


# Cardiac Early Repolarization Pattern Anomalies Among Children and Adolescents With and Without Attention-Deficit Hyperactivity Disorder: A Community Observational Study

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## Abstract

Our research had 2 aims, first, to determine if electrocardiographic early repolarization pattern anomalies (ERPAs) were more likely present among children and adolescents diagnosed with attention-deficit hyperactivity disorder (ADHD;  $n = 416$ ) when compared with non-ADHD children ( $n = 187$ ), and second, to assess if ADHD patients whose parents report severe ADHD psychometric scores were more likely to have ERPA in their surface ECG (electrocardiography) when compared with other ADHD patients with mild to moderate dysfunction or no dysfunction. In our unmatched case-control study, ERPA was recognized when there was an end QRS notch (J wave) or slur on the downslope of a prominent R wave with and without ST-segment elevation and the peak of the notch or J wave ( $J_p \geq 0.1$  mV in  $\geq 2$  contiguous leads, excluding VI-V3 anterior lead, and QRS duration (measured in leads in which a notch or slur is absent)  $< 120$  ms or ST-segment elevation  $> 0.1$  mV in  $\geq 2$  contiguous leads, excluding VI-V3, and QRS duration  $< 120$  ms. The *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition) criteria were used to diagnose ADHD. Our data analysis suggested a significant association between ERPA presence and ADHD ( $n = 603$ ,  $P = .020$ ). Our logistic regression model suggests that patients with ERPA ( $n = 167$ ) were 2.778 times more likely to have a diagnosis of ADHD after controlling for age, gender, and ethnicity (95% confidence interval for odds ratio 1.087-7.100,  $P = .033$ ). Multiple regression models suggested that age,  $P < .001$ ; gender,  $P < .001$ ; ERPA,  $P = .004$ ; and ERPA leads number,  $P = .022$ , were significant predictors of global parental ADHD worry scale. Hispanic and black ethnicity were not significant predictors. Consequently, the presence of ERPA should be reported in all ECGs done in children and adolescents for prospective behavioral phenotype and/or arrhythmia risk stratification analysis.

## Keywords

ADHD, ERP, early repolarization, arrhythmia, ECG

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## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. It is presently believed that a dysfunction of frontal-striatal brain pathways that contribute to the executive function, including attention, is the cause for this behavioral phenotype.<sup>1</sup> Twin studies suggest a rather robust inheritance pattern

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for ADHD.<sup>2</sup> The genetic complexity of ADHD patients cannot be overstated when we consider that likely environmental factors interact with genetic substrate to modulate the phenotypic behavioral expression of this condition. Once diagnosed, children with ADHD are likely treated with stimulant medications that are known to cause dopamine receptor-transporter mediated cardiovascular effects. Early repolarization (ERP) was once thought of as a benign variant of no clinical significance, but recent studies have called that into question. The characterization, definition, and clinical implications of early repolarization are gaining greater scrutiny in the adult cardiology community. These developments will affect our decision to prescribe children psychostimulant medication for the treatment of ADHD. Certain early repolarization pattern anomalies (ERPAs) have been suggested to be potentially arrhythmogenic in nature.<sup>3-5</sup> Consequently, knowledge of ERPA presence among ADHD children and adolescents have prospective clinical importance. There is paucity in the literature regarding the prevalence and clinical significance of ERPA among ADHD patients. We could find only one study that suggested that ERPA is associated with ADHD. After analyzing the electrocardiogram (ECG) tracings in a small sample of children ( $n = 50$ ), Nahshoni et al<sup>6</sup> suggested that “the rates of early repolarization (ER) in children with ADHD is significantly higher than in normal controls (32% vs 13%,  $P = .012$ ).” Our study had 2 aims: first, to determine if ERPAs were more likely present among children and adolescents diagnosed with ADHD when compared with non-ADHD children of similar demographic backgrounds. Second, to assess if children and adolescents with ADHD whose parents report severe attention difficulties and/or hyperactivity/impulsivity or “significant worry regarding their child behavior” (Parental Worry) are more likely to have ERPAs in their surface ECG when compared with other ADHD patients with mild to moderate dysfunction.

