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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Evidence supporting the role of telomerase, MMP-9, and *SIRT1* in attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Growing evidence suggests that telomeres, telomerase, matrix metalloproteinase-9 (MMP-9), and *SIRT1* (sirtuin1) are involved in the pathophysiology of neuropsychiatric and neurodevelopmental disorders. However, whether these molecules are contributors to attention-deficit/hyperactivity disorder (ADHD) has been little explored and poorly understood. This study aimed to determine the potential role of telomerase, MMP-9, and *SIRT1* in children with ADHD. The study was performed on 46 children with ADHD aged between 8 and 14 and 43 healthy children matching in age and gender. Children were evaluated by Kiddie-Sads-Present and Lifetime Version, Conners' Parent Rating Scale-Revised Short Form (CPRS-RS) and Stroop test. Serum telomerase, MMP-9, and *SIRT1* levels were measured by a quantitative sandwich enzyme-linked immunosorbent assay. MMP-9 and telomerase levels were significantly higher and *SIRT1* levels were significantly lower in patients with ADHD than those of controls. All three molecules were significantly associated with both the severity of ADHD symptoms and cognitive functions. This is the first attempt to indicate that the important role of telomerase, MMP-9, and *SIRT1* in ADHD, and the association of all these molecules with the severity of ADHD and cognitive functions, but future studies are required to verify these results.

Keywords Attention-deficit/hyperactivity disorder (ADHD) · Telomerase · *SIRT1* · MMP-9 · Cognitive · Child/adolescence

Introduction

Attention-deficit/hyperactivity disorder (ADHD), one of the most common childhood-onset neurodevelopmental conditions, is characterized by developmentally inappropriate levels of persistent inattention, and/or hyperactive–impulsive behavior (American Psychiatric Association (APA) 2013). The worldwide prevalence of ADHD is approximately 5% with a male:female ratio of 2.28:1 (Danielson et al. 2018). The cognitive and behavioral symptoms of ADHD interfere with psychosocial functioning and academic performance and are often far-reaching enough to impair quality of life and well-being (Dunn et al. 2019; Leffa et al. 2018). An extensive study has revealed that these children more frequently experience stressful and distressing life events compared to typically developing children since ADHD has many complications including psychological dysfunctions, academic failure, problems in familial, social and peer relationships, and risky behaviors (Hartman et al. 2019). Moreover, ADHD involves some kinds of well-established cognitive deficits in working memory and executive functions such as response inhibition, error monitoring, attentional disengagement, and decision-making processes. However, despite comprehensive studies that have been conducted on this matter, both the etiopathogenesis of ADHD and the etiological roots of cognitive deficits in ADHD have not still been clarified (Gupta and Kar 2010).

The enzyme telomerase (telomere deoxynucleotidyl transferase and telomere terminal transferase) is responsible for the lengthening of telomeres which shorten during cell division and also has a crucial role in neuronal differentiation, neuronal survival, and neuritogenesis (Amano and

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Sahin 2019; Anitha et al. 2019). Numerous studies have revealed that cognitive deficits and some neuropsychiatric conditions including autism spectrum disorders, schizophrenia, Alzheimer's disease, and depression are associated with shorter telomeres (Amano and Sahin 2019; Anitha et al. 2019; Kim et al. 2016). Furthermore, some researchers have suggested a strong association between telomere length and chronic psychosocial stress (Mathur et al. 2016). Telomerase plays an extremely important part in many cancers and is a central regulator of all of the hallmarks of cancer, but recent studies have suggested that telomere/telomerase is dysfunctional in many chronic conditions characterized by chronic inflammation such as diabetes, renal failure, chronic obstructive pulmonary disease, and some nonmalignant proliferative skin diseases including psoriasis (Jurk et al. 2014; Kordinas et al. 2015, 2016; Liu et al. 2008). Although most adult cells display low basal telomerase activity, a growing body of evidence indicates that the catalytic subunit TERT (telomerase reverse transcriptase: abbreviated to TERT, or hTERT in humans) is tightly regulated in its expression and inducible in various cell types in response to changes in environmental cues (Ducrest et al. 2002). For example, some cell types, including germ cells, endometrium, cervical epithelium, epidermis, esophageal epithelium, intestinal crypts, dendritic cells, renewable tissues (e.g., hair follicles), bone marrow cells, hematopoietic stem cells, and activated lymphocytes are exceptions to this rule and they exhibit telomerase activity (Burger et al. 1997; Collins and Mitchell 2002; Ducrest et al. 2002; Ping et al. 2003). However, whether there is a relationship between telomerase activity and symptoms and neuropsychological processes of ADHD has been little explored up to now. Few published studies have indicated that childhood ADHD, in particular, with hyperactivity–impulsivity symptoms, are associated with telomere length (Costa de et al. 2015; Momany et al. 2019).

SIRT1 (sirtuin1) which is functionally tightly interconnected and intertwined with telomerase, is one of nicotinamide adenine dinucleotide (NAD)-dependent deacetylase enzymes. It has recently been reported that while telomere shortening suppresses *SIRT1*, increased *SIRT1* activity stabilizes telomere and mitigates telomere-dependent dysfunction (Amano and Sahin 2019; Amano et al. 2019). In addition, *SIRT1* is also involved in a wide range of normal brain functions including cognitive functions, synaptic plasticity, learning and memory as well as the neuroprotective property (Amano and Sahin 2019; Elibol and Kilic 2018). However, the potential role of *SIRT1* in childhood psychiatric disorders has been still poorly figured out and has been studied mostly in many adult psychiatric disorders such as schizophrenia, mood disorders, anxiety disorders, and addiction (Elibol and Kilic 2018; Herskovits and Guarente 2014; Kishi et al. 2011; Lu et al. 2018). There is no study examining the association of ADHD with *SIRT1* in both children and adults in the literature based on the available databases at the time of the study.

Matrix metalloproteinase-9 (MMP-9), another enzyme negatively regulated by *SIRT1*, is one of the endopeptidases necessary for the dynamic remodeling and degradation of the extracellular matrix. It has also been suggested that while MMP-9 plays a pivotal role in functions such as brain development, synaptic plasticity, and learning and memory, it is associated with various neuropsychiatric conditions including addiction, epilepsy, mood disorders, autism spectrum disorders, ADHD, and neuroinflammation (Kadziela-Olech et al. 2015; Reinhard et al. 2015; Vafadari et al. 2016). But unfortunately, data on whether MMP-9 is implicated in ADHD remain considerably unknown. In this context, there is only one study in the literature investigating the level of MMP-9 in ADHD and supporting that there is an association between elevated serum MMP-9 levels and the severity and impulsivity of ADHD symptoms (Kadziela-Olech et al. 2015).

Telomerase, MMP-9, and *SIRT1* are involved in a wide range of physiological and pathological processes and increasing number of data have suggested that these three molecules are also associated with cognitive deficits and several neuropsychiatric disorders. Regarding the association between MMP-9, *SIRT1*, and telomerase, these three biomarkers are independently involved in a great deal of neuronal physiological functions and diseases including psychiatric disorders but also they are tightly intertwined (Amano and Sahin 2019; Amano et al. 2019; Ding et al. 2013; Mendes et al. 2017). It is known that a dramatically increased and activated MMP-9 plays an apoptotic role by damaging mitochondria. While the MMP-9 levels increase in inflammation, hypoxia or damages of the brain, *SIRT1* redresses the imbalance of MMP-9 by regulating MMP-9 expression; therefore, it is recognized as a negative regulator of MMP-9 and protects against the increased and activated MMP-9 (Lee and Kim 2011; Reinhard et al. 2015). Furthermore, MMP-9 expression is up-regulated by telomerase, independently of telomerase activity, and telomerase promotes MMP-9 mRNA expression in neoplastic illnesses and induces cancer cell invasion (Ding et al. 2013). In regard to the relationship between *SIRT1* and telomerase, the depletion of *SIRT1* is associated with a substantial reduction of telomerase mRNA and protein expression and it has been revealed that *SIRT1* is necessary for proficient telomere elongation and increases the transcription of human telomerase reverse transcriptase, while telomere shortening affects *SIRT1* expression and suppresses the sirtuins (Amano and Sahin 2019; Amano et al. 2019; Chen et al. 2012).

Since the mechanisms of cognitive dysfunction in ADHD have not been clarified, the telomerase, *SIRT1,* and MMP-9 which have important roles in cognitive abilities and functions, may play a part in cognitive deficits in ADHD. In

addition, these three molecules are related to inflammation as well as learning, memory and other cognitive functions mentioned above (Jurk et al. 2014; Vafadari et al. 2016; Xie et al. 2013). In the setting of an inflammatory process, the intracellular enzymes (e.g., telomerase) are released into the extracellular fluid as a result of cell destruction and functional damage in the membrane (Chen et al. 2017). Moreover, accumulating evidence indicates that neuroinflammation and peripheral inflammation are risk factors in the etiopathogenesis of ADHD (Danielson et al. 2018; Dunn et al. 2019; Leffa et al. 2018). Therefore, these inflammation-related molecules may be involved in ADHD, which is emphasized to have inflammation in its etiopathogenesis, and the measurement of their serum levels can bring along new explanations related to the mechanism of cognitive dysfunction of ADHD.

In this study, we sought to investigate whether the serum levels of *SIRT1* and MMP-9 and telomerase alter in children with ADHD. We further explored whether there is an association between telomerase, *SIRT1*, and MMP-9 levels and the type and severity of ADHD symptoms and cognitive deficits in children with ADHD. This study would shed light on the understanding of the mechanisms involved in the development of ADHD. Thus, the hypothesis of the present study is as follows:

Increased serum telomerase and MMP-9 levels and decreased serum *SIRT1* levels may be associated with the type and severity of symptoms and the presence of cognitive deficits in children with ADHD.

