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Surface Electrocardiographic Parameters of Children and Adolescents Diagnosed with Attention-Deficit/Hyperactivity Disorder in an Ambulatory Community Pediatric Center: A Focus on Cardiac Repolarization Electrocardiogram Intervals

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Abstract

Objectives: Our research aims were to determine if repolarization measures (QTcF, QTcB, JTcF, and JTcB) in attention-deficit/hyperactivity disorder (ADHD) children and adolescents differ from normal subjects and determine if the JTc interval duration, as a purer repolarization measure than QTc, strengthens the differentiation between ADHD and normal children and adolescents.
Methods: This study included 418 subjects aged 5–18 years who were diagnosed with ADHD, and 1948 subjects in a historical normal control group. One-way analysis of variance (ANOVA) was performed to compare the independent groups on normal continuous outcomes. Means and standard deviations (SDs) were reported and interpreted for the ANOVA. Logistic regression analysis was performed to test the ability of four variables (QTcB, QTcF, JTcB, and JTcF) to predict an ADHD diagnosis, with age and gender as independent covariates. The log odds with standard errors for each variable were reported and interpreted for the logistic models.
Results: In the nominal logistic regressions with JTcF ≥322 or JTcB ≥335 (values 1 SD above the mean of the control group), age and sex were significant contributors to the models that showed that subjects with a JTcF ≥322 ms had a statistically and significantly higher probability to be diagnosed with ADHD in comparison with normal control subjects (odds ratio [OR]: 2.6, 95% confidence interval [95% CI] 2.02–3.33, $p < 0.0001$). Similarly, those subjects with a JTcB ≥335 ms were 2.7 times more likely to be diagnosed with ADHD than normal control subjects (OR: 2.7, 95% CI 2.1–3.45, $p < 0.0001$).
Conclusions: JTc provided a clearer separation of the groups than QTc. JTcB and JTcF 1 SD above the control group means are strong predictors of ADHD diagnosis and remain so even when strong demographic predictors of longer QTc (age and sex) are included in the regression models. Consideration should be given to recording a pretreatment electrocardiogram in all children and adolescents with ADHD, and to measuring and monitoring JTc in patients with ADHD, especially when considering the addition of QT prolonging drugs.

Keywords: children, ADHD, electrocardiogram, repolarization, QTc, JTc

Introduction

Stimulant drugs, including amphetamines, especially when misused, carry a risk of sudden cardiac death or serious cardiovascular adverse warning (FDA 2011; Zukkoor 2015). Nevertheless, they are routinely prescribed to patients with attention-deficit/hyperactivity disorder (ADHD) (Vetter et al. 2008). Drugs that prolong QT or JT have varying warning levels and recommendation in their labels, depending on the extent and circumstances of the effect. A recent study reported that methylphenidate

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and atomoxetine caused QTc prolongation after 8 weeks of treatment and suggested that ADHD patients have ''potential discrete abnormalities in cardiac functioning associated with dopaminergic and noradrenergic genes'' (Snircova et al. 2017). A nationwide self-controlled case study series of a large insurance data base analysis in South Korea suggested an increase in the relative risk of cardiac arrhythmias in ADHD children treated with methylphenidate (Shin et al. 2016). Regarding cardiovascular events in children taking QT prolonging medications alone or in combination with stimulants, there is little literature information on this topic (Kaltman and Berul 2015; Rohatgi et al. 2015; Zhang et al. 2015). It was suggested by Zhang et al. that ADHD subjects with long QT syndrome (LQTS) who were treated with stimulants or nonstimulant medications had a ''62% cumulative probability of cardiac events in the ADHD treatment group compared to 28% of the matched LQTS control group not exposed to ADHD medications'' (Zhang et al. 2015). Presently, a routine electrocardiogram (ECG) test before stimulant treatment is not mandated (Perrin et al. 2008; Vetter et al. 2008; Hamilton et al. 2012). There is a paucity in the research regarding electrocardiographic repolarization duration in children with ADHD. Psychoactive drugs with QT prolonging effects are often prescribed in ADHD, such as antidepressants (e.g., fluoxetine and amitriptyline) and antipsychotics (e.g., aripiprazole, risperidone, and haloperidol), along with many other commonly prescribed drugs, such as loperamide, ondansetron, and metoclopramide macrolides (e.g., clarithromycin and erythromycin). These drugs have an increased risk in patients with preexisting QT prolongation of inducing long-QT-associated ventricular arrhythmias-torsades de pointes (Ackerman et al. 2013). This additional risk supports the routine recording of a pretreatment ECG in ADHD patients being prescribed stimulants, QT prolonging drugs, or both. It has been suggested that the ECG JTc interval (J point to the end of the T wave) reflects more accurate myocardial repolarization changes than the QTc interval during ventricular pacing (Tsai et al. 2014). Moreover, JTc, if significantly prolonged, serves as a better potential ''independent predictor of cardiovascular events in men with wide QRS complex'' (Crow et al. 2003), although this may not be the case for children and adolescents.