## Methods

Kids ‘N Teen Clinics, PA (KNT), is a community pediatric clinic (since 1997) caring for mostly minority inner-city children. Our population sample included children and adolescents (5 years to 18 years of age) evaluated for ADHD who had an ECG done and those who had an ECG for other reasons excluding ADHD during the study period ( $n = 603$ , 2008-2017). Most subjects were referred by public school counsellors 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 Parents

Vanderbilt Scales<sup>7</sup> and the Pediatric Symptom Checklist.<sup>8</sup> Verbal and written health information regarding ADHD and the benefits and risks of stimulant treatment were given during the exit clinical visit. Of note, the “selective warning” on stimulants safety was verbally shared with patients. Most if not all parents were given the option of having an ECG done on their child prior to starting stimulant treatment. With few exceptions, most children completed ECGs. The present research study was approved by the institutional review board for Baylor College of Medicine and Affiliated Hospitals, Houston, TX (Protocol: H-40256, 2016). It is our understanding that with their approval the Institutional Review Board 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. The initial case list for medical record review included a print out of the names of patients whose billing records included the ADHD diagnosis from 2008 to 2017 (International Classification of Diseases, Ninth Revision [ICD-9-CM], clinical modification 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 (FAI) and blindly by a senior pediatric cardiologist (FR) 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, our study group included all pediatric patients who met the *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition)<sup>9</sup> criteria for attention-deficit disorder (home and school dysfunction) and whose legal guardians verbally agreed to have an ECG done on their child ( $N = 416$ ). Most parents and teachers completed a Vanderbilt psychometric scale. Our non-ADHD (control) group included those patients who had an ECG done for cardiovascular symptoms that included the following: chest pain, heart murmurs, palpitation, high blood pressure, or routine sports physicals ( $N = 187$ ). None of the control patients were on stimulants at the time the ECG was performed. Children and adolescents in the case and control groups had their medical record reviewed by the Clinic Medical Director (FAI) only. Only those whose record review and/or psychometric scale (PSC or other) did not suggest the ADHD diagnosis were included in the study as controls. Patients excluded from the study were those with ADHD who did not have an ECG done. Cases and controls were excluded when a structural heart defect was found. Our record review did not find any documentation of the current use of potential cardiovascular stimulants such as decongestants, caffeinated beverages, or any

metabolic or electrolyte imbalance in our study subjects at the time the ECG was performed.

### ADHD Assessment

ADHD was diagnosed utilizing all available body of clinical information that included the NICHQ (National Institute for Children's Health Quality) Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)<sup>7</sup> and the NICHQ Vanderbilt ADHD Diagnostic Teacher Rating Scale (scales: 0 = never, 1 = occasionally, 2 = often, and 3 = very often). Abnormal "cluster" behavior was scored according to the bright future tool for professionals (VADPRS) and counted as abnormal those that scored 2 (often) or 3 (very often).<sup>7</sup> The reliability and cost-effectiveness of the VADPRS are well accepted in research and clinical settings.<sup>7</sup> The diagnosis of ADHD required 6 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." All individual raw scores pertaining to attention, hyperactivity-impulsivity, and total raw score were tabulated. The parental worry psychometric report was stratified according to severity regarding the number of times a parent gave a score of 2 or 3 in each of the 9 "behavior cluster" questions of attention or hyperactivity/impulsivity: 0 = no ADHD, 1 = mild (score of 1-3), 2 = moderate (score of 4-6), and 3 = severe (score of 7-9). Scales were also studied as a combination of attention and hyperactivity concerns as total numbers (total parental worry). Our output generated global scales of total parental worry as follows: If a subject was classified as mild in attention = 1 and was further classified as moderate in hyperactivity = 2, his total parent worry (global scale) was 1 + 2 = 3. As a result, since the maximum score in attention deficit is 3 and the maximum score in hyperactivity is 3, a patient may have a maximum global score of 6. This global ordinal score was further nominally classified as follows: 0 = no ADHD, 1 = mild (global score of 1-2), 2 = moderate (global score of 3-4), and 3 = severe (global score of 5-6).

Early Repolarization (ER) was recognized if: There was an end QRS notch (J wave) or slur on the downslope of a prominent R wave with and without ST-segment elevation and the peak of the notch or J wave (Jp)  $\geq 0.1$  mV in  $\geq 2$  contiguous leads, excluding V1-V3, and QRS duration (measured in leads in which a notch or slur is absent)  $< 120$  ms, or ST-segment elevation  $> 0.1$  mV in  $\geq 2$  contiguous leads, excluding V1-V3, and QRS duration  $< 120$  ms.<sup>10</sup>