Subjects and methods

Participants

After power analysis, this study was conducted on 46 outpatients with "pure" ADHD [the mean (SD) age: 10.67 ± 2.56 years, min–max: 8–14 years, 31 males–15 females, 67.4% males], at the Child and Adolescent Psychiatry Clinic of Sivas Cumhuriyet University Hospital. First diagnosed patients were included in the study. The patients had no chronic medical conditions, drug or alcohol abuse, and smoking habits and were not using the medication(s). Within the ADHD group, 9 children (19.6%) (5 males, 4 females) had predominantly inattentive presentation (ADHD-PI), 12 (26.1%) (9 males, 3 females) had predominantly hyperactive-impulsive presentation (ADHD-PH), and 25 (54.3%) (17 males, 8 females) had combined presentation (ADHD-C) for those with both inattentive and hyperactive/impulsive symptoms. The control group consisted of 43 healthy volunteer children [the mean (SD) age: 10.95 ± 2.71 years, min–max: 8–14 years, 31 males–12 females, 72.1% males] who had no present or past psychopathology and no chronic medical condition. All participants were included in the study between March and September 2019. After a verbal explanation of the study, all participants accepted to participate in the study, and their parents/legal guardians gave written informed consent. The study was conducted in agreement with the ethical standards of the Declaration of Helsinki and Good Clinical Practice procedures and approved by the Human Research Ethics Committee of our institution (Date: 05.12.2019, No: 2019–02/01).

Clinical assessment and neuropsychological measures

The diagnosis of ADHD was established according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (APA 2013) and confirmed by two child and adolescent psychiatrists. Also, participants and their parents underwent a semi-structured interview (Turkish version of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version, KSADS-PL) (Gokler et al. 2004) to identify whether the child has any current and past psychiatric disorder (Kaufman et al. 1997). In addition, the participants' sociodemographic characteristics and clinical data were collected using a form prepared by the researchers.

The severity of ADHD was assessed using the Conners' Parent Rating Scale-Revised Short Form (CPRS-RS). The CPRS-RS consists of 27 questions that help to screen for a child's behaviors and includes three subscales (Hyperactivity Subscale, Cognitive Problems/Inattention Subscale, and Oppositional Subscale) and an auxiliary scale (ADHD Index) (Kumar and Steer 2003). These questions are rated from 0 to 3 (0 = never, 1 = rarely, 2 = frequently, and 3 = always) according to the frequency of problems. Higher scores represent severe problematic behaviors. The Turkish validity and reliability study was performed by Kaner et al. (2013).

The Stroop test TBAG form (ST-TBAG), whose reliability and validity have been proved, was employed to measure the severity of attention deficit (selective attention) and basic cognitive speed (Karakas et al. 1999; Stroop 1935). ST-TBAG consists of five subtests and errors, corrections, and completion time (duration) are calculated for each subtest. The increasing number of total errors and corrections and/or total completion duration indicates a more severe attention deficit and more impairment of cognitive functions. In the present study, total time, total error, and total correction scores of Stroop were used.

Biochemical measurements and procedures

Peripheral venous blood samples (10 mL) were collected in a vacutainer without anticoagulant between 09:00 and 12:00 a.m. The tubes were left at room temperature for 10 min, the blood samples were centrifuged at 3000 rpm for 15 min and stored at − 80 °C until the analysis. All experiments were performed by a two-site sandwich ELISA (enzyme-linked immunosorbent assay) method using Human ELISA Kits (SinoGeneClon Biotech Co.,Ltd; catalog number is SG-11444 for Human Telomerase(TE) (hTERT) ELISA Kit, catalog number is SG-10458 for Human Sirtuin 1(*SIRT1*) ELISA Kit, and catalog number is SG-10412 for Human Matrix metalloproteinase 9 (MMP-9) ELISA Kit, respectively) and expressed in µg/L (MMP-9) or ng/ml (*SIRT1* and telomerase). All measurements were performed on the same day in accordance with the manufacturer's instructions to minimize assay variance. The optical density of each well was measured under 450 nm wave length using a microplate reader. The samples from each patient were tested in duplicate. The sensitivity was determined as 0.05 ng/ml, 0.18 ng/ml, and 10 µg/L for telomerase, *SIRT1*, and MMP-9, respectively. The intra- and inter-assay coefficients of variation of the different assays were 4.92% and 6.98%, 5.81% and 5.22%, and 4.6% and 4.99% for telomerase, *SIRT1*, and MMP-9, respectively.

Results

Demographic and clinical characteristics of the participants

Table 1 shows the selected clinical characteristics of the participants. The ADHD and control groups did not differ significantly in terms of age, gender, parents' education level, family income level, and residence place (all p values > 0.05). On the other hand, a significant difference was determined for the family history of ADHD ($p < 0.001$) (Table 1).