Objectives of This Study

The objectives of this study were to (1) determine if the ECG repolarization times (QTcB, QTcF, JTcB, and JTcF) of ADHD patients are different from normal controls considering age and sex differences; and (2) determine if the JTc interval is a better repolarization measure than QTc in comparing ADHD with normal children and adolescents.

Materials and Methods

Our research protocol was approved by the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals, Houston, TX (protocol: H-40256, 2016). The IRB committee agreed with our request to waive the need for ethics approval and the need to obtain informed consent for the medical records review, data analysis, and publication of the retrospectively obtained and anonymized data for this noninterventional study. Our methodology had been previously published (Isart et al. 2019). Our population research sample ($N=2366$) included two groups: Group 1 with children and adolescents (5–18 years of age) evaluated for ADHD at an urban community clinic (Kids 'N Teen Clinics, PA, Houston, TX) who had an ECG done ($n=418$, 2008–2017); and Group 2 is the historical control group that included 1948 children and adolescents of 5–18 years of age from a large group of healthy children and adolescents who were subjects in pharmaceutical company-sponsored clinical trials with centralized management and interpretation of their ECGs by a core ECG laboratory (Covance, Reno, NV, 2003–2005, Table 1), reported by Mason et al. (2007). We also compared our findings with baseline ECG values of a large ADHD pediatric sample

Table 1. Demographic and Study Variables of Subjects ($N=2366$)

Group Demographic and study variables (N = *2366*)	*1 ADHD patients* (n = *418*), n *(%)*	*2 Normal controls*[a] (n = *1948*), n *(%)*	*Significance* p < *0.05**
Age <10 years	257 (61.60)	963 (49.4)	<0.001*
Male	316 (75.80)	1160 (59.5)	<0.001*
Black	160 (38.40)	—	—
Recent stimulant or psychotropic therapy	31 (7.40)	—	—
QRS ≥94 ms (≥1 SD)	40 (9.57)	310 (15.91)	0.004*
QTcB ≥430 ms (≥1 SD)	107 (25.60)	285 (14.63)	<0.001*
QTcB ms, mean (SD)	415.99 (19.15)	407.90 (21.34)	<0.001*
QTcF ≥410 ms (≥1 SD)	103 (24.64)	291 (14.94)	<0.001*
QTcF ms, mean SD	397.98	391.09 (18.76)	<0.001*
Male	398.93 (1.11)	390.39 (0.55)	
Female	395.15 (1.92)	392.13 (0.67)	
JTcB ms, mean (1 SD)	326.47 (19.73)	314.07 (20.52)	<0.0001*
(335 ms ≥1 SD, # subjects)	134 (32.06)	288 (14.78)	<0.0001*
JTcF ms, mean (1 SD)	312.47 (22.74)	301.07 (20.54)	<0.0001*
(322 ms ≥1 SD, # subjects)	125 (29.90)	284 (14.58)	<0.0001*
Reasons for ECG test			
ADHD stimulant monitoring	395 (94.5)	—	
ADHD with cardiovascular symptoms or signs	23 (5.5)	—	
General health screening	0	1948 (100)	

[a]Of the control sample, 75.56% were North American children (2003–2005). The 2000 U.S. census reported 12.3% of the U.S. population as African American, 12.5% as Latin American, and 75.1% as white.

ADHD, attention-deficit/hyperactivity disorder; ECG, electrocardiogram; SD, standard deviation.

of subjects enrolled in 20 clinical trials (including atomoxetine registration) in global outpatient academic centers ($n=5930$, 77.3% male, 22% non-Caucasian, 6–10 years (38.4%), 10–18 years (61.6%) (Table 2) (Prasad et al. 2007).

