

Epilepsy duration is an independent factor for electrocardiographic changes in pediatric epilepsy

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Abstract

Objective: Cardiac alterations represent a potential epilepsy-associated comorbidity. Whether cardiac changes occur as a function of epilepsy duration is not well understood. We sought to evaluate whether cardiac alterations represented a time-dependent phenomenon in pediatric epilepsy.

Methods: We retrospectively followed pediatric epilepsy patients without preexisting cardiac conditions or ion channelopathies who had history of pediatric intensive care unit admission for convulsive seizures or status epilepticus between 4/2014 and 7/2017. All available 12-lead electrocardiograms (ECGs) from these patients between 1/2006 and 5/2019 were included. We examined ECG studies for changes in rhythm; PR, QRS, or corrected QT intervals; QRS axis or morphology; ST segment; or T wave. Data were analyzed using multivariable models containing covariates associated with ECG changes or epilepsy duration from the univariate analyses.

Results: 127 children with 323 ECGs were included in the analyses. The median epilepsy duration was 3.9 years (IQR 1.3-8.4 years) at the time of an ECG study and a median of 2 ECGs (IQR 1-3) per subject. The clinical encounters associated with ECGs ranged from well-child visits to status epilepticus. We observed changes in 171 ECGs (53%), with 83 children (65%) had at least 1 ECG with alterations. In a multivariable logistic regression model adjusting for potentially confounding variables and accounting for clustering by patient, epilepsy duration was independently associated with altered ECGs for each year of epilepsy (OR: 1.1, 95% CI: 1.0-1.2, $P = .002$). Extrapolating from this model, children with epilepsy durations of 10 and 15 years had 2.9 and 4.9 times the odds of having ECG changes, respectively.

Significance: Cardiac alterations may become more common with increasing epilepsy duration in select pediatric epilepsy patients. Future studies are needed to determine the potential clinical implications and the generalizability of these observations.

KEYWORDS

cardiac, ECG, epilepsy, pediatric, temporal

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1 | INTRODUCTION

Childhood-onset epilepsy is a common neurological condition affecting more than 20 million children worldwide, with a disproportionately high rate of years living with disability.¹ In addition to the developmental and cognitive impairments associated with epilepsy, cardiac alterations may constitute a potential epilepsy-associated comorbidity, including interictal and periictal rhythm disturbances,²⁻⁷ corrected QT interval (QTc) changes,⁸⁻¹³ and ventricular conduction and repolarization abnormalities.¹⁴⁻¹⁹ These cardiac alterations can be detrimental, supported by the increased arrhythmogenic potential under conditions of periictal hypoxemia^{13,20} and seizure-associated fatal and near-fatal arrhythmias.²¹⁻²³ Despite these associations of cardiac abnormalities with potentially deleterious consequences, whether cardiac changes occur as a function of epilepsy duration is not well understood.

In small cohorts of adult epilepsy patients and in children with Dravet syndrome, worsening indices of cardiac electrophysiology with increasing epilepsy duration suggest that cardiac electrical alterations may be progressive in epilepsy.^{19,24} Using standard 12-lead electrocardiogram (ECG), we previously reported that children with epilepsy admitted to the pediatric intensive care unit (PICU) for convulsive status epilepticus had increased odds for ECG alterations.²⁵ In this study, we seek to investigate whether ECG abnormalities are associated with duration of time since epilepsy diagnosis in a cohort of pediatric epilepsy subjects with history of PICU admission for convulsive seizures and status epilepticus.

2 | METHODS

2.1 | Patient selection and data collection

The Baylor College of Medicine Institutional Review Board approved this retrospective, longitudinal study with a waiver of consent. The study cohort was selected from children with epilepsy who had a history of admission to the Texas Children's Hospital PICU between 4/2014 and 7/2017 with primary diagnosis of convulsive seizures or status epilepticus. Children were included if they had at least one standard 12-lead ECG study following their diagnosis of epilepsy in the electronic medical record between 1/2006 and 5/2019 and excluded if they had preexisting cardiac conditions or known ion channelopathies.

