Assessment of Autonomic Nervous System in Children with Celiac Disease: A Heart Rate Variability Study

SEYMA KAYALI[1] AND SUNA SELBUZ[2]

From Departments of [1]Pediatric Cardiology and [2]Pediatric Gastroenterology, Health Sciences University, Kecioren Training and Research Hospital, Ankara, Turkey.

Correspondence to: Dr Seyma Kayali, Department of Pediatric Cardiology, Kecioren Training and Research Hospital, Pýnarbasi Mah, Sanatoryum Cad, Ardahan Sok No.25, 06380 Kecioren, Ankara. ak-seyma@hotmail.com
Received: November 14, 2019;
Initial review: January 20, 2020;
Accepted: April 28, 2020.

Objective: We evaluated the activity of autonomic nervous system in children with celiac disease by using heart rate variability (HRV) analysis. **Methods:** HRV parameters of 37 children with celiac disease were compared to 36 age- and sex-matched healthy controls. None of the participants had a systemic, central or peripheral neurological disease. **Results:** Statistically significant differences were present in two parameters; standard deviation of all RR intervals (SDNN) and standard deviation of 5-minute RR interval means (SDANN). Age was negatively correlated with mean, minimum and maximum heart rate. Duration of disease was positively correlated with low frequency power-high frequency power ratio. No correlation was found between anti-tissue transglutaminase IgA level and HRV parameters. **Conclusion:** Celiac disease may affect autonomic nervous function in children even if there are no symptoms of dysautonomia.

Keywords: *Complications, Comorbidity, Extra-intestinal, Neurological involvement.*

Celiac disease, an autoimmune inflammatory enteropathy, has manifestations beyond the gastrointestinal system with neurological manifestations such as cerebellar ataxia and peripheral neuropathy present in up to 10% of the patients [1]. The data about the frequency of involvement of autonomic nervous system (ANS) in celiac disease are still insufficient, in particular for the pediatric age group. In adult studies, it was shown that the frequency of associated ANS disorder in patients with celiac disease was up to 45% [2]. Some of these patients were asymptomatic or existing symptoms were ascribed to some other cause.

Sympathetic and parasympathetic components of ANS can be tested by heart rate variability (HRV) analysis, which is a reliable and selective method [3]. In this study, we evaluated the activity of ANS in children with celiac disease by using 24-hour rhythm Holter monitoring and compared the results with healthy controls.

METHODS

We included patients with celiac disease under follow up at the Pediatric gastroenterology department of Kecioren Training and Research hospital, between January, 2018 and January, 2019. Written informed consent was obtained from parents of all participants. The control group was selected from attendees of general outpatients clinic who were considered to be healthy based on history, examination and routine laboratory tests. Children with congenital and/or acquired heart disease, arrhythmia, with a history of either gastrointestinal and neurological disorders or other chronic illnesses, and taