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Chronotypical characteristics and related miR-142-3p levels of children with attention deficit and hyperactivity disorder

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ABSTRACT

To compare children with Attention Deficit and Hyperactivity Disorder (ADHD) and a healthy control group in terms of chronotype characteristics and miRNA-142-3p/miRNA-378 levels. 50 children with ADHD and 44 healthy children were included in the study. Childhood Chronotype Questionnaire was used to identify the chronotype preferences of children. Serum miR-142-3p and miR- 378 levels were determined. Preference for nighttime was higher in children with ADHD. Additionally, a night preference was found to be associated with attention deficit in both groups. While a significant correlation was found between the psychopathology rate in mothers and the presence of ADHD, there was no such correlation in fathers. In the comparison between children with ADHD and the control group, no significant difference was found between miRNA levels. Both the miR-142-3p and miR-378 values of the children with ADHD that have immediate relatives with a psychiatric disorder were lower, compared to control group. We found that shift to night preference in the circadian rhythm was higher and this preference was associated with attention deficit in the children with ADHD. In addition, the presence of psychopathology in the family and the mother's psychopathology affected the miR-142-3p and miR378 levels

1. Introduction

Interest in circadian rhythm is increasing every day, and Jeffrey Hall, Michael Rosbash and Michael Young received the 2017 Nobel Physiology and Medicine Award for their work on circadian rhythm. Circadian rhythm includes the 24-hour behavioral and physiological changes caused by the endogenous biological hours (pacemaker), and is synchronized by environmental stimuli (Tomas A., 2000). The center and regulator of the circadian cycle in mammals is the suprachiasmatic nucleus (SCN) in the anterior hypothalamus (Dibner et al., 2010). The main rhythm regulator is light, and 24-hour light information reaches the suprachiasmatic nucleus through the retinohypothalamic tract from the ganglions in retina (Hughes et al., 2015). The external indicator of the circadian rhythm is called *chronotype*. Chronotype was defined in 1900s, and consists of elements such as sleep- wake preferences specific to the person (Kalmbach et al., 2017). Chronotype has three different types; morning type, intermediate form, and evening type. Individuals with the morning type prefer doing their activities in the early hours of the day and start the day early whereas individuals with the evening type prefer doing activities in the afternoon or evening, and end and start the day late (Lange and Randler, 2011). Intermediate form is the name given to the group that does not fit either the morning or evening group (Adan and Natale, 2002).

Circadian rhythm is controlled by a set of time genes. These genes are CLOCK (circadian locomotor output cycles kaput), BMAL1 (Brain, muscle ARNT-like protein 1), PER (Period 1 and 2), CRY (Cryptochrome), REV-ERB alpha and ROR alpha (retinoic acid–related orphan receptor response elements alpha) (Dibner et al., 2010). In circadian rhythm, BMAL1, one of the locomotive genes, can regulate the behavioral rhythms together with CLOCK genes by regulating the ignition rate of the SCN neurons (Deboer et al., 2003). Studies show that individuals with ADHD have circadian rhythm disorders, and are more often of the evening people in their chronotype preferences (Kooij and Bijlenga, 2013; Park et al., 2011; Voinescu et al., 2012). In a genetic study performed by Baird et al. in 2012, rhythmic expression of BMAL1 and PER2 genes was evaluated in ADHD patients matched controls. The study observes that rhythmic expression disappeared in ADHD patients (Baird et al., 2012).

MicroRNAs (miRNA) play an active role both in the etiology of ADHD and circadian preferences. miR-142-3p is among the best

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modulators of 3′-UTR activity and extracellular expression of BMAL1, which is one of the main CLOCK genes. A study on rats in 2013 has shown that miR-142-3p might play a role in the post-transcriptional modulation of BMAL1, and the regulation of the release of molecules that mediate the circadian function of SCN (Shende et al., 2013). In addition, CLOCK/BMAL1 heterodimers regulate the expression of miR-142-3p (Tan et al., 2012). A study on whether the miRNA-378 was effective on circadian rhythm examined 57 miRNAs released from the rat liver. The study observes an overexpression of miR-378 had high level of influence on the expression of circadian rhythm genes, such as the BMAL1/CLOCK protein complex (Wang et al., 2016).