As expected, both scores of all the subscales and ADHD Index scores in the CPRS-RS were significantly higher in the ADHD group compared to the control group ($p < 0.001$) (Fig. 1a). Similarly, a statistically significant difference was determined in Stroop Test—total time, total error, and total correction scores. All three scores of the Stroop test were

Table 1 Sociodemographic characteristics of the sample

	ADHD group ($N=46$)	Control group ($N=43$)	Statistic	p value
Age (mean-years ± SD)	10.67 ± 2.56	10.95 ± 2.71	$U=914.00$*	0.534
Gender (n, %)			$\chi^2=0.232$**	0.630
Male	31 (67.4)	31 (72.1)		
Female	15 (32.6)	12 (27.9)		
Level of education of the mother (n, %)			$\chi^2=0.855$**	0.652
Elementary school level or lower	15 (32.6)	13 (30.2)		
Primary education	21 (45.7)	17 (39.5)		
High school and higher	10 (21.7)	13 (30.2)		
Level of education of the father (n, %)			$\chi^2=0.527$**	0.768
Elementary school level or lower	10 (21.7)	8 (18.6)		
Primary education	16 (34.8)	13 (30.2)		
High school and higher	20 (43.5)	22 (51.2)		
Family income level (n, %)†			$\chi^2=1.434$**	0.488
Low	16 (34.8)	16 (37.2)		
Middle	18 (39.1)	12 (27.9)		
High	12 (26.1)	15 (34.9)		
Place of residence (n, %)			$\chi^2=0.058$**	0.809
Urban	31 (67.4)	30 (69.8)		
Rural	15 (32.6)	13 (30.2)		
Family history of ADHD (n, %)			$\chi^2=23.731$**	**< 0.001**
Yes	31 (67.4)	7 (16.3)		
No	15 (32.6)	36 (83.7)		

ADHD attention-deficit hyperactive disorder, *SD* standard deviation

*Mann–Whitney U test. **χ^2 test, Bold font indicates statistical significance $p < 0.05$

†The level of income was determined by the minimum wage value on the date of the study

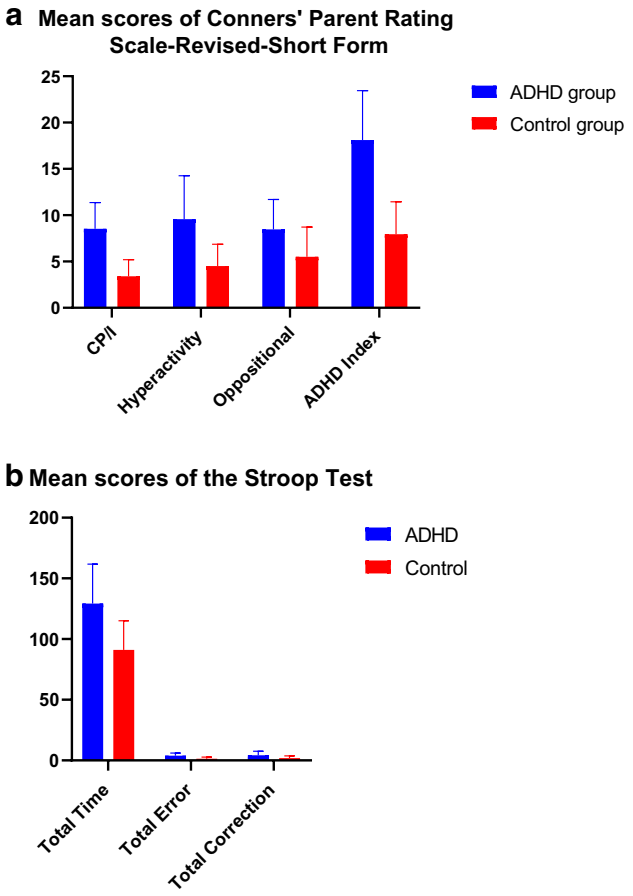

Fig. 1 **a** Mean scores of subjects' Conners' Parent Rating Scale-Revised Short Form (CPRS-RS). Blue column: ADHD patients, red column: healthy controls, *CP/I* cognitive problems/inattention. The mean scores were significantly higher in the ADHD group compared to the control group ($p < 0.001$). **b** Mean scores of participants' Stroop Test Scores. Blue column: ADHD patients, red column: healthy controls. The mean scores were significantly higher in the ADHD group compared to the control group ($p < 0.001$)

significantly higher in the ADHD group than the control group, suggesting that the ADHD group completed the test in a longer time (later, lower performance compared to the control group), with a greater number of errors and corrections ($p < 0.001$) (Fig. 1b). Table 2 shows Conners' Parent Rating Scale and Stroop Test TBAG Scores.

Biochemical measurements

The mean (SD) telomerase and MMP-9 levels of ADHD cases were significantly higher than the levels of the control group (0.394 ± 0.141 vs. 0.324 ± 0.102; $p = 0.018$ and 338.70 ± 102.80 vs. 270.22 ± 79.39; $p = 0.002$, respectively) (Fig. 2a, b). On the other hand, the mean (SD) *SIRT1* levels were significantly lower in ADHD cases compared to the control group (2.78 ± 1.23 vs. 4.39 ± 0.75; $p < 0.001$) (Fig. 2c). Table 3 summarizes serum levels of *SIRT1*, MMP-9, and telomerase in ADHD cases and healthy controls.