### Definitions

(1) *Notching*: + distinct Jp deflection of  $> 1$  mm at the end of QRS. (2) *Slurring*: Terminal QRS gradual angle change ( $> 10^\circ$ ) of R wave to ST-segment or abrupt change in the slope of the last deflection at the end of QRS. (3) *ST-Segment Elevation*: Elevation at the end of the QRS complex or J point  $> 0.1$  mV or 1 mm in at least 2 contiguous leads, to be measured from the voltage-time point offset from the isoelectric line prior to the start of the Q wave. ST elevation only in V1, V2, or V3, but it will not be classified as ERPA unless this anomaly is also noted in other leads. (4) *ST-Segment Pattern*: Horizontal/descending defined as  $\leq 0.1$  mV elevation of the ST-segment within 100 ms after the J point. Concave/ascending defined as  $> 0.1$  mV elevation of ST-segment within 100 ms after the J point or a persistent elevated ST-segment of  $> 0.1$  mV throughout the ST-segment.<sup>10</sup> If the ST-segment is ascending in at least 2 leads in each territory and is horizontal or downward slopping in 1 lead, it should be defined as ascending and vice versa. If the ST-segment is horizontal in the inferior leads and ascending in the lateral leads, the final interpretation will depend on the extent (more leads) and the (higher) amplitude of the end QRS slur or notch, that is, on the territory where the ERP is most prominent.

### Number of ERPA ECG Leads Affected

This is the absolute number of ECG leads where ERP was noted excluding V1, V2, and V3. This number will range from 0 to a maximum of 9 leads.

### Statistical Analysis

Data were meticulously entered in Excel by a third-party coder and data manager (d-stats, Cambridge, MA) and analyzed utilizing SPSS by a third-party senior biostatistician (REH). Categorical variable substratified analysis was done utilizing the  $\chi^2$  statistic at a significance level of .05 and 0.8 power. Categorical predictor and outcome variables were analyzed with frequency and cross-tabulation statistics to describe the sample and check for coding errors. Skewness and kurtosis statistics were conducted on continuous predictor and outcome variables to check for the assumption of normality. Logistic regression analysis was used to predict for a diagnosis of ADHD. The outcome variable was coded as 0 = no ADHD and 1 = ADHD. Age, gender, race, and ERPA were entered in the logistic model as predictor variables. Statistical assumptions were assessed using normal probability plots and residual analysis. Reference categories were chosen and coded accordingly. Adjusted

**Table 1.** Demographic Variables, ECG Indication, and Prevalence of ERPA in Study Subjects (N = 603).

Variables	ADHD (n = 416)	Non-ADHD (n = 187)	ERP Present (n = 167)	ERP Absent (n = 436)
Age <10 years	257 (61%, $P < .001$ )	81 (42.4%)	84 (50.3%, $P = .12$ , ns)	250 (57.3%)
Male	316 (75%, $P < .001$ )	111 (58.1%)	121 (72.4%, $P = .4$ , ns)	301 (69.0%)
Black	160 (38%, $P = .23$ , ns)	27 (14.1%)	76 (45.8%, $P < .001$ )	108 (24.8%)
ECG indications				
ADHD monitoring	394 (100%)	0	120 (30.5%)	274 (69.5%)
ADHD cardiovascular symptoms or signs	23 (100%)	0	8 (34.8%)	15 (65.2%)
Non-ADHD cardiovascular symptoms or signs	0	59 (100%)	17 (28.8%)	42 (71.2%)
Heart murmur	0	54 (100%)	13 (24%)	41 (76%)
General screening	0	73 (100%)	8 (11%)	61 (89%)
Study subjects, n = 603				
ERP present (+) <sup>a</sup>	127 (76.0%)	40 (24.0%)	167 (100%)	—
ERP absent (-)	289 (66.3%)	147 (33.7%)	—	436 (100%)
Total	416	187		
ERPA prevalence	30.5%	21.4%	27.7%	

Abbreviations: ECG, electrocardiography; ERPA, early repolarization pattern anomaly; ADHD, attention-deficit hyperactivity disorder; ERP, early repolarization pattern; ns, not significant.

<sup>a</sup>Odds ratio = 1.615, 95% confidence interval = 1.0749-2.4264,  $P = .021$ .

odds ratios (ORs) with 95% confidence intervals (CIs) were reported and interpreted for the logistic model. Simultaneous multiple regression was used to predict for continuous survey outcomes. Polychotomous categorical variables were dummy-coded for the analysis, and reference categories were chosen. Change in  $R^2$  was tested using the  $F$  test. Unstandardized beta coefficients with standard errors and standardized beta coefficients for each regression model were presented and interpreted. Multicollinearity was assessed using tolerance and variance inflation factor statistics. Durbin-Watson was used to test for autocorrelations. Normal probability plots and residual analysis were analyzed. Statistical significance was assumed at a  $\alpha$  value of .05 and all analyses were conducted using SPSS Version 21 (IBM Corp, Armonk, NY).<sup>10</sup>

