Original article / *Araştırma*

Heart rate variability as an indicator of autonomous nervous system activity in children with attention deficit hyperactivity disorder

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ABSTRACT

Objective: *The aim of the present study was to evaluate heart rate variability (HRV) in children newly diagnosed as attention-deficit/hyperactivity disorder (ADHD).* ***Methods:*** *A total of 51 children with new ADHD diagnosis who were not received any treatment formed the study group and 51 age and sex-matched healthy children were enrolled as the control group. 24-hour heart rate (HR) recordings were performed with rhythm Holter monitoring and HRV parameters indicating autonomous nervous system (ANS) functions were evaluated. Children in ADHD group were further divided into two groups as 'severe' and 'mild' ADHD according to Clinical Global Impressions-ADHD-Severity scale.* ***Results:*** *HRV parameters were comparable between ADHD and control groups. Whereas, percentage of consecutive NN intervals over 50 msn (pNN50) and minimum Spectral Power per hour (minSPH) values were lower; while, maximum 1-hour heart rate Holter (maxHRH) and mean heart rate (HR) values were higher in severe ADHD group than those of control group.* ***Conclusion:*** *These results support that as the severity of ADHD increases, ANS dysfunction becomes more overt. Further large scale, multi-centered, randomized-controlled clinical trials are needed to clarify possible role of ANS dysfunction in ADHD etiopathogenesis.* ***(Anatolian Journal of Psychiatry 2018; 19(5):493-500)***

Keywords: *attention-deficit/hyperactivity disorder, heart rate variability, autonomic nervous system, pNN50, minSPH, maxHRH*

Dikkat eksikliği hiperaktivite bozukluğu olan çocuklarda otonom sinir sistemi aktivitesinin bir göstergesi olarak kalp hızı değişkenliği

ÖZ

Amaç: *Bu çalışmanın amacı, yeni tanı konan ve hiç ilaç kullanmamış dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan çocuklarda kalp hızı değişkenliğini (KHD) değerlendirmektir.* ***Yöntem:*** *Ölçütlere uyan toplam 51 DEHB'li çocuk çalışma grubunu oluşturdu ve bunlarla benzer yaş ve cinsiyetteki 51 sağlıklı çocuk kontrol grubu olarak çalışmaya alındı. Yirmi dört saatlik ritm Holter kayıtları yapıldı ve otonom sinir sistemi (OSS) işlevlerini gösteren HRV parametreleri değerlendirildi. DEHB grubundaki çocuklar, klinik global değerlendirme-DEHB ciddiyet ölçeğine göre 'ciddi' ve 'hafif' DEHB gruplarına ayrıldı.* ***Bulgular:*** *DEHB ve Kontrol grubu arasında KHD parametreleri açısından anlamlı bir fark saptanmadı. Ciddi DEHB grubunun, 50 msn'nin üzerindeki ardışık NN aralıklarının tüm NN sayısına oranı (pNN50) ve minimum spectral power per hour (minSPH) değerlerinin ortalamaları kontrol grubuna göre daha düşük iken, maksimum 1-hour heart rate Holter (maksHRH) ve ortalama kalp hızı (KH) değerleri daha yüksekti.* ***Sonuç:*** *Bu sonuçlar, DEHB şiddeti arttıkça, OSS işlev bozukluğunun daha fazla olduğunu desteklemektedir. DEHB etiyopatogenezinde OSS işlev bozukluğunun olası rolünü açıklığa kavuşturmak için daha büyük ölçekli, çok merkezli, randomize-kontrollü klinik çalışmalara gerek vardır.* ***(Anadolu Psikiyatri Derg 2018; 19(5):493-500)***

Anahtar sözcükler: *Dikkat eksikliği ve hiperaktivite bozukluğu, kalp hızı değişkenliği, otonom sinir sistemi, pNN50, minSPH, maksHRH*