Mean values of telomerase, MMP-9, and *SIRT1* levels were similar among the three presentations of ADHD in the Kruskal–Wallis test. The positive family history for ADHD did not change the telomerase, MMP-9, and *SIRT1* levels (all p values > 0.005, data not shown).

Table 4 shows the correlations between telomerase, MMP-9, and *SIRT1* levels and Conners' Parent Rating Scale-Revised Short Form and Stroop Test. As can be seen in the table, there was a positive correlation between telomerase and MMP-9 levels and the scores of all the subscales and ADHD Index in the CPRS-RS, and Stroop Test—total time, total error and total correction scores. On the other hand, *SIRT1* was negatively correlated with all scores of the CPRS-RS and Stroop Test (all p values < 0.001). In addition, while there was a significant negative correlation between serum *SIRT1* levels and both telomerase and MMP-9 levels, a positive correlation was determined between MMP-9 and telomerase (Table 4).

Table 2 Comparison of the CPRS-RS and Stroop Test Scores between the study and control groups

	ADHD group ($N = 46$)	Control group ($N = 43$)	p value*
CPRS-RS-cognitive problems/inattention scores (mean ± SD)	8.54 ± 2.82	3.4 ± 1.79	**< 0.001**
CPRS-RS-hyperactivity scores (mean ± SD)	9.57 ± 4.68	4.51 ± 2.35	**< 0.001**
CPRS-RS-oppositional scores (mean ± SD)	8.46 ± 3.23	5.51 ± 3.20	**< 0.001**
CPRS-RS-ADHD index scores (mean ± SD)	18.11 ± 5.34	7.95 ± 3.49	**< 0.001**
Stroop test—total time scores (mean- seconds ± SD)	129.24 ± 32.43	91.00 ± 24.10	**< 0.001**
Stroop test—total error scores (mean ± SD)	3.91 ± 2.17	1.47 ± 1.20	**< 0.001**
Stroop test—total correction scores (mean ± SD)	4.24 ± 3.36	1.93 ± 1.76	**< 0.001**

ADHD Attention deficit hyperactive disorder, *CPRS-RS* Conners' Parent Rating Scale-Revised Short Form, *SD* standard deviation

*Mann–Whitney *U* test. Bold font indicates statistical significance $p < 0.05$

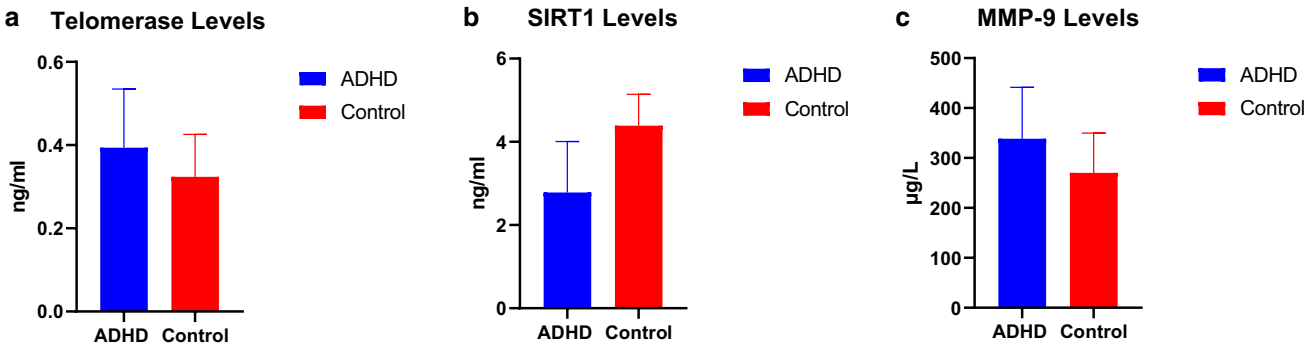

Fig. 2 **a** Serum telomerase levels in ADHD cases and healthy controls. Blue column: ADHD patients, red column: healthy controls. The mean (SD) telomerase levels in ADHD cases was significantly higher than of the control group (0.394 ± 0.141 vs. 0.324 ± 0.102; p = 0.018). **b** Serum *SIRT1* levels in ADHD Cases and Healthy Controls. Blue column: ADHD patients, red column: healthy controls. The mean (SD) *SIRT1* levels in ADHD cases were significantly lower than of the control group (2.78 ± 1.23 vs. 4.39 ± 0.75; $p < 0.001$). **c** Serum MMP-9 levels in ADHD cases and healthy controls. Blue column: ADHD patients, red column: healthy controls. The mean (SD) serum MMP-9 levels in ADHD cases was significantly higher than of control group (338.70 ± 102.80 vs. 270.22 ± 79.39; $p = 0.002$)

