groups, exclusion criteria were a history of psychotropic medication, intellectual disability, and the presence of chronic disease diagnosis (diabetes mellitus, asthma, epilepsy, etc …). Except for the combined type of ADHD in the case group, any psychiatric disorder was an exclusion criterion for both groups. Due to the genetically heterogeneous nature of ADHD (Todd and Lombroso, 2003), some subtypes were reported to have stronger associations with some genetic factors than the others (Smith, 2010; Waldman et al., 1998), and our relatively small study sample, only the patients with combined type ADHD were included with the aim to create a homogenous group as much as possible. Based on the studies demonstrating the effects of psychiatric disorders (Haramati et al., 2011; Whalley et al., 2012; Xu et al., 2010), physical diseases (Butz et al., 2016; Chistiakov et al., 2016; Jimenez-Mateos and Henshall, 2013; Wu et al., 2014) and psychotropic drugs (Seo et al., 2014) on miRNA expression levels, we excluded any individuals with any physical or psychiatric comorbidities (including oppositional defiant disorder), and psychotropic drug use history. Peripheral blood samples have been used in clinical studies because brain tissue is not readily accessible. The transcriptional changes in peripheral mononuclear cells have been shown to reflect molecular and cellular changes in the brain (Fan et al., 2015; Fisar and Raboch, 2008). Based upon the previous literature data we expected to show miRNA level variations from the blood samples.

The study was approved by the Medical Ethics Board of Medical School of Pamukkale University and performed in accordance with the Declaration of Helsinki. The parents' of the participants signed written informed consent prior to the study procedures. Blood sampling was made once for both groups.

2.2. Molecular genetic studies

Peripheral blood samples were collected from each study participant (2 mL from each). Total RNA was obtained from whole peripheral blood with EXIQON miRCURY RNA Isolation Kit (Exiqon A/S, Vedbaek, Denmark) according to the instructions of the manufacturer. EXIQON miRCURY LNA Universal RT microRNA PCR (Exiqon A/S, Vedbaek, Denmark) kit was used for cDNA synthesis. The RNA samples were adjusted to contain 20 ng/μL of template RNA, and 5x Reaction buffer, nuclease-free water, enzyme mix, and RNA spike-in were added to make a total reaction volume of 10 μL. The mixture was incubated in a thermal cycler at 42 °C for 60 min followed by inactivation of reverse transcriptase for 5 min at 95 °C. Template cDNA samples were diluted to 1:80 with nuclease-free water for real-time PCR. Diluted template cDNA, PCR Master Mix, and PCR primers set (Table 2) were added to microtubes to a final volume of 10 μL. Samples were prepared for each

Table 1
The miRNAs and their rationale for the study.

miRNA	The rationale for the study	Reference
miR-5692b	Targets Homer1a	(Dweep and Gretz, 2015; Wong and Wang, 2015)
miR-let-7d	Levels increased in ADHD	Wu et al. (2015)
miR-107	Levels decreased in ADHD	Kandemir et al. (2014)
miR-124-3p	Targets *DRD4*	Dweep and Gretz (2015)
miR-4447	Targets *DAT1*	Wong and Wang (2015)

Table 2
Primer sequences of the miRNAs analyzed by qRT-PCR.

miRNA	Target sequence	Sequence reference
U6	Reference gene primer set	
hsa-miR-5692b	AAUAAUAUCACAGUAGGUGU	MIMAT0022497
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	MIMAT0000065
hsa-miR-124-3p	UAAGGCACGCGGUGAAUGCC	MIMAT0000422
hsa-miR-107	AGCAGCAUUGUACAGGGCUAUCA	MIMAT0000104
hsa-miR-4447	GGUGGGGGCUGUUGUUU	MIMAT0018966

Table 3
Real-time PCR cycle conditions.