Patient demographics and the age of epilepsy onset were collected. For each ECG study, we extracted chronic seizure types, maintenance antiseizure medications (ASM), inotropic medications, reason for the clinical encounter, indication for

Key points

- ECG alterations are common in a select cohort of pediatric epilepsy patients.
- Epilepsy duration is an independent risk factor for ECG alterations.
- Children with 10 and 15 years of epilepsy have 3 and 5 times the odds of having ECG changes compared to those with <1 year of epilepsy.
- Studies are needed to determine the clinical implications and the generalizability in the pediatric epilepsy population.

ECG, location where the ECG study was performed, whether there was a documented seizure episode within 24 hours prior to the ECG study, and laboratory data. When applicable, we also estimated the time interval between the most recent clinical or electrographic seizure and the ECG study. The age at epilepsy diagnosis was determined based on either neurology service documentation or the first appearance of International Classification of Diseases, 9th revision (ICD-9) diagnostic or 10th revision (ICD-10) codes for epilepsy. Refractory epilepsy was determined based on the documentation by the neurology service, operationally defined as failure of adequate trials of two appropriately chosen and tolerated ASMs.²⁶ All ECGs were read by a pediatric cardiac electrophysiologist per our institutional clinical standards. We extracted these official ECG interpretations to identify heart rate, measurements of PR, QRS, and QTc intervals, rhythm abnormalities (atrial or ventricular arrhythmias, heart block, or junctional rhythms), PR interval shortening or prolongation, QRS axis abnormalities (right or left axis deviation, northwest axis, indeterminate axis), QRS morphologic or interval abnormalities (right or left bundle branch block, incomplete right or left bundle branch block, interventricular conduction delay, or low voltage), QTc interval shortening or prolongation, ST segment abnormalities (nonspecific changes, early repolarization, ischemic changes), or T-wave abnormalities (inverted T wave, nonspecific changes, notched T wave, late peaking T wave). An ECG study was considered to be abnormal if abnormalities in rhythm, PR interval, QRS axis, QRS interval, QTc interval, ST segment, or T wave were present.

2.2 | Statistical analyses

The primary outcome was the odds of having an abnormal ECG as function of epilepsy duration. We reported patient demographics, clinical and laboratory data, and details of ECG abnormalities using descriptive statistics. In univariate

analyses, we evaluated associations between clinical characteristics and presence of abnormal ECG using the Pearson chi-square test for categorical variables and the Mann-Whitney *U* test and generalized linear modeling for continuous variables. We evaluated univariate associations between clinical characteristics and epilepsy duration using linear regression with robust standard errors. Multivariable logistic regression, adjusting for potentially confounding variables and accounting for multiple observations (clustering) by patient, was used to evaluate the association of epilepsy duration with the odds of having an ECG abnormality. Prespecified model covariates included reason for the clinical encounter and number of ASMs based on clinical concerns for confounding. Additional covariates associated with epilepsy duration and with abnormal ECG with $P < .1$ in univariate analyses were also included in the multivariable model. The final model therefore also included the chronic seizure type, presence of abnormal electrolytes or acidosis, and ionotropic therapy. Age at ECG was excluded, as it was highly collinear with epilepsy duration, with older patients having longer durations of epilepsy. Since age at epilepsy onset was not associated with the presence of abnormal ECG, the association between abnormal ECG and age was attributable to increasing epilepsy duration. We performed a sensitivity analysis restricted to the first ECG study following epilepsy diagnosis and constructed a multivariable model using the same methodological approach. Statistical computations were performed using STATA, version 14.2 (StataCorp LP). Two-sided P values of $<.05$ were considered statistically significant.

3 | RESULTS

Between 4/2014 and 7/2017, 427 children were admitted to the PICU with the primary diagnosis of convulsive seizures or status epilepticus. Two hundred forty-four of the 427 children had epilepsy (57%). Of those, 102 children had preexisting cardiac condition/known channelopathy ($n = 38$) or no ECG study ($n = 64$) and were excluded. One hundred forty-two had the diagnosis of epilepsy and had at least one standard 12-lead ECG study between 1/2006 and 5/2019. Fifteen children with epilepsy had ECG studies only prior to the diagnosis and were excluded. The remaining 127 children had ECG studies ($n = 323$) at or following the diagnosis of epilepsy and were included in the study.