Table 3 Serum levels of MMP-9 and *SIRT1* and telomerase in ADHD cases and healthy controls

	ADHD group ($N = 46$)	Control group ($N = 43$)	p value*
Telomerase (mean ± SD)	0.394 ± 0.141	0.324 ± 0.102	**0.018**
MMP-9 levels (mean ± SD)	338.70 ± 102.80	270.22 ± 79.39	**0.002**
SIRT1 levels (mean ± SD)	2.78 ± 1.23	4.39 ± 0.75	**< 0.001**

ADHD attention-deficit hyperactive disorder, *MMP-9* matrix metalloproteinase-9, *SD* standard deviation, *SIRT1* Sirtuin 1

*Mann–Whitney *U* test. Bold font indicates statistical significance $p < 0.05$

Discussion

This study is the first attempt to examine blood telomerase, MMP-9, and *SIRT1* levels together in children with ADHD. To date, there is only one study examining the level of MMP-9 in ADHD (Kadziela-Olech et al. 2015), but, to the best of our knowledge, both telomerase and *SIRT1* have not been studied. Therefore, there is still a lack of data about whether or not these molecules have any role in ADHD. The main results of the present study are that (1) children with ADHD had significantly higher telomerase and MMP-9 levels and significantly lower *SIRT1* levels, (2) all three molecules were significantly associated with both the severity

Table 4 Correlations (as Spearman's *r* correlation coefficients) between telomerase, MMP-9 and SIRT1 levels and CPRS-RS and Stroop Test

Parameters	Telomerase (ng/ml)		MMP-9 levels (µg/L)		*SIRT1* levels (ng/ml)	
	*r**	*p**	*r*	*p*	*r*	*p*
CPRS-RS-cognitive problems/inattention scores	0.513	**< 0.001**	0.503	**< 0.001**	− 0.636	**< 0.001**
CPRS-RS-hyperactivity scores	0.770	**< 0.001**	0.746	**< 0.001**	− 0.706	**< 0.001**
CPRS-RS-oppositional scores	0.810	**< 0.001**	0.770	**< 0.001**	− 0.630	**< 0.001**
CPRS-RS-ADHD index scores	0.734	**< 0.001**	0.728	**< 0.001**	− 0.802	**< 0.001**
Stroop test—total time scores	0.768	**< 0.001**	0.735	**< 0.001**	− 0.718	**< 0.001**
Stroop test—total error scores	0.608	**< 0.001**	0.677	**< 0.001**	− 0.686	**< 0.001**
Stroop test—total correction scores	0.666	**< 0.001**	0.605	**< 0.001**	− 0.603	**< 0.001**
Telomerase	–	–	0.839	**< 0.001**	− 0.654	**< 0.001**
MMP-9 levels	0.839	**< 0.001**	–	–	− 0.634	**< 0.001**
SIRT1 levels	− 0.654	**< 0.001**	− 0.634	**< 0.001**	–	–

ADHD attention-deficit hyperactive disorder, *CPRS-RS* Conners' Parent Rating Scale-Revised Short Form, *MMP-9* matrix metalloproteinase-9, *SD* standard deviation, *SIRT1* Sirtuin 1

*Spearman's Correlation Analysis

of ADHD and cognitive functions in ADHD, and (3) while *SIRT1* levels had a significant negative correlation with both telomerase and MMP-9 levels, a positive correlation was observed between MMP-9 and telomerase. Until now, these outcomes offer a unique finding to the literature; however, we cannot make an adequate comparison between the results of the present study and prior studies investigating these molecules in other neuropsychiatric disorders. Telomerase, MMP-9, and *SIRT1* perform a broad range of physiological and pathological functions. The mounting evidence suggests that these three molecules are also associated with cognitive deficits and a number of neuropsychiatric disorders including autism spectrum disorders, schizophrenia, Alzheimer's disease, and mood disorders. Specifically, it is known that shorter telomeres, considerable increased MMP-9 and reduced levels of *SIRT1* exacerbate and/or contribute to many neuropsychiatric disorders (Amano and Sahin 2019; Anitha et al. 2019; de Costa et al. 2015; Kim et al. 2016; Kishi et al. 2011; Lu et al. 2018; Mathur et al. 2016; Momany et al. 2019). However, only a few studies have explored the possible role of telomere length, MMP-9 and *SIRT1* in ADHD, one of the most common psychiatric disorders in childhood (de Costa et al. 2015; Momany et al. 2019; Vafadari et al. 2016). These studies have revealed that shortened telomere length and increased MMP-9 levels are associated with ADHD, in particular, hyperactivity–impulsivity type. In the present study, we tried to find out whether or not telomerase, MMP-9, and *SIRT1* are involved in cognitive and attentional problems in ADHD. This is because cognitive dysfunction is a known feature of ADHD and all of these enzymes have a remarkable role in brain development, cognitive functions, and executive functioning. More importantly, the causes of cognitive deficits in ADHD have not been clarified, yet. Hence, figuring out that these cognitive problems may be related to the mentioned enzymes may open up new horizons for us from the etiological aspect.

