QT intervals in metabolic dilated cardiomyopathy

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OBJECTIVES: The present study determined the prevalence of dilated cardiomyopathy together with prolonged corrected QT (QTc) intervals in children. The study also examined whether an association exists between prolonged QTc intervals and ventricular dysrhythmia in a patient cohort with dilated cardiomyopathy.

BACKGROUND: The morbidity and mortality for pediatric patients with dilated cardiomyopathy remains high and is a clinical challenge. The patient population includes a significant number of Hutterite patients with metabolic disease associated with dilated cardiomyopathy.

METHODS: Thirty-eight pediatric patients with dilated cardiomyopathy were reviewed for the presence of prolonged QTc and dysrhythmias. Eleven patients had a metabolic etiology for their dilated cardiomyopathy.

RESULTS: Thirty-six per cent of the patient cohort had a long QTc interval. After 50 months of follow-up, the probability of survival for a child with a long QTc interval was approximately 50%. The probability of survival for a child with a normal QTc interval was 72%. Seventy per cent of the patients who died had a metabolic etiology for their dilated cardiomyopathy and a long QTc.

CONCLUSIONS: Dilated cardiomyopathy may be associated with a prolonged QTc and may increase the patient's risk for sudden death. The presence of a metabolic etiology for dilated cardiomyopathy increases the risk of death.

Key Words: Dilated cardiomyopathy; Long QT; Metabolic disease; Pediatric

Dilated cardiomyopathy (DCM) is a rare disease in infants and children with a generally unfavourable outcome. Predominant etiologies in the pediatric age group are either idiopathic or the sequelae of myocarditis. Other causes include familial disease, drug therapy, or metabolic, rheumatological, neurological, renal or endocrine disease. DCM is diagnosed by the presence of dilation of the left or both ventricles, with accompanying systolic dysfunction. The prevalence of DCM in infants and children is 36 per 100,000 (1). Survival at one year and five years is approximately 65% and 51%, respectively (2).

Cardiac dysrhythmias have been suggested as a risk factor for poor outcome in children with DCM (3-6). The reported incidence of cardiac dysrhythmias in pediatric DCM patients ranges from 19% to 46% on standard electrocardiogram (ECG), Holter monitoring or both (2-12). The prognostic significance of dysrhythmias in children with DCM is controversial (2-11).

Les segments QT dans la cardiomyopathie dilatée d'origine métabolique

OBJECTIFS : La présente étude a évalué la prévalence de la cardiomyopathie dilatée et de l'allongement du segment QT corrigé (QTc) chez les enfants et a aussi tenté de déterminer s'il y a un lien entre l'allongement du QTc et les dysrythmies ventriculaires chez une cohorte de patients présentant une cardiomyopathie dilatée.

HISTORIQUE : Chez les patients pédiatriques atteints de cardiomyopathie dilatée, la morbidité et la mortalité demeurent élevées et représentent un important défi clinique. La population de patients incluait un nombre important de patients hutteriens souffrant d'une maladie métabolique associée à la cardiomyopathie dilatée.

MÉTHODES : Trente-huit patients pédiatriques souffrant de cardiomyopathie dilatée ont été examinés pour relever la présence d'un allongement du QTc et de dysrythmies. Onze patients présentaient une cardiomyopathie dilatée d'origine métabolique.

RÉSULTATS : Trente-six pour cent de la cohorte de patients présentaient un QTc allongé. Après 50 mois de suivi, la probabilité de survie chez les enfants qui avaient un QTc allongé était d'environ 50 %, contre 72 % chez les enfants dont le QTc était normal. Soixante-dix pour cent des patients décédés présentaient une cardiomyopathie dilatée et un allongement du QTc d'étiologie métabolique.

CONCLUSIONS : La cardiomyopathie dilatée peut être associée à un allongement du QTc et peut exacerber le risque de mort subite chez ces patients. La présence d'une cardiomyopathie dilatée d'étiologie métabolique accroît le risque de mortalité.

The purpose of the present study was to identify the prevalence of DCM along with a prolonged corrected QT (QTc) interval, and to determine whether an association exists between prolonged QTc and reduced survival in this cohort of pediatric patients with DCM. The sample includes a number of patients from the Hutterite community in southern Alberta, which is considered to be an inbred population. There is a high incidence of autosomal recessive disease, including metabolic disease, in this population. In this population, we are not aware of a primary disease affecting the QT interval.

