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Evaluation of QT Dispersion and Tp-e interval in Children with Hypothyroidism

Mohamed Hesham Hassan Ezzat[1], Mohamed Samy Abdel-Samae[1], Mohamed Basiony Taha[*2]

[1]Department of Cardiology, Faculty of Medicine. Al-Azhar University, [2]Department of Cardiology, Matrouh Specialized Cardiothoracic and Interventional Catheterization Center, Egypt.

***Corresponding author**: Mohamed Basiony Taha, **Mobile**: 002-01093149693, **Email:** dr.mohamedbasiony@gmail.com

ABSTRACT

Background: Several studies in adults, showed increased dispersion of QT and corrected QT (QTc), peak-to-end interval of the T wave (Tp-e), Tp-e/QT ratio and Tp-e/QTc ratio in hypothyroidism. However, there were few studies in children with hypothyroidism. **Objective**: This study aimed to evaluate the relationship between hypothyroidism in children and increased QTd, QTc, Tp-e, Tp-e/QT ratio and Tp-e/QTc ratio. z**Patients and methods:** In this study we compared 50 hypothyroid children with 30 healthy children in respect of serum thyroid stimulating hormone (TSH), serum level of free triiodothyronine (fT3) and level of free thyroxine (fT4). Hypothyroidism diagnosed with TSH above the laboratory accepted upper limit and normal or decreased fT4 values. The patient and control group data were compared by calculating the QT interval, corrected QT(QTc), QT dispersion (QTd), QTc dispersion (QTcd), Tp-e, Tp-e/QT ratio and Tp-e/QTc ratio on 12-lead surface electrocardiogram (ECG).

Results: In the hypothyroid group, the mean age was 10.36 ± 4.18 years old (ranged from 1-17 years). Regarding the control group, the mean age was 9.09 ± 4.58 years old (ranged from 1-17 years). The QT max, QTc max, QTd, QTcd, Tp-e, Tp-e/QT and Tp-e/QTc values were determined to be significantly higher in hypothyroid children than the control children (p=0.03, p=0.026, p< 0.001, p=0.004, p=0.003, p=0.034 and p=0.027 respectively). QT max, QTc max, QTd and QTcd in the hypothyroid group were 330 ± 38 ms, 406 ± 26 ms, 37 ± 17 ms and 39 ± 17 ms respectively. While in the control group, they were 315 ± 23 ms, 393 ± 26 ms, 18± 13 and 27 ± 16 respectively. **Conclusion:** It could be concluded that there was a significant increase in QTd, QTcd, Tp-e, Tp-e/QT ratio and Tp-e/QTc ratio values in children with hypothyroidism similar to that seen in adults. The use of 12- lead ECG for the measurements of QTd, QTcd and Tp-e can be considered necessary for the monitoring of children with hypothyroidism and in the evaluation of the risk of cardiovascular disease.

Keywords: Hypothyroidism, QT dispersion, thyroid stimulating hormone, children.

INTRODUCTION

Hypothyroidism is the most common disorder arising from hormone deficiency. About 4.6% of the U.S. population age 12 and older has hypothyroidism, according to the National Health and Nutrition Examination Survey (NHANES III) [(1)]. According to the time of onset it is divided into congenital and acquired. Congenital hypothyroidism affects 1 in 1,500-3,000 newborns in the U.S. each year [(2)]. According to the level of endocrine dysfunction it is divided into primary and secondary or central and according to the severity into clinical and subclinical hypothyroidism. Therapy of choice is the administration of thyroxine and the prognosis is very good [(3)]. Cardiac repolarization impairment was observed in ECG and action potential of hypothyroid patients and experimental animal models [(4, 5)]. Several clinical groups correlated serum TSH levels with the repolarization abnormalities [(6)]. Studies have shown that QT, QTc, QTd and QTcd are increased in adult hypothyroidism patients [(7, 8)]. The mechanism of the cardiac effect in these patients is a matter of debate. It has been reported that cardiac K^+ and L-type Ca^{++} channels affection related to serum T3 and T4 in hypothyroid patients and in turn repolarization anomalies develop [(4)]. The Tp-e interval, which is the distance between the T-wave peak and the end of the T-wave, is considered as the transmural dispersion index of ventricular repolarization. In addition, the Tp-e/QT and Tp-e/QTc ratio can be used as predictors of ventricular arrhythmogenesis [(9)]. Studies have shown that Tp-e interval, Tp-e/QT and Tp-e/QTc are prolonged in hypothyroidism patients [(8, 10)].

