Bundle branch block – a monogenic inherited ECG trait in chromosome patients

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An electrocardiographic investigation was made for 1004 individuals: for 297 Down syndrome (DS) patients (average age 14.1 yrs), their 269 healthy siblings (average age 18.7 yrs), and for 438 parents (average age 49.0 yrs). An increased frequency of tachicardy, ventricular preexcitation, and bundle branch block was found in DS patients compared with their siblings. The bundle branch block in DS patients was inherited in autosome dominant way with penetrance 0.6. It was supposed that chromosome trisomy lowers the threshold for multifactorial pathology and therefore allows to reveal the prevalent influence of inheritance. The investigation of familial patterns in families of chromosome patients seems to have greater resolution than the traditional twins' method which is used for investigation of multifactorial inheritance.

Key words: electrocardiogram, Down syndrome, familial pattern, multifactorial inheritance

INTRODUCTION

Electrocardiogram (ECG) reflects major heart functions such as automatism, irritability, and conductivity. Each of the latter is determined in a multifactorial way. The incidence of multifactorial pathology differs among the families and in geographic regions. Ethnic differences in ECG were shown [1] – even though attempts have been made to deny their presence [2].

However, persistent exceptions do occur when multifactorial signs in the familial pattern show Mendelian inheritance. Familial cases with ECG alterations have been known for decades. As a matter of fact, they are the result of cardiomyopathy [3, 4] or hereditary syndromes accompanied by the following pathology: Holt–Oram atriodigital syndrome [5, 6], Friedreich ataxy combined with congenital glaucoma [7] or with Charcot–Marie–Tooth peroneal muscular atrophy [8].

Beside these and multiple other rare syndromes with nontypical ECG distortions, there are known some hereditary syndromes for which ECG test is a single or leading diagnostic sign. Solely electrocardiographic Wolff–Parkinson–White syndrome is inherited in autosomal dominant type [9], the linkage of the disorder to DNA markers on band 7q3 having been demonstrated [10]. Abnormally prolonged QT interval is common to both of the other purely electrocardiac cases: Ward–Romano syndrome, which is inherited in autosomal dominant type, as well as to autosomal recessive Jervell and Lange–Nielsen cardioauditory syndrome. In spite of synonymous changes in ECG and obvious monogenic inheritance, the syndromes of long QT turned out to be heterogenic in genetic sense [11].

Based on nonsystemic reports on inheritance of ECG parameters, we attempted to evaluate ECG in Down syndrome (DS) patients and their first range relatives.

MATERIALS AND METHODS

In order to detect multifactorial traits with prevalent inherited factors, one must choose (*i*) a sufficiently frequent chromosome disease and (*ii*) a sufficiently frequent multifactorial sign which could be additionally divided into several smaller units. The most frequent of autosomal diseases accompanied by multiple congenital malformations is Down syndrome (DS). About 650 alive patients are known in Lithuania. Almost 300 of these (about 46%) were covered by our investigation. ECG was used as a typical multifactorial sign. Standard 12-lead ECG was recorded for all of 1004 DS patients and their relatives in regional hospitals. The "formal" ECG diagnosis was divided into 21 traits.

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The ECGs were studied in a group of 297 DS patients (156 male and 141 female) with cytogenetically proven additional chromosome 21. The karyotype of 271 patients (91.2%) contained 47 chromosomes with trisomy 21, 14 patients (4.7%) were chromosome mosaics 46/47, +21, 12 patients (4.0%) contained 46 chromosomes with Robertsonian translocation. The youngest DS patient was 1 year and the oldest 48 years old (average age 14.1 years).

For such an age-ranged contingent it is rather difficult to choose an adequate control group (especially considering the fact that in hospitals and outpatient departments ECG is usually recorded when heart pathology is suspected). In our opinion, sibling control is the most acceptable in many aspects. ECG was taken for 269 siblings (135 brothers and 134 sisters) with normal karyotype. The youngest sibling was 1 year old, the oldest 58 years old (average age, 18.7 years). The age difference of 4.6 years between the DS group and the sibling group can be easily explained by the widely known fact that these patients are often born by women of older age.