PATIENTS AND METHODS

Thirty-eight infants, children and adolescents (22 male and 16 female patients) with DCM were retrospectively studied. Both inpatient and outpatient charts from the Alberta Children's Hospital (Calgary, Alberta) were searched for a DCM diagnostic code and cross-referenced with echocardiographic data. The criteria

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TABLE 1
Mean scores for clinical variables

Variable	Normal QTc group (n=21)	Long QTc group* (n=12)
Age at diagnosis, years	6.3	1.0
Heart rate, beats/min	104	142
QTc, ms	391	486
LVEDD, cm	4.20	3.97
FS, %	26.0	16.2

*Corrected QT interval (QTc) cutoff was 440 ms for males and 450 ms for females. FS Fractional shortening; LVEDD Left ventricle end diastolic dimension

for a diagnosis of DCM were based on echocardiographic data demonstrating a nonhypertrophied dilated left ventricle. ECGs and echocardiograms were recorded at six-month intervals. A prolonged QTc interval was defined as 450 ms or greater for female patients and 440 ms or greater for male patients.

Patients were excluded from the study if they had a diagnosis of another form of cardiomyopathy, such as hypertrophic or restrictive cardiomyopathy, any structural heart disease or an underlying chronic dysrhythmia. Five patients were subsequently excluded from the analysis because of ECG abnormalities that altered their QT interval (one patient with a congenital third-degree heart block, two patients with ventricular pacemakers, one patient with left bundle branch block and one patient with Wolff-Parkinson-White syndrome and a wide QRS).

The etiology of DCM in the patient cohort included idiopathic causes (n=8), myocarditis (n=5), metabolic causes (n=11), anthracycline toxicity (n=6), ischemic causes (n=1), renal failure (n=1) and unknown causes (n=1). Metabolic cardiomyopathy was defined as DCM secondary to metabolic disease, such as Pompe's disease (n=1), 3-methylglutaconic aciduria (n=5), lipodystrophy (n=1), mitochondrial disease (n=1) and Fryn syndrome (n=1). The remaining two patients, classified as having metabolic cardiomyopathy, were part of the Hutterite community of southern Alberta, had a positive family history of DCM, specifically 3-methylglutaconic aciduria, and died suddenly without prior DNA testing. Patients were classified with DCM secondary to myocarditis based on clinical presentation, and the myocarditis was not proven by myocardial biopsy in each case to confirm diagnosis.

Statistical analysis

The initial phase of the analysis consisted of descriptive statistics, such as frequencies, means and SDs. Children were divided into two groups at presentation, one group with a normal QTc interval and a second group with a prolonged QTc interval. Continuous variables were compared between these two groups using Student's *t* tests, while between-group comparisons for categorical variables used χ^2 tests of association. Analyses were also conducted to determine whether there was an association between a prolonged QTc interval and ventricular dysrhythmias. Kaplan-Meier survival curves were used to compare survival rates between children with normal QTc and children with prolonged QTc intervals. The last set of between-group comparisons involved comparing two different groups, children still alive at last follow-up and those who had died. A discriminant function analysis was also conducted to determine which variables best discriminated between children who had survived and those who were deceased. Statistical significance at $P < 0.05$ was used and trends at $P < 0.10$ were also reported.

TABLE 2
Frequencies of clinical variables by group

Variable	Normal QTc group (n=21) (%)	Prolonged QTc group (n=12) (%)
Family history of DCM	4.8	41.7
Mortality	14.3	58.3
Mitral regurgitation	36.8	88.9
Abnormal ST segment (ECG)	33.3	66.7
Right ventricular hypertrophy (ECG)	14.3	41.7
Metabolic etiology of DCM	19.1	58.3

DCM Dilated cardiomyopathy; ECG Electrocardiogram; QTc Corrected QT interval

RESULTS

The mean age $\pm$ SD at diagnosis in the 33 patients was 4.5 ± 5.4 years. The range of age at diagnosis included birth to 16 years. There were 19 male patients and 14 female patients. Patients were followed for a mean $\pm$ SD of 44.5 ± 50.4 months (range of follow-up was zero to 199 months). Groups were defined by QTc scores at presentation. There were 12 children in the long QTc group (eight male and four female children) and 21 children in the normal QTc group (11 male and 10 female children).