Cardiac electrical activity has been shown to be affected in subclinical hypothyroidism patients with normal serum T3 and T4 levels. It has been considered that this effect could be associated with TSH [(4)].

AIM OF THE WORK

This study aimed to evaluate the relationship between hypothyroidism in children and QTd, QTc, Tp-e, Tp-e/QT ratio and Tp-e/QTc ratio.

PATIENTS AND METHODS

The study was a case-control one that was carried out on 50 children with hypothyroidism and (30) children with normal thyroid function as control group. The study was conducted in Cardiology department of Al-Azhar University Hospital. The study included both sexes below the age of 18 years old. Patients with structural heart diseases were excluded by trans-thoracic echocardiography. Subjects complaining of any hepatic

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or renal function disorder or hypertension or diabetes mellitus were excluded too. Subjects on medications were excluded except for treatment of hypothyroidism. Euthyroid patients were excluded from the hypothyroid group. Approval for the study was granted by the Ethics Committee and informed consent was obtained from the parents or legal guardians of all children in both groups.

Thyroid profile was done for all subjects on Cobas 411 immunoassay auto analyzer by a kit supplied by Roche diagnostic. It is a one-step sandwich assay Electro Chemiluminescene assay (ECL). The reference ranges provided by the kits manufacturer are shown in table (1).

Table (1): Reference ranges for TSH, FT4 and FT3

TSH	**µIU/mL**
> 1 ≤ 6 Years	0.7: 6
> 6 ≤ 11 Years	0.6: 4.8
> 11 ≤ 20 Years	0.51 : 4.3
FT4	**µg/dL**
> 1 ≤ 6 Years	12.3 : 23
> 6 ≤ 11 Years	12.5 : 22
> 11 ≤ 20 Years	12.6 : 21
FT3	**pg/mL**
> 1 ≤ 6 Years	3.69 : 8.5
> 6 ≤ 11 Years	3.88 : 8
> 11 ≤ 20 Years	3.93 : 7.7

Resting standard 12 leads electrocardiogram was done for each participant for assessment of the rate, rhythm and the items in table (3). Measurements were not taken in ECG leads where the finishing point of the T wave could not be selected. ECG intervals and segments are demonstrated in **figure (1**).

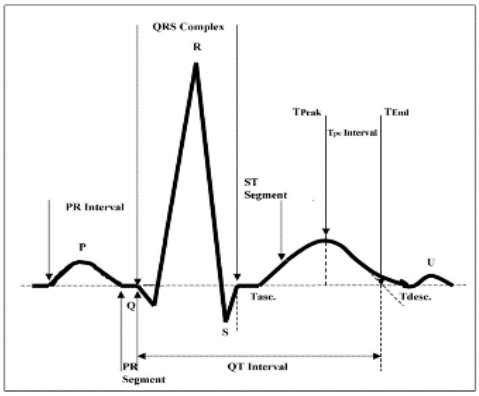

Figure (1): ECG intervals and segments.

QT interval was defined as the distance from the onset of the QRS complex to the end of the T wave [(11)]. The corrected QT interval (cQT): calculated by using Bazett formula, divides the measured QT by the square root of the RR interval ($QT/\sqrt{R.R}$ [(12)]. QT dispersion (QTd) was defined as the difference between the longest and shortest QT intervals [(13)]. The corrected QT dispersion (QTcd) was calculated as the difference between the shortest and the longest cQT values [(14)].