Males predominated (57%), and the median age of epilepsy diagnosis was 1.8 years (IQR 0.5-5 years) with a median of 2 ECGs (IQR 1-3) per subject following the diagnosis of epilepsy (Table 1). Sixty-five children had refractory epilepsy. The median epilepsy duration at the time of a given ECG study was 3.9 years (IQR 1.3-8.4 years) (Table 1). Reasons for the clinical encounters, ECG indications and locations, chronic seizure types, and number and names of maintenance

TABLE 1 Demographic and clinical characteristics of 127 patients with epilepsy

| | N (%) or median [IQR] |
|---|-----------------------|
| Male gender | 73 (57) |
| Race | |
| White | 32 (25) |
| Black | 23 (18) |
| Hispanic | 67 (53) |
| Asian | 5 (4) |
| Age at epilepsy diagnosis (years) | 1.8 [0.5-5] |
| Number of ECGs per subject | 2 [1-3] |
| Epilepsy duration at the time of ECG ^a | 3.9 [1.3-8.4] |
| Refractory epilepsy | 65 (51) |
| Reason for clinical encounters ^a | |
| Increased seizure frequency/status epilepticus | 110 (34) |
| Office visits | 86 (27) |
| Respiratory concerns | 40 (12) |
| New-onset seizure | 19 (6) |
| Other | 68 (21) |
| ECG locations ^a | |
| Outpatient | 88 (27) |
| Emergency center | 84 (26) |
| Regular inpatient floor | 34 (11) |
| Intensive care unit | 114 (35) |
| Unknown | 3 (1) |
| ECG indications ^a | |
| Tachycardia/Bradycardia | 60 (19) |
| Arrhythmias | 59 (18) |
| Heart evaluation | 40 (12) |
| Evaluate QT/ST segment | 18 (6) |
| Seizures | 36 (11) |
| CNS abnormalities | 24 (7) |
| Medication evaluation | 16 (5) |
| Respiratory concerns | 4 (1) |
| Other | 66 (20) |
| Chronic seizure types ^{a,b} | |
| Focal onset | |
| Aware | 6 (2) |
| Impaired awareness | 90 (28) |
| Focal to bilateral tonic-clonic | 13 (4) |
| Generalized onset | |
| Tonic-clonic | 53 (16) |
| Tonic, clonic, or atonic | 87 (27) |
| Myoclonic and others | 43 (13) |
| Epileptic spasm | 26 (8) |

(Continues)

TABLE 1 (Continued)

| | N (%) or median [IQR] |
|---|-----------------------|
| Absence | 9 (3) |
| None of the above/not available | 96 (30) |
| Maintenance ASM^{a,b} | |
| Levetiracetam | 166 (51) |
| Carbamazepine/Oxcarbazepine | 74 (23) |
| Zonisamide | 73 (23) |
| Clobazam | 60 (19) |
| VNS/Surgery | 46 (14) |
| Clonazepam | 45 (14) |
| Topiramate | 38 (12) |
| Phenobarbital | 33 (10) |
| Rufinamide | 26 (8) |
| Lacosamide | 24 (7) |
| Lamotrigine | 22 (7) |
| Valproic acid | 20 (6) |
| Vigabatrin | 11 (3) |
| Ketogenic diet | 9 (3) |
| Other | 48 (15) |
| Not available/missing | 31 (10) |
| Number of maintenance ASMs^a | |
| 0 | 20 (6) |
| 1 | 81 (25) |
| 2 | 82 (25) |
| 3 | 43 (13) |
| 4+ | 65 (20) |
| Not available/missing | 31 (10) |

Abbreviations: ASM, antiseizure medication; CNS, central nervous system; ECG, electrocardiogram; IQR, interquartile range; VNS, vagal nerve stimulator.

^aAmong the 323 individual ECGs obtained among the 127 patients following the diagnosis of epilepsy.