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly encountered psychiatric disorder of childhood, and is also a neuropsychiatric disorder laying the foundations for other psychiatric problems in adolescence and adulthood.[1] Autonomic nervous system is essential in maintaining attention, self-regulation, social connection and emotional stability, which are usually affected in children with ADHD.[2] Inattention and behavioral disinhibition are the main symptoms in ADHD which may be associated with autonomous nervous system (ANS) dysregulation; however, the results of previous studies about this issue are unclear.[3] Generally diminished sympathetic modulation has been proposed in children with ADHD or conduct disorder (CD).[4-6] However, alterations in the parasympathetic tonus in subjects with ADHD remains controversial.[5,7-9]

Parasympathetic system controls the heart rate (HR) through the vagus nerve which is known as cardiac vagal control (CVC).[10] This theory generally defines the relationship between autonomic functions and behaviors.[11] Social compliance is related with attention capacity, empathy ability, and emotional regulation. Therefore, it has been proposed that CVC might be related to ADHD, which presents itself with attention deficit, impulsivity, behavioral inhibition, and difficulties in targeted behaviors.[12-17] The 'Polyvagal Theory', which aims to explain CVC, was developed to understand the mutual communication between the heart and brain. According to this theory, the myelinated vagus is a structure, which has a role in social communication, attention, and self-regulation, and ends up in visceral organs. It also have critical roles in emotional expression such as the soft palate, larynx, pharynx, and facial muscles, and in communication.[18,19]

A change in heart rate from beat to beat is defined as heart rate variability (HRV).[20, 21] HRV provides information about sympathetic and parasympathetic balance, and it is accepted as the marker of cardiac autonomic tonus. HRV can be easily calculated using a rhythm Holter recording, a non-invasive method that converts CVC to measurable data.[22]

Autonomic activity variations in children with ADHD have been investigated in previous studies resulting in conflicting data. It was suggested that autonomic dysregulation plays a role in the pathogenesis of destructive behavioral disorders.[8,9,23,24]

The aim of the present study was to evaluate HRV in children newly diagnosed with ADHD, and to investigate whether an autonomic nervous system (ANS) dysfunction is present or not in children with ADHD compared to the healthy controls.

METHODS

A total of 51 children aged between 8 and 12 years, who applied to the outpatient clinic of the Child and Adolescent Psychiatry Department at the Medical School of İnönü University between January 2012 and January 2013, and complied with the DSM-IV diagnostic criteria, and were diagnosed as ADHD according to the Turkish version of the Schedule for Affective Disorders and Schizophrenia for School-age Children (6-18 years)-present and lifetime version (K-SADS-PL-T),[25] were included in the study. The children were newly diagnosed with ADHD and no treatment was initiated yet. An age and gender matched control group was formed, comprising 51 healthy and volunteering children. The study was approved by the Local Ethics Committee and informed consents were obtained from the parents.

Children with chronic medical illnesses (such as, neurological and/or cardiologic diseases), diffuse developmental disorders, mental retardation, or psychotic disorder were excluded from the study. The patients using drugs or substances affecting heart rate, sympathetic-parasympathetic nervous system activity, and QT interval in electrocardiography were also excluded.

A sociodemographic information form, the Conners' Parent Rating Scale-Revised Long Version (CPRS-RLV) was given to the parents. Children diagnosed with ADHD were divided into two groups as 'severe ADHD' and 'mild' ADHD according to Clinical Global Impressions-ADHD-Severity (CGI) scale.

Twenty-four hours heart rhythm recordings were performed with rhythm Holter monitorization starting from 9.00 a.m. to 9.00 a.m. of the following day using the rhythm Holter device.

Measurement of the HRV

Heart rhythm recordings were conducted for 24 hours both in the patient and control groups using a 3-channel rhythm Holter monitorization device. HRV parameters were analyzed by a computer program.