Should any of the ECG parameters occur with the same frequency in siblings and parents and be present more frequently in DS patients, we might affirm that it reflects hereditary damage in this ontogenetic channel. Therefore ECG was also studied in 438 parents (258 mothers and 180 fathers). The youngest of parents was 21 years old, the oldest 81 years old (average age was 48.4 years for mothers and 49.6 years for fathers).

The largest age groups were six-to-ten years (21.7%) in DS patients, 11-to-15 years (21.8%) in siblings, and beyond 46-to-50 years (17.2%) in parents.

RESULTS AND DISCUSSION

ECG changes have been found in 77.8% of DS patients, 63.6% of siblings and 69.2% of parents. The increased incidence of ECG pathology was observed in DS patients aged 30 years and beyond, whereas in the parents it occurred much later, at age over 70 years. The age-dependent incidence curve in siblings precisely corresponded to that of parents in the age interval between 20 and 40 years, *i.e.* where the ages of both groups were overlapping.

The ECG-based diagnoses for the three groups of patients are displayed in Table 1. The increased frequencies for cicatrix, repolarisation abnormalities and low QRS voltage in parents as compared with healthy offsprings were most likely due to aging. The DS patients, as compared with their siblings, showed an increased incidence of sinus tachicardy ($P < 0.002$ according to Student's t test), right ($P < 0.002$) and left ($P < 0.001$) bundle branch block (BBB) and ventricle preexcitation ($P < 0.001$ when assumed short-PQ and Wolff–Parkinson–White syndromes).

About 80% of manifestations in chromosome diseases are so-called minor anomalies which in isolation occur also in normal population or accompany non-chromosomal pathology. There is no one clinical sign that would be typical of chromosome diseases in general or of a single disease. The incidence of the same symptoms among chromosome disease patients is reported to be quite variable, from several to dozens per cent.

This phenomenon was determined as delayed ontogenesis [12] or as nonspecific amplified developmental instability [13] caused by chromosome aneuploidy or any other teratogenic factor. The concept of decreased buffering in development pathways [14] allows us to predict that developmentally less stable traits are also

Table 1. **ECG diagnoses in Down syndrome families**

Diagnosis	DS patients (297 ECG)		Siblings (269 ECG)		Parents (438 ECG)	
	n	%	n	%	n	%
1. Sinus bradicardy	5	1.7	4	1.5	10	2.3
2. Sinus tachicardy*	39	13.1	15	5.6	13	3.0
3. Sinus arrhythmia	4	1.3	5	1.9	0	0.0
4. Extrasystoly	7	2.4	10	3.7	23	5.3
5. Atrial fibrillation	3	1.0	1	0.4	4	0.9
6. Sinoauricular block	1	0.3	2	0.7	4	0.9
7. Atrioventricular block	6	2.0	8	3.0	5	1.1
8. Right bundle branch block*	47	15.8	21	7.8	25	5.7
9. Left bundle branch block**	28	9.4	8	3.0	22	5.0
10. Intraventricular block	22	7.4	19	7.1	44	10.0
11. Short PQ**	21	7.1	8	3.0	14	3.2
12. Wolff-Parkinson-White syndr**	7	2.4	0	0.0	5	1.1
13. Left ventricular hypertrophy	23	7.7	27	10.0	36	8.2
14. Right ventricular hypertrophy	5	1.7	0	0.0	2	0.5
15. Left atrial hypertrophy	0	0.0	1	0.4	0	0.0
16. Right atrial hypertrophy	4	1.3	0	0.0	0	0.0
17. Ischemia	11	3.7	13	4.8	22	5.0
18. Cicatrix	1	0.3	0	0.0	16	3.7
19. Deviation of electric axis	31	10.4	26	9.7	43	9.8
20. Repolarisation abnormalities	34	11.5	24	8.9	68	15.5
21. Low QRS voltage	0	0.0	4	1.5	19	4.3
Total	299	–	196	–	372	–

Significance level: *$P < 0.002$, according to t test
**$P < 0.001$, according to *t*-test

more liable to variation in trisomy syndromes. If so, then we can prove that chromosome imbalance in DS patients lowers the threshold for appearance of familial multifactorial pathology. Therefore, in our opinion, for the appearance of three ECG signs – tachicardy, bundle branch block, and ventricular preexcitation – hereditary factors are responsible predominantly, while other ECG disturbances are basically determined by environmental factors.