^bSome patients exhibited multiple seizure types and were on multiple ASMs. Percentages do not add to 100% accordingly.

ASMs are summarized in Table 1. Increased seizure frequency/status epilepticus was the most common reason for the clinical encounter associated with an ECG study (34%), followed by routine office visits (27%). The PICU (35%) and outpatient setting (27%) represented the most common locations where ECG studies were performed. The two most common seizure types were focal onset-impaired awareness/focal onset to bilateral tonic-clonic seizures (33%), followed by generalized onset tonic-clonic seizures (16%). The most common maintenance ASM was levetiracetam (51%), followed by carbamazepine/oxcarbazepine (23%), zonisamide (23%), and clobazam (19%) (Table 1).

Eighty-three of 127 children (65%) had at least 1 abnormal ECG study, and 171 of 323 ECG studies (53%) exhibited 1 or

TABLE 2 ECG characteristics of 323 ECGs obtained in 127 patients with epilepsy

| | N (%) |
|--|----------|
| ECG abnormality present | |
| By patient (n = 127) | 83 (65) |
| By individual ECG study (n = 323) | 171 (53) |
| Rhythm abnormalities | |
| Premature ventricular contractions | 4 (1) |
| Junctional rhythm | 1 (0.3) |
| Abnormal PR interval | |
| Long PR interval (1st degree AV block) | 7 (2) |
| Short PR interval | 8 (2) |
| QRS axis | |
| Right axis deviation | 14 (4) |
| Left axis deviation | 9 (3) |
| QRS morphology | |
| Interventricular conduction delay | 5 (2) |
| Right bundle branch block | 4 (1) |
| Low voltage | 4 (1) |
| Incomplete right bundle branch block | 2 (0.6) |
| Widening | 1 (0.3) |
| Prolonged QTc interval | 7 (2) |
| ST segment abnormalities | |
| Nonspecific changes | 60 (19) |
| Early repolarization | 9 (3) |
| T-wave abnormalities | |
| Nonspecific changes | 98 (30) |
| Inverted T wave | 5 (2) |
| Inverted T wave +nonspecific changes | 3 (1) |

Abbreviations: ECG, electrocardiogram; QTc, corrected QT interval.

more abnormalities (Table 2; Figure 1). We observed a spectrum of ECG abnormalities including rhythm disturbances and alterations in interval duration, axis, and morphology. Changes in the ST segment and T-wave abnormalities were the most common abnormalities observed (Table 2).

Univariate analyses revealed that epilepsy duration was associated with increased likelihood of having an abnormal ECG study (unadjusted RR for each year of epilepsy: 1.05, 95% CI: 1.03-1.07, *P* < .0005) (Table 3). Abnormal ECG studies were also associated with age at which ECG was obtained, chronic seizure type, reason for clinical encounter, the presence of abnormal electrolytes or acidosis, and the presence of inotropes. Age of epilepsy onset, diagnosis of refractory epilepsy, presence of recent seizures, interval between seizures and ECG, location where ECG studies were obtained, and number of chronic ASMs were not associated with abnormal ECG studies (Table 3). Epilepsy duration was associated with seizure semiology, increasing number