Tp-e interval was defined as the distance from the peak of the T wave to the end of T wave, which was defined as the intersection of the isoelectric line with the tangent to the down slope of the T wave [(15)].

Ethical approval

The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant in the study.

Statistical analysis

Recoded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Independent-samples t-test of significance was used when comparing between two means. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the P-value <0.05 was considered significant.

RESULTS

Data given in table 2 showed demographic, clinical and laboratory results of the hypothyroid group and control group. No statistically significant difference was detected between the hypothyroid and control groups in respect of age, gender, body weight, body mass index (BMI) and heart rate. Data are given as mean ± SD.

Table (2): Demographic data and thyroid profile for hypothyroid and control children

Variables		Hypothyroid group (n:50)	Control group (n:30)	P-value
Age (years)		10.36 ± 4.18	9.09 ± 4.58	0.22
Sex	M	23	15	0.73
	F	27	15	
weight/kg		33.07 ± 11.66	30.13 ± 13.45	0.32
BMI (Kg/m^2)		16.5 ± 1.40	17.01 ± 1.44	0.13
HR (bpm)		93.06 ± 15.51	94.36 ± 14.3	0.71
R.R (cycle/minute)		20.18 ± 3.59	29.03 ± 3.24	<0.001
SBP (mmHg)		110.4 ± 6.6	102.7 ± 7.8	<0.001
DBP (mmHg)		67.8 ± 8.4	65.3 ± 6.28	0.14
TSH (µIU/ml)		10.7 ± 1.50	2.846 ± 0.826	<0.001
FT4 (µg/dL)		13.64 ± 2.89	13.6 ± 3.76	0.96
FT3 (pg/ml)		6.30 ± 1.26	6.58± 0.744	0.21

Regarding the age the hypothyroid group mean age was determined as 10.36 ± 4.18 years (ranged from 1-17 years). Males represented 46 % (23 patients) of the study population while females represented 54 % (27 patients). The control group mean age was 9.09 ± 4.58 years (ranged from 1-17 years). Males represented 50 % (15 child) of the study population and females represented 50 % (15 child).

The TSH level was determined to be statistically significantly higher in the hypothyroid group than the control group. There was no difference between the hypothyroid group and the control group in the level of FT3 and FT4.

Table 3 showed the measurements of QT max, QT min, QTc max, QTc min, QTd, QTcd, Tp-e, Tp-e/QT ratio and Tp-e/QTc ratio in the hypothyroid children and the control children.

Table (3): ECG measures of hypothyroid and control children

Variables	Hypothyroid group (n:50)	Control group (n:30)	P value
QT max (s)	0.330 ± 0.038	0.315 ± 0.023	0.03
QT min (s)	0.293± 0.034	0.297± 0.024	0.534
QTc max (s)	0.406 ± 0.026	0.393 ± 0.026	0.026
QTc min (s)	0.368 ± 0.024	0.365 ± 0.024	0.656
QTd (s)	0.037 ± 0.017	0.018 ± 0.013	< 0.001
QTcd (s)	0.039 ± 0.017	0.027 ± 0.016	0.004
Tp-e (s)	0.065 ± 0.014	0.0553 ± 0.0135	0.003
Tp-e/QT	0.2 ± 0.043	0.18 ± 0.045	0.034
Tp-e/QTc	0.160 ± 0.032	0.142 ± 0.037	0.027

The QT max, QTc max, QTd, QTcd, Tp-e, Tp-e/QT and Tp-e/QTc values were significantly higher in hypothyroid children than the control children (p=0.03, p=0.026, p< 0.001, p=0.004, p=0.003, p=0.034 and p=0.027 respectively). QT max, QTc max, QTd and QTcd in the hypothyroid group were 330 ± 38 ms, 406 ± 26 ms, 37 ± 17 ms and 39 ± 17 ms respectively. While they were in the control group 315 ± 23 ms, 393 ± 26, 18 ± 13 and 27 ± 16 respectively.

A positive correlation was determined between the QTd and QTmax and QTcd and QTc max values and TSH values. A strong positive correlation between the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio and serum TSH levels was determined.