Although the results of the present study cannot be adequately compared, they can be discussed based on the foregoing. First, these molecules related to neuroinflammation may be involved in the pathophysiology of ADHD; a growing number of findings indicate the involvement of neuroinflammation and peripheral inflammation in both the pathophysiology and progression of ADHD. In this regard, it has been proven that early environmental insults (maternal infection, smoking, obesity and poor diet, maternal exposure to pollutants, viral infections, asphyxia, neurotoxins, etc.) identified as risk factors for ADHD are associated with elevated neuroinflammation (Danielson et al. 2018; Dunn et al. 2019). By means of various ways including glial activation, blood–brain barrier disruption, increased oxidative stress, impaired neurogenesis, neuronal damage and degeneration and altered neurotransmitter function/metabolism, neuroinflammation is involved in the neuropathological cascade, affects brain development, increases the risk of neurodevelopmental disorders, and has detrimental effects on cognitive performance (Crotti and Ransohoff 2016; Leffa et al. 2018). Increasing number of evidence have suggested that *SIRT1* has anti-inflammatory and anti-oxidative properties, but *SIRT1* deficiency, reduced levels of *SIRT1* or the lack of *SIRT1* in the brain contributes to the inflammatory process and cognitive deficits. In this regard, it has been proposed that treatment and/or prevention of inflammation in the brain through increasing *SIRT1* or pharmacological activation of *SIRT1* would be a promising strategy; thus, there is currently a great interest pharmacologically in targeting sirtuin pathways in neuropsychiatric disorders (Michán et al. 2010; Xie et al. 2013). Moreover, some researchers have revealed that overexpression of *SIRT1* stimulates cognitive enhancements and has protective effects on memory in animal models (Wang et al. 2017). The existing clinical information present that the *SIRT1* activator, resveratrol or synthetic *SIRT1*-activating compounds such as SRT2104 have anti-inflammatory and neuroprotective effects, improve cognitive and memory performance, and could alleviate hyperactivity/non-compliance of autism patients (Hendouei et al. 2019). However, there is currently no study assessing the use of these compounds as adjuvant therapy in ADHD. Given these crucial data about *SIRT1*, we can suggest that *SIRT1* may have a role in ADHD symptoms by means of its effect on neurogenesis and cognitive abilities as well as its anti-inflammatory effect.

More importantly, MMP-9 negatively regulated by *SIRT1* is also one of the key molecules that contributes to neuroinflammation by activating proinflammatory cytokines. MMP-9 enzymatic activity drastically increases following several pathological stimuli and insults, and in turn, this improperly activation is involved in a number of brain disorders including neurodevelopmental and neuroinflammatory disorders (Huntley 2012; Vafadari et al. 2016). Fragile X syndrome (FXS), a neurodevelopmental disorder, is characterized by cognitive deficits, inattention, impulsivity and hyperactivity, anxiety, seizures, autism, abnormal elevated expression of MMP-9 in the brain, and high plasma activity of MMP-9. Tetracycline, derivative minocycline (MMP-9 inhibitor) treatment reduces anxiety and eases atypical behaviors in individuals with FXS (Dziembowska et al. 2013). To the best of our knowledge, no study has evaluated the usefulness of the minocycline in patients with ADHD. Little is already known about the effect of MMP-9 on ADHD symptoms. In this regard, the study by Kadziela-Olech et al. (2015) revealed a correlation between elevated serum concentrations of MMP-9 and the severity of ADHD symptoms and impulsivity, which is similar to the results of the present study. The authors explained this finding by the notion that elevated concentrations of MMP-9 are seen in conditions such as inflammation and hypoxia and attributed its possible role in ADHD to the fact that MMP-9

may be partly responsible for the reduced or irregular levels of extracellular dopamine. In addition to the hypothesis of the researchers, given that there is a significant negative correlation between *SIRT1* and MMP-9 (one of the results of the present study) and *SIRT1* is a negative regulator of MMP-9, high levels of MMP-9 in the ADHD group would be explained by decreased *SIRT1* concentration. Again, another interesting finding indicates that telomerase regulates MMP expression independently of telomerase activity, stimulates MMP-9 mRNA expression in neoplastic illnesses, and induces cancer cell invasion through the up-regulation of the metalloproteinases (Ding et al. 2013). Although the population of the present study is different, based on this important finding and our result showing a significant positive correlation between telomerase and MMP-9, it can be assumed that elevated MMP-9 levels in ADHD patients may be the result of high telomerase levels, or vice versa, however, our hypothesis needs to be verified.

