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Atrial and Ventricular Electrocardiographic Dromotropic Disturbances in Down Syndrome Patients with Structurally Normal Heart: A Cross-Sectional Study

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Abstract

Background: We designed a cross-sectional study to determine electrocardiographic disorders in Down syndrome patients with congenitally normal hearts in a bid to predict fatal cardiac arrhythmia in the future.

Materials and Methods: We investigated 60 children with DS without congenital abnormal hearts. Sixty healthy juveniles were also included in the study as a control group. Physical examination, electrocardiography, and echocardiography were performed in all subjects. Corrected QT interval (QTc) was measured according to Bazett's formula.

Results: Patients with DS consisted of 32 males (53.33%), and 28 females (46.66%), aged 6–13 (9.21 ± 6.24) years old. Healthy subjects comprised 31 males (51.66%), and 29 females (48.33%) with a mean age of 9.15 ± 5.01. The two groups were significantly different in terms of heart rate (P=0.006), maximum P-wave duration (P=0.001), and P-wave dispersion (PWd, P=0.0001). There was no statistically significant difference regarding minimum P-wave duration (P=0.176). The patients with DS had a greater maximum QTc interval, QT dispersion, and corrected QT interval dispersion (QTc-d) than the healthy control subjects (P=0.001). However, there was no difference in maximum QT interval and minimum QTc interval between the two groups (P=0.67 and P=0.553, respectively). A positive correlation was found between age, heart rate, and all electrocardiographic variables.

Conclusion: All DS patients, even in the absence of concomitant congenital heart disease should be followed up carefully by electrocardiography, looking for increased PWd and QTc-d to detect predisposed cases to arrhythmia.

Key Words: Cardiovascular Abnormalities, Children, Down syndrome, Congenital Heart Defects.

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1- INTRODUCTION

Down syndrome (DS) is the most common autosomal trisomy abnormality. Despite routine prenatal screening, the incidence of Down syndrome is 1 per 700–800 live births (1, 2). The congenital heart abnormalities such as ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular septal defect (AVSD), and tetralogy of Fallot (TOF) are commonly encountered in DS patients. Approximately half of Down syndrome patients have congenital heart disease (CHD) (3). Over the last decade, the field of congenital cardiac surgery has progressed a great deal and life expectancy of these patients has been prolonged up to 60 years (4). Recent studies have shown that the Down syndrome patients with structurally normal hearts may develop various cardiac problems such as bradycardia, atrioventricular block, and autonomic dysfunction (5, 6). The latter has been reported in Down syndrome patients with structurally normal hearts (7, 8). However, with the exception of few investigations, P-wave dispersion (PWd), and QT interval dispersion (QTd) has not been studied in pediatric Down syndrome patients (9). This study aimed to predict cardiac disturbances in children with Down syndrome lacking congenital heart disease, analyzing PWd and QTd.

2- MATERIALS AND METHODS

2-1. Study design and population

This cross-sectional study was performed in Amir-Kabir Hospital in Arak city, Iran, between October 2015 and September 2016. The study included 60 children with Down syndrome without congenital heart disease that referred to our pediatric cardiology department for cardiac evaluation. Down syndrome diagnosis was established in most cases based on physical examination. Genetic study and consultation was requested in suspicious patients. The control group consisted of 60 age and sex-matched healthy children selected from relatives of patients. Their healthiness, particularly in terms of undiagnosed cardiac problems, was affirmed by physical as well as echocardiographic examination.

2-2. Methods

All subjects underwent an electrocardiographic examination. The standard 12-lead electrocardiogram (ECG) was recorded with a sweeping rate of 25 mm/s and amplitude of 1 mV/cm in either group.

2-3. Measuring tools

First of all, a standard 12-lead ECG was recorded with the patient lying in the supine position. At the second step, the P-wave and QT interval were measured and as a result, QTd and PWd were calculated. The P-wave duration is defined as the interval between the starting and ending points of P-wave deflection. The PWd is by definition, the difference between the duration of maximum (max) and minimum (min) P-waves interval (9). At the third stage, the QT interval was determined which is the time from the beginning of the QRS complex to the end of the T-wave. QTc was measured according to Bazett's formula (5). The difference between the maximum and minimum QTc intervals is expressed as QTc-d (QTc dispersion) (5). In the presence of the U-wave, the lowest point between the T and U-waves was considered (9). In addition to the above variables, QT onset was calculated. QT onset is defined as the interval from the beginning of Q-wave to the beginning of T-wave. The QT onset maximum was the longest and QT onset minimum was the shortest distance.

2-4. Ethical considerations

The study was approved by our Institutional Review Board (ID code: 1394-232). Informed written consent was

obtained from parents or guardians of all minors participated in our research.

2-5. Inclusion and exclusion criteria

Inclusion criteria including: Iranian Children with Down syndrome without congenital heart disease. Exclusion criteria including: Individuals with an unsuitable standard ECG or indefinite T-wave termination were excluded. Again, we eliminated cases with congenital heart defects, cardiac dysfunction, significant valvular abnormalities and any atrial or ventricular arrhythmia on ECG.