Group 1 subjects were either referred by public school counselors or were noted to have learning difficulties during the yearly clinical intake. As part of clinical care, legal guardians and teachers of children with behavioral difficulties were instructed to complete psychometric scales that included the pediatric Symptom Check list (Murphy et al. 2016) and the Parents Vanderbilt Scales (Wolraich et al. 2003). The initial case list for medical record review (Group 1) included a printout of the names of patients whose billing records included an ADHD diagnosis from 2008 to 2017 (ICD-9-CM, *International Classification of Diseases*, ninth revision, code 314.0x and ICD 10-CM). For confidentiality reasons, a copy of the psychometric scales and the ECG was coded. Each coded ECG was read by a senior pediatrician (F.A.I.) and blindly by a senior pediatric cardiologist (F.R., who did not know the case or control status of each ECG). Those ECGs with significant abnormalities were referred to a pediatric cardiologist for further evaluation. As a result, Group 1 included all pediatric patients who met the *Diagnostic Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (American Psychiatric Association 2000) criteria for Attention-Deficit Hyperactive/Disorder (home and school dysfunction), and whose legal guardians verbally agreed to have an ECG done on their child ($N=418$). Most parents and teachers completed a Vanderbilt psychometric scale. ADHD study subjects were excluded when a structural heart defect was found. Our record review of Group 1 did not find any documentation of the current use of potential cardiovascular stimulants such as decongestants, caffeinated beverages, or any metabolic or electrolyte imbalance at the time the ECG was performed.

ADHD assessment

ADHD was diagnosed utilizing all available clinical information that included the NICHQ Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) and the NICHQ Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS) (Wolraich et al. 2003). Abnormal ''cluster'' behavior was scored according to the bright future tool for professionals (VADPRS) and those who scored 2 (often) or 3 (very often) are counted as abnormal (Wolraich et al. 2003). The reliability and cost-effectiveness of the VADPRS are well accepted in research and clinical settings (Wolraich et al. 2003). The diagnosis of ADHD requires six or more counted behaviors with a score of 2 or 3 in a ''behavioral cluster'' in the areas of inattention (IN), hyperactivity/impulsivity (HI), or both for the combined type (IN/HI). Thus, a minimum score of 12 was needed for the ADHD diagnosis on that behavioral ''cluster.''

Electrocardiography

The Welch-Allyn CP200 Electrocardiograph was used using standard Welch-Allyn electrodes on most ADHD study subjects according to the CP200 instruction manual (Welch Allyn, Inc. 2005). Most if not all ECGs were recorded with all filters ON (muscle tremor [35 Hz], baseline [high pass 0.5 Hz], mains [AC interference 50–60 Hz] at 25 ms and 10 mV). The automatically calculated heart rate (HR, beats per minute), PR, QRS, QT, and QTcB that use the global median beat from all 12 leads were used for the study (Kors and Herpan 2009). A few ECGs done elsewhere also reported automated HR, PR, QRS, and QTcB utilizing the Marquette ECG automated algorithm 12SL (General Electric Marquette 12 SL 2005). The JT segment duration was calculated by subtracting the QRS duration from the QT interval. When QT values were missing, they were extrapolated using the reported HR and QTcB from the database. The QTcB and JTcB intervals of each subject were calculated by applying Bazett's formula (QT or JT/RR^{-2} in seconds) (Berul et al. 1994). The QTcF and JTcF intervals among ADHD subjects were derived by applying Fridericia formula (QT or JT/RR^{-3} in seconds). ECGs in Group 1 with significant abnormalities were referred to a pediatric cardiologist for further evaluation. ECGs of ambulatory ''normal'' children (Group 2 = 2049) were done using two electrocardiographs, the MTX-2 and the General Electric MAC 1200. QTc was calculated in the control group by the semiautomated method. The ECG algorithm first displayed automated annotations of the waveform onsets and offsets of three consecutive beats, usually in lead 2. The cardiologist then overread the ECGs, adjusting these annotations, if necessary. Then QTc was calculated by the Fridericia formula. JTc was calculated by subtracting QRS from QT, and then applying the Fridericia formula to the JT interval. According to Mason et al., no statistical difference in the ECG intervals of the MTX-2 and MAC 1200 was found (Mason et al. 2007).