Demographic and clinical variables

There was no significant association between QTc group and patient sex. There was a significant group difference in age at diagnosis ($t[23]=3.96$; $P < 0.01$), with the long QTc group having a younger age at diagnosis. There was also a significant group difference in heart rate at baseline ($t[31]=-3.46$; $P < 0.01$), with the long QTc group having a higher heart rate at baseline as well as at diagnosis. There was a significant group difference in fractional shortening by echocardiogram at baseline ($t[28]=2.55$; $P < 0.05$). There was a trend toward an increased left ventricular end diastolic dimension (LVEDD) in the long QTc group, but no significant difference was found (Table 1).

There was a significant association between group and family history of DCM ($\chi^2[1]=6.99$; $P < 0.01$), with significantly more children in the long QTc group having a positive family history than children in the normal QTc group (Table 2). A trend was present for an association between group and mortality ($\chi^2[1]=3.46$; $P < 0.10$). Despite the trend for an association between QTc group and mortality, there was no significant association between group and sudden cardiac death. Of 11 patients with a metabolic etiology for their DCM, seven had a long QTc interval at diagnosis. During follow-up, another child developed a long QTc interval for a total of eight children, seven of whom died.

A significant association was found between QTc group and the presence of mitral regurgitation by echocardiogram ($\chi^2[1]=6.65$; $P < 0.05$). There was a trend for an association between group and right ventricular hypertrophy at baseline ($\chi^2[1]=3.12$; $P < 0.10$). A trend existed for an association between group and abnormal ST segment at baseline ECG ($\chi^2[1]=3.42$; $P < 0.10$). There was no observed significant association between group and any kind of arrhythmia (arrhythmia during Holter monitoring or exercise), with only two children noted to have an arrhythmia during follow-up, and both were in the normal QTc group.

Figure 1) Kaplan-Meier curves showing the probability of survival for patients with a normal corrected QT (QTc) interval and patients with a long QTc interval

Survival analysis

The long QTc and normal QTc survival curves are shown in Figure 1. Results showed that after 50 months of follow-up, the probability of survival for a child with a long QTc interval was approximately 50%, compared with 72% for a child with a normal QTc interval. Additional results showed that after 100 months of follow-up, the probability of survival for a child with a long QTc interval was approximately 39%, compared with 72% for a child with a normal QTc interval.

Comparison of survivors with deceased patients

Additional analyses comparing children who had survived with those who were deceased showed a significant association with family history ($\chi^2[1]=9.76$; $P<0.01$) (Table 3). One-half of the children who died had a positive family history of DCM. There was a significant association between mitral regurgitation by echo at baseline and death ($\chi^2[1]=3.88$; $P<0.05$). There was also a significant association of right ventricular hypertrophy by echo and death ($\chi^2[1]=5.64$; $P<0.05$), as well as between left atrial dilation at baseline and death ($\chi^2[1]=6.81$; $P<0.01$). Children who died were significantly younger at diagnosis ($t[30]=-2.58$; $P<0.01$), had a significantly longer QTc interval ($t[31]=2.82$; $P<0.01$), and had a significantly lower fractional shortening ($t[28]=-2.05$; $P=0.05$). There was a trend for an association between cause of DCM and death ($\chi^2[5]=10.70$; $P=0.058$). Six patients who died with a long QTc interval had a metabolic etiology for their DCM. Of these six patients, the mean $\pm$ SD QTc at diagnosis was 490 ± 0.016 ms (range 465 ms to 500 ms). During follow-up, the mean $\pm$ SD longest QTc was 498 ± 0.019 ms (range 465 ms to 520 ms). Two other deceased patients also had a metabolic etiology for their DCM; one patient developed a long QTc in follow-up, whereas the other patients' QTc intervals remained normal. Only two patients were treated with a beta-blocker and neither survived.

