QTc Dispersion in Children with Congenital Hypothyroidism

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ABSTRACT
Background: The effects of thyroid hormones on the cardiovascular system have been well documented. Chronotropic response and normal tone of the heart muscle during diastole are due to T3. Moreover, triiodothyronine affects the number of B adrenergic receptors and their sensitivity to catecholamines. Increased corrected QT (QTc) dispersion has been found to be associated with cardiac arrhythmias and sudden cardiac death in patients with myocardial infarction, left ventricular hypertrophy, congestive heart failure, diabetes and end-stage renal disease.
Objective: The objective of this study was to evaluate QTc dispersion in children with congenital hypothyroidism.
Patients and Methods: This was a case-control study that was carried out at Pediatric Cardiology and Endocrinology Units, Zagazig University Children's Hospital. The study included 74 children with hypothyroidism and control subjects. Twelve lead ECG was performed to all participants. Serum T4 and TSH were measured to all study members.
Results: There was statistically significant increase among case than control groups regarding QTc dispersion ($P < 0.05$), while there was no statistically significant difference ($P \geq 0.05$) regarding longest QTc, shortest QTc and QRS amplitude. The current study showed that, there was no statistically significant difference ($P \geq 0.05$) regarding longest QT, shortest QT, QRS amplitude and QTc dispersion in cases with low versus those with high TSH level. There was no significant correlation between TSH and QTc dispersion.
Conclusion: QTc dispersion was higher in our patients compared to control group, which indicates heterogeneity of ventricular repolarization that could contribute to increased risk of ventricular arrhythmias.
Keywords: QTc dispersion, Assessment, Congenital hypothyroidism.

INTRODUCTION

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation. In most cases, the disorder is permanent. Less commonly, the altered neonatal thyroid function is transient, attributable to the transplacental passage of maternal medication and maternal blocking antibodies [1]. In rare cases, CH may result from a pituitary or hypothalamic abnormality (central or secondary/tertiary hypothyroidism) [2]. The thyroid hormone is important for normal growth and development in infancy [3].

Since cardiovascular system is rich in TSH receptors and is one of the major sites of action for TSH, it is relatively sensitive to changes in the levels of TSH [4]. The effects of thyroid hormones deficiency on the cardiovascular system include pericardial effusion, weak arterial pulse, bradycardia, hypotension, facial and peripheral edema, deepened cardiac sounds, and congestive heart failure manifestations such as ascites, orthopnea, and paroxysmal dyspnea [5]. Congenital heart disease (CHD) is the most frequent disease condition associated with congenital hypothyroidism. CHD is also reported to be a risk factor for non-autoimmune hypothyroidism in children [6].

QTc dispersion, the difference between the maximum and minimum QTc interval on the 12-lead electrocardiogram (ECG), is a marker of heterogeneity of ventricular repolarization [7].
The objective of this study was to evaluate QTc dispersion in children with congenital hypothyroidism.

PATIENTS AND METHODS

This case-control study was performed at Pediatric Cardiology and Endocrinology Units, Zagazig University Hospitals on 74 participants that were divided into patients and control groups.

Study population: The study retrospectively enrolled 48 patients with congenital hypothyroidism between April 2021 and May 2022. They were regularly followed up at Outpatient Clinic of Ministry of Health, Zagazig, Egypt. The control group included 26 asymptomatic healthy children selected from Inpatients/Outpatients Units of Zagazig University Children's Hospital.

Patients: Forty-eight children with congenital hypothyroidism that were diagnosed to have high TSH and low T4 levels and who were getting hormonal replacement treatment were included in the study. The patients' group was divided into two subgroups: patients with TSH levels < 40 uIU/ml and cases with TSH > 40 uIU/ml. Patients were divided into two subgroups based on duration of illness: duration of illness <12 months and duration of illness >12 months.
Control subjects: Twenty-six children of comparable age and sex to cases served as controls. Control children had been investigated to exclude congenital or acquired heart disease and their physical examination and Echocardiography were found to be uneventful.

Inclusion criteria: Patients with congenital hypothyroidism from birth (full term) to 3 years of age.

Exclusion criteria: Other endocrinal or CNS dysfunction, patients on antiepileptic drugs, and congenital or acquired heart diseases. Patient with surgical intervention of thyroid gland.

All patients were subjected to the following:
(1) Full history taking. (2) Serum T4 and TSH estimation. (3) Twelve lead ECG.