Statistical analysis

Chi-square statistics were used to compare the ADHD group and the normal control group on dichotomous categorical outcomes. Frequencies and percentages were reported and interpreted for the chi-square analyses. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated for the chi-square statistics. One-way analysis of variance (ANOVA) was performed to

Table 2. Cardiac Repolarization Measures (QTcF and JTcF Means and Standard Deviations) of Attention-Deficit/Hyperactivity Disorder Groups and Normal Controls, According to Pubertal Status and Gender

Age group[a]	*Sex*	*QTcF*[b] *Prasad ADHD*	*QTcF Isart ADHD*	*QTcF Mason normal*	*JTcF Isart ADHD*	*JTcF Mason normal*
Prepubertal	M	393 ± 17.1	398 ± 21.3	388 ± 18.5	314 ± 25.0	299 ± 20.1
Pubertal	M	399 ± 19.0	400 ± 19.6	394 ± 18.0	312 ± 23.5	304 ± 19.0
Postpubertal	M	402 ± 18.5	406 ± 16.1	388 ± 19.1	309 ± 22.2	291 ± 19.6
Prepubertal	F		389 ± 16.1	388 ± 19.3	309 ± 16.8	301 ± 20.8
Pubertal	F		399 ± 15.8	393 ± 18.0	314 ± 17.4	304 ± 18.9
Postpubertal	F		401 ± 16.6	398 ± 18.4	307 ± 15.6	305 ± 20.5

[a]Prepubertal = age <9 for F and <10 for M; pubertal = age 9 to 13 for F and 10 to 14 for M; postpubertal = >13 for F and >14 for M.
[b]Prasad values for M and F combined, with F representing 24% of the total.
ADHD, attention-deficit/hyperactivity disorder; F, females; M, males.

compare the independent groups on normal continuous outcomes. Means and standard deviations (SDs) were reported and interpreted for the ANOVAs. Logistic regression analysis was performed to test the ability of four variables (QTcB, QTcF, JTcB, and JTcF) to predict an ADHD diagnosis, with age and gender as independent covariates. The log odds with standard errors for each variable were reported and interpreted for the logistic models. Statistical significance was assumed at an alpha value of 0.05 and all analyses were performed using SPSS Version 26 (IBM Corp., Armonk, NY).

Results

Out of 2366 subjects (5–18 years of age), 418 (17.7%) were diagnosed with ADHD (Group 1). There were 1948 (82.3%) subjects in the historical normal control group (Group 2) (Table 1). When the ADHD (Group 1) was compared with the large sample of normal controls (Group 2), contingency analysis suggested a greater proportion of ADHD subjects with more than 1 SD above the QTcF and JTcF means ($n = 103$ [24.64%] vs. $n = 291$ [14.94%] and JTcF $n = 125$ [29.90%] vs. $n = 284$ [14.58%], $p < 0.0001$). On the other contrary, the proportion of subjects with more than 1 SD above the mean QRS (≥94 ms) was lower in the ADHD group than the normal control group ($n = 40$ [9.5%] vs. $n = 310$ [15.9%], $p < 0.004$, Table 1).

There was a significant difference between the ADHD group and the control group on QTc measurements. ANOVA showed that the ADHD group had significantly higher QTcF and QTcB mean values than normal controls, $p < 0.0001$. Moreover, ADHD subjects were more likely to have a QTcF (OR: 1.86, 95% CI 1.44–2.40, $p < 0.0001$) and QTcB (OR: 2.01, 95% CI 1.55–2.58, $p < 0.0001$) more than 1 SD of the mean ($p < 0.0001$) than normal subjects. When predicting for ADHD diagnosis, QTcF (>410 ms), QTcB (>430 ms), age, and male sex were significant predictors of ADHD diagnosis in the nominal logistic fit, $p < 0.0001$. Similarly, we found a significantly higher proportion of subjects with JTcF and JTcB above 1 SD of mean in the ADHD group when compared with the normal control group, $p < 0.0001$. See Table 1 for the proportions of each group. Unadjusted differences of extreme QTc values (≥450 ms) between ADHD subjects and normal controls demonstrate no statistically significant differences between study groups. Of the 418 ADHD subjects, 11 (2.63%) had a QTcB of 450 ms or more. Only one had a QTcB >460 ms (0.4%). Similarly, of the 1948 normal controls, 60 (3.08%) had a QTcB ≥450 ms, and only 21 (1.08%) had a QTcB longer than 460 ms ($p = 0.377$). Our logistic regression analysis for the models predicting for ADHD diagnosis demonstrated that JTcF and JTcB were significant predictors when age and male sex were considered in the models in comparison with normal controls ($p < 0.0001$, Table 3).

In the nominal logistic regressions with JTcF ≥322 or JTcB ≥335 (values 1 SD above the mean of the control group), age and sex were significant contributors to the models that showed that subjects with a JTcF ≥322 ms had a statistically and significantly higher probability to be diagnosed with ADHD in comparison with normal control subjects (OR: 2.6, 95% CI 2.02–3.33, $p < 0.0001$). Similarly, those subjects with a JTcB ≥335 ms were 2.7 times more likely to be diagnosed with ADHD than normal control subjects (OR: 2.7, 95% CI 2.1–3.45, $p < 0.0001$, Table 4).