## Results

Of 612 children and adolescents with and without ADHD who had an ECG done, 9 were excluded from our ERP data analysis. Of those, 7 were excluded due to suboptimal ECG quality (5 were controls and 2 were ADHD patients). A total of 603 patients were included, 416 cases (69%) and 187 (31%) controls. Note that 23 (5.5%) of our ADHD study group also had cardiovascular concerns during the intake evaluation. Additionally, 51 ADHD patients (12.2%) reported having taken a stimulant medication (time and date was not recorded) prior to

electrocardiography testing. A significant number of our patients in the control group, 59 (30.9%) had an ECG done due to cardiovascular symptoms or signs. Our research sample included 69.8% males, 30.2% females, 65% Hispanics, 30.6% African Americans, and 4.4% Caucasians. Within our study groups, 55.2% were children between 5 and 9 years old and 44.8% were adolescents between 10 and 17 years old (Table 1). Of 416 patients diagnosed with ADHD, 127 (30.5%) had ERPA, whereas only 40 (21.4%) of 187 control patients had ERPA ( $P = .020$ ). Similarly, among 167 subjects with ERPA, the frequency of ERPA was higher among those with ADHD when compared with unmatched controls (76% vs 66.3%,  $P = .020$ ; Table 1). Of interest, ADHD parental worry psychometric reports showed a trend for higher scores among those with ERPA when compared with those without ERPA (Table 2). Likewise, of 161 children who had ERPA in their ECGs, 97 (60.2%) were categorized as having severe ADHD in the total parental worry scale, much higher than those with mild-moderate dysfunction (16.1%) or no apparent ADHD dysfunction (23.6%,  $P = .023$ ; Table 3). Regarding the extent of ERPA encountered, only 11 (9%) of ADHD patients ( $n = 121$ ) had ST-segment elevations  $>0.2$  mV ( $>2$  mm), compared with only 4 (10.5%) controls. Most patients with ERPA had ST elevation in the range of 1 to 2 mV ( $n = 159$ , 90.5%,  $P = .792$ , ns). Standard multiple regression models were conducted to assess the degree to which age, race-ethnicity, gender, ERPA status, and

**Table 2.** ERPA Presence and Severity Trend of Parental Worry Vanderbilt Scale ( $P = ns$ ).

	0	1	2	3	4	5	6	Total
ERPA absent (-), n (%)	141 (33.3%)	1 (0.2%)	7 (1.7%)	21 (5.0%)	51 (12.0%)	55 (13.0%)	148 (34.9%)	424 (100%)
ERPA present (+), n (%)	38 (23.0%)	1 (0.6%)	4 (2.5%)	6 (3.7%)	15 (9.3%)	25 (15.5%)	72 (44.7%)	161 (100%)
Total, n (%)	179 (30.6%)	2 (0.3%)	11 (1.9%)	27 (4.6%)	66 (11.3%)	80 (13.7%)	220 (37.6%)	585 (100%)

Abbreviations: ERPA, early repolarization pattern anomaly; ns, not significant.

**Table 3.** ERPA Presence and Severity of ADHD ( $P = .023$ ).

Scale/Score	No ADHD, Score = 0	Mild–Moderate ADHD, Score = 1-4	Severe ADHD, Score = 5-6	Total
ERPA absent (-), n (%)	141 (33.3%)	80 (18.9%)	203 (47.9%)	424 (100%)
ERPA present (+), n (%)	38 (23.6%)	26 (16.1%)	97 (60.2%)	161 (100%)
Total, n (%)	179 (30.6%)	106 (18.1%)	300 (51.3%)	585 (100%)

Abbreviations: ERPA, early repolarization pattern anomaly; ADHD, attention-deficit hyperactivity disorder.

number of ERPA-affected ECG leads predicted those patients who had the highest Global Parent Worry Scores (GPWS), Attention Parent Worry Scores (APWS) and Hyperactivity-Impulsivity Parent Worry Scores (HIPWS; Table 4). Preliminary analysis noted that there were no violations of the assumption of normality, linearity, multicollinearity, and homoscedasticity. The results indicated that the independent variables combine to significantly predict changes in Global Parent Worry ADHD scores,  $F(6, 576) = 20.17, P < .001$ . The model explained 16.5% of variance in these scores and four of the independent variables, including ERPA and number of ERPA affected ECG leads, significantly predicted changes in ADHD Total Parental Worry scores (severity index) outcome variable when controlling for other variables (Table 4). Hispanic and black race-ethnicity were not significant predictors of ADHD Parental Worry,  $P = .05$  and  $P = .27$ , respectively. Likewise, a standard multiple regression model also indicated similar results for Attention Parental Worry (adjusted  $R^2 = 13.5\%$ ,  $F(6, 576) = 16.08, P < .001$ ; Table 4) and for Hyperactivity-Impulsivity Parental Worry scores alone (adjusted  $R^2 = 18.1\%$ ,  $F(6, 575) = 21.12, P < .001$ ; Table 4) for age, gender, and ERPA. Of note, African American race-ethnicity was not a contributor in the 3 models,  $P = .27, .44$ , and  $.13$ , respectively. Hispanic ethnicity was a contributor in Attention Parental Worry model only ( $P = .04$ ). The number of ERPA-affected ECG leads was a borderline contributor in the Hyperactivity-Impulsivity model ( $P = .06$ ). A direct logistic regression model to assess the degree to which age, race-ethnicity, gender, ERPA status, and number of ERPA-affected ECG leads predicted those patients who had an ADHD diagnosis (0 = no, 1 = yes) was analyzed. Preliminary analysis noted that there were

