Heart rate variability in children with congenital sensorineural deafness

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SUMMARY: Uçar T, Tutar E, Tekin M, Atalay S. Heart rate variability in children with congenital sensorineural deafness. Turk J Pediatr 2010; 52: 173-178.

We hypothesized that decreased sympathetic/parasympathetic balance as a result of the absence of auditory stimuli on the autonomic nervous system might be an explanation for our previous finding of lower mean heart rate in congenitally deaf children. To test our hypothesis, we obtained heart rate variability (HRV) data of 23 children with congenital sensorineural deafness from 24-hour Holter ECG recordings and compared them to data of 18 healthy children. HRV was measured by calculating time-domain and frequency-domain indexes from 24-hour recordings and from 6 hours of recordings obtained while subjects were sleeping. We additionally compared the HRV values obtained from children with and without *GJB2* gene mutations. We did not find any significant difference in HRV parameters between deaf children and healthy children. There were also no significant differences in HRV parameters between deaf children with and without *GJB2* mutations. We conclude that cardiac autonomic dysfunction does not seem to be present in patients with congenital sensorineural deafness.

Key words: sensorineural deafness, heart rate variability, autonomic nervous system.

Heart rate variability (HRV) represents a noninvasive parameter for studying cardiac autonomic control[1,2]. Decreased HRV is a sign of autonomic imbalance and is an independent predictor of increased morbidity and mortality with various forms of heart disease and sudden death. Decreased variability was found in adult patients with myocardial infarction[3,4], chronic heart failure[5,6], left ventricular dysfunction[5], low cardiac output[7], and diabetic neuropathy[8]. In the pediatric age group, HRV has been investigated in diabetes mellitus[9], respiratory distress syndrome of the newborn[10,11], sudden infant death syndrome[12], congenital heart disease both before and after operation[13], critically ill children following cardiac surgery[14], and normal infants and children[2,15,16], but has not yet been extensively investigated in children with congenital sensorineural deafness. The most common cause of congenital hearing impairment has been shown to be impairment of the function of different gap junction proteins[17]. Mutations in the beta types of gap junction genes, GJB2 and GJB3 genes, encoding connexin 26 and connexin 31 proteins, respectively, are commonly detected in different populations[17].

In our previous study, which was conducted in order to investigate repolarization abnormalities, consisting of approximately 800 children, we surprisingly found that congenitally deaf children had lower mean heart rate than their healthy counterparts[18]. We proposed that decreased sympathetic tone as a result of the absence of auditory stimuli on the autonomic nervous system in deaf children might be an explanation. To test that hypothesis, we obtained HRV data from 24-hour Holter ECG recordings in a group of children with congenital sensorineural deafness and compared data to those of healthy school children. To exclude the effect of acoustic stimuli on the autonomic nervous system, we also compared the HRV data obtained during the daytime with that during sleep. In order to evaluate the effect of mutations in the GJB2 and GJB3 genes, we

compared the values obtained in patients with and without a mutation in these genes.

Material and Methods

We evaluated 23 children with congenital sensorineural deafness (male/female: 13/10, mean age: 12.7±2.4 years, range: 8-16 years). All children were screened for mutations in the *GJB2* and *GJB3* genes using previously published polymerase chain reaction (PCR)-single strand conformational polymorphism (SSCP) methods[19,20]. The control group included 18 age- and sex-matched healthy school children (male/female: 11/7, mean age: 12.1±4.2 years, range: 6.5-17 years). Children with syndromic forms of congenital deafness or having acute or chronic illnesses were excluded. Family histories of children were negative for syncope, seizure or premature sudden death. All children had a normal medical history and physical examination except for hearing impairment. Sinus rhythm was confirmed before entering the protocol. This study was approved by the ethics committee of our institution.

