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ORIGINAL ARTICLE

Increased P-Wave and QT Dispersions Necessitate Long-Term Follow-up Evaluation of Down Syndrome Patients With Congenitally Normal Hearts

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Abstract Reports state that Down syndrome (DS) patients with congenitally normal hearts might experience the development of cardiac abnormalities such as cardiac autonomic dysfunction, valvular lesions, bradycardia, and atrioventricular block. However, the presence of any difference in terms of P-wave dispersion (PWd) and QT dispersion (QTd) was not evaluated previously. This study prospectively investigated 100 DS patients with structurally normal hearts and 100 age- and sex-matched healthy control subjects. Standard 12-lead electrocardiograms were used to assess and compare P-wave and QT durations together with PWd and QTd. The median age of the DS patients and control subjects was 48 months. Heart rates and P-wave and QT dispersions were significantly greater in the DS group than in the control group (113 ± 22.9 vs 98.8 ± 16.6 bpm, $p < 0.001$; 31.3 ± 9.5 vs 24 ± 8.6 ms, $p < 0.001$; and 46.6 ± 15.9 vs 26 ± 9.1 ms, $p < 0.001$, respectively). A positive correlation was found between PWd and age in the DS patients ($p < 0.05$; $r = 0.2$). All children with DS should be followed up carefully with electrocardiography in terms of increased P-wave and QT dispersions even in the absence of concomitant congenital heart disease for management of susceptibility to arryhthmias.

Keywords Congenital heart disease · Down syndrome · Electrocardiography · P-wave dispersion · QT dispersion

Trisomy 21, also called Down syndrome (DS), is the most common chromosomal abnormality, with an incidence of 1 per 700–800 live births [33]. Down syndrome is characterized by dysmorphic features, cognitive impairment, and various congenital abnormalities [18, 30]. Approximately 40–50 % of affected individuals have congenital heart defects. The most common defects are atrioventricular septal defect, ventricular septal defect, isolated atrial septal defect, and tetralogy of Fallot [32, 33, 35].

The life expectancy of DS patients is affected mainly by the severity of cardiac anomalies [21]. Because of advances in congenital cardiac surgery and postoperative care, the life span of DS patients has progressively increased from 12 to 60 years [6]. However, possibly because of this prolongation and improvement in diagnostic methods, the development of various cardiac problems among DS patients with congenitally normal hearts, including autonomic dysfunction [14, 22], valvular abnormalities [20, 23], bradycardia, and atrioventricular block [7, 29], have been reported in recent years.

As studies have shown, P-wave dispersion (PWd) and QT dispersion (QTd) represent the heterogeneity of atrial depolarization and ventricular repolarization, respectively. An increase in PWd is associated with a higher risk of atrial arrhythmias [12, 27]. An increase in QTd results in susceptibility to ventricular arrhythmias and sudden cardiac death among patients with myocardial infarction, diabetes mellitus, chronic heart failure, and pulmonary arterial hypertension [8, 28, 31]. Although alterations in autonomic

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function and some of the aforementioned cardiac abnormalities among DS patients with structurally normal hearts have been reported [1, 2, 9, 13, 15, 16, 19], PWd and QTd among these patients have not been studied.

This study aimed to assess PWd and QTd in children with Down syndrome. To the best of our knowledge, this is the first study to investigate PWd and QTd in this population.

Materials and Methods

Patients

This prospective case-control study was conducted in the pediatric cardiology departments of Izmir Dr Behcet Uz and Diyarbakır Children's Hospitals between August 2013 and November 2013. The study enrolled 100 children with Down syndrome referred to these pediatric cardiology departments for cardiac evaluation and found to have no echocardiographic abnormalities. The control group consisted of 100 age- and sex-matched children who had evaluation of their heart murmurs.

The study excluded patients with congenital heart defects, ventricular dysfunction, arrhythmia, and indefinite T-wave termination on electrocardiogram (ECG), as well as those taking any medication that could affect the QT interval. Patients who had ECG recordings with less than nine derivations also were excluded. The study was approved by the ethics committee of Behcet Uz Children's Hospital. All the participants underwent an electrocardiographic (ECG) examination.