The main objective of this study is to assess whether there is a difference in chronotype preferences between children and adolescents with ADHD, and a healthy control group. Children and adolescents with ADHD who received ADHD medication before were excluded from the study, because ADHD medications may influence the circadian rhythm and sleep patterns in both children (Sangal et al., 2006) and adults (Snitselaar et al., 2017). The secondary objective is to assess the miR-142-3p and miR-378 levels which are associated with the BMAL1 gene, one of the main genes playing a role in ADHD etiology and the regulation of the circadian rhythm, in both the ADHD group and the control group.

2. Method

2.1. Participants

This is a cross-sectional study that aims to compare miR-142-3p/miR-378 levels and chronotypical characteristics between a control group and children with ADHD that presented to Gaziantep University Child and Adolescent Psychiatry Department who had not received any prior medication for ADHD. An approval was obtained from the Ethical Committee of Gaziantep University (No: 2016/219). The study included 44 healthy controls and 50 ADHD patients that presented for therapeutic purposes between September 2016 and January 2017, the study group consisted of those who were diagnosed with ADHD according to the DSM-5, and the control group consisted of those were not diagnosed with a psychopathology according to DSM-5. Participants and their parents were involved in the study after signing the informed consent form. The inclusion criteria for the study were willingness to participate in the study, and being at an age range of 6 to 17. The exclusion criteria were as follows: unwillingness to participate in the study, mental retardation, pervasive developmental disorder, psychotic disorder, mood disorder, anxiety disorder, tic disorder, and presence of an additional chronic physical disease (DM, asthma, cancer, epilepsy, etc.) in the child. Disruptive behavioral disorders were not added as an exclusion criteria for the study group, since these disorders present a very high comorbidity with ADHD (Frick and Nigg, 2012). Chronic physical diseases and developmental disorders were excluded as potential causes of secondary sleep disorders. All children who met these criteria and for whom appropriate consent could be taken were included in the study within the specified time period. The control group was not age and sex matched during the study, however on post-hoc analysis, there was not a statistically significant difference between the study and control groups in terms of gender and age.

In order to establish an ADHD diagnosis, investigators filled out the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version—Turkish Adaptation (SADS-PL-T). (Birmaher et al., 2009; Kaufman et al., 1997; Gökler et al., 2004). Parents were provided with a Sociodemographic Data Form and the Turkish versions the Conner's Parent Rating Scale (CPRS), and the Childhood Chronotype Questionnaire (CCQ) (Dereboy et al., 1998; Dursun et al., 2015). The data form included information about age, gender, educational status, known medical or psychiatric disorders and prior presentation to child and adolescent psychiatry for the presenting child, number of siblings, level of income, parental status, parental age, educational status, prior psychiatric presentation, history of psychiatric diagnoses and medications, and known psychiatric disorders in first degree relatives for the family. The study on the validity and reliability of the Turkish form of CPRS included 5355 children and adolescents (aged 3–17), resulting in a Cronbach's alpha coefficient of 0.85—0.55 and a Cronbach's split half coefficient of 0.80–0.50, with a test-retest reliability of the range 0.073—0.35. The study on the validity and reliability of the Turkish form of CCQ included 101 children (aged 9–18) and observed that the correlation with the Morningness Eveningness Scale for Children (MESC) was significant.

2.2. Procedure

miRNA isolation: Plasma output was performed on all blood samples taken at 9:00 from patients and healthy controls. Total RNA including miRNA was obtained from the plasma of patients and controls using the miRNeasy Mini Kit (Qiagen, California, USA). *cDNA output:* Isolated RNA samples were converted to complementary DNA (cDNA) using TaqMan miRNA Reverse Transcription Kit (Life Technologies, Foster City, CA) in a 384- well Thermal Cycler (BioEr, China). *Preamplification:* Prior to qRT-PCR reactions, cDNA samples were amplified using TaqMan PreAmp Master Mix (Life Technologies, Foster City, CA). Preamplification protocol will be as follows: 10 minutes at 95 °C, 2 minutes at 55 °C, 2 minutes at 72 °C and, 15 seconds at 95 °C and 4 minutes at 60 °C for 14 cycles as the cycle stage. Amplified cDNAs were kept at −80 °C for further analysis. *Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR):* ***ν***QRT-PCR reactions were realized using a device with high process capacity (BioMark; Fluidigm, San Francisco, CA). Amplified cDNA samples were mixed with TaqMan Universal PCR Master Mix and Sample Loading Reagent, and put in the sample inputs of 96.96 chip Dynamic Array (Fluidigm, San Francisco, CA). QRT-PCR reactions were realized by following the protocol in the BioMark Real-Time PCR system (10 minutes at 95 °C, 15 seconds at 95 °C, and 1 minute at 60 °C for 30 cycles). The outputs were analyzed with the Fluidigm Real-Time PCR Analysis Software. miR-142-3p and miR-378 expression levels were investigated and compared between the groups.