Turkish Version of Schedule for Affective Disorders and Schizophrenia for School-age Children (6-to-18 years of age)-Present and Lifetime Version (K-SADS-PL-T): This is a semi-structured scale for screening psychopathology in children and adolescents aging between 6-18 years, which was developed by Kauffman et al. The scale has three parts; the first part is an unstructured initial interview, the second part is the screening interview of approximately 200 symptoms for diagnosis, and the third part is the general rating scale for children who are being evaluated for functionality. Gökler et al. conducted the reliability and validity of K-SADS-PL-T in Turkey.[25]

Sociodemographic Information Form: This form was developed by the researchers, and it includes gender, age, education level, the places where the child was raised and lives, family type, social security, body disorders requiring continuous treatment, psychiatric illnesses in personal and family histories, symptoms, duration and onset age of symptoms, stress factors, and an accompanying psychiatric diagnosis. These forms were read out by the investigator, and completed with the participating subjects or their families.

Conners' Parent Rating Scale-Revised Long Form (CPRS-R): This is a scale containing a total of 80 items. The validity and reliability of this scale was performed in Turkey by Kaner et al.[26] It is composed of defiance, cognitive problems/ inattention, hyperactivity, anxiety, shyness, perfectionism, social problems, and psychosomatic complaint subscales. Questions were replied in a quadruple Likert scale by the parents. The options of never, rarely, frequently and always were scored as 0, 1, 2, and 3 points, respectively.

Statistical analysis

The SPSS 17.0 for Windows (SPSS Inc, Illinois, Chicago) package program was used for statistical analysis. The normal distribution of nümerical data was examined using the Kolmogorov-Smirnov test. Normally distributed parameters were compared using the Student-t test. Numerical variables that do not fit the normal distribution were tested with the Mann-Whitney U test. The chi-square test was used for comparisons of the groups in terms of categorical data. The level of statistical significance was accepted as $p<0.05$.

RESULTS

Of the enrolled 51 patients in the ADHD group, 8 (16%) were female, and 43 (84%) were male; the gender distribution in the healthy control group comprising 51 children was the same (16% female and 84% male). The mean ages of the control and ADHD groups were comparable (9.7±1.4 years vs. 9.6±1.4 years, p=0.981).

The distribution of accompanying disorders in children with ADHD was determined as defiant disorder (DD) in 45%, behavioral disorder (BD) in 6%, anxiety disorder in 18%, specific learning difficulties in 16%, and nocturnal enuresis in 2% of the study group.

Parental scores of the ADHD group were determined higher in all subscales of Conners' Parent Rating Scale except for perfectionism compared to those of the parents of the controls (p=0.289 for perfectionism, while p<0.001 for others) (Table 1).

Parameters of the HRV

Heart rate variability parameters were comparable between ADHD and control groups (Table 2). ADHD group was further divided into 2 according to their CGI scale as 'severe ADHD' and 'mild ADHD'. pNN50 and minSPH values were lower; while, maxHRH and mean HR values were higher in severe ADHD group than those of the control group, which indicate lower parasympathetic activity among children with

Table 1. Comparison of the scale scores of the study population

Scale scores	ADHD group Mean±SD	Control group Mean±SD	p
State anxiety	37.1±7.0	31.6±7.1	<0.001
Constant anxiety	33.0±6.7	28.7±5.6	<0.001
CDI	11.7±6.4	6.0±3.4	<0.001
CASI	31.5±6.5	29.8±7.4	0.179