no violations of the assumption of normality, linearity, multicollinearity, and homoscedasticity. The results indicated that the independent variables combine to significantly predict changes in ADHD diagnosis,  $\chi^2(9, n = 603) = 98.875, P < .001$ , indicating that the model distinguished between respondents who were and were not diagnosed with ADHD. As shown in Table 5, only 3 of the variables, age, gender, and ERPA, made a unique statistically significant contribution to the model. The strongest predictor of ADHD diagnosis was ERPA, with an OR of 2.778 ( $P = .033$ ). Patients with ERPA were 2.778 times more likely to have a diagnosis of ADHD (95% CI for OR = 1.087-7.100,  $P = .033$ ; Table 5).

## Discussion

The main aim of our research was to determine if children and adolescents diagnosed with ADHD were more likely to have ERPA when compared with non-ADHD children of similar age, gender, and ethnic background. With this construct in mind, our literature review confirmed the paucity of scientific studies regarding ERPA prevalence in children. We could find only a recent published “prevalence” study of ERPA among pediatric patients.<sup>11</sup> Sager et al<sup>11</sup> found that of 719 children of 8 to 12 year of age attending a large university-affiliated hospital, 17% had ERPA in their surface ECGs. Most of the group reported were males (62%), blacks (52%), had an ECG done for cardiac symptoms (48%), arrhythmia (6%), structural heart disease (13%), and noncardiac condition (11%), but only 23% had the ECG done for screening purpose. Our research analysis suggested that of 416 patients with ADHD, 127 (30.5%) had ERP (Table 1). Our logistic regression model that controlled for age,

**Table 4.** Multiple Regression Coefficients for GPWS, ADPWS, and HIPWS Outcome Models.

Outcome	Predictor	Regression Coefficients for Predictive Models		
		B (SE)	$\beta$	P
GPWS	Constant	6.04 (0.54)	—	<.001
	Age	-0.19 (0.31)	-0.230	<.001
	Ethnicity			
	Hispanic	-0.915 (0.47)	-0.172	.050
	African American	0.534 (0.48)	0.097	.269
	Gender	-1.027 (0.211)	-0.185	<.001
	ERPA			
	ERPA present (+)	1.271 (0.444)	0.223	.004
ERPA leads	-0.286 (0.125)	-0.180	.022	
ADPWS	Constant	3.091 (0.289)	—	<.001
	Age	-0.086 (0.017)	-0.197	<.001
	Ethnicity			
	Hispanic	-0.523 (0.250)	-0.187	.037
	African American	0.199 (0.259)	0.068	.443
	Gender	0.471 (0.113)	-0.162	<.001
	ERPA			
	ERPA present (+)	0.647 (0.238)	0.215	.007
ERPA leads	-0.145 (0.067)	-0.174	.030	
HIPWS	Constant	2.951 (0.277)	—	<.001
	Age	-0.107 (0.016)	-0.250	<.001
	Ethnicity			
	Hispanic	-0.337 (0.240)	-0.122	.161
	African American	0.375 (0.248)	0.131	.132
	Gender	-0.591 (0.108)	-0.206	<.001
	ERPA			
	ERPA present (+)	0.529 (0.228)	0.228	.021
ERPA leads	-0.119 (0.064)	-0.145	.064	

Abbreviations: GPWS, Global Parental Worry Scale; ADPWS, Attention-Deficit Parental Worry Scale; HIPWS, Hyperactivity-Impulsivity Parental Worry Psychometric Scale; ERPA, early repolarization pattern anomaly.

**Table 5.** Logistic Regression Model of ERPA, Number of ERPA Leads Affected, and Demographic Variables as Predictors of ADHD Diagnosis.