2.3. Measures and statistical analysis

Normal distribution of numerical data was tested by the Shapiro–Wilk test. In the comparison of the normally distributed variants in both groups, Student *T* test was used. Mann Whitney *U* test and Kruskal Wallis tests were used in the comparison of the non- normally distributed variants in 2 groups, and 3 and 5 groups, respectively. Correlation between categoric variants, and correlation between digital variants were tested with the Chi- Square test and, Spearman correlation coefficient, respectively. SPSS 22.0 package software was used for the analyses. $p < 0.05$ was accepted as statistically significant.

3. Results

3.1. Description of the sample

There were 50 and 44 participants in the ADHD group and control group, respectively. While 40 (80%) were boys and 10 (20%) were girls in the ADHD group, the control group included 33 (75%) boys and 11 (25%) girls. The mean age was 8.24 ± 2.19 in the patient group, and 8.45 ± 2.78 in the control group. There was no significant difference between groups in terms of gender ($p = 0.561$) and age ($p = 0.677$). There was no statistically significant difference between groups in terms of income level ($p = 0.052$).

3.2. Sociodemographic factors

Statistically significant difference was found between the ADHD group and control group in terms of a previously diagnosed psychiatric

Table 1
Distribution of sociodemographic data by groups.

		ADHD (*n*, (%))	Control (*n*, (%))	*p*
Gender	Male	40 (80)	33 (75)	0.561
	Female	10 (20)	11 (25)	
Psychiatric disorder in mother	Yes	9 (18)	0 (0)	0.003*
	No	41 (82)	44 (100.0%)	
Psychiatric disorder in father	Yes	3 (6)	1 (2.3)	0.372
	No	47 (94)	43 (97.7)	
Psychiatric disorder in first degree relatives	Yes	12 (24)	1 (2.3)	0.002*
	No	38 (76)	43 (97.7)	

ADHD: attention deficit hyperactivity disorder.

disorder among the first degree relatives as reported by the parent. A psychiatric disorder was found in the first degree relatives of 12 (24%) cases in the ADHD group, and 1 (2.3%) case in the control group ($p = 0.002$). When considered in terms of the presence of a psychiatric disorder, a significant correlation was found between the patient group and control group in mothers, which refers to a higher degree in mothers of those with ADHD ($p = 0.003$) but there was no such correlation in fathers ($p = 0.372$) (Table 1)**.** Furthermore, in the analysis performed within the group with ADHD, it was found that those with a history of psychiatric disorder among the first degree relatives were individuals in the evening group ($p = 0.018$).

When the ADHD group and the control group were compared based on their CPRS sub-scale scores as a confirmation of the clinical ADHD diagnosis in the study group, the scores taken by the ADHD group in all sub-scales were higher in a statistically significant manner (with $p < 0.001$) as compared to the control group.

3.3. Factors related to chronotype

There was no statistically significant difference between the mean sleep times of both groups ($p = 0.336$). 50%, 12% and 38% of the ADHD group were morning, intermediate form and evening types, respectively. In the control group, 70.5%, 13.6% and 15.9% of the participants were morning, immediate form, and evening types, respectively. When groups were examined in terms of morning, intermediate form and evening type distribution, no statistical difference was found between the ADHD group and the control group ($p = 0.054$); however, it could be clearly observed that percentage of ADHD group's evening preference is much higher than percentage of control group's evening preference. Additionally, when the groups were divided into morning and other sub-types, the control group was observed to include more patients of the morning type ($p < 0.05$) (Table 2).

In patient ($p = 0.034$) and control ($p = 0.006$) groups, a significant difference was found between the chronotype sub-groups in terms of the measurements of Attention Deficit sub-scale of the CPRS, and evening persons were associated with high attention deficit sub- scale scores. No difference was seen between genders in terms of chronotype preferences.