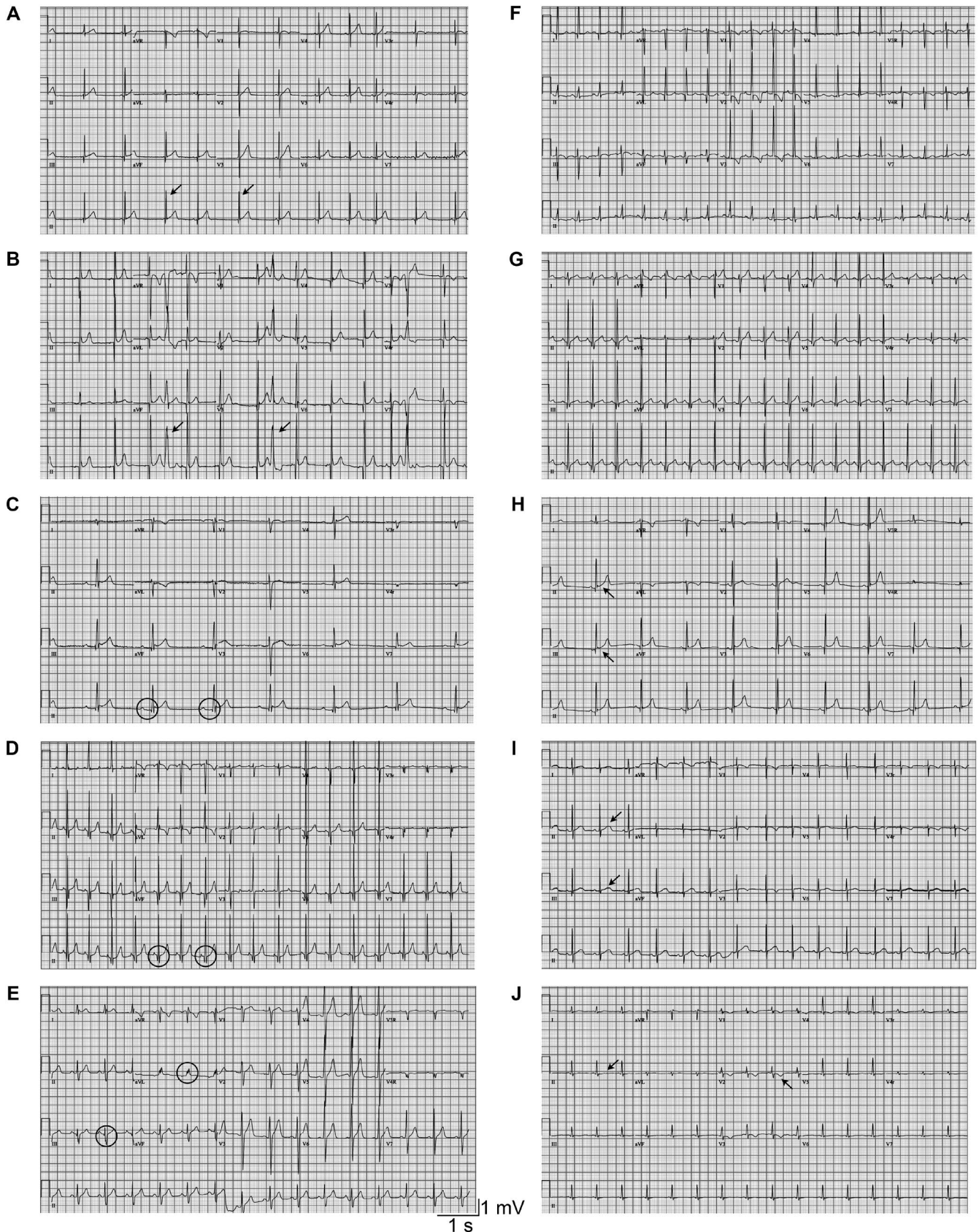


FIGURE 1 ECG abnormalities in pediatric epilepsy. Sample ECG tracings that illustrate diverse abnormalities. A, Junctional rhythm (arrows). B, Premature ventricular contractions (arrows). C, 1st degree AV block (circles). D, Short PR interval (circles). E, Interventricular conduction delay (circles). F, Left axis deviation. G, Right axis deviation. H, Nonspecific ST segment changes (arrows). I, Nonspecific T-wave abnormalities (arrows). J, Flatten T wave and inverted precordial T wave (arrows)