ECG Examination

A standard 12-lead ECG was recorded with a sweeping rate of 25 mm/s and an amplitude of 1 mV/cm with the patients lying in the supine position. Measurements of the P-wave and QT interval and calculations of QTd and PWd were performed by a blinded pediatric cardiologist. All the durations of these variables were measured with a 5× magnifying glass.

The time between starting and ending points of P-wave deflection was measured as the P-wave duration. We calculated PWd as the difference between the duration of maximum (max) and minimum (min) P-waves [31]. The time from the beginning of the QRS complex to the end of the T-wave was measured as the QT interval. In the presence of the U-wave, the end point of the T-wave was accepted as the lowest point between the T- and U-waves.

Corrected QT (QTc) was calculated according to Bazzet's formula [4]. The QT and QTc dispersions were calculated as the difference between the maximum and minimum QT and QTc intervals, respectively [4]. The mean of three separate measurements of the P-wave, QT, and QTc durations was used to calculate the P-wave, QT, and QTc dispersions.

Table 1 Features and electrocardiographic findings for Down syndrome (DS) patients and control subjects

	DS patients ($n = 100$)	Controls ($n = 100$)	p value
Gender (M/F)	54/46	54/46	>0.05
Median age (months)	48	48	>0.05
Heart rate (bpm)	113 ± 22.9	98.8 ± 16.6	<0.001
P_{max} (ms)	71.4 ± 10.2	66.8 ± 11.3	<0.05
P_{min} (ms)	40.1 ± 7.4	42.9 ± 9.1	<0.001
PW dispersion (ms)	31.3 ± 9.5	24 ± 8.6	<0.001
QT_{max} (ms)	294 ± 31.5	303 ± 29.5	<0.05
QT_{min} (ms)	247 ± 31.5	276 ± 29.7	<0.001
QT dispersion (ms)	46.6 ± 15.9	26 ± 9.1	<0.001
QTc_{max} (ms)	422 ± 24.1	404 ± 25.2	<0.001
QTc_{min} (ms)	357 ± 26.2	371 ± 25.5	<0.001
QTc dispersion (ms)	65.3 ± 26.6	33.7 ± 13.3	<0.001

PW P-wave, *QTc* corrected QT

Statistical Analysis

The SPSS 18.0 computer package program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numeric data are shown as mean ± standard deviation, and categorical variables are shown as number and frequency. The distribution pattern of data was assessed by the Shapiro–Wilk test and graphic methods. The normally distributed numeric parameters of the two groups were assessed by Student's t test. Pearson's correlation test was applied for numeric data, and point biserial analysis was used for correlation between numeric and categorical data. A p value lower than 0.05 was considered statistically significant.

Results

The demographic and ECG characteristics of the patients with DS and the healthy control subjects are shown in Table 1. The median age of the patients with DS was 48 months. The groups were similar in terms of age and sex ($p > 0.05$). Comparison of ECG measurements between the two groups showed a significantly higher heart rate ($p < 0.001$), longer P_{max} duration ($p < 0.05$), and greater PWd ($p < 0.001$) as well as a shorter P_{min} duration ($p < 0.001$) in the patients with DS than in the control subjects. The difference in PWd between the two groups is shown in Fig. 1.