Predictor	AOR (95% CI)	P
Age	0.845 (0.795-0.898)	<.001
Ethnicity		
White	Reference	
Hispanic	0.431 (0.160-1.157)	0.095, NS
African American	1.850 (0.645-5.307)	0.253, NS
Gender		
Male	Reference	
Female	0.412 (0.276-0.616)	<.001
ERPA		
ERPA absent (-)	Reference	
ERPA present (+)	2.778 (1.087-7.100)	.033
Number ERPA lead affected	0.819 (0.630-1.063)	.133 NS

Abbreviations: ERPA, early repolarization pattern anomaly; ADHD, attention-deficit hyperactivity disorder; AOR, adjusted odds ratio; CI, confidence interval; NS, not significant.

race, and gender indicated that patients with ERPA were 2.78 times more likely to have a diagnosis of ADHD ( $P = .033$ ). Our results are applicable to a mostly minority vulnerable young urban population with ADHD who had an ECG done for cardiac screening purposes. The overall prevalence of ERPA in our ADHD patients (30.5%) suggest that our study group had similar results to those reported by Nahshoni et al<sup>6</sup> (32%) in Israel. They reported that a small group of children with ADHD ( $n = 50$ ) had significantly higher proportion of early repolarization (ST elevation) when compared with apparently healthy control subjects (32% vs 13%,  $P = .012$ ).<sup>6</sup> Interestingly, our control population had much higher proportion of ERPA (21%) than the one reported by Nahshoni et al (13%).<sup>6</sup> Our global ERPA prevalence (27.7%) was also higher than the whole prevalence reported by Sager et al (17%).<sup>11</sup> Interestingly, our sub-analysis suggested that those patients who had ADHD and cardiovascular symptoms ( $n = 20$ , 4.5%) had higher prevalence of ERPA than those ADHD patients without cardiovascular symptoms or signs ( $n = 402$ , 95.5%; 42.1% vs 30.3%,  $P = <.08$ , ns). We speculated that ADHD patients might have greater J point deflections than controls, but our results did not bear that out (9.1% vs 10.5%,  $P = .79$ ). Most ERPA J point elevations in our group of patients were between 0.1 and 0.2 mV ( $P = .792$ ). Our findings are of interest, considering that certain ERPA in a selected group of adults was found to be associated with potentially lethal rhythm disturbances especially when present in the inferolateral leads, a risk factor for torsade's de point that may cause sickle cell disease (SCD).<sup>3</sup> Moreover, during 2005, the perceived safety of stimulants was questioned when several patients that had SCD were also found to have been treated with stimulant medication.<sup>12</sup> This potential arrhythmogenic concern prompted the Food and Drug Association to issue a selective safety warning label regarding the possibility of SCD among children and adolescents especially those with structural cardiac abnormalities treated with stimulants.<sup>12</sup> Our personal experience with targeted stimulant prescription is that stimulants are usually safe and effective. As our study protocol was of retrospective nature, we did not account for the current use of potential cardiovascular stimulants such as decongestants and/or consumption of caffeinated beverages at the time the ECG was performed among our study subjects, nor did we obtain any metabolic studies prior to ECG testing. Reflecting that a significant percentage of the control sample when compared with our case sample had cardiovascular concerns (31.5% vs 5.5%), it is biologically plausible that our control group was more likely to have ECG abnormalities including ERPA. This is a methodological weakness but also a strength of our research, as

we found that ADHD patients were more likely to have ERPA when compared with our controls. It has been suggested that males and African Americans have a higher proportion of ERPA when compared with females and Caucasians.<sup>11</sup> These findings were corroborated with our demographic findings (African Americans 41.3% vs Caucasian 25% vs 21.3% Hispanics,  $P < .001$ ). To our knowledge, our study is the first that reports the smaller but significant presence of ERPA among Hispanic young patients with ADHD. Prevalence of ERPA was similar among males and females (28.7% vs 25.4%,  $P = .41$ , ns). Children older than 10 years of age tended to have a higher proportion of ERPA than those younger than 10 years (30.9% vs 25.1%), but the difference was not statistically significant ( $P = .12$ , ns). However, this tendency may be explained by the fact that non-ADHD patients were significantly older than ADHD patients (11 years vs 9 years, median ages,  $P < .001$ ). The odds ratio for predicting the presence of ADHD status increased from 1.67 to 2.78 for the ERPA independent variable when age, gender, and ethnicity were inserted into the logistic regression model ( $P = .03$ ). Age ( $P < .001$ ), gender ( $P < .001$ ), and ERPA ( $P = .03$ ) were significant predictors for ADHD, but in fact, ERPA was the strongest predictor. In this model, ethnicity was not a significant logistic regression predictor when African Americans and Hispanics were used as predictor variables and white ethnicity as the reference variable. This came as a surprise as we expected that African American patients would have a strong contribution to the model considering that 41.3% had ERPA (Table 1), and our literature review suggested a robust prevalence of ERPA among African American children in comparison to Caucasian children, 22% and 11%, respectively.<sup>11</sup> Looking at ADHD parental psychometric scores, our data analysis included multiple regression models predicting the severity of ADHD parental worry on a scale from 0 to 6. Our models suggested that ERPA ( $P = .004$ ), number of ECG leads with ERPA ( $P = .022$ ), age ( $P < .001$ ), and gender ( $P < .001$ ) were significant predictors of the global severity on the ADHD parental worry scale when controlling for each other. Race-ethnicity was not a statistically significant predictor (Table 4). We could not find any other study to compare our logistic regression and multiple regression models. Some research peers and clinicians may be cautious in the interpretation of our results, considering that our method of defining ADHD severity has not been formally validated. On the other hand, the VADPRS for the diagnosis of ADHD has been validated for research purposes.<sup>7</sup> As a result, it is likely that our severity scale has intrinsic validity. We hope that in the future our severity ADHD construct may be used by others and prospectively validated in different