Our ADHD group mean repolarization interval measures are compared with those reported by Prasad et al. (2007) in pediatric patients with ADHD. Their observations in ADHD subjects are similar to ours (Table 2).

Table 3. Logistic Regression of JTcF, JTcB, Age, and Male Sex As Predictors of Attention-Deficit/Hyperactivity Disorder Diagnosis Using Normal Controls ($N = 1948$) As Reference Outcome Variable

Outcome ADHD group versus normal control group	*Predictor*	B *(SE)*	p
	Constant	−9.04 (0.88)	<0.0001*
	JTcF	0.027 (0.003)	<0.0001*
	Age	−0.11 (0.02)	<0.0001*
	Male sex	0.36 (0.06)	<0.0001*
	Constant	−10.21 (0.97)	<0.0001*
	JTcB	0.029 (0.003)	<0.0001*
	Age	−0.07 (0.018)	<0.0001*
	Male sex	0.39 (0.063)	<0.0001*

*Statistically significant, $p < 0.05$.
ADHD, attention-deficit/hyperactivity disorder; SE, standard error.

Discussion

We sought to analyze the repolarization intervals of ADHD patients, as they often are prescribed drugs for comorbid conditions that could prolong repolarization and predispose them to arrhythmias. For example, risperidone in high doses has been shown to prolong myocardial repolarization (Gluais et al. 2004). The QT segment measures the heart's total depolarization and repolarization time, while the JT segment excludes the QRS interval and has been proposed as a more appropriate measurement for repolarization risk stratification than the QT (Berul et al. 1994). A JTcB interval higher than 340 ms has been suggested to be a robust predictor of repolarization abnormalities in patients with long QT syndrome (Berul et al. 1994). We found that there was a significant proportion of ADHD subjects with a JTcB interval duration of 1 SD above the mean of normal controls (≥335 ms). Moreover, JTcB (1 SD above the control mean, ≥335 ms) and JTcF (1 SD above the control mean, ≥322 ms) were strong predictors of ADHD diagnosis even when additional strong QT predictors, age and sex, were included in the regression models. We found that the Akaike's information criterion for the JTc nominal fit was lower (i.e., better) than the QTc fit and that adding QTcF to the nominal fit for the JTcF fit did not improve the model. The shared variances (R^2) were larger in the JTc ANOVA compared with the QTc ANOVA. This suggests

Table 4. Logistic Regression of JTcF, JTcB, Male Sex, and Age As Predictors of Attention-Deficit/Hyperactivity Disorder Group ($N = 418$) with Normal Controls ($N = 1948$) As Reference Outcome Variable

Outcome	*Predictor*	*AOR*	*95% CI*	p
ADHD group versus normal control group				
	JTcF ≥322 ms	2.59	2.02–3.32	<0.0001*
	Male sex	2.02	1.58–2.57	<0.0001*
	Age	0.90	0.93–1.11	<0.0001*
ADHD group vs. normal control group				
	JTcB ≥335 ms	2.69	2.10–3.45	<0.0001*
	Male sex	2.12	1.66–2.71	<0.0001*
	Age	0.91	0.94–1.09	<0.0001*

*Statistically significant, $p < 0.05$.
95% CI, 95% confidence interval; ADHD, attention-deficit/hyperactivity disorder; AOR, adjusted odds ratio.

that JTc is a better parameter to address repolarization differences between ADHD subjects and normal controls.