CASI: Childhood Anxiety Sensitivity Index; CDI: Children's Depression Inventory

Table 2. Comparison of Conners Parental Rating Subscales

Subscales	ADHD mother	Control mother	p	ADHD father	Control father	p
Conners 1	15.0±6.7	6.9±5.0	<0.001	14.7±7.1	7.1±5.0	<0.001
Conners 2	19.6±7.3	6.5±5.4	<0.001	19.0±8.3	6.8±5.9	<0.001
Conners 3	13.8±6.2	4.7±4.2	<0.001	13.0±6.8	5.4±4.6	<0.001
Conners 4	9.9±5.4	5.7±4.1	<0.001	9.3±6.0	5.3±3.7	<0.001
Conners 5	6.9±4.3	6.0±3.6	0.289	7.3±3.8	6.8±3.8	0.411
Conners 6	5.4±3.6	1.9±2.0	<0.001	5.1±3.6	1.6±1.8	<0.001
Conners 7	4.7±3.5	2.9±3.0	0.005	4.8±3.9	2.8±2.6	0.004
Conners 8	21.8±6.9	7.8±6.5	<0.001	21.1±8.4	7.8±5.8	<0.001
Conners 9	11.7±4.6	4.5±4.0	<0.001	11.3±4.8	4.7±3.7	<0.001
Conners 10	4.4±2.6	1.8±1.7	<0.001	4.1±2.7	1.7±1.9	<0.001
Conners 11	16.1±6.4	6.3±4.9	<0.001	15.3±6.7	6.4±5.0	<0.001
Conners 12	15.2±5.5	4.7±3.8	<0.001	14.1±6.3	4.6±4.1	<0.001
Conners 13	15.1±6.4	5.4±4.5	<0.001	14.5±6.9	5.9±4.9	<0.001
Conners 14	30.3±10.1	10.1±7.6	<0.001	28.7±12.3	10.5±8.0	<0.001

Conners 1 accounts for 'oppositional defiant' subscale; Conners 2, 'cognitive problems/inattention' subscale; Conners 3, 'hyperactivity' subscale; Conners 4, 'anxiety-shyness' subscale; Conners 5, 'perfectionism' subscale; Conners 6, 'social problems' subscale; Conners 7, 'psychosomatic' subscale; Conners 8, 'ADHD index' subscale; Conners 9, 'Conners global index-restlessness -impulsivity' subscale; Conners 10, 'Conners global index-emotional lability' subscale; Conners 11, 'conners global index-total' subscale; Conners 12, 'DSM-IV symptoms subscale-inattention' subscale; Conners 13, 'DSM-IV symptoms subscale-hyperactivity-impulsivity' subscale; Conners 14, 'DSM-IV symptoms subscale-total' subscale.

Table 3. Comparison of HRV parameters between study groups

HRV parameters	ADHD group (n=51)	Control group (n=51)	p
MinHR , bpm	51.0±5.4	49.7±6.3	0.144
MaxHR, bpm	161.8±15.5	163.4±21.5	0.516
minHRH	69.8±8.7	68.0±10.6	0.161
Analyzed beat	113775±22268	101663±32513	0.109
Analyzed min	1306±201	1223±364	0.106
SDNN24h	128.2±32.0	132.4±39.1	0.482
SDANN	112.1±31.9	111.9±39.3	0.828
SDNNI	64.6±16.3	68.6±16.1	0.191
rMSSD	45.7±13.6	50.3±14.7	0.204
pNN50	21.0±10.6	24.4±11.0	0.174
SpectralP24h	4157±2057	4551±2131	0.352
maxSPH	9053±5724	9147±4730	0.625
maxQTc	471.4±30.2	464.0±21.1	0.543
ULF	57.7±30.7	66.6±34.3	0.271
VLF	2649±1719	2979±1592	0.240
LF	875.0±320.6	1034.1±451.1	0.099
HF	569.4±246.9	637.3±268.2	0.269