research and clinical settings. Even though ERPA is suggested by field experts to be a benign and common ECG finding,<sup>13</sup> we postulate that ERPA may represent an important cardiac repolarization anomaly. Furthermore, ERPA may be an electrical cardiac phenotypic expression of an autonomic nervous system imbalance or dysregulation, especially among ADHD patients. It is a pathophysiological challenge to elucidate why our ADHD patients were more likely to have ERPA than our control sample, especially when a significant percentage of our control sample had an ECG done for potential cardiovascular problems. It is speculative that ADHD patient may have intrinsic cardiac nervous system differences at the level of the cardiomyocyte where dopaminergic receptors are present that may manifest as ERPA. The potential explanation for these findings draws on observations from previous published basic science research. It has been suggested that brain dopamine receptor (DRD4) defects are clinically associated to the behavioral phenotypic expression of ADHD. Particularly, Tovo-Rodriguez et al<sup>14</sup> found “a contribution of DRD4 7R rare variants to high hyperactivity-inattention scores in a population base sample from a large birth cohort.” Dopamine receptors (DR) are also found in other organs including kidneys, heart, and vascular system. Cavallotti et al<sup>15</sup> found D1, D2, D3, and D4 subtypes of DR in the human heart tissues including the endocardium, myocardium, and epicardium. The authors suggested that “dopamine receptors by subtype may have uneven concentration in cardiac tissues. Particularly, D1 is more concentrated in the epicardium.”<sup>15</sup> Ionic outward currents differentials are important in the repolarization process.<sup>5,16</sup> Of note, it is suggested that dopamine modulates ion currents differentials at the cardiomyocyte level.<sup>17</sup> This current is likely affected by ionic and molecular variables including genetic make-up giving the typical ECG morphological phenotype of ERPA noted on ECGs in those affected. Considering that dopamine-DRs exert neurotropic effects in cardiovascular nerves and tissues, it is biologically plausible that an anomaly of their signaling may also cause atypical ionic current differentials of cardiac action potentials between endocardium-myocardium-epicardium that may be registered as early repolarization currents on surface ECGs (ERPA). If our research findings are corroborated by carefully designed electrophysiological studies, it may be prudent to suggest that ERPA be considered a phenotypic expression of an abnormal ADHD gene in a subset of ADHD patients causing autonomic nervous system (ANS) dysregulation and/or intracardiac dopaminergic or adrenoceptor dysfunction. Current literature supports the clinical recommendation of behavioral treatments such as cognitive behavioral therapy, bio feedback, intensive counselling, daily

moderate exercise, and medications such as those that restore ANS balance. Those therapies that may interact positively in decreasing the risk of significant cardiovascular events including SCD, hyperactivity, and improving the executive skills of individuals.

## Study Strengths and Limitations

Unmatched case-control studies cannot prove cause, and in this study the number of cases far outnumbered controls. Thus, we could only suggest certain predictability of an outcome variable (ADHD) by variables of interest that included age, gender, ethnicity, and ERPA. The results are not generalizable to the US population due to sample size (N = 603) and a skewed demographic sample (mostly Hispanic and African American patients). A weakness of this study is that the bilingual psychometric scales were filled 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. Although psychometric scales have been validated and contribute to the diagnosis of ADHD and its behavioral phenotype, our definition scale of mild, moderate, and severe ADHD has not been validated, but we believe it has intrinsic validity as we noted a biological trend in the prevalence of ERPA. Clinical ECGs such as the one used in our study have limitations. A print-out or copy of ECGs may lead to a higher risk of interobserver variability especially if the tracings are not perfectly recorded or if motion artifacts are recorded. Review of ECGs in an electronic form allows for magnification of waveforms that can facilitate ERPA detection but may not accurately reflect the real-world interpretation of ECGs in a clinical setting by practitioners that are not cardiologists. Doing meaningful research with vulnerable populations is also a challenge. There are other comorbid neuropsychiatric conditions that occur in higher association with an ADHD diagnosis, such as anxiety, depression, bipolar disorder, and oppositional defiant disorder, than may present an additional layer of confounding when evaluating the correlation of ERPA with ADHD. Furthermore, we assumed that our control group did not have ADHD based on medical record review including other psychometric scales (PSC or VADPRS) when available. We did not have other important information of controls such as psychoeducational information including teacher reports. Selection bias was likely present, as the control group was more likely to have cardiovascular findings in their ECGs. Perhaps this bias at the end was a study strength. This is especially factual, considering that the control group was potentially more likely to have ECG abnormalities. Our study did not include in the logistic regression model the medications that our sample



