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Analysis of electrocardiograms in individuals with *CDKL5* deficiency disorder

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Abstract

CDKL5 deficiency disorder (CDD) is an epileptic encephalopathy associated with medically refractory epilepsy. We sought to determine whether prolonged corrected QT interval (QTc) or other cardiac conduction abnormalities were seen in CDD in a clinical cohort. A cohort of individuals with CDD was evaluated in the Children's Hospital Colorado's International Foundation for CDKL5 Research designated Center of Excellence clinic with routine electrocardiograms obtained as part of routine clinical care. Retrospective review of electrocardiograms was completed. ECGs from 44 individuals (7 male, 37 female, age range 0–34.5 years) with pathogenic mutations and findings consistent with CDD were evaluated. Multiple ECGs were available from the 44 individuals obtained from 1996 to 2020. Prolonged QTc was found in two individuals (4.5%) and either resolved or was not confirmed on Holter monitor; no additional interventions were performed. A total of 11 individuals had echocardiograms for a variety of indications including unexplained tachycardia and ECG abnormalities; all were normal. Two individuals in the cohort died during the study with no abnormal findings on ECG. The incidence of prolonged QTc or other significant actionable cardiac abnormalities was rare in a cohort of individuals with CDD though was higher than the prevalence seen within the general population. Further studies in a larger, confirmatory cohort over a longer period are needed.

Keywords

CDD; CDKL5; long QT

1 | INTRODUCTION

CDKL5 deficiency disorder (CDD) is a developmental encephalopathy caused by pathogenic variants in cyclin-dependent kinase-like 5 (CDKL5). While initially thought

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to be the early seizure variant of Rett Syndrome, CDD is now identified as its own entity (Kadam et al., 2019). Phenotypic features include infantile-onset refractory epilepsy, hypotonia, developmental delay, intellectual disability, and visual impairment. Given the phenotypic neurologic similarities between CDD and Rett Syndrome, it is possible that the cardiac manifestations may also be similar. However, the cardiac manifestations in CDD, including the incidence of prolonged QTc, have not been well defined (Olson et al., 2019). In a cohort of individuals with CDKL5, 19 out of 29 were investigated with electrocardiography (ECG) and echocardiogram. ECG abnormalities were identified in 11 of them, though the exact findings and whether any clinical management changes resulted are not noted in the article (Amin et al., 2017). Cardiac conduction abnormalities, primarily prolonged QT interval, have been described in ~10%–18% of individuals with Rett Syndrome (Fu, Armstrong, Marsh, Lieberman, Motil, Witt, Standridge, Nues, et al., 2020). Prolonged QT interval dictates the presence of a repolarization abnormality that can predispose to the development of a fatal cardiac arrhythmia and is one hypothesized cause of death in Rett Syndrome. The severity of QTc prolongation may be associated with a higher risk of potentially fatal cardiac arrythmias and an association between QTc prolongation and sudden death in individuals with Rett Syndrome has been described (Clark et al., 2020). In addition to prolonged QT interval, individuals with Rett Syndrome have also been reported to have other repolarization abnormalities and reduced heart rate variability. Single individuals with Rett Syndrome have been reported to have sinus bradycardia, ventricular tachycardia, and asymptomatic sinoatrial block (Acampa & Guideri, 2006). The true clinical significance of these findings is uncertain. Echocardiographic imaging is typically normal, though subtle features of systolic and diastolic function have been reported (Fu, Armstrong, Marsh, Lieberman, Motil, Witt, Standridge, Lane, et al., 2020). The goal of this study was to retrospectively evaluate electrocardiograms and other related studies in a cohort of individuals with CDD to determine whether significant and actionable cardiac abnormalities were found.

2 | METHODS

Individuals with pathogenic or likely pathogenic variants in *CDKL5* described in the CDKL5 database at Children's Hospital Colorado were included in this retrospective chart review. Out of the original 49 identified, five were excluded due to missing or unreadable electrocardiograms. Standard 12-lead electrocardiograms (ECGs), obtained as part of routine clinical care, were reviewed and abnormalities were classified into Long QT, Borderline Long QT, Nonspecific Repolarization Abnormalities, and Other. The “Other” category included all other ECG abnormalities which did not involve QT interval or repolarization. Review was performed independently by two board-certified pediatric cardiologists. The QT interval was measured either by hand or by using on-screen calipers. The observed QT was corrected for heart rate by Bazett's correction utilizing the preceding RR interval. Prolongation was defined as QTc > 460 ms (Moss, 1993). Borderline prolongation was defined as between 445 and 460 ms. Additional data obtained from the ECGs included QRS duration and T-wave morphology. Clinical data were obtained from review of the electronic medical record and included age at time of the ECG, CDKL5 variant, and variant classification (pathogenic or likely pathogenic), whether patient was living or deceased, and

cause of death if known. Electrocardiograms were obtained in a portion of patients due to a variety of reasons including tachycardia, hemodynamic abnormalities, and abnormal ECG.