Process step	Instrument Settings
Polymerase Activation/Denaturation	95 °C, 10 min
Amplification Cycles	40 cycles at 95 °C, 10 s 60 °C, 1 min, 72 °C, 8 s, ramp-rate 1.6 °C/s6

miRNA and control miRNA (U6), and real-time PCR amplification was performed with the following protocol: polymerase activation/denaturation at 95 °C for 10 min, followed by 40 amplification cycles at 95 °C for 10 s, at 60 °C for 1 min, at 72 °C for 8 s (ramp-rate 1.6 °C/s^6), using a QIAGEN Corbett Rotor-Gene 6000 (Corbett Research, Australia) (Table 3). Cq and Ct values of all miRNAs were obtained using Rotor-Gene Q Series Software. Using ΔΔCt method, expression levels of miR-5692b, miR let-7d, miR 124-3p, miR-107, and miR-4447 were compared between the groups.

2.3. Statistical analysis

Statistical analysis was performed with SPSS 15.0. Software (Chicago, SPSS Inc.). Descriptive data were obtained by using descriptive statistical methods such as mean, standard deviation, median, frequency, ratio, minimum, and maximum. Quantitative data comparison between groups was made using Student's t-test for parameters with a normal distribution, and Mann-Whitney *U* test for parameters with a non-normal distribution. Pearson Chi-square test, Fisher's exact test, and Yates' continuity correction test were used to perform qualitative data comparison. A *p*-value < 0.05 was considered statistically significant for all statistical tests. For fold change analysis We first calculated the relative expression (E) of the target miRNAs using the ΔΔCt method in which U6 miRNA was used as the reference. Then we used these relative expression values to calculate the expression levels as ratio figures using the following formula: $(E_{target})^{\Delta C\ (control\ -\ ADHD)}_{t\ target} / (E_{Ref})^{\Delta C\ (control\ -\ ADHD)}_{t\ Ref}$.

3. Results

There was no statistically significant difference in sex and age between the patient and the control groups ($p > 0.05$). Table 4 presents the age and sex characteristics of the study participants. Socio-demographic characteristics (parents' education level, family structure, physical and psychiatric disease in family, household income) were similar in both groups, and no known ADHD related risk factors (prematurity, childbirth type, gestational weight at birth, exposure to smoking during pregnancy, and maternal disease during pregnancy) were found to be statistically significantly different between the groups in the sample of this study (Supplementary Tables 1, 2, and 3). The levels of miR-5692b were statistically significantly higher, and the levels of miR-let-7d were significantly lower in the ADHD group compared to controls ($p < 0.05$) (Table 5, and Fig. 1). The relative levels of miR-107, miR124-3p, miR-5692b, miR-let-7d, miR-4447 in ADHD group were respectively 1.13, 4.81, 3.07, 0.26, and 1.26 as fold changes compared to the control group (Fig. 2).

The relative level of miRNAs in ADHD group was shown as fold changes compared to the control group.

4. Discussion

ADHD is a major health problem and its etiology has not been fully elucidated yet (Thapar et al., 2009). Recent evidence suggests that miRNAs may play a role in the etiology of ADHD (Srivastav et al., 2017). In this study, we aimed to show an association of miR-5692b, miR-let-7d, miR-124-3p, miR-4447 and miR-107 levels with ADHD. Compared to controls, we found an increase in miR-5692b levels ($p = 0.006$) and a decrease in miR-let-7d levels ($p = 0.017$) in the ADHD group. However, there were no statistically significant differences between the groups regarding the miR-124-3p, miR-107, and miR-4447 expression levels. To the best of our knowledge, we demonstrated an association between miR5692b levels and ADHD for the first time.