The 24-hour Holter ECG recordings were obtained using a three-channel ambulatory electrocardiographic monitor. The records included a complete day and night cycle, and the children were encouraged to perform their normal daily activities at home and school. HRV was measured by calculating time-domain and frequency-domain indices from 24-hour recordings, from 6 hours of recordings obtained while subjects were sleeping (midnight - 6 AM) and from 12-hour recording obtained while subjects were undertaking normal daily activities (8 AM - 8 PM).

A digital Holter scanner (Pathfinder 700 Series, Reynolds Medical LTD, Hertford, United Kingdom) was used to analyze rhythm and HRV from the Holter tapes. Holter tapes were reviewed by two authors (TU and ET) and QRS complexes identified. Abnormal beats, significant pauses and areas of artifact were excluded.

Six time-domain indices were examined: (1) Mean RR: mean of all normal sinus R-R intervals, (2) SDNN: standard deviation of all normal sinus R-R intervals, (3) SDNN-i: mean of the standard deviation of all normal sinus R-R intervals for all 5-min segments, (4) SDANN: standard deviation of the averaged normal sinus R-R intervals for all 5-min segments, (5) rMSSD: root mean square of the successive normal sinus R-R interval difference, and (6) pNN50: percentage of successive normal sinus R-R intervals longer than 50 ms. Three frequency-domain indices were examined as: (1) LF: low frequency power (frequency range 0.04 to 0.15 Hz), (2) HF: high frequency power (frequency range 0.15 to 0.40 Hz), and (3) LF/HF ratio[1,2,13,15].

Statistical Analysis

All data were expressed as mean ± SD. Student's t test or Mann-Whitney U test was used where appropriate. A two-tailed p value <0.05 was considered statistically significant.

Results

The length of analyzable Holter recording was 22.3±1.2 hours for deaf children and 22.7±1.4 hours for the control group ($p>0.05$). The mean time-domain indices and frequency-

Table I. HRV Parameters of Deaf Children and the Control Group on 24-Hour Recordings

Variables	Deaf children (n:23)	Control group (n:18)	P Value
Mean RR (ms)	698.96 ± 63.49	710.8 ± 116.11	0.67
SDNN (ms)	94.093 ± 29.472	94.505 ± 34.374	0.96
SDNN-i (ms)	76.74 ± 26.33	80.83 ± 29.01	0.63
SDANN (ms)	48.18 ± 14.67	49.39 ± 15.06	0.79
rMSDD (ms)	64.04 ± 42.53	66.83 ± 34.32	0.82
pNN50 (%)	21.30 ± 12.99	24.39 ± 14.65	0.47
LF (ms^2)	653.35 ± 424.49	743.16 ± 463.44	0.52
HF (ms^2)	547.49 ± 531.60	615.12 ± 556.53	0.69
LF/HF	1.71 ± 0.93	1.70 ± 0.96	0.97

Mean RR: Mean of all normal sinus R-R intervals. SDNN: Standard deviation of all normal sinus R-R intervals. SDNN-i: Mean of the SD of all normal sinus R-R intervals for all 5-min segments. SDANN: SD of the averaged normal sinus R-R intervals for all 5-min segments. rMSDD: Root mean square of the successive normal sinus R-R interval difference. pNN50: Percentage of successive normal sinus R-R intervals longer than 50 ms. LF: Low frequency. HF: High frequency.

domain indices of the deaf children and control group on 24-hour recordings are shown in Table I and nighttime values are shown in Table II. We did not determine any significant difference in either time- or frequency-domain HRV parameters from 24-hour recordings or from the 6 hours of recordings obtained during sleep between the children with congenital sensorineural deafness and hearing school children. When the nighttime and daytime time- and frequency-domain indices were compared in deaf children, the vagal tone indices were found more powerful at nighttime (HF: $p<0.001$, rMMSD: $p=0.003$, pNN50: $p<0.001$). We also found similar results in healthy children (HF: $p<0.001$, rMMSD: $p<0.001$, pNN50: $p<0.001$). The mean time-domain indices and frequency-domain indices of deaf children in daytime and nighttime are shown in Table III and of healthy children are shown in Table IV.