Descriptive statistics were performed on the data to collect the minimum, maximum, average, and SD of the QTc data. A Pearson correlation coefficient was calculated to quantify the relationship between age and the initial prolonged QTc. An alpha level of $\alpha = 0.05$ was chosen to determine if the correlation coefficient was statistically significant.

3 | RESULTS

A total of 44 patients with CDD (7 males, 37 females) who had at least one electrocardiogram were included in the study. Ages ranged between 0 days to 34.54 years (average 6.95 years; Figure 1). The majority had a single ECG which was obtained as a baseline, in total 96 ECGs in 44 patients. However, 17/44 (39%) had more than 1 ECG and 1 patient had as many as 8 ECGs. Across all ECGs, mean QTc was 422 m ± 20 SD, range 375–465, $n = 96$. A total of 12 ECGs in a total of nine patients (9/44 or 20%) had a QTc which fell within the borderline range (445–460 ms).

The data were plotted to look at age (in years) at ECG versus the QTc recorded at that ECG (Figure 1 below). The minimum age included in the graph above was 0 years while the maximum age included was 34.54 years, (mean = 6.95, SD = 6.97). The average QTc score across all patients was 422.42 with a minimum of 375 and a maximum of 465. The data follow a relatively normal distribution. There is a slight right skew due to the lack of QTc scores in older patients. Only two patients had a QTc longer than 460 msec (2/44, 4.5%). One of these patients had a normal initial ECG with a QTc of 439 ms at 3 months of age but developed a prolonged QTc when a second ECG was obtained at 6 years of age. A Holter monitor was obtained in this patient which was interpreted as normal. Three subsequent ECGs were collected on this patient up until the age of 13 years, with a QTc ranging from 450 to 460 ms. The second patient with prolonged QTc had a repeat ECG which had normalized 10 months later. No further cardiac evaluation was pursued following the normal ECG. A medication list from the time of the ECG (2013) was not available for the first patient. The second patient was not prescribed any medications known to prolong QT interval at the time of the ECG based on the electronic medical record.

In total, 50/96 (52%) of obtained ECGs were normal, 11/96 (12%) had nonspecific repolarization abnormalities but normal QTc interval, and 21/96 (22%) had other abnormalities which included sinus tachycardia ($n = 8$), left ventricular hypertrophy ($n = 2$), right ventricular hypertrophy ($n = 2$), left atrial enlargement ($n = 1$), and deep septal q waves ($n = 8$).

A total of 13 electrocardiograms were completed in 11 individuals (including individuals with ECG abnormalities such as LVH [$n = 3$], left atrial enlargement [$n = 1$], and deep septal q waves [$n = 4$]). There were no structural or functional cardiac abnormalities found in any patient. Six Holter monitors were performed with no documented arrythmias. One transient arrythmia monitor was also obtained, again with no documented arrythmias. Two deaths occurred in the study population, one due to a respiratory infection and the second occurred

at home due to an unknown cause. Both individuals had a single normal ECG obtained in early childhood (3 years and 1 year of age, respectively).

4 | DISCUSSION

This cohort of patients with CDD demonstrated an incidence of borderline prolonged QTc (445–460 ms) in 20% and prolonged QTc (>460 ms) in only 4.5%. This is significantly below the incidence of prolonged QTc reported by Clark et al. (2020) paper evaluating a large cohort of 129 female patients with Rett Syndrome, who had an incidence of 9.3% (12/129) with a defined prolonged QTc of greater than or equal to 460 ms. Also of note, these patients had prolonged QTcs that were longer than any patient in our study (median 474 ms, interquartile range 470–486 ms vs. median 463.5 ms) (Clark et al., 2020). Crosson et al. (2017) noted an incidence of prolonged QTc of 7% in their cohort of 100 patients with Rett Syndrome, but used a lower cutoff of >450 ms. These findings suggest that while patients with CDD have borderline prolonged QTc at an incidence similar to or higher than has been previously reported in patients with Rett Syndrome, the actual incidence of prolonged QTc may be much lower.

While the Crosson et al. study noted a trend toward increased QTc with age, this was not seen in the Clark et al. study. As QTc increases with age in the normative population, the clinical significance of this trend is uncertain. Most of the patients in our study had a single ECG obtained in infancy or childhood (mean 6.95 years) and there was no statistically significant linear correlation with prolonged QTc and age ($r = 0.177$, $p = 0.22$). Additionally, in our patients with serial ECGs, there was no trend toward prolonged QTc with age, including the patient with a normal initial ECG who had prolonged QTc at the age of 6 and was followed with serial ECGs until 13.9 years. Resolution of prolonged QT occurred in one individual and this has not been reported previously to our knowledge.