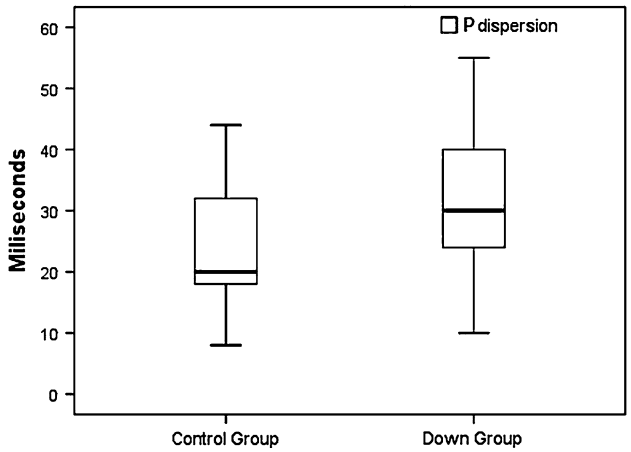

Fig. 1 P-wave dispersion durations in Down syndrome and control groups

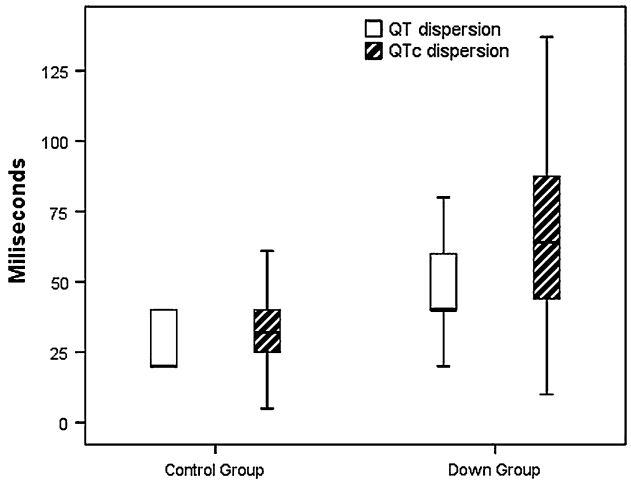

Fig. 2 Dispersion durations of QT and QTc in Down syndrome and control groups

The patients with DS had a greater QTc maximum duration, QTd, and QTc dispersion than the healthy control subjects (all $p < 0.001$). However, the control group had significantly longer QT_{max} ($p < 0.05$), QT_{min} ($p < 0.001$), and QTc_{min} ($p < 0.001$) durations than the DS group (Table 1). The differences in QTd and QTc dispersion between the groups are shown in Fig. 2.

A positive correlation was found between PWd and age in the patients with DS ($p < 0.05$; $r = 0.2$). However, age was not associated with QTd and QTc dispersion in these patients (all $p > 0.05$), and sex was not correlated with PWd, QTd, or QTc dispersion (all $p > 0.05$).

Discussion

A large proportion of persons with DS have congenital cardiac malformations, which are associated with some morbidities and decreased life expectancy [21]. The current study evaluated DS patients with structurally normal hearts. We found that DS patients had a significantly greater heart rate, maximum P-wave duration, P-wave dispersion, QTd and QTc dispersion than healthy volunteers. A correlation between P-wave dispersion and aging also was found.

Two important ECG parameters, P-wave dispersion and maximum P-wave duration, are used to evaluate the homogenous propagation of sinus node impulses through the right and left atrial myocardium [27]. These parameters are markers reflecting the tendency of the atrial myocardium to atrial fibrillation [12]. Both P-wave duration and PWd are affected by physiologic changes such as a decrease in heart rate and an age-related increase in the size and mass of the heart [31]. An increase in PWd also results from various clinical conditions including electrolyte imbalance, distention of the atria due to pressure or volume overload, and imbalance of cardiac autonomic control [11, 31].

Both QTd and QTc dispersions have been suggested as two other ECG parameters related to a tendency for potentially fatal ventricular arrhythmias [8, 28]. In a previous study, children with ventricular ectopy who had structurally normal hearts showed significantly greater QTc dispersion than the control group [10].

Down syndrome adults with structurally normal hearts have altered autonomic cardiac regulation. These patients have depressed heart rates and blood pressure responses to exercise, as well as reduced heart rate recoveries after maximal exercise. These abnormalities are attributed to inadequate sympathetic activation, blunted vagal withdrawal, and catecholamine response [9, 15, 16, 19]. Autonomic dysfunction is suggested to be associated with increased PWd and QTd [5, 26]. We therefore consider that a higher PWd and QTd in our DS patients might have resulted from a higher incidence of autonomic dysfunction in this population. Because DS is a consequence of a chromosomal abnormality, the presence of some intrinsic pathologies affecting myocardial production and conduction of electrical impulse also may be possible.

Some authors have stated that vagal modulation at rest is more prominent in DS patients with a structurally normal heart than in control subjects [3, 17]. They found that DS patients had a lower resting heart rate and lower blood pressure levels, attributable to an increased parasympathetic influence on the sinoatrial node.