Eight children (34.8%) were found to have homozygous 35delG mutation in the *GJB2* gene, indicating that deafness in these persons was caused by impairment of the connexin 26 protein. One child (4.3%) was demonstrated to carry heterozygous 35delG mutation. None of the children was positive for *GJB3* mutations. The mean time-domain indices and frequency-domain indices of deaf children with and without homozygous *GJB2* mutations during 24-hour recordings are shown in Table V. The nighttime recordings of these groups are shown in Table VI. There were no significant differences in either time- or frequency-domain HRV parameters from 24-hour recordings or

Table II. HRV Parameters of Deaf children and the Control group at Night

Variables	Deaf children (n:23)	Control group (n:18)	P Value
Mean RR (ms)	887.48 ± 113.0	874.22 ± 181.32	0.77
SDNN (ms)	117.08 ± 45.32	117.25 ± 45.65	0.99
SDNN-i (ms)	97.47 ± 41.73	99.89 ± 41.92	0.85
SDANN (ms)	50.70 ± 21.05	47.45 ±19.50	0.61
rMSDD (ms)	86.61 ± 51.90	93.70 ± 53.19	0.67
pNN50 (%)	38.36 ± 21.49	40.03 ± 23.60	0.81
LF (ms^2)	878.69 ± 750.88	947.93 ± 760.63	0.77
HF (ms^2)	968.50 ± 888.29	1067.34 ± 1081.06	0.75
LF/HF	1.38 ± 1.04	1.30 ± 0.83	0.81

Mean RR: Mean of all normal sinus R-R intervals. SDNN: Standard deviation of all normal sinus R-R intervals. SDNN-i: Mean of the SD of all normal sinus R-R intervals for all 5-min segments. SDANN: SD of the averaged normal sinus R-R intervals for all 5-min segments. rMSDD: Root mean square of the successive normal sinus R-R interval difference. pNN50: Percentage of successive normal sinus R-R intervals longer than 50 ms. LF: Low frequency. HF: High frequency.

Table III. HRV Parameters of Deaf Children in Nighttime and Daytime

Variables	Nighttime (n:23)	Daytime (n:23)	P Value
Mean RR (ms)	887.48 ± 113.0	676.66 ± 60.32	<0.001
SDNN (ms)	117.08 ± 45.32	96.09 ± 30.42	<0.01
SDNN-i (ms)	97.47 ± 41.73	79.70 ± 25.68	0.01
SDANN (ms)	50.70 ± 21.05	49.91 ± 14.88	0.23
rMSDD (ms)	86.61 ± 51.90	60.24 ± 40.12	0.003
pNN50 (%)	38.36 ± 21.49	20.36 ± 11.74	<0.001
LF (ms^2)	878.69 ± 750.88	683.30 ± 404.02	0.29
HF (ms^2)	968.50 ± 888.29	552.30 ± 520.42	<0.001
LF/HF	1.38 ± 1.04	1.72 ± 0.90	0.001

Mean RR: Mean of all normal sinus R-R intervals. SDNN: Standard deviation of all normal sinus R-R intervals. SDNN-i: Mean of the SD of all normal sinus R-R intervals for all 5-min segments. SDANN: SD of the averaged normal sinus R-R intervals for all 5-min segments. rMSDD: Root mean square of the successive normal sinus R-R interval difference. pNN50: Percentage of successive normal sinus R-R intervals longer than 50 ms. LF: Low frequency. HF: High frequency.