Holter monitors were obtained on a select portion of patients (6/44 or 13%) for a variety of reasons including tachycardia, palpitations, and prolonged QT. None of these showed clinically significant abnormalities. Echocardiograms were also completed in 11/44 (25%). The reasons stated for obtaining the imaging include abnormal ECG, hypertension, hypotension, tachycardia, CDD, and “Rett Syndrome.” All had normal cardiac structure and function. This suggests that congenital heart disease and ventricular dysfunction are not common in CDD and that an echocardiogram may not be necessary, even in those with an abnormal ECG suggesting structural heart disease. This is consistent with a previous study reported by Guideri et al. (2004) where 32 girls with Rett Syndrome were evaluated by echocardiogram due to cardiac dysautonomia and had normal cardiac structure and function.

This study has several limitations. This is a retrospective chart review and relies on the accuracy and completeness of the medical record. The patient sample size is small so further studies are necessary to ensure the accuracy and generalizability of these findings to the entire CDD population. The Bazett formula was chosen as it is the current clinical standard, acknowledging that there can be overcorrection at high heart rates and undercorrection at lower heart rates (Vandenberk et al., 2016). Finally, many patients lacked longitudinal follow-up, so it is possible that prolonged QTc developed later or that cardiac-related deaths

occurred in the study group that was not documented in the available electronic medical record.

5 | CONCLUSION

The cardiac manifestations of CDD need to be fully defined with a longitudinal study, though this retrospective study provides some new insights. This study suggests that structural and functional cardiac disease is not common in CDD, even in those with abnormal ECGs or clinical findings which suggest structural or functional cardiac abnormalities. Similar to what has been reported in the Rett Syndrome population, mild QTc prolongation is present in a portion of patients with CDD. However, the incidence may be lower than what has been reported previously in the Rett Syndrome population and the degree of QTc prolongation less severe. The clinical significance of this finding remains uncertain as a direct causal relationship between prolonged QTc and sudden death in Rett Syndrome or CDD has yet to be established. Further studies are necessary to guide clinical management in these individuals. Nevertheless, given the increased prevalence of prolonged QT interval in our cohort compared to the incidence of LQTS in the general population, it is reasonable to obtain at least an initial baseline ECG on all individuals with CDD at the time of diagnosis and to follow those individuals who have a prolonged QTc. Our clinic obtains an annual ECG given that one of the individuals followed developed prolonged QT after a normal initial ECG and another later had resolution of their prolonged QT. Echocardiography is likely necessary only if there are clinical cardiac concerns beyond the diagnosis of CDD.

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DATA AVAILABILITY STATEMENT

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

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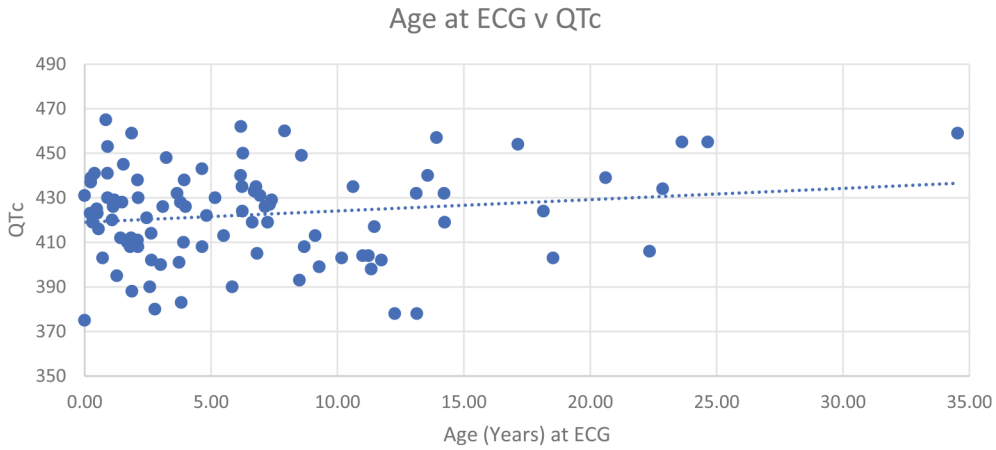

FIGURE 1.

Age (in years) at ECG versus the QTc recorded at that ECG. The minimum age included in the graph above was 0 years while the maximum age included was 34.54 years, ($\mu = 6.95$, $\sigma = 6.97$). The average QTc score was $\mu = 422.42$, $\sigma = 21.016$ with a minimum of 375 and a maximum of 465. Based on the graph above, the data follow a relatively normal distribution. There is a slight skew due to the lack of QTc scores in older patients.