To the extent of our knowledge, there has been no study investigating the *in vivo* relationship between any endogenous miRNAs targeting Homer 1a and ADHD, and this is the first report demonstrating an association between ADHD and miR-5692b levels. ADHD group had 3.07 fold higher miR-5692b levels than the controls, and the two group comparisons achieved statistical significance level. Homer 1a, targeted by miR-5692b (Dweep and Gretz, 2015; Wong and Wang, 2015), is one of the most important scaffolding proteins in Homer family (Qiu et al., 2010). It has been shown to take part in dopamine, norepinephrine, and glutamate signaling pathways (De Bartolomeis and Tomasetti, 2012; Iasevoli et al., 2009), as well, in synaptic rearrangement through multiple mechanisms (De Bartolomeis et al., 2014; Tu et al., 1999). There is an important amount of data in the literature, suggesting Homer 1a- ADHD association. Firstly, Homer 1a neuronal protein was found to be significantly decreased in the prefrontal cortex (PFC) of spontaneously hypertensive rats (Hong et al., 2009), which is currently accepted as an animal model for studying ADHD (Kantak et al., 2008). Also, Homer 1 knockout mice showed impairments in learning, and working memory (Jaubert et al., 2007; Szumlinski et al., 2005), and an increase in the expression of Homer 1a was associated with improved cognitive function (Lominac et al., 2005). Furthermore, methylphenidate (MPH), the first line treatment of ADHD (Leonard et al., 2004), has been reported to increase Homer 1a expression (Hong et al., 2011, 2009; Zhang et al., 2007) and might contribute to the therapeutic efficacy through Homer 1a expression in attention-related corticostriatal pathways (Yano and Steiner, 2005). The only miRNA study that investigated Homer 1a was an animal study by Yang et al. The authors found a significant decrease in striatal and hippocampal

Table 4
Sex and age characteristics.

	ADHD (n = 30)	Controls (N = 30)	Comparison
Sex male/female	23/7	16/14	$p = 0.104$ ($\chi^2 = 3.59$)
Age mean ± SD (years)	9 ± 2.77	10.4 ± 3.64	$p = 0.216$ ($z = -1.238$)
Age median (min-max)	8 (6–16)	10.5 (6–17)	

For sex data analyses χ^2 test and Yates' continuity correction were performed, for age data analyses Mann Whitney *U* test was performed ($p < 0.05$ statistically significant).

Table 5
Comparison of miRNA levels.

	ADHD (n = 30)		Controls (n = 30)		z	p
	Mean ± SD	Median	Mean ± SD	Median		
miR-5692b	928.41 ± 1563.13	344.05	126.69 ± 187.72	4.98	−2.735	0.006
miR-let-7d	2.54 ± 2.09	1.75	9.83 ± 34.16	2.58	−2.381	0.017
miR-124-3p	1066.6 ± 2198.44	0.64	32.82 ± 97.51	0	−1.301	0.193
miR-4447	527.08 ± 1079.85	50.52	417.6 ± 615.35	163.21	−1.042	0.297
miR-107	9.67 ± 15.23	4.42	8.57 ± 6.51	7.52	−1.013	0.311

Mann Whitney *U* test was performed ($p < 0.05$ statistically significant).

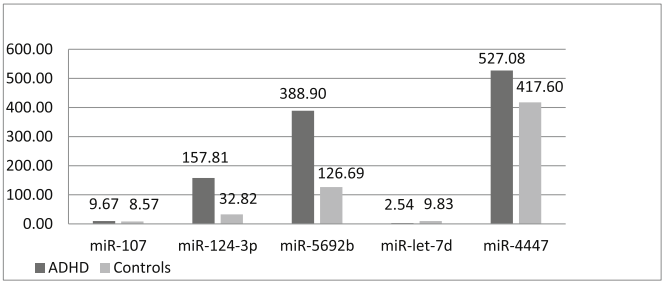

Fig. 1. Mean miRNA expression levels.

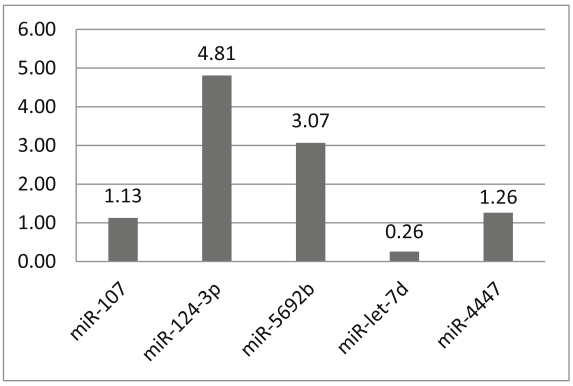

Fig. 2. Fold changes (ADHD/Control).