Table IV. HRV Parameters of Healthy Children in Nighttime and Daytime

Variables	Nighttime (n:18)	Daytime (n:18)	P Value
Mean RR (ms)	874.22 ± 181.32	680.8 ± 102.1	<0.001
SDNN (ms)	117.25 ± 45.65	98.50 ± 32.40	<0.05
SDNN-i (ms)	99.89 ± 41.92	92.54 ± 26.01	0.05
SDANN (ms)	47.45 ±19.50	48.40 ± 16.10	0.44
rMSDD (ms)	93.70 ± 53.19	63.81 ± 31.21	<0.001
pNN50 (%)	40.03 ± 23.60	24.40 ± 17.71	<0.001
LF (ms^2)	947.93 ± 760.63	739.18 ± 451.40	0.07
HF (ms^2)	1067.34 ± 1081.06	598.10 ± 515.36	<0.001
LF/HF	1.30 ± 0.83	1.78 ± 0.91	<0.001

Mean RR: Mean of all normal sinus R-R intervals. SDNN: Standard deviation of all normal sinus R-R intervals. SDNN-i: Mean of the SD of all normal sinus R-R intervals for all 5-min segments. SDANN: SD of the averaged normal sinus R-R intervals for all 5-min segments. rMSDD: Root mean square of the successive normal sinus R-R interval difference. pNN50: Percentage of successive normal sinus R-R intervals longer than 50 ms. LF: Low frequency. HF: High frequency.

Table V. HRV Parameters of Deaf Children With and Without *GJB2* Mutation on 24-hour Recordings

Variables	GJB2 (+) (n:9)	GJB2 (-) (n:14)	P Value
Mean RR (ms)	724.44 ± 65.84	682.57 ± 58.43	0.12
SDNN (ms)	100.05 ± 27.20	90.26 ± 31.20	0.45
SDNN-i (ms)	82.78 ± 23.01	72.86 ± 28.38	0.39
SDANN (ms)	47.70 ± 13.64	48.49 ± 15.79	0.90
rMSDD (ms)	76.00 ± 47.99	56.36 ± 38.49	0.29
pNN50 (%)	24.28 ± 12.41	19.39 ± 13.45	0.39
LF (ms^2)	800.21 ± 475.89	558.94 ± 375.56	0.19
HF (ms^2)	640.43 ± 380.01	487.75 ± 616.09	0.51
LF/HF	1.61 ± 1.19	1.77 ± 0.76	0.71

Mean RR: Mean of all normal sinus R-R intervals. SDNN: Standard deviation of all normal sinus R-R intervals. SDNN-i: Mean of the SD of all normal sinus R-R intervals for all 5-min segments. SDANN: SD of the averaged normal sinus R-R intervals for all 5-min segments. rMSDD: Root mean square of the successive normal sinus R-R interval difference. pNN50: Percentage of successive normal sinus R-R intervals longer than 50 ms. LF: Low frequency. HF: High frequency.

Table VI. HRV Parameters of Deaf Children With and Without *GJB2* Mutation at Nighttime

Variables	GJB2 (+) (n:9)	GJB2 (-) (n:14)	P Value
Mean RR (ms)	946.69 ± 134.18	849.41± 80.87	0.07
SDNN (ms)	129.05 ± 49.01	109.39 ± 42.84	0.32
SDNN-i (ms)	112.96 ± 45.31	87.51 ± 37.56	0.15
SDANN (ms)	48.40 ± 18.60	52.18 ± 23.05	0.66
rMSDD (ms)	98.08 ± 47.59	79.23 ± 54.91	0.40
pNN50 (%)	46.56 ± 22.78	33.09 ± 19.64	0.14
LF (ms^2)	1195.24 ± 1011.63	675.19 ± 458.72	0.10
HF (ms^2)	1225.70 ± 881.43	803.16 ± 884.31	0.27
LF/HF	1.17 ± 0.83	1.51 ± 1.17	0.47

Mean RR: Mean of all normal sinus R-R intervals. SDNN: Standard deviation of all normal sinus R-R intervals. SDNN-i: Mean of the SD of all normal sinus R-R intervals for all 5-min segments. SDANN: SD of the averaged normal sinus R-R intervals for all 5-min segments. rMSDD: Root mean square of the successive normal sinus R-R interval difference. pNN50: Percentage of successive normal sinus R-R intervals longer than 50 ms. LF: Low frequency. HF: High frequency.

from the 6 hours of recordings obtained during sleep between children with and without *GJB2* mutations.