TABLE 3 Univariate analysis of clinical factors associated with abnormal ECG

| | Abnormal ECG (n = 171) ^a | Normal ECG (n = 152) ^a | RR | 95% CI | P |
|---|--|--------------------------------------|------|-----------|--------|
| Epilepsy duration (years) ^b | 6 [2-10] | 3 [1-6] | 1.05 | 1.03-1.07 | <.0005 |
| Age at ECG (years) ^b | 9 [4-15] | 6 [2-11] | 1.03 | 1.02-1.05 | <.0005 |
| Age of epilepsy onset (years) ^b | 1.3 [0.5-5] | 1 [0.5-4] | 1.00 | 1.00-1.00 | .6 |
| Seizure semiology | | | | | |
| Focal impaired awareness or focal to bilateral tonic-clonic | 61 (36) | 38 (25) | | | .01 |
| Generalized tonic-clonic | 24 (14) | 20 (13) | | | |
| Generalized tonic | 33 (19) | 20 (13) | | | |
| Other/missing | 53 (31) | 74 (49) | | | |
| Number of maintenance ASMs | | | | | |
| 0 | 10 (6) | 10 (8) | | | .9 |
| 1 | 46 (28) | 35 (27) | | | |
| 2 | 46 (28) | 36 (28) | | | |
| 3 | 22 (14) | 21 (16) | | | |
| 4+ | 39 (24) | 26 (20) | | | |
| Refractory epilepsy | 82 (48) | 68 (45) | 1.06 | 0.9-1.3 | .6 |
| Reason for clinical encounter | | | | | |
| Routine visit | 42 (25) | 44 (29) | | | .03 |
| New seizure | 7 (4) | 12 (8) | | | |
| Increase in seizure/SE | 62 (36) | 48 (32) | | | |
| Respiratory | 29 (17) | 11 (7) | | | |
| Other | 31 (18) | 37 (24) | | | |
| ECG locations | | | | | |
| Outpatient | 39 (23) | 49 (32) | | | .1 |
| Emergency Center | 42 (25) | 42 (28) | | | |
| Regular inpatient floor | 19 (11) | 15 (10) | | | |
| Pediatric intensive care unit | 68 (40) | 46 (30) | | | |
| Unknown | 3 (2) | 0 (0) | | | |
| History of seizures in prior 24 h ^c | | | | | |
| No | 76 (51) | 63 (53) | | | .7 |
| Yes | 73 (49) | 55 (47) | | | |
| Seizures to ECG interval (min) ^d | 262 [102-489] | 255 [85-393] | | | .8 |
| Abnormal electrolytes or acidosis ^e | 59 (35) | 28 (18) | 1.4 | 1.2-1.7 | .001 |
| Inotropes | 1 (1) | 9 (5) | 1.7 | 1.4-2.2 | .017 |

Note: Categorical variables were analyzed using Pearson chi-square test. Seizures to ECG interval was analyzed using a Mann-Whitney *U* test.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; ECG, electrocardiogram; RR, relative risk; SE, status epilepticus.

^aResults presented as n (%) or median [interquartile range].

^bRR and CI estimated using generalized linear models; the RR describes the additional average risk of abnormal ECG associated with each additional year of age or epilepsy duration.

^cNormal ECG: n = 118 and abnormal ECG: n = 149.

^dNormal ECG: n = 40 and abnormal ECG: n = 58.

^eIncludes any of the following: serum potassium <3 or >6 mmol/L, magnesium <2 mg/dL, phosphorus <2.5 mg/dL, total calcium <7.5 mg/dL, or base excess <-5.

of chronic ASMs, refractory epilepsy, age at which ECG was performed, and electrolyte abnormalities or acidosis (Table S1).

In a multivariable logistic regression model, epilepsy duration was independently associated with the presence of ECG abnormalities (OR: 1.1, 95% CI: 1.0-1.2, *P* = .002)

TABLE 4 Multivariable logistic regression analysis evaluating the association of epilepsy duration with odds of abnormal ECG^a

| | OR | 95% CI | P |
|---|-----|---------|------|
| Epilepsy duration (years) | 1.1 | 1.0-1.2 | .002 |
| Abnormal electrolytes or acidosis | 1.8 | 0.9-3.4 | .09 |
| Inotropes | 4 | 0.3-46 | .3 |
| Number of maintenance ASMs | 0.9 | 0.7-1.1 | .2 |
| Reasons for clinical encounter | | | |
| New seizure | 0.7 | 0.2-2.6 | .6 |
| Increasing seizure/SE | 1.3 | 0.6-2.7 | .5 |
| Respiratory | 2.6 | 0.9-7.6 | .1 |
| Other | 0.8 | 0.4-1.8 | .6 |
| Seizure semiology | | | |
| Focal impaired awareness or focal to bilateral tonic-clonic | 1.4 | 0.7-2.9 | .3 |
| Generalized tonic-clonic | 1.2 | 0.5-2.8 | .7 |
| Generalized tonic | 1.8 | 0.9-3.8 | .1 |

Abbreviations: ASM, antiseizure medication; CI, confidence interval; ECG, electrocardiogram; OR, odds ratio; SE, status epilepticus.