DISCUSSION

Cardiac repolarization impairment was observed in ECG and action potential of hypothyroid patients and experimental animal models [4, 5]. The calcium current is regulated by T3 at transcriptional and posttranscriptional level. The voltage dependent L-type Ca^{++} channel expression is reduced by the thyroid hormone. The calcium current is also modulated by T3 through cAMP [16]. In the last decade, several clinical groups correlated serum TSH levels with the repolarization abnormalities [6]. This correlation is also supported by the fact that subclinical hypothyroidism, with normal T3 and T4 levels but elevated TSH, share most of the cardiac repolarization abnormalities with subclinical hypothyroidism [17].

In our study, a correlation between ECG changes and the TSH level was detected however no significant relation was determined between ECG changes and FT4 level in the ECG changes. QT dispersion, QTc max, QTc dispersion, Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were detected to be higher in hypothyroid children than the control children and a significant positive correlation between TSH level and QT dispersion and Tp-e interval and Tp-e/QT ratio and Tp-e/QTc ratio was detected.

In the current study QTc max, QTd, QTcd, and Tp-e were detected as 406 ±26, 37 ± 17 ms, 39 ± 17 ms and 65± 14 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, p= 0.003).

Unal *et al.*[6] and Bakiner *et al.* [7] studies evaluated the relationship between subclinical hypothyroidism (SH) and repolarization disorder. **Unal *et al.* [6]** measured QTd and QTcd in SH patients as 54.2 ± 8.2 ms and 56.3 ± 7.4 ms respectively, while **Bakiner *et al.* [7]** measured QTcd as 100 ± 30 ms in SH patients. When the Tp-e interval was > 85 ms, this has been defined as increased Tp-e interval [18].

Findikli *et al.* [8] study in 2019 evaluated the relationship between the TSH level and the duration of Tp-e interval in hypothyroid patients and also evaluated the relationship between the TSH level and the QTc and compared them with control group. The patients were divided into two groups as hypothyroid (HT) and euthyroid. The HT group was 42 female patients and the euthyroid group, 39 female patients who had received LT4 treatment for a previous hypothyroid period and now had thyroid function test results within the normal reference range. The results of this study showed that The Tp-e and QTc intervals of the hypothyroid group were significantly prolonged compared to those of the euthyroid and control groups ($p < 0.001$) and the values of the euthyroid and control groups were similar. A positive correlation was determined between TSH levels and Tp-e and QTc intervals.

Gürdal *et al.* [10] determined the Tp-e interval to be 87 ± 5 ms in adults with SH. It remains controversial as to which QTc, QTd, QTcd and Tp-e values increase the risk of cardiac disease. **Okin *et al.* [19]** showed that QTc > 46 ms increased the risk of cardiac mortality 2.6-fold and QTd > 58 ms was reported to increase cardiac mortality 2-fold. In a study by **Bruyne *et al.* [20],** QTcd > 59.6 ms was reported to be reflected in an increase of 2.1-fold in cardiac death risk compared to those with QTcd < 39.0.

Hetland *et al.* [21] showed that there was a greater frequency of arrhythmic events in patients with Tp-e interval >100 ms after myocardial infarct. As there is no consensus on the reference limits of QTd, QTcd and Tp-e, it is difficult to determine which QTd, QTc and Tp-e values are pathological and which values reflect an increased risk of cardiac disease or at what TSH level, QTd has started.

In **Akin *et al.* [14]** study QTd, QTcd, and Tp-e were determined as 38.00 ± 12.77 ms, 58.73 ± 29.23 ms and 75.95 ± 11.87 ms respectively in children with SH and these values were found to be statistically significantly higher compared to those of an age and gender-matched control group.

Oner *et al.* [22] 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. However, no association was detected between TSH levels and QTc dispersion.

In the current study, no statistically significant correlation was determined between QTd, QTcd, Tp-e and age and gender. While there are studies which reported that dispersion is not affected by age and gender. Others have reported that values are higher in males and are affected by age [23].