Of interest was the fact that all patients with a positive family history of DCM had a metabolic etiology for their disease. Given the fact that having a metabolic etiology and a positive family history of DCM seemed to be important factors in the relationship to survival, a discriminant function analysis was conducted to determine which variables best discriminated

TABLE 3
Group comparison of children alive versus children deceased

Variable	Children alive (n=23)	Children deceased (n=10)
Mean LVEDD, cm	4.2	3.8
Mean age at diagnosis, years	5.7	1.8
Mean heart rate, beats/min	114	128
Mean QTc, ms	409	464
Mean FS, %	24.7	15.9
Family history of DCM, %	4.3	50.0
Mitral regurgitation, %	4.8	85.7
Right ventricular hypertrophy, %	0	25.0
Left atrial dilation, %	33.3	87.5
Long QTc, %	13.0	70.0
Metabolic etiology of DCM, %	17.4	80.0

DCM Dilated cardiomyopathy; FS Fractional shortening; LVEDD Left ventricular end diastolic dimension; QTc Corrected QT interval

between children who had survived to those who were deceased. Results showed that the child's QTc interval, family history and whether the etiology of DCM was metabolic were the best variables to discriminate between children still alive and those who died ($\chi^2[3]=15.95$; $P<0.01$). In total, 87.9% of children were correctly classified as surviving or deceased using these three variables.

DISCUSSION

The present study confirms the previously described poor clinical outlook for pediatric patients with DCM. The study examined the possible relationship of a prolonged QTc interval and negative outcomes such as sudden cardiac death in a cohort of pediatric DCM patients. We hypothesized that prolongation of the QTc interval was an element in the causal pathway of sudden cardiac death in pediatric patients with DCM and that this may be an important factor in the clinical management of these patients.

Dubin et al (13) reported that prolonged QT dispersion and QT SD identify pediatric patients with DCM at a higher risk for subsequent ventricular dysrhythmias. They reported 26 patients with severe DCM referred for poor cardiac output and heart transplantation. Their results supported a relation between DCM and a prolonged QT dispersion (QT dispersion is defined as the duration of the shortest QT subtracted from that of the longest) (14). The QT dispersion was prolonged as LVEDD increases and as the cardiomyopathy disease worsens. Therefore, a prolonged QT dispersion can identify patients at increased risk of developing a malignant dysrhythmia.

The relationship between the QT interval and cardiomyopathy is not well examined in the literature. Martin et al (14) examined the relationship between the QT interval and ventricular hypertrophy or dilation. They reported that a statistically significant proportion of their pediatric patients with DCM had a long QTc interval. Huh et al (15) retrospectively reviewed ECG data of 33 children with idiopathic DCM and found that QRS duration positively correlated to left ventricular dimensions. QT dispersion was also significantly prolonged in patients with DCM compared with controls (15).

Our survival data demonstrate the importance of the QTc interval in that the probability of survival for a child with a long QTc interval was approximately 50% compared with 72% for a child with a normal QTc interval. This observation

appears to hold true over short-term follow-up; after 100 months of follow-up, the probability of survival for a child with a long QTc interval was approximately 39% compared with 72% for a child with a normal QTc interval. The role of a positive family history of DCM is important in the survival analysis. Our results demonstrate that the child's QTc, the family history and whether the etiology of DCM was metabolic were the best variables to discriminate between children still alive and those who died ($\chi^2[3]=15.95$; $P<0.01$). In total, 87.9% of children were correctly classified as surviving or deceased using these three variables.

Similar to the Martin et al study (14), in our DCM group, there was no relation of QTc to age, shortening fraction or LVEDD. While there were no significant associations between long QTc and normal QTc grouping with dysrhythmia or sudden death, with a larger patient population, one may uncover a significant difference, and this deserves further study. Similar to Huh et al's (15) study results, the LVEDD was not significantly higher in our long QTc interval group, but a trend existed.

All patients who died with a long QTc had a metabolic etiology for their DCM, including five patients with known 3-methylglutaconic aciduria. A metabolic etiology for DCM,

together with a positive family history, would seem to be important risk factors for long QTc and death. Our patient population does include a significant inbred Hutterite population.

The present study was limited by its retrospective design, including a lack of DNA data on some of our patients who died before the discovery of the gene for 3-methylglutaconic aciduria.

CONCLUSION

DCM is a rare disease in infants and children with a poor outcome. More than one-third of children with DCM in the present study had a long QTc interval. The cohort of patients demonstrated a significantly reduced survival compared with patients with a normal QTc. Patients with a positive family history and metabolic etiology for DCM are at a particularly high risk of death. The study was limited by a small sample size.

However, the results suggest that the relationship between QTc intervals and outcome measures in pediatric patients with a metabolic etiology of DCM warrants further study.

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