2-6. Data Analyses

The continuous data are presented as mean ± standard deviation. The Student's t-test compared continuous data between the two groups. Pearson's correlation test was applied to assess the correlation between electrographic parameters and age (quantitative variables). The SPSS software version 24.0 (SPSS Inc. Chicago, IL, USA) was used for all statistical analyses. The P values less than 0.05 were considered statistically significant.

3- RESULTS

The Sixty patients with DS including 32 males (53.33%), and 28 females (46.66%) aged 6–13 years old (mean: 9.21 ± 6.24) were compared with 60 healthy subjects of whom 31 males (51.66%) and 29 females (48.33%) with a mean age of 9.15 ± 5.01. The two groups were similar with respect to age and sex (P =0.811, and P=0.951, respectively). The ECG characteristics of the patients with DS and the control subjects are summarized in **Table.1**. As noted in **Table.1**, ECG variables revealed a significant difference between the two groups in terms of heart rate (HR) (P=0.006), P-max duration (P=0.001), and PWd (P=0.0001). However, there was no statistically significant difference concerning P-min duration (P=0.176). The patients with DS had a greater QTc-max, QTd, and QTc-d than the healthy control children (P=0.0001). However, there was not a considerable difference regarding QT max and QTc min between the two groups (P=0.67, and P=0.553, respectively). Using Pearson correlation coefficient, in DS cases, a positive correlation was found between the age and HR, as well as all ECG parameters including QT-min, QT-max QTd, QTc-max, QTc-min, QTc-d, QT-max onset, QT-min onset, P-max, P-min, and PWd (**Table.2**).

Table-1: The electrocardiographic parameters for Down syndrome (DS) and control subjects

Parameters	(n = 60)DS patients,	(n = 60)Controls,	P-value
HR (bpm)	105.60 ± 23.43	94.83 ± 18.35	0.006
QT-max (ms)	301.00 ± 18.07	299.70 ± 15.51	0.67
QT-min (ms)	251.00 ± 13.58	276.02 ± 24.61	0.0001
QTd (ms)	45.15 ± 7.99	31.18 ± 8.10	0.0001
QTc-max (ms)	420.20 ± 12.94	408.90 ± 12.58	0.0001
QTc-min (ms)	352.20 ± 16.36	350.00 ± 22.55	0.553
QTc-d (ms)	69.93 ± 11.14	44.87 ± 8.75	0.0001
QT-max (onset) (ms)	200.15 ± 26.10	169.80 ± 28.31	0.0001
QT-min (onset) (ms)	149.86 ± 21.64	115.58 ± 29.69	0.0001
P-max (ms)	70.47 ± 10.53	65.20 ± 4.84	0.0001
P-min (ms)	38.44 ± 5.07	37.05 ± 6.02	0.176
PWd (ms)	29.42 ± 6.94	23.98 ± 4.05	0.0001

HR*:* heart rate, QT-max: maximum QT interval, QT-min: minimum QT interval, QTd: QT dispersion, QTc-max*:* maximum corrected QT, QTc-min*:* minimum corrected QT, QTc-d*:* corrected QT dispersion, QT-max (onset)*:* maximum interval from the beginning of Q-wave to the beginning of T-wave, QT-min (onset)*:* minimum interval from the beginning of Q-wave to the beginning of T-wave, P-max*:* maximum P-wave interval, P-min*:* minimum P-wave interval, PWd*:* P-wave dispersion.

Table-2: The correlation between age and ECG parameters in DS patients

Parameters	Pearson Correlation	P-value
HR (bpm)	0.83	0.0001
QT-max (ms)	0.922	0.0001
QT-min (ms)	0.702	0.0001
QTd (ms)	0.868	0.0001
QTc-max (ms)	0.899	0.0001
QTc-min (ms)	0.568	0.0001
QTc-d (ms)	0.773	0.0001
QT-max (onset) (ms)	0.604	0.0001
QT-min (onset) (ms)	0.373	0.004
P-max (ms)	0.604	0.0001
P-min (ms)	0.695	0.0001
PWd (ms)	0.703	0.0001

HR*:* heart rate, QT-max: maximum QT interval, QT-min: minimum QT interval, QTd: QT dispersion, QTc-max*:* maximum corrected QT, QTc-min*:* minimum corrected QT, QTc-d*:* corrected QT dispersion, QT-max (onset)*:* maximum interval from the beginning of Q-wave to the beginning of T-wave, QT-min (onset)*:* minimum interval from the beginning of Q-wave to the beginning of T-wave, P-max*:* maximum P-wave interval, P-min*:* minimum P-wave interval, PWd*:* P-wave dispersion.