Electrocardiography:
Twelve-lead ECG recordings were obtained for all patients. The QT interval was taken as the period from the beginning of the Q wave to the end of the T wave. QT dispersion was calculated as the difference between the maximal and minimal QT intervals on 12-channel standard ECG. The QT intervals on ECGs were corrected using Bazett's formula [corrected QT interval (QTc) = QT/√R-R] and were expressed as corrected QT interval (QTc) [7].

Ethical consent:
An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Written informed consents to participate in study were obtained from all parents. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All data were collected, tabulated, and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean ± SD. Independent samples Student's t-test was used to compare between two groups of normally distributed variables, while Mann-Whitney U test was used for comparison of median (interquartile range) of non- normally distributed variables. Qualitative data were presented as absolute frequencies (number) & relative frequencies (percentage). Percent of categorical variables were compared using Chi-square test. Spearman's rank and Person correlations coefficient were utilized to assess relationship between various study variables, (+) sign indicate direct correlation & (-) sign indicate inverse correlation, also values near to 1 indicate strong correlation and values near to 0 indicate weak correlation. All tests were two sided. $P < 0.05$ was considered statistically significant (S), p-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS
As shown in table (1), there were no statistically significant differences between the studied groups regarding age (years) and sex ensuring groups homogeneity ($p > 0.05$).

Statistical analysis:

Table (1): Demographic characteristics of the two studied groups

Variable	Cases group (n=48)		control group (n=26)		Tests	
					z	P value
Age (years) Median (IQR)	16.5 (7-30)		15 (7.5-36)		-0.738	0.460 (NS)
Variable	No	(%)	No	(%)	x^2	P value
Sex Female	25	52.1	14	53.8	0.021	0.885 (NS)
Male	23	47.9	12	46.2		

(**NS**): non-significant - (**X^2**): chi-square test - (**z**): Mann-Whitney U test

Table (2) showed that there was statistically significant difference ($P < 0.001$) between case and control groups regarding QTc dispersion while there was no statistically significant difference ($P > 0.05$) between them regarding longest QTc, shortest QTc and QRS amplitude.

Table (2): QTc dispersion of studied groups

Variable	Cases group (n=48)	Control Group (n=26)	tests	
			z	P value
Longest QTc (sec) Mean ± SD	0.55 ± 0.07	0.52 ± 0.07	1.521	0.133 (NS)
Shortest QTc (sec) Mean ± SD	0.42 ± 0.07	0.45 ± 0.06	-1.894	0.062 (NS)
QTc dispersion (sec) Mean ± SD	0.13 ± 0.23	0.08 ± 0.01	-3.724	<0.001* (S)
QRS amplitude (mv) Mean ± SD	0.8 ± 0.17	0.8 ± 0.16	-0.115	0.909 (NS)

(**NS**): non-significant >0.05 - (**S**): Significant <0.05* - (**t**): independent sample t-test - (**z**): Mann-Whitney U test
There was no statistically significant difference ($P > 0.05$) between the TSH levels subgroups regarding longest QTc, shortest QTc, QRS amplitude and QTc dispersion **(Table 3).**

Table (3): serum TSH value and ECG readings of studied cases

Variable	TSH		tests	
	<40(uIU/ml) (n=25)	≥40(uIU/ml) (n=23)	z/t	P value
Longest QTc (sec) Mean ± SD	0.57 ± 0.08	0.53 ± 0.05	1.730	0.090 (NS)
Shortest QTc (sec) Mean ± SD	0.42 ± 0.06	0.42 ± 0.09	0.092	0.927 (NS)
QTc dispersion (sec) Mean ± SD	0.14 ± 0.31	0.11 ± 0.019	-1.150	0.250 (NS)
QRS amplitude (mv) Mean ± SD	0.8 ± 0.15	0.8 ± 0.016	-1.693(z)	0.091 (NS)

(**mv**): millivolt - (**NS**): non-significant >0.05 – (**RV**): right ventricle - (**S**): Significant <0.05* (**t**): independent sample t-test - (**z**): Mann-Whitney U test
There was no significant relationship between TSH and T4 serum levels with any of the studied clinical and ECG parameters ($P > 0.05$) as shown in table (4).