patients reported taken the day of the ECG. Of note, few of our ADHD patients might have been on stimulants prior the ECG testing (8.5%). If there was an effect, is likely to negligible. Negrao et al<sup>18</sup> 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.” Nevertheless, the use of stimulant medication prior to ECG testing represents a potential confounding variable that needs to be controlled for in future studies.

## Conclusion

The observation that DRs are found in the brain and heart together with the biochemical plausibility that DR variants may influence myocardial repolarization raises the possibility that patients with ADHD may have a higher incidence of ERPA on their ECGs. In addition, new reports showing an association between certain ERPA and cardiovascular events in adults have clinical implications for the treatment of children with ADHD given that many of these patients are treated with stimulant medication that may modulate myocardial repolarization even further. Our research corroborated that ADHD patients have a statistically significant higher proportion of ERPA when compared with a group of non-ADHD patients. We also found a weak but interesting ERPA proportion trend increase with higher parental psychometric behavior worry scores. Multiple regression models also suggested that ERPA and number of ECG leads with ERPA were strong predictors of higher psychometric scores and/or ADHD severity.

While our results are of research interest, they are not likely to be of major clinical significance due to the limitations of our study. As a result, our findings only suggest that a subset of ADHD patients may also have a neurotransmitter signaling anomaly at the heart tissue and/or autonomous nervous system levels that may explain their high proportion of ERPA.

It is prudent to analyze if certain ERPA morphology in the inferolateral leads, especially the horizontal/descending, is significantly present in our ADHD group of patients. This is clinically important, as certain ERPA morphology may be a considerable arrhythmogenic stratified risk factor for prospective cardiovascular events in a unique sample of patients, as suggested by Chen et al<sup>4</sup> adult data. The morphology and pattern of early repolarization currents among patients with a neurodevelopmental syndrome including those with ADHD will likely be the focus of future research. Our research supports the relevance of controlling for age, gender, and race-ethnicity when doing any prospective ERPA risk stratification in vulnerable populations. Considering our limitations and

results, we recommend that a meaningful population-based prospective relative risk cardiovascular study among ADHD-ERPA patients be completed and that the presence of nonanterior lead ERPA be reported in all ECGs done in children and adolescents for prospective behavioral and/or cardiac risk stratification analysis.

## Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder  
ANS: Autonomous Nervous System  
APWS: Attention Parental worry scale  
DSM: Diagnostic Statistical Manual of Mental Disorders  
ECG: Electrocardiogram  
ERPA: Early Repolarization Pattern Anomaly  
GPWS: Global Parental worry scale  
HIPWS: Hyperactivity-Impulsivity parental worry scale  
KNT: Kids ‘N Teen Clinics PA  
PSC: Pediatric Symptom Check List  
VADPRS: Vanderbilt Attention Deficit/Hyperactivity Disorder Parent Rating Scale

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## Author Contributions

FAI: MD FAAP, Kids ‘N Teens Clinics, Houston, TX, Medical director, is the principal investigator. He provided the initial master list of study sample and completed the medical record review of all ADHD cases and controls. With the help of his research assistant, He copied-coded ECGs and Psychometric scales for proper data entry and management. He did the initial master write up of the manuscript and presented it to the BCM IRB for approval. He coordinated the data to be analyzed by senior bio-statistician and implemented document revisions as suggested by co-investigators.  
FGR: MD UT health, Houston, TX, Pediatric Cardiologist, is the co-investigator who contributed by helping define methods for the study, read all ECGs, reviewed and provided wise editing of manuscript.  
FII: BA MS, Houston, TX, was the clinical research assistant. Along with the principal investigator-medical director, he participated by supervising and/or performing ECGs, pulled medical records, copied and assisted in the coding of ECGs and psychometric scales. He completed the initial pilot study sample data collection,

entering data in the preliminary excel and systat file that lead to the final hypothesis under study. He helped with the preliminary data analysis using systat for this purpose. He downloaded and read several research articles pertinent to the research presented.

### Declaration of Conflicting Interests

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