Discussion

Children with congenital sensorineural hearing loss have inherent repolarization abnormalities including QT/QTc prolongation and increased

QT/QTc dispersion[21,22]. In our previous study, we examined ECGs of children who were students of the schools for the deaf, and compared them to those of age- and sex-matched healthy school children, with special emphasis on repolarization status[18]. We found that the mean heart rate of deaf children was significantly slower than that of healthy children. We hypothesized that decreased sympathetic/parasympathetic balance as a result of the absence of auditory stimuli on the autonomic nervous system in deaf children may be an explanation[23,24].

Heart rate variability depends on the influence of sympathetic and parasympathetic activity on the sinus node, and it is primarily modulated by parasympathetic nervous system activity. HRV measures have received a great deal of attention with regard to the autonomic control of the heart rate[15,25]. The high frequency (HF) component of the frequency-domain analysis and rMSSD and pNN50 in the time-domain analysis are well-known HRV parameters that are dependent on the vagal tone. The low frequency (LF) component of the frequency-domain analysis and SDNN, SDNN-i, and SDANN-i of the parameters of the time-domain analysis are dually influenced by vagal and sympathetic tones. The ratio of low- to high-frequency power (LF/HF) reflects sympathetic-parasympathetic balance[13,15,16]. In this study, we examined sympathetic-parasympathetic balance in children with congenital sensorineural deafness.

Our results showed that there was no difference in time-domain and frequency-domain indices between children with sensorineural deafness and the control group over 24 hours. El Habbal et al.[21] carried out a similar study. They obtained only LF/HF ratio in 52 children with congenital sensorineural deafness and compared them to that observed in healthy children. Similar to our results, they did not find significant difference between the two groups.

We speculated as to whether or not the influence of auditory stimuli on the autonomic nervous system was important. One can assume that there are no auditory stimuli at night. Thus, we separately analyzed the HRV parameters during both night and day. Both deaf children and healthy children had more powerful vagal tone during the nighttime than during the daytime. There were no significant differences for either time- or frequency-domain HRV parameters between deaf children and healthy counterparts during the night (Table II). Therefore, we conclude that auditory stimuli have no effect on the autonomic activity of the heart.

Genetic factors account for at least half of all cases of profound congenital deafness. To date, 80 loci for nonsyndromic hearing loss have been mapped and more than 30 genes have been identified. These genes belong to a wide variety of protein classes such as ion channel and gap junction components, transcription factors, extracellular matrix proteins, and genes with an unknown function[17,26]. Ion channel dysfunction and dysfunction of fluid-ions homeostasis in the inner ear are the most important mechanisms for sensorineural hearing loss, and these dysfunctions can involve not only the inner ear but also other organs. For example, similar potassium ion channels are present in the heart, and their dysfunction is responsible for sensorineural hearing loss and Jervell and Lange-Nielsen syndrome[27]. Connexins and potassium channel proteins control key physiological processes in the heart and inner ear, demonstrating that similar electrically excitable tissues are present in both localizations. Mutations in the *GJB2* gene have been established as a major cause of inherited and sporadic nonsyndromic hearing impairment in different populations. Connexins belong to a family of gap junction proteins responsible for the intracellular transport of ions, metabolites, and second messengers[26,28]. Their role has been shown in cardiac impulse conduction[29]. However, a previous ECG study in 11 children with congenital sensorineural deafness due to *GJB2* mutations did not demonstrate any ECG abnormality[30]. We similarly could not find any ECG or HRV abnormalities in children with deafness due to either *GJB2* mutations or other etiologic factors (Tables V, VI).

We conclude that cardiac autonomic dysfunction does not seem to be present in patients with congenital sensorineural deafness.

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