^aAccounting for multiple observations (clustering) by patient.

adjusting for abnormal electrolytes or acidosis, ionotropic therapy, number of ASMs, reason for clinical encounter, chronic seizure type, and accounting for multiple observations (clustering) by patient (Table 4). Extrapolating from this model, children with 5 years of epilepsy duration have an estimated 1.7 times the odds of having abnormal ECGs compared to children within 1 year of epilepsy diagnosis. Children with 10 years and 15 years of epilepsy duration have an estimated 2.9 times and 4.9 times the odds of having abnormal ECGs, respectively.

In a sensitivity analysis restricted to the first ECG study following epilepsy diagnosis, epilepsy duration and electrolyte abnormalities or acidosis were associated with abnormal ECG studies. In a multivariable model adjusting for abnormal electrolytes or acidosis, number of maintenance ASMs, and reason for clinical encounter, longer epilepsy duration had higher odds of abnormal ECG (OR = 1.1, 95% CI: 1.0-1.3, $P = .06$; Table S2), although this finding did not reach statistical significance.

4 | DISCUSSION

In this study, we retrospectively assessed a select group of children with epilepsy and history of ICU admission who underwent formal ECG assessment for different indications, in different clinical locations, at different times during their epilepsy. We found that epilepsy duration is an independent risk factor for ECG changes in these 127 children with a history of

PICU admission for convulsive seizures or status epilepticus suggesting that cardiac alterations may be a time-dependent phenomenon in pediatric epilepsy patients with a history of severe seizure exacerbation that requires ICU level care.

Epilepsy-associated cardiac electrical alterations represent a well-known systemic comorbidity in adult epilepsy^{4-15,17-20,27,28} and to a lesser extent in childhood-onset epilepsy.^{2,3,16,25} Additionally, recent observations in small cohorts of adult epilepsy individuals and children with Dravet syndrome suggest that epilepsy-associated cardiac electrical alterations may worsen over time. Specifically, adults with long-standing epilepsy have been shown to exhibit interictal and postictal pathological T-wave alternans, an indicator of cardiac electrical instability and a risk marker for sudden cardiac death^{18,19}; whereas adults with newly diagnosed epilepsy do not exhibit pathological T-wave alternans.¹⁹ Similarly, epilepsy duration of 5 years or greater is associated with longer QTc intervals and worse spatial-temporal ventricular repolarization heterogeneity in children with Dravet syndrome.²⁴ Our findings in this cohort of pediatric epilepsy patients without ion channelopathy or cardiac conditions add to the growing clinical evidence for cardiac electrical alterations as a function of epilepsy duration.

We found that ECG changes were common in this cohort of pediatric epilepsy patients. Nonspecific ST segment and T-wave changes represented the most common alterations with the prevalence of 19% and 30%, respectively. In comparison, the prevalence of nonspecific ST elevation and T-wave changes is approximately 10% and 5% in over 48,000 school-age children participating in an ECG screening program.²⁹ In adult population-based studies, the prevalence of early repolarization (characterized by the ST segment alterations) and nonspecific ST-T changes is approximately 6% and 10%, respectively.^{30,31} Although nonspecific ECG changes are generally considered to have indeterminate clinical significance, they may nevertheless reflect underlying cardiac electrophysiological changes such as increased ventricular repolarization complexity,³² which could have future clinical impact. Accordingly, population-based, longitudinal studies in adults have revealed nonspecific ST segment and T-wave changes to be independent risk factors for cardiac mortality decades following the ECG studies.^{30,31} Together, these observations suggest that minor ST/T-wave abnormalities may represent early indicators of altered cardiac electrophysiology and risk biomarkers. The clinical implication of the observed ECG changes and the underlying cardiac electrophysiological alterations in pediatric epilepsy are currently unknown. Future prospective studies are needed to further characterize cardiac electrophysiological alterations represented by the minor ECG changes and to evaluate their potential long-term impact in the overall pediatric epilepsy population.