Table (4): Correlation between serum TSH and T4 with clinical and ECG parameters

Variable	TSH (uIU/ml)		T4 (ng/dl)	
	R	P	R	P
Duration of illness (months)	-0.166	0.259	0.035	0.813
Systolic BL/P mmHg	0.006	0.969	-0.054	0.715
Diastolic BL/P mmHg	-0.013	0.932	0.094	0.524
Heart rate(beat/minute)	-0.037	0.803	0.278	0.056
Hb (gm/dl)	0.247	0.090	0.095	0.521
O2 saturation (%)	0.104	0.484	0.015	0.921
Longest QTc (sec)	-0.230	0.116	-0.069	0.641
Shortest QTc (sec)	0.081	0.585	0.024	0.874
QTc dispersion (sec)	-0.258	0.077	-0.090	0.543
QRS amplitude (mv)	0.186	0.205	-0.221	0.131

DISCUSSION

Our study showed a female mild predominance among cases group (52.1%). This agrees with **Abdelmoktader** [8] who confirmed the already known higher prevalence of CH among females than males. This also coincides with **Rezaeian et al.** [9] who indicated the role of the female gender as a risk factor for CH. Moreover, **Medda et al.** [10] conducted a case-control study in order to determine risk factors for CH and reported higher prevalence of CH among females than males. Similarly, **Akha et al.** [11] reported that the female/male ratio of CH was approximately 1.0. On the other hand, **Abbasi et al.** [12] reported that, 53.5% of neonates with transient CH were boys and 46.5% girls, with male to female ratio of 1.14. In permanent CH, male to female was 1.19 (54.5% boys and 45.5% girls). In their study, there was no significant difference between male and female sex among neonates with CH.

Previous studies have shown increased QT dispersion to be a predictor of adverse outcomes in various cardiac disease states. Increased QT dispersion has been found to be associated with cardiac arrhythmias and sudden cardiac death in patients with myocardial infarction, left ventricular hypertrophy,

congestive heart failure, diabetes and end-stage renal disease. [13]

The present study showed that there was statistically significant increase among case than in control groups regarding QTc dispersion ($P < 0.001$), while there was no statistically significant difference between them regarding longest QTc, shortest QTc and QRS amplitude ($P > 0.05$). **Ezzat et al.** [14] aimed to evaluate the relationship between hypothyroidism in children and increased QTc dispersion. They reported that, maximal QTc and QTc dispersion were higher in children with hypothyroidism than in the control subjects. In their study maximal QTc, QT dispersion and QTc dispersion were detected as 406 ± 26, 37 ± 17 and 39 ± 17 ms respectively in children with hypothyroidism and these values were found to be statistically significantly higher compared to those of an age and gender-matched control group ($p = 0.03$, $p < 0.001$, $p = 0.004$ respectively). **Unal et al.** [15] and **Bakiner et al.** [18] studies evaluated the relationship between subclinical hypothyroidism (SH) and repolarization disorders. **Unal et al.** [15] measured QT dispersion and QTc dispersion in subclinical patients as 54.2 ± 8.2 and 56.3 ± 7.4 ms respectively, **Bakiner et**

al. [16] measured QTc dispersion as 100 ± 30 ms in patients with subclinical hypothyroidism. **Oner *et al.*** [7] showed in a study done on 27 children with congenital hypothyroidism that QTc dispersion was increased significantly in the patient group compared to control group.

The current study showed that there was no statistically significant difference regarding **longest QT, shortest QT, QRS amplitude and QTc dispersion** in cases with low versus those with high TSH level **(P value ≥ 0.05)**. This is in agreement with **Oner *et al.*** [7] who showed no association between TSH levels and QTc dispersion. On the contrary, QT dispersion was reported by **Bakiner *et al.*** [16] to be directly related to TSH levels in overt hypothyroidism. In agreement with our finding, mean QTc was reported to be significantly increased in subclinical hypothyroidism compared to controls. The increase of QTc dispersion was greater in patients with TSH > 10 mIU/l and with a return to normal TSH levels, the QTc dispersion was detected to fall to a level similar to that of the control group [16]. **Rifaz and Bahat** [17] showed that the corrected QT was increased in hypothyroid patients. In that study, an increase in QTc was detected in 64 hypothyroid patients diagnosed as primary hypothyroidism. The mean corrected QT interval in cases and controls were 436 and 402 ms respectively (P value < 0.001). The current study showed that there was no significant correlation between TSH or T4 serum levels and QTc dispersion (P > 0.05). This is in line with **Öner *et al.*** [7] who reported that, no association was detected between TSH levels and QTc dispersion. Unlike **Ezzat *et al.*** [14] who suggested a correlation between ECG changes and the TSH level however, no significant relation was determined between ECG changes and T4 level.

CONCLUSION

QTc dispersion was higher in our patients compared to control group, which indicates heterogeneity of ventricular repolarization that could be associated with increased risk of ventricular arrhythmias.

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