Interestingly, in contrast to these studies, we found a higher resting heart rate in the DS patients than in the control subjects. Because the parasympathetic nervous system gradually matures from birth to adulthood [25], the higher heart rate found in our DS patients may have been associated with a slower maturation of the cardiac autonomic system in these patients.

Aging is associated with increased P-wave duration, conduction time, and atrial refractoriness, possibly due to progressive deposition of fibrous tissue between myocytes. This deposition of fibrous tissue might be one cause for a higher incidence of atrial fibrillation in adults [24]. In the current study, we also observed a correlation between age and PWd. However, despite the presence of similar correlations between age and QTd as well as between male sex and QTd reported previously [34, 36], no such correlations were observed in our study.

We consider that determination of increased PWd, QTd, and QTc dispersion in persons with DS may have some clinical implications. The fact that an increase in these parameters is related to atrial and ventricular arrhythmias, which have the potential for fatal outcomes, necessitates long-term follow-up evaluation of DS patients, even in the absence of structural cardiac anomalies. The probability of age-related prolongation in these parameters and a potential resultant increase in cardiovascular risk suggests the importance of such follow-up assessment.

In conclusion, individuals with DS may be more prone to ventricular and atrial arrhythmias due to prolonged duration of the P-wave, QTd, and QT dispersions. Therefore, with the prolongation of life expectancy, DS patients, even those with structurally normal hearts, should be followed up for many years because of such proarrhythmic conditions.

The current study is the first to demonstrate increased PWd, QTd, and QT dispersion in patients with DS. Further studies are warranted to exhibit the mechanisms and prognostic implications of these ECG parameters.

References

1. Agiovlasitis S, Collier SR, Baynard T, Echols GH, Goulopoulou S, Figueroa A et al (2010) Autonomic response to upright tilt in people with and without Down syndrome. Res Dev Disabil 31:857–863
2. Agiovlasitis S, Baynard T, Pitetti KH, Fernhall B (2011) Heart rate complexity in response to upright tilt in persons with Down syndrome. Res Dev Disabil 32:2102–2107
3. Baynard T, Guerra M, Pitetti KH, Fernhall B (2004) Heart rate variability at rest and exercise in persons with Down syndrome. Arch Phys Med Rehabil 85:1285–1290
4. Bazett HC (1920) An analysis of the time relations of electrocardiograms. Heart 7:353–370
5. Bissinger A, Grycewicz T, Grabowicz W, Lubinski A (2011) The effect of diabetic autonomic neuropathy on P-wave duration, dispersion, and atrial fibrillation. Arch Med Sci 7:806–812
6. Bittles AH, Bower C, Hussain R, Glasson EJ (2007) The four ages of Down syndrome. Eur J Public Health 17:221–225
7. Blom NA, Ottenkamp J, Deruiter MC, Wenink ACG, Gittenberger-De Groot AC (2005) Development of the cardiac conduction system in atrioventricular septal defect in human trisomy 21. Pediatr Res 58:516–520
8. Bluzaite I, Brazdzionyte J, Zaliunas R, Rickli H, Ammann P (2006) QT dispersion and heart rate variability in sudden death risk stratification in patients with ischemic heart disease. Medicina Kaunas 42:450–454
9. Bricout VA, Guinot M, Faure P, Flore P, Eberhard Y, Garnier P et al (2008) Are hormonal responses to exercise in young men with Down's syndrome related to reduced endurance performance? J Neuroendocrinol 20:558–565
10. Das BB, Sharma J (2004) Repolarization abnormalities in children with a structurally normal heart and ventricular ectopy. Pediatr Cardiol 25:354–356
11. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O et al (1992) Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 20:1251–1260
12. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M et al (1998) Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 135:733–738
13. Esbensen AJ, Seltzer MM, Greenberg JS (2007) Factors predicting mortality in midlife adults with and without Down syndrome living with family. J Intellect Disabil Res 51:1039–1050
14. Fernhall B, Otterstetter M (2003) Attenuated responses to sympathoexcitation in individuals with Down syndrome. J Appl Physiol 94:2158–2165
15. Fernhall B, Renaud M, Holden H, Slotter C (2000) Autonomic control during exercise is altered in Down syndrome. Sci Sports 15:288
16. Fernhall B, Baynard T, Collier SR, Figueroa A, Goulopoulou S, Kamimori G et al (2009) Catecholamine response to maximal exercise in persons with Down syndrome. Am J Cardiol 103:724–726
17. Goldsmith RL, Bloomfield DM, Rosenwinkel ET (2000) Exercise and autonomic function. Coron Artery Dis 11:129–135
18. Gorlin RJ, Cohen MM, Hennekam RCM (2001) Syndromes of the head and neck, 4th edn. Oxford University Press, Oxford, pp 35–76
19. Guerra M, Llorens N, Fernhall B (2003) Chronotropic incompetence in persons with Down syndrome. Arch Phys Med Rehabil 84:1604–1608
20. Hamada T, Gejyo F, Koshino Y, Murata T, Omori M, Nishio M et al (1998) Echocardiographic evaluation of cardiac valvular abnormalities in adults with Down's syndrome. Tohoku J Exp Med 185:31–35
21. Hayes C, Johnson Z, Thornton L, Fogarty J, Lyons R, O'Connor M et al (1997) Ten-year survival of Down syndrome births. Int J Epidemiol 26:822–829
22. Iellamo F, Galante A, Legramante JM, Lippi ME, Condoluci C, Albertini G et al (2005) Altered autonomic cardiac regulation in individuals with Down syndrome. Am J Physiol Heart Circ Physiol 289:2387–2391
23. Karadeniz C, Ozdemir R, Yozgat Y, Mese T (2013) An unexpected aortic valve in trisomy 21. Am J Med Genet Part A 161:2670–2671
24. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK et al (2004) Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol 44:109–116
25. Migliaro E, Contreras P, Bech S, Etxagibel A, Castro M, Ricca R et al (2001) Relative influence of age, resting heart rate, and sedentary lifestyle in short-term analysis of heart rate variability. Braz J Med Biol Res 34:493–500
26. Nakagawa M, Takahashi N, Iwao T, Yonemochi H, Ooie T, Hara M et al (1999) Evaluation of autonomic influences on QT