In the current study, a significantly positive correlation was detected between the QTd, QTcd, QTmax and QTcmax values and TSH values (r= 0.187, r=0.389, r=0.296, r=0.355) respectively.

A study by **Galetta *et al.* [24]** showed that QT dispersion was increased in hypothyroidism. In that study, an increase in QTd was determined in 42 adult patients diagnosed with SH. A positive relationship was determined between QTd and QTcd and TSH and

these relationships were shown to recover following treatment with L-thyroxine.

A study by **Rifaz and Bahat** [25] 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 ms and 402 ms respectively. It was found that corrected QT had P-value < 0.001 and was statistically significant. In another study by **Bakiner *et al.*** [7]**,** which evaluated QTd in hypothyroid patients. QTcd was seen to be statistically significantly increased in 58 female patients and this was shown to be significantly correlated with TSH levels. This increase was greater in patients with TSH > 10 mIU/L and with a return to normal TSH levels, the QTcd was detected to fall to a level similar to that of the control group.

A study by **Sarma *et al.*** [26] showed that QTc was prolonged (p less than 0.02) and heart rate decreased (p less than 0.005) during the hypothyroid state. The study used 24-hour Holter tapes before and after (8 to 12 weeks) thyroxine replacement therapy in 10 patients with hypothyroidism. The findings were compared to 6 normal control subjects. QTc interval remained significantly prolonged after 8 to 12 weeks of T4 replacement, when biochemical indices of hypothyroidism had returned to normal values.

Unal *et al.* [6] determined a significantly positive relationship between QTd and serum TSH levels in 80 female patients diagnosed with SH and a significant drop was found in both QT interval and QTd in patients treated with levothyroxine. **Nathaniel *et al.*** [27] reported that significant prolongation of the QTc interval occurred in inadequately treated hypothyroidism and the degree of the QTc prolongation was directly related to the severity of hypothyroidism. **Altun *et al.*** [28] showed that QT prolongation and increased QTd were directly related to the TSH levels in hypothyroidism. Besides, **Kweon *et al.*** [29] showed that the QTc and QT dispersions improved after the L-thyroxine treatment in patients with primary hypothyroidism. This suggests that the thyroid hormone affects ventricular inhomogenicity, and subsequent L-thyroxine replacement therapy may reduce malignant ventricular arrhythmia and sudden cardiac death in primary hypothyroidism. However, **Akin *et al.*** [14] found that the QTd and QTcd values were increased in SH patients, but no relationship was seen with TSH values and a significant positive correlation was determined between QTmax values and TSH and this showed that the serum TSH values could be the cause of ventricular repolarization anomaly.

In the current study a significant correlation between the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio and serum TSH levels was detected (r=0.704, r=0.541, r=0.641) respectively. **Gürdal *et al.*** [10] showed that the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were increased in a sample of 28 adults with hypothyroidism compared to a control group and this was correlated with TSH levels. Similarly **Akin *et al.*** [14] showed a significant correlation between the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio and serum TSH levels.

Although the increase in these parameters in adults shows an increased risk of ventricular arrhythmia, there is a need for further studies to confirm these results in pediatric patients. In addition, although the TSH level necessary for the treatment of hypothyroid patients is debatable, it has been reported that the repolarization anomaly in SH patients could be corrected with L-thyroxine treatment and this was particularly evident in patients with TSH >10 mIU/L [6, 7].

There have been no enough studies evaluating the relationship between hypothyroidism and repolarization anomaly in children and there is a need for much more research as it may not be valid to recommend this treatment for children.

CONCLUSION

It could be concluded that there is a significant increase in QTd, QTcd, Tp-e, Tp-e/QT ratio and Tp-e/QTc ratio values in children with hypothyroidism similar to that seen in adults. The use of 12- lead ECG for the measurements of QTd, QTcd and Tp-e can be considered necessary for the monitoring of children with hypothyroidism and in the evaluation of the risk of cardiovascular disease.

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