SDNN: standard deviation of all NN intervals; SDANN: standard deviation of 5 min averaged NN intervals; SDNNI: the mean of the 5-min standard deviation of the NN intervals calculated over 24 h; rMSSD: the square root of the sum of squares of differences of consecutive NN intervals; LF: low frequency; HF: high frequency; VLF: very low frequency; pNN50: proportion of NN50 divided by the total number of NN (R-R) intervals; NN50: the number of pairs of successive NN (R-R) intervals that differ by more than 50 msec; maxQTc: maximum value of QT interval corrected according to heart rate;
RMSSD: square root (mean (diff-RR x diff-RR)); SDNN: standard deviation of the NN (R-R) intervals; NN50: the number of pairs of successive NN (R-R) intervals that differ by more than 50 ms; pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals
Here's a quick run-down of what they mean (NN or R-R intervals means the time between two successive heart beats). RMSSD: root mean square of the successive differences - used for a good snapshot of the autonomic nervous system's parasympathetic branch and is the basis of our 'HRV score'. RMSSD is strongly backed by research and is considered the most relevant and accurate measure of autonomic nervous system activity over the short-term.

Table 4. Comparison of HRV parameters of severe ADHD and control groups

	Severe ADHD (n=23)	Controls (n=51)	p
minHR	51±5	50±6	0.445
maxHR	165±14	163±22	0.693
AverageHR	91±9	85±8	0.016
minHRH	71±9	68±11	0.334
maxHRH	119±11	111±12	0.007
SDNN24h	132±36	132±39	0.939
SDANN	116±36	112±39	0.642
SDNNI	67±20	69±16	0.664
rMSSD	45±14	50±15	0.115
pNN50	19±10	24±11	0.050
spectralP24h	4524±2676	4551±2131	0.963
minSPH	1365±921	1828±865	0.043
maxSPH	10383±7591	9147±4730	0.401
maxQTc	473±37	464±21	0.279

SDNN: standard deviation of all NN intervals; SDANN: standard deviation of 5 min averaged NN intervals; SDNNI: the mean of the 5-min standard deviation of the NN intervals calculated over 24 h; rMSSD: the square root of the sum of squares of differences of consecutive NN intervals; HR, heart rate; HF: high frequency; LF: low frequency; VLF: very low frequency; pNN50: proportion of NN50 divided by the total number of NN (R-R) intervals; NN50: the number of pairs of successive NN (R-R) intervals that differ by more than 50 msec; maxQTc: maximum value of QT interval corrected according to heart rate.

with overt ADHD (Table 3).

DISCUSSION

In the present study, the HRV parameters of the children with newly diagnosed ADHD and healthy controls were measured using 24-hour rhythm Holter monitorization. Though no statistically significant difference was determined in these parameters between with the entire ADHD group and healthy controls; we found that pNN50 and minSPH values of children 'severe' ADHD were lower than those of the control group; while, maximum HRH and mean HR values of the former group were higher than that of the latter group. These results suggest that as the severity of ADHD increases, ANS dysfunction become more overt, which possibly reflects dysregulation in vagal activity.

Heart rate variability parameters provide information about the status of the ANS. Among these parameters, RMSSD and pNN50 indicate specifically parasympathetic parts of autonomic tonus, which are regulated by the vagal route; while SDNN generally reflects the sympathetic tonus.[4,21,23] In some studies, it has been proposed that autonomous dysregulation might play a role in the pathogenesis of destructive behavioral disorders.[20,27] Changes in autonomic activity were investigated in children with ADHD, but conflicting results were obtained. Since autonomic nervous system activities play an essential role in sustaining attention, self-regulation, establishing social connections and emotional stability, which are usually affected in children with ADHD,[2] these may be associated with ANS dysregulation. However, the results of previous studies about this issue are unclear.[3] Generally diminished sympathetic modulation has been proposed in children with ADHD or conduct disorder (CD).[4-6] Whereas, alterations in the parasympathetic tonus in subjects with ADHD remains controversial.[5,7-9] Musser et al. found that[9] children with ADHD had ineffective parasympathetic responses in both induction and suppression conditions. However, it was reported that the behavioral disorders were related to aggressive and negligent behaviors, and decreased sympathetic and parasympathetic activities.[6,28-30] Consistently, in a recent study, Wang et al. reported that preschool-age boys with more severe inattentive and hyperactive behavioral characteristics had lower sympathetic and higher parasympathetic activity.[31]