Homer1a expression in rats which were given a lentiviral vector containing Homer 1a-specific miRNA by intracerebroventricular injection. These rats exhibited increased locomotor activity and non-selective attention, as well as impaired learning and memory abilities. These are in line with the behavioral findings of ADHD animal models. Moreover, these abnormal behaviors were ameliorated by MPH (Yang et al., 2013). Based on the findings of our study and the previous literature findings, it can be suggested that increased miR-5692b levels that act to alter Homer 1a expression may be associated with ADHD. We should note that our sample size was relatively small to generalize this association. Thus, this finding should be interpreted cautiously, until it is replicated in future studies.

Another important finding of the study was the decreased miR-let-7d levels in the ADHD group in comparison to the controls. Let-7 was found as the first known human miRNA (Roush and Slack, 2008) Let-7 and its family members have been defined as brain miRNAs that play a role in neuronal differentiation (Pasquinelli and Ruvkun, 2002; Rougvie, 2001). The activity of let-7 is increased in parallel with neuronal differentiation (Wulczyn et al., 2007), and let-7d stops cell proliferation to progress the cells in the direction of neuronal differentiation (Zhao et al., 2013). It is known that synaptic density in the brain increases with age, and neuronal firing creates a permanent network that is established by repetitive experiences. Connections no longer being used are eliminated with synaptic pruning process (Gao et al., 2012). Cell proliferation, neuronal differentiation, and migration of neurons to target regions are almost complete in the first few years of life in humans. Then, beginning from middle childhood, brain region-specific overproduction and pruning of synapses and receptors occur (GIEDD, 2004). The synaptic density of the PFC reaches its peak at 3.5 years but gradually decreases during adolescence (Huttenlocher and Dabholkar, 1997). It is reported that the problems during the selection of the rapidly increasing prefrontal cortex synapses in childhood are contributing to the emergence of ADHD and its life-long physiopathology. This abnormal synapse structure is involved in the neurobiological model of ADHD (Stahl, 2013). Synaptic overproduction and pruning errors may also explain the differences seen as gray matter density changes in brain regions in children with ADHD when compared to controls (Sowell et al., 2003; Teicher, 2001). Overproduction of synapses and receptors occurs in a lesser extent in girls than boys (Andersen, 2003). This was reported as one of the many reasons for girls being less affected by ADHD than boys in childhood (Teicher, 2001). It's hypothesized that the significantly decreased miR-let-7d levels that we reported in the ADHD patients, may contribute to the ADHD pathogenesis through the neuronal differentiation and synaptic pruning errors. In contrast to decreased miR-let-7d levels that we found in our study, two previous studies identified an association between increased miR-let-7d levels and ADHD in humans [20], and rats [68]. In spontaneously hypertensive rats' PFC, increased levels of miR-let-7d were shown to decrease tyrosine hydroxylase expression which is important in dopamine metabolism, through down-regulation of galectin-3; linking the miR-let-7d to ADHD (Wu et al., 2010). Similarly, in ADHD children and adolescents, high levels of miR-let-7d and down-regulated galectin-3 levels were found to be significantly associated with ADHD (Wu et al., 2015). Based on the heterogeneous nature of ADHD, it may be possible that miR-let-7d may have an impact on the ADHD pathogenesis in multiple ways and via different pathways. It is known that miR-let-7d plays either physiological and pathological role in the brain, backing this hypothesis (Di et al., 2014). Another possible explanation for these contradicting findings between the studies could be that different genetic backgrounds and stressors have unequal effects on gene expression. Once more, we should emphasize that this is a preliminary finding and our comments should be taken into account by keeping the limitation of small sample size in mind. Future studies will help to clarify any possible association of miR-let-7d and ADHD.