Similarly, the result of the present study revealing higher telomerase in ADHD, whose etiopathogenesis is increasingly associated with inflammation (Dunn et al. 2019; Leffa et al. 2018), may also be attributed to inflammation. A great number of evidence shows a bidirectional association between inflammation and telomerase system: inflammation induces telomere dysfunction, and telomere dysfunction or telomere attrition leads to inflammation (Ding et al. 2013; Jurk et al. 2014). However, up to the present, a limited number of studies investigating telomere length in ADHD has been conducted. One of these few studies reported that telomere length was negatively correlated with hyperactive–impulsive symptoms (de Costa et al. 2015). Another study, contrary to expectations, revealed a positive relationship between longer telomere length and childhood hyperactive–impulsive symptoms (Momany et al. 2019). These inconsistent findings may be associated with the age and background of the participants, methodological differences, and covariates. In the present study, another result indicated that the elevated telomerase in the ADHD group may be due to decline in *SIRT1*, just like MMP-9. It has been recently revealed that *SIRT1* depletion causes telomere dysfunction, while telomere shortening leads to suppressed *SIRT1*. Also, it has been reported that increasing SIRT1 stabilizes the telomeres and rescues DNA damage and mitigates telomere-dependent diseases through regulating DNA repair pathways (Amano and Sahin 2019; Amano et al. 2019).

Second, a number of studies have notified that children with ADHD experience greater stress in social and academic contexts compared to their peers without ADHD (Hartman et al. 2019). All of the three molecules we measured are linked to stress and stressful life events. A number of previous studies revealed an association between telomere length, telomerase activity, and chronic psychosocial stress. The majority of these studies have shown that stress and adversity are major causes of accelerated telomere shortening, and telomere shortening increases telomerase activity (Beery et al. 2012; Coimbra et al. 2017; Kim et al. 2016). However, the studies conducted to evaluate the effects of psychological stress on telomerase activity until today have yielded contradictory results that may be caused by different physical processes including stress hormones, chronic stress, inflammation, and oxidative stress (de Punder et al. 2019). Several studies have also reported a suppressive effect of stressful conditions on telomerase activity (Epel et al. 2004, 2010). Likewise, evidence has indicated that chronic stress-induced social and cognitive alterations are related to an increased release and activity of MMP-9 (Kooij et al. 2014; Huntley 2012). Concerning the relationship of chronic stress with *SIRT1*, recent studies have reported that while *SIRT1* activity in the brain decreases upon chronic stress, activation of *SIRT1* could prevent or block chronic stress-induced unfavorable conditions such as abnormal dendritic structures (Abe-Higuchi et al. 2016; Lu et al. 2018). However, we cannot establish an association between the obtained results and chronic stressful events, conditions, and adversities since we did not evaluate the stress level in this study.

The strengths of the present study are that (1) the present study is the first attempt to investigate telomerase, MMP-9, and *SIRT1* molecules, which are associated with cognitive functions, stress resistance and neuroinflammation, in children with ADHD, (2) patients were sampled predominantly from non-treatment and non-comorbid settings, thus leading the general population to be more representative and enabling the adjustment for potential confounders, (3) psychopathology was comprehensively assessed using the structured interview techniques instead of relying on scales only. However, this study has some limitations, as well. First, biochemical measurements were not repeated after the treatment of ADHD. Second, we did not evaluate the self-perceived stress and psychosocial adversity which may be predictive of telomerase activity, MMP-9, and *SIRT1* levels. Bearing these limitations in mind, the results of this study should be interpreted carefully and these matters should be addressed in further studies.

In conclusion, this study is important since telomerase, MMP-9, and *SIRT1* are compared between children with and without ADHD for the first time. Based on the results of this initial study, it can be asserted that telomerase and MMP-9 levels are significantly higher and *SIRT1* levels are significantly lower in patients with ADHD, and all three molecules are significantly associated with both the severity of ADHD and cognitive functions in ADHD. We, thus, suggest that these molecules play an important role in ADHD's etiology. In addition, taken all together, the results of the present study indicate that novel therapeutic applications such as *SIRT1* activator, resveratrol or synthetic *SIRT1*-activating compounds, and minocycline (MMP-9 inhibitor) might lead

to alleviated clinical symptoms in ADHD. Therefore, future studies supporting and detailing whether or not telomerase, MMP-9 and *SIRT1* are involved in ADHD, will pave the way for new insights into ADHD's pathophysiology and new therapeutic interventions. Also, further prospective studies are required to determine any relationship between ADHD drugs and telomerase, MMP-9 and *SIRT1* as well as the possible involvement of these molecules in the clinical course of ADHD and treatment response.

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Author contributions The study was planned by AUC, SB, and CMI. AUC, CMI, and SAS assessed psychopathology and neuropsychological status, collected the data; SB, DU, and DB measured and analyzed all serum data; SC performed the statistical analysis of the data. AUC and SAS wrote the main paper and SC designed the tables. CMI, SB, DU, and DB reviewed the paper and gave technical support and conceptual advice. All authors read and approved the final manuscript.

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Data accessibility The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Compliance with ethical standards

Conflict of interest The authors reported no conflict of interest related to this article.

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