Although there are controversial reports about hypo-sympathetic activation in children with ADHD,[24] it has been recently reported in many basal heart activity studies that parasympathetic activities were determined to be lower in children with ADHD.[23,27,32] In a study where circadian rhythm analysis was performed, high heart rates were shown during nighttime in children with

ADHD.[32] Also, Tonhajzerova et al. reported higher heart rates together with lower rMSSD values in short-term HRV analyses during resting states and orthostatic provocation.[8] Consistently, our results regarding RMSSD and pNN50 values, which indicate parasympathetic activity in overt ADHD patients, were lower in AHDH group, whereas their mean HR was higher than that of the healthy controls. According to Porges' Polyvagal Theory, our autonomic nervous system does not only control our heart rates and peristaltism in our bodies, but also our social and emotional behaviors. In this context, decreased vagal activity has negative effects on the social and emotional development of children.[19] In the light of these results, consistent with our study; decreased vagal tonus in children with ADHD may have negative effects on social and emotional development of these children.

The majority of researches have proposed that autonomic signs determined in ADHD are related to the accompanying behavioral disorders (BD) rather than ADHD itself.[33] It was determined that the most common accompanying psychopathology in our study population was defiance disorder (DD). It is observed that 45% of ADHD patients were diagnosed additionally with DD, and 6% with BD. As the BD ratio was low in all ADHD patients in our sample size, it is thought to have led to the result that both ADHD and control groups had similar HRV values. Decreased vagal activity was determined more markedly in children with severe ADHD, in which BD was more frequently observed than the control group.

Various physiological parameters such as blood pressure, skin transduction rate (STR), HRV and pupil light reflex have been used to investigate relationships between ANS and ADHD. Decreases in HRV and electro-dermal response were observed in adults with antisocial behaviors, and children with BD, due to less autonomic stimulation.[34] In spite of this, in a study performed by Kara et al. on ANS functions in boys aged 6 to 11 years and who were diagnosed with ADHD using pupilometric measurement, it was reported that pupillary diameters measured under photopic and mesopic conditions were similar to those in the healthy controls.[35]

One of basic research subjects in ADHD and HRV studies were the investigation of the effects of psycho-stimulants on the cardiovascular system. The psycho-stimulant, Methylphenidate, is commonly used in ADHD treatment. In another study performed by Buchorn et al., decreased pNN50 and RMSSD values and increased HR in children with ADHD were reported as returned to normal levels after methylphenidate treatment.[17] Only newly diagnosed ADHD children who are treatment naive were enrolled to the present study, since psycho-stimulant drugs have substantial effect on HRV. We thereby aimed to evaluate whether children with ADHD have any difference regarding ANS functions compared to those of healthy peers.

One of the limitations of our present study was that HRV analysis had not been performed during task; instead, we recorded 24-hour heart rhythm during an ordinary day. Secondly, we did not exclude anxiety disorder accompanying ADHD, which may affect heart rhythm. However, only nine children had concomitant anxiety disorder in ADHD group. On the other hand, children with 'pure' ADHD are relatively rarely encountered and are not representative of typical ADHD population. This makes it difficult to compare the results of the relevant studies. These children may also have sub-threshold symptoms of comorbidities that are not accounted for.[36]

CONCLUSION

In our study, we determined that pNN50 and minimum SPH values, which show parasympathetic activity, were lower in children with severe ADHD than their healthy peers, whereas their maximum HRH and mean HR values were higher than the control group. These results support that as the severity of ADHD increases, ANS dysfunction becomes more overt. However, further studies are required to investigate ANS dysfunction in ADHD patients.

Authors' contributions: *T.Y.: planning, literatüre review, conducting the research, statistics, writing manuscript; Ö.Ö.: finding the issue, planning, reviewing the manuscript.*

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