4- DISCUSSION

The pathophysiology of cardiac abnormalities in Down syndrome patients has not yet been elucidated accurately (10). To reduce the incidence of cardiovascular events, early diagnosis of electrical disturbances in these patients is essential. The comprehensive analysis of 12-lead ECG could be used as a screening of electrocardiographic abnormalities which may present in some instances with peculiar patterns such as Wolf-Parkinson-White, long QT interval or pre-excitation disorders (11). In the present study, we assessed DS patients with structurally normal hearts. We showed that DS patients had a significantly greater HR, P-max wave duration, P-wave dispersion, QTd and QTc-d than the healthy control individuals. Furthermore, we detected a positive correlation between the increased age and atrial and ventricular ECG parameters. The heterogeneity of ventricular repolarization and atrial depolarization are estimated with QTd and PWd, respectively. The increase in QTd predisposes the patient to the development of ventricular arrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF) (12). PWd and P-max duration are used to evaluate the homogeneous propagation of depolarization through the right and left atrial myocardium. According to recent studies, prolongation of these parameters could precede atrial fibrillation or other atrial arrhythmias. Enlargement and hypertrophy of atria can alter the physiology of depolarization. Both P-max and PWd are indicators of depolarization changes in atria (13). Increased PWd occurs in various circumstances, e.g. atrial enlargement due to pressure or volume overload or disorders of the cardiac autonomic system (14). Cardiac Autonomic dysfunction is associated with increased PWd and QTc-d. Both PWd and QTc-d have been suggested as two critical ECG parameters potentially capable of predicting atrial and ventricular arrhythmias such as atrial fibrillation or ventricular fibrillation with ensuing fatal outcomes (12). We affirmed that even in the absence of structural anomalies of the heart, long-term follow-up of DS patients is mandatory to prevent lethal cardiac arrhythmia. It has been suggested that increased PWd and QTc-d in the DS

patients, results from autonomic dysfunction. Some studies have shown that in DS cases, even with a structurally normal heart, the parasympathetic nervous system (vagal tone) is more prominent, at rest (13). Some derangements in catecholamine response during exercise have been suggested, in the Down syndrome patients without CHD, which includes attenuated heart rate and blood pressure response to exercise, inadequate sympathetic activation, and decreased vagal tone (8).

Generally, the parasympathetic nervous system gradually matures from newborn to the adolescence period in a healthy flourishing child. Hence, heart rate is slower in the adulthood as a result of increased parasympathetic tone (6). Our study showed enhanced heart rate in the DS patients compared to control subjects. As mentioned above, DS patients even in the absence of structural heart disease may manifest with inadequate heart rate response to exercise due to the impaired cardiac autonomic nervous system (6, 15).

Iellamo et al. (6) investigated the probable occurrence of derangements in the autonomic nervous system of the heart in patients with Down syndrome but without structural heart disease. Ten patients with Down syndrome were compared with 10 healthy controls in terms of blood pressure and R-R interval variability at rest and during active orthostatism. During standing, the decrease in the R-R interval was significantly lower in the Down syndrome group compared with the control group. These data corroborate the reduced heart rate response to orthostatic stress in DS cases owing to blunted sympathetic activation and reduced vagal withdrawal and to some extent decreased baroreflex sensitivity in response to active orthostatism (6). Recent studies have further emphasized an imbalance of the autonomic nervous system in these patients' category with reduced sympathetic activity and persistent vagal tone during exercise, along with impaired baroreflex sensitivity (16, 17). Giagkoudaki et al. (18) demonstrated the improved autonomic nervous system dysfunction by exercises enhancing the parasympathetic modulation. Following 6 months' exercise-training program, they showed that sympathovagal imbalance improved due to increasing vagal activity. Again, Mendonca et al. (19) indicated the 12 weeks of combined aerobic and resistance exercise training augmented the heart rate recovery and cardiovagal modulation in adults with DS. The higher basic heart rate found in our DS patients can be explained by a slower maturation of the parasympathetic nervous system in DS cases. We demonstrated a positive correlation between the age, PWd, QTc-d and other ECG parameters. The age-related disturbances in atrial and ventricular ECG parameters which are potentially associated with increased risk of cardiac arrhythmias emphasize the importance of regular follow-up of the DS patients even in the absence of congenital heart disease.

4-1. Limitations of the study

We did not perform 24-hour Holter monitoring in our patients to precisely diagnose rhythm disorders. Moreover, we did not establish subclinical cardiac dysfunction by evaluation of systole and diastole phases of Pulse Waved Doppler echocardiography. Lack of follow-up in DS cases is another drawback of the present study. Likewise, blinding could not be done for examining cardiologist due to the obvious general appearance of DS cases. This might have resulted in more precise cardiac evaluation in the latter group. Undoubtedly more comprehensive investigations are warranted to follow DS patients with ECG abnormalities to determine the exact rate of cardiac arrhythmia. In conclusion, patients with Down syndrome, even those with

structurally normal hearts may be more prone to atrial and ventricular arrhythmias. Therefore, they should be followed up for many years because of the existence of pro-arrhythmic conditions.

5- CONCLUSION

In conclusion, patients with Down syndrome, even those with structurally normal hearts may be more prone to atrial and ventricular arrhythmias. Therefore, they should be followed up for many years because of the existence of pro-arrhythmic conditions.

6- CONFLICT OF INTEREST: None.

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