Table 2
Distribution of chronotypes in 2 groups as morning type and intermediate-evening type.

	ADHD		Control		
	n	%	*n*	%	*P*
Morning type	25	50.0%	31	70.5%	0.044*
Intermediate- evening type	25	50.0%	13	29.5%	

CPRS: Conners Parent Rating Scale; ODD: oppositional defiant disorder; CD: conduct disorder; HA: hyperactivity; SLD: specific learning disability).

3.4. Factors related to miRNA

Among the patient and control groups, miR-142-3p ($p = 0.971$) measurement showed a statistically significant similarity and miR-378 ($p = 0.063$) measurement did not show a statistically significant difference. However, both the miR-142-3p ($p = 0.011$, $r = 0.37$), and miR378 ($p = 0.007$, $r = 0.38$) levels were significantly lower in those with a psychiatric disease among the immediate relatives (Table 3). In the correlation analysis performed, it was seen that presence of any psychiatric disease in the families of the ADHD group reduced miR-142-3p and miR-378 levels.

4. Discussion

One of our objectives was to evaluate the chronotype preferences of children and adolescents with ADHD, and healthy controls. 50%, 12% and 38% of the ADHD group in our study were of morning, intermediate form and evening types, respectively. In the control group, 70.5%, 13.6% and 15.9% of the participants were morning, immediate, and evening types respectively. When groups were examined in terms of morning, intermediate and evening types, even though there was no statistically significant difference between the ADHD group and the control group, the evening type ratio was higher in the ADHD group. Failure to find any difference might be associated with more frequent morning preference in children in our study, or the examination of chronotype under three subgroups, morning/intermediate form/evening. When the groups were divided into two as morning and intermediate/evening types, a significant difference was seen between patients and controls ($p = 0.044$). In a study carried out by Durmus et al., 52 individuals with ADHD aged between 7 and 12, and 52 controls were compared, which led to similar results with our study (Durmuş et al., 2017). Rybak et al. claimed that more than 40% of the adults with ADHD preferred evening whereas only 18.5% preferred morning (Rybak et al., 2007). In another study published in 2017, three groups with ADHD, Autism Spectrum Disorder, and a typical development were compared. No chronotypical difference was found between cases; however, the evening type was higher among individuals with ADHD (van der Heijden et al., 2017). In a study by Golan et al., there was a delayed circadian cycle and also sleep initiation difficulties in the ADHD patients. Accordingly, it was suggested that morning sleepiness was higher in ADHD patients, and methylphenidate treatment could be beneficial (Golan et al., 2004). A correlation was observed between the circadian preference and attention deficit both in the ADHD group and the control group. Evening type children received a high score from the Conner's Attention Deficit sub-scale whether ADHD was present or not. In a study performed with ADHD patients, it was stated that evening preference had a higher effect on attention deficit, and no apparent effect on the hyperactivity and impulsivity, in parallel with the findings of our study (Caci et al., 2009). In our study between the patient ($p = 0.034$) and the control ($p = 0.006$) groups, a significant difference was found between the chronotype sub-groups in terms of the measurements of Attention Deficit sub-scale of the CPRS, and evening persons were associated with high attention deficit sub- scale scores. In another study performed on 550 adults in 2012, attention deficit was shown to be associated with sleeplessness and evening preference (Voinescu et al., 2012).

Evening preference was shown to be associated with attention deficit and impulsivity in a study conducted in 2007 (Rybak et al., 2007).

Another aim of our study was the compare the ADHD group and controls in terms of the associated miRNA levels. However, no statistically significant difference was seen in our study. We also observed a statistically significant difference between the group that had and did not have a psychiatric pathology among the first degree relatives in terms of miRNA levels. In our study, while there was no difference between ADHD and control group in the psychopathology of fathers, a difference was observed in mothers. Similar results were obtained from

Table 3
miRNA levels distribution among ADHD patients by the presence of any psychiatric disease among immediate relatives.