The present study is the first to show that ADHD children and adolescents have longer repolarization times than normal controls of similar age and sex. Therefore, the risk of repolarization-related arrhythmias must be considered before prescribing drugs that are known to prolong the QT interval (Martin et al. 2012). Consideration should be given to measuring and monitoring JTc in ADHD subjects, especially when QT prolonging drugs are prescribed. There is no reported agreement regarding safe JTcB or JTcF values in this setting. Some clinicians may elect to use our 1 SD above the mean as a benchmark. We are not aware of any study reporting QTcF, JTcF, and JTcB means and SDs for children and adolescents according to age and gender. Consequently, we are not able to compare our parameters of interest with reference data except for QTcB. Mason et al. (2007) reported important sex differences among 2308 children and adolescents in the 98th percentile for QTcB. The QTcB for females was more prolonged than males (457–461 ms vs. 448–452 ms) (Mason et al. 2007). Rijnbeek et al. (2001) reported similar results (447–457 ms in females vs. 440–449 ms in males) in 5–16-year-old children and adolescents. Our data analysis did not concur with this trend. Our ADHD mean repolarization interval measures are comparable with those reported by Prasad et al. (2007) in pediatric patients with ADHD. Although QTcF and QTcB means in patients with ADHD were statistically and significantly different from normal controls, the differences are not clinically important, except when considering adding QT prolonging drugs. Whereas the ADHD group had higher representation in the extreme group (445–459 ms) when compared with normal controls, the unadjusted differences of extreme QTc values between ADHD subjects and normal controls did not demonstrate a statistically significant difference between them. The lack of statistical significance may be explained by the small sample size and shorter QRS segments in the ADHD group. The unadjusted data analysis emphasizes the need of larger sample sizes when studying extreme QTC measurements and the importance of JTC measuring when doing risk stratification before recommending QTC prolonging drugs. Even though we found that JTcB and JTcF above 1 SD of the mean are strong predictors of the diagnosis of ADHD, the design of our study did not allow us to explore the possibility that the severity of the ADHD behavioral phenotype and/or other comorbid conditions such as anxiety or oppositional defiant disorder correlates with the extent of the increase in JTc. We can only speculate about the biological plausibility of our findings. We postulate that longer cardiac repolarization times in ADHD subjects may be a phenotypic expression of the underlying genetic and/or epigenetic abnormality causing ADHD. This is a research question that needs to be explored.

Conclusions

QTc and JTc intervals are longer in patients with ADHD than in normal subjects. Older subjects and females are well-known predictors of longer QT. Inclusion of these demographic predictors in the models showed them to be strong contributors to the models, as expected, but JTc remained a strong independent predictor of the ADHD diagnosis. Our observations suggest that treatment of comorbid conditions, including depression, which is common in patients with ADHD, with QT prolonging drugs should be undertaken with caution. Consideration should be given to measuring and monitoring JTc in those patients. The JTc interval is simple to calculate, noninvasive, and more likely to detect repolarization abnormalities than QTc alone.

Clinical Significance

Finally, given the fact that the commonly used stimulants for treatment of ADHD and the relative QT prolongation in patients with ADHD both pose a proarrhythmia risk, we recommend that ECGs should be considered in patients with ADHD before use of these drugs. A prospective study is needed to rule out a measurement algorithm difference as a contributor to our findings. In addition, the present research supports the need for future prospective studies looking at the effects of stimulants +/− QT prolonging drugs on electrocardiographic parameters, including QTcF, QTcB, JTcF, and JTcb.

Study strengths and limitations

Causality cannot be proven with unmatched case/control studies. Our results may not be generalizable to the U.S. population due to our small sample size of ADHD cases ($N=418$) and a skewed demographic sample (mostly Hispanic and African American patients in the ADHD group). Of the control sample, 75% were North American children and it is likely that <12% represented the African American children. However, having a large normal control sample strengthens our conclusions. A weakness of this study is that the bilingual psychometric scales were filled out by the parents within the context of a high-pace general pediatric clinic. We assumed that parents understood the content of the questionnaire and that they gave us reliable answers. The psychometric scales we used have been validated and contributed to the diagnosis of ADHD and its behavioral phenotype (Wolraich et al. 2003). Some of our ADHD patients might have been on stimulants before the ECG testing (up to 7.4%). If there was an effect, it is likely to have been negligible, especially with regard to repolarization effects. Prasad et al.'s (2007) mean ECG values among stimulant-experienced and stimulant-naive pediatric subjects were not clinically significant. Negrao et al. suggested that in a small group of patients ($n=19$) ''methylphenidate indeed caused increase in HR and BP but no change in cardiac depolarization and repolarization duration of homogeneity'' (Negrao et al. 2009). Yet, the use of stimulant medication before ECG testing represents a potential confounding variable that needs to be controlled for in future studies as suggested by a recently published study (Snircova et al. 2017). ECG parameter interobserver variability was not present, as all measurements were automated. We assumed high correlation among ECG algorithms generated by the FDA-approved ECG equipment, but there are known, small, systematic differences among commercial ECG machines (Klingfield et al. 2014, 2018; McFarlane et al. 2017), which could have contributed negatively or positively to our observations. Because of this, our findings should be evaluated in a prospective study using uniform ECG equipment.

Disclosures

No competing financial interests exist.

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