This is the first study to evaluate the miR-124-3p levels in ADHD patients. miR-124 is the most abundant miRNA in the brain (Sun et al., 2015). miR-124-3p targets *DRD4* gene (Dweep and Gretz, 2015), an

important candidate gene for ADHD (Faraone et al., 2001; Li et al., 2006). Mature miR-124 was shown to cause changes in *DRD4* regulation, which is one of the various protein-encoding genes related to neuro signalization and neuroplasticity (Forero et al., 2010; Oak et al., 2000). Animal studies showed that neuronal differentiation was enhanced by the effect of miR-124 in the developing brain regions and the spinal cord (Cheng et al., 2009; Conaco et al., 2006; Visvanathan et al., 2007). miR-124 binding regions of several genes were associated with cognitive performance (Lim et al., 2005). In accordance, miR-124 was associated with learning and memory-related processes and long-term plasticity of the synapses in the mature nervous system (Rajasethupathy et al., 2009). Regarding these, we would expect to find a significant difference between the groups, since we know that ADHD is a neurodevelopmental disorder in which neurocognitive processes are distorted. As well, higher values were observed in the ADHD diagnosed children's samples than the healthy ones (Fig. 1), and ADHD/control group fold changes were recorded as 4,81 (Fig. 2). However, we were not able to show a statistically significant difference between ADHD patients and the controls with nonparametric tests. The small sample size might have constituted an obstacle to confirm our hypothesis, as the miR-124 levels were dispersed in a wide range in the ADHD group, in contrast to the controls. Future studies with larger samples are needed to test the miR-124 ADHD association, specifically in combination with neurocognitive assessments.

Our study is also the first study to question the relationship between miR-4447 and ADHD as well as other psychiatric disorders to our knowledge. Dopamine pathways are crucial in many psychiatric disorders including ADHD. *DAT1* gene, functioning in dopamine metabolism, is found to have an impact in ADHD etiopathogenesis (Li et al., 2006; Purper-Ouakil et al., 2005; Yang et al., 2007), and it is targeted by miR-4447 (Wong and Wang, 2015). In the future, miR 4447 levels may be studied in a larger number of ADHD patients in comparison to controls.

A previous study by Kandemir et al. searched for an association between some candidate miRNAs and ADHD in children and adolescents. They reported a significant relation between miR-107 levels and ADHD. Also, the authors suggested miRNA 107 as a biological biomarker and reported that this biomarker could be related with minimal brain change in ADHD since it had been previously shown that miR107 was related with neurodegenerative diseases and traumatic brain injury (Wang et al., 2010; Wong and Wang, 2015). This previous finding based the rationale for selection miR107 in our study; however, we were not able to show any statistical difference between the ADHD and the control groups. It should be emphasized that the patient group in our study was composed of only combined type ADHD patients as it had been previously mentioned. The inconsistency between the studies may be related to this methodological difference.

Our study has several limitations. Firstly, we had a small sample size. Future studies with larger samples may contribute to generalize these findings. Also, the expression levels of the genes that the selected miRNAs target were not assessed in terms of the biological actions of miRNAs. In the future, further studies investigating the miRNA expression levels together with the measurement of gene expression or their end-product proteins and combining these procedures with neurocognitive test and neuroimaging findings will help us to understand the role of miRNAs in the ADHD pathogenesis more clearly.

Conclusively, we found statistically significantly altered circulating miR-5692b and miR-let-7d levels in ADHD children and adolescents compared to controls, as well as higher miR-124 levels although not significant statistically. Collectively, findings in this study support previous studies suggesting the importance of miRNAs in the understanding of the complex etiopathogenesis of ADHD. Specifically, we believe that it was important to report those alterations in ADHD for miR-5692b with its potential role in dopamine, norepinephrine, and glutamate signaling pathways, and miR-let-7d with its role in neuronal differentiation. Our results can be taken into consideration as preliminary to construct a base for future studies conducted with ADHD children and adolescents to test the possible role of miR-5692b, miR-let-7d and miR-124 in the ADHD etiopathogenesis.

Conflicts of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Role of funding source

Our study has been supported by Pamukkale University Coordination of Scientific Research Projects (Funding Number: 2016TIPF024).

Acknowledgments

We gratefully thank Dr. Ömer Başay and Hande Şenol for their work in statistical analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.05.021.

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