		Psychiatric history in immediate relatives (24%, *n*:12) (RFU)	No psychiatric history in immediate relatives (76%, *n*:38) (RFU)	*p*	*r*
miR-142-3p	IQR(25–75)	17.95–18.51	19.82–21.32	0.011	0.37
	Median	20.52	22.75		
miR-378	IQR(25–75)	22.90–23.47	24.18–25.36	0.007	0.38
	Median	24.14	26.16		

miR: micro RNA, RFU: relative fluorescence unit.

two studies conducted in 2016, and it was stated that mothers of ADHD patients experienced more stress and their psychopathology rate was higher as compared to the controls (Babakhanian et al., 2016; Borden et al., 2016). A large Finland-based study examining the presence of any psychopathology in the parents of ADHD children found a similar result. In this study conducted in 2017, it was claimed that the correlation between children with ADHD and the mothers' psychopathology might be associated with genetic inheritance (Joelsson et al., 2017). Further studies are needed to understand if this difference between mother and father is associated with genetics and environmental factors. The presence of a psychiatric pathology was found in families of 24% of the ADHD cases and 2.3% of the control group. It is known that psychiatric disorders also have a genetic basis. Therefore, the high rate in the patient group seems to be compliant with the literature and the clinical information (Biederman and Faraone, 2005; Mukaddes, 2015).

In our study, ADHD patients that had a psychiatric disorder among their first degree relatives were found to tend to be evening persons as compared to those with no such history. Family studies performed show that chronotype preferences are also hereditary characteristics (Kalmbach et al., 2017).

No difference was found between the genders in our study in terms of chronotype preferences. In literature, on the other hand, there are many studies in which a difference was found between males and females in terms of chronotype preference. In two studies performed, it was found that females in adolescence and early adulthood had more morning chronotype as compared to males (Baehr et al., 2000; Boivin et al., 2016). The amplitude of the melatonin release in males was lower as compared to females in other studies that investigated the circadian differences between genders (Cain et al., 2010; Santhi et al., 2016). Since a low amplitude indicates a weaker intrinsic oscillator, it can explain the high volatility of males in behavioral rhythm phases (Cain et al., 2010).

Many studies were performed on miRNAs both in psychiatry and other medical areas. The results of these studies vary. Similarly, inconsistencies were observed in the studies performed on the circadian rhythm. As is known, one of the pathways in the regulation of transcription of miRNAs related to the circadian rhythm is the effect of transcription factors such as BMAL1 /CLOCK and REV-ERBα / β. Due to such effect, adult miRNAs are either not released or are released in a low amplitude. Inconsistency in various studies might be attributed to the difference (Wang et al., 2016). And yet, also in our study, we concluded that the difference in the levels of miR-142-3p, which was previously shown to affect BMAL1 directly, (Shende et al., 2013; Tan et al., 2012) and miR-378 (Wang et al., 2016)found in the feedback mechanism of the CLOCK/BMAL1 transcription factor was not statistically significant between the ADHD and control groups. In a comparison made between ADHD patients, both the miR-142-3p and miR-378 levels of the patients with any psychiatric disorder history in their first degree relatives were found to be significantly lower. While such difference was attributed to the genetic load in psychiatric diseases, no other study was found in the literature review showing the correlation between miRNA levels and family history. Therefore, there is a need for new studies to explain correlation of miRNAs and genetic load in psychiatric diseases.

Given the restrictions of our study, one of our limitations was the relatively few number of patients, which could be an explanation for miRNA levels with no significant difference and lack of difference in chronotype preference. Another reason behind the lach of statistical difference between miRNA levels might be a procedural restriction, as MiRNA levels measured from the plasma samples. The fact that miRNA levels on the periphery have an undetermined release, and those on the plasma are not stable might have led us to the conclusion that there is no significant difference between the groups. Another restriction is the effect of sleep hygiene and sleeping problems on chronotype preference. Children with ADHD experience more sleep problems than their typically developing peers (Cortese et al., 2013). Sleep problems are experienced by up to 70% of children with ADHD (Sung et al., 2008). While sleep hygiene problems (as an externalization factor) and specific sleeping problems were higher in the individuals with ADHD, the fact that this affected the chronotype preferences and created a difference might be another factor affecting our conclusions. Even though we excluded children with sleep and waking related disorders from the study as a psychiatric comorbidity, given the literature on the field, the ADHD group might have had a higher proportion of subsyndromal sleep problems or more significant sleep difficulties that may have been under-reported. Finally, there is a need for studies performed on a larger sample in order to better understand the correlation between ADHD, miRNA and chronotype.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.175.

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