dispersion using the head-up tilt test in healthy subjects. Pacing Clin Electrophysiol 22:1158–1163
27. Ozer N, Aytemir K, Atalar E, Sade E, Aksöyek S, Ovünç K et al (2000) P-wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 23:1109–1112
28. Pye M, Quinn AC, Cobbe SM (1994) QT interval dispersion: a noninvasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? Br Heart J 71:511–514
29. Raveau M, Lignon JM, Nalesso V, Duchon A, Groner Y, Sharp AJ et al (2012) The App-Runx1 region ıs critical for birth defects and electrocardiographic dysfunctions observed in a Down syndrome mouse model. PLoS Genet 8:e1002724
30. Roizen NJ, Patterson D (2003) Down's syndrome. Lancet 361:1281–1289
31. Sap F, Karataş Z, Altin H, Alp H, Oran B, Baysal T et al (2013) Dispersion durations of P-wave and QT interval in children with congenital heart disease and pulmonary arterial hypertension. Pediatr Cardiol 34:591–596
32. Seal A, Shinebourne E (2004) Cardiac problems in Down syndrome. Curr Pediatr 14:33–38
33. Stoll C, Alembik Y, Dott B, Roth MP (1998) Study of Down syndrome in 238,942 consecutive births. Ann Genet 41:44–51
34. Tran H, White CM, Chow MS, Kluger J (2001) An evaluation of the impact of gender and age on QT dispersion in healthy subjects. Ann Noninvasive Electrocardiol 6:129–133
35. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ (2011) The changing epidemiology of congenital heart disease. Nat Rev Cardiol 8:50–60
36. Yavuz B, Deveci OS, Yavuz BB, Halil M, Aytemir K, Cankurtaran M et al (2006) QT dispersion increases with aging. Ann Noninvasive Electrocardiol 11:127–131