If trisomy-21 provokes manifestation of multifactorial pathology, one can expect that inheritance of some ECG parameters in chromosome patients would be close to Mendelian. For 10 ECG diagnoses parental trait was inherited by offsprings: DS patients and their healthy siblings as well (Table 2). Left ventricle hypertrophy was inherited by DS patients twice and the bundle branch block (BBB) four times as often as by their siblings.

Only the difference between the frequencies of inherited BBB in DS patients and their siblings was statistically significant ($P \leq 0.004$ according to Fisher's *arcsinus* test; Table 3). Parents with BBB (right or left, complete or incomplete) had 41 offsprings suffering from DS, and for 12 (29.3%) of these patients BBB was established. In 42 healthy siblings this block was found only in three cases (7.1%). The analysis of familial patterns enabled to conclude that the BBB was inherited in autosome dominant type with penetrance of 60%. The more phylogenetically recent features are more variable in general population as well as in DS patients. Investigation of ECG in DS families showed that BBB, being undoubtelly phylogenetically more recent [15], is more likely to be inherited compared with other ECG traits.

Traditionally, the influence of inheritance on multifactorial signs is investigated using the twins' method. Both the ECG method, which is used in cardiology, and the twins' method, which is used in genetics, are well known classical methods. Probably this is why there are a few new publications and almost all of them refer to a study of the year 1939 [16]. The subject of the study was a sample of 50 pairs of twins (32 monozygotic and 18 dizygotic), young adults without cardiac pathology. The amplitudes of P wave and QRS complex were measured and the ECGs were estimated as "closely similar", "somewhat similar" or "non-similar". The conclusion of the mentioned investigation was that the ECG of monozygotic twins is influenced by inheritance.

We suppose we have suggested a new approach to investigation of inheritance in multifactorial pathology. Investigation of familial pattern in families of chromosome patients seems to be more informative and having a higher resolution than the twins' method.

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Table 2. **Familial ECG alterations**

Diagnosis	Number of parental traits found in children		
	DS patients	Siblings	Total
1. Sinus bradicardy	1	0	1
2. Sinus tachicardy	4	3	7
3. Right bundle branch block	4	1	5
4. Left bundle branch block	4	1	5
5. Intraventricular block	3	4	7
6. Short PQ	3	2	5
7. Left ventricular hypertrophy	9	5	14
8. Ischemia	1	0	1
9. Deviation of electric axis	6	9	15
10. Repolarisation abnormalities	5	10	15
Total	40	35	75

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Table 3. **Familial cases of right and left bundle branch block (BBB)**

Diagnosis in parents	DS patients (total 41) Siblings (total 42)							
	with BBB		without BBB		with BBB		without BBB	
	n	%	n	%	n	%	n	%
Right BBB	4	9.8	15	36.6	1	2.4	25	59.5
Left BBB	4	9.8	14	34.1	1	2.4	11	26.2
BBB (in children – block of another branch)	4	9.8	0	0.0	1	2.4	3	7.1
Total*	12	29.3	29	70.7	3	7.1	39	92.8

Significance level: * $P \leq 0.004$, according to Fisher's *arcsinus* test

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HISO PLUOŠTO KOJYČIŲ BLOKADA – MONOGENIŠKAI PAVELDIMAS CHROMOSOMINIŲ LIGONIŲ EKG POŽYMIS

S a n t r a u k a

Buvo išanalizuotos 1004 elektrokardiogramos: 297 probandams, sergantiems Dauno sindromu, 269 jų sveikiems sibsams ir 438 tėvams. Probandams dažniau negu jų tėvams ir sibsams nustatyta sinusinė tachikardija, skilvelinės ekstrasistolės ir Hiso pluošto kojyčių blokada. Genealoginės analizės duomenimis, probandai, sergantys Dauno sindromu, Hiso pluošto kojyčių blokadą paveldi autosominiu dominantiniu būdu su 60% penetrantiškumu. Manome, kad 21-os chromosomos trisomija mažina daugiaveiksnės patologijos pasireiškimo slenkstį, todėl pasireiškia paveldėjimas. Daugiaveiksnės patologijos tyrimas chromosominių ligonių šeimose aiškiau negu dvynių metodas rodo paveldimų veiksnių poveikį.