The observed association between epilepsy duration and ECG changes may be attributable to several factors.

Univariate analyses revealed that chronic seizure type, abnormal electrolytes or acidosis, and the presence of inotropes were associated with ECG alterations. Other potential contributing factors include the number of ASM and their mechanisms of action, as many ASMs modulate ion channel activities and could thereby impact cardiac electrophysiology.^{33,34} Adjusting for these potential contributing factors in our analysis, epilepsy duration remained independently associated with ECG changes. The observed ECG alterations could also simply represent an acute effect of seizures or status epilepticus. However, in this cohort, these changes were not associated with the presence of a seizure episode or time since last recorded seizure, and the prevalence of ECG studies with alterations was similar across various clinical locations where ECGs were obtained (outpatient, emergency center, inpatient, PICU). Together, these findings suggest that, while well-described ECG alterations do arise from seizures or status epilepticus, the observed ECG changes in this study are not likely due to transient seizure-related phenomena.

Because some ECG features evolve with age in the pediatric population,³⁵ these ECG alterations may simply represent the expected developmental changes. We utilized the official reports by the pediatric cardiac electrophysiologists who reviewed all ECG studies as part of routine clinical practice at our institution. Their evaluation would have accounted for the expected age-dependent ECG norms. Furthermore, we did not observe an association between age of epilepsy onset and abnormal ECG studies. Together, these findings suggest that the observed ECG alterations do not simply reflect age-dependent changes.

Several mechanisms may underlie epilepsy duration and ECG abnormalities. For instance, aberrant sympathovagal balance with sympathetic predominance, represented by alterations in heart rate variability, has been extensively described in epilepsy.²⁷ Persistent sympathetic predominance in adults with long-standing epilepsy can adversely affect cardiac function such as increased cardiac stiffness and decreased exercise tolerance.³⁶ Similarly, myocardial molecular remodeling suggestive of persistent sympathetic predominance has been described in the animals with early as well as long-standing epilepsy.^{37,38} These observations indicate that epilepsy may adversely affect the heart through aberrant autonomic regulation leading to myocardial remodeling. Future studies are needed to gain further mechanistic insights into the association of epilepsy duration with cardiac abnormalities.

This cohort of pediatric epilepsy patients with a history of PICU admission and ECG studies performed for specific clinical indications represents a selective group, which limits the generalizability of our findings. Studies in more general pediatric epilepsy cohorts will be necessary to further ascertain whether epilepsy duration is an independent factor associated with cardiac alterations in the overall pediatric

epilepsy population. Although we excluded children with known ion channelopathy, we did not explore other genetic influences that might also contribute to the observed ECG changes. Furthermore, we could not exclude cumulative seizure burden as a factor that underlies the association between epilepsy duration and abnormal ECG studies. Similarly, we could not evaluate the combined effects of chronic seizure type and epilepsy duration on the observed ECG changes or the cumulative ASM exposure as a factor that might underlie the association between epilepsy duration and abnormal ECG studies. The sensitivity analysis failed to meet statistical significance. However, the magnitude and direction of the odds ratio were similar to the final, larger-sample multivariable model. Therefore, these results are consistent and support our primary findings.

This study provides the first description of epilepsy duration as an independent risk factor for ECG changes in a highly selective group of pediatric epilepsy patients without cardiac conditions or ion channelopathies. Our findings add to the emerging clinical evidence suggesting that cardiac alterations may be a time-dependent phenomenon. Future prospective studies are needed to determine the incidence of ECG alterations as a function of epilepsy duration in the overall pediatric epilepsy population, provide mechanistic insights into progressive cardiac alterations, and determine their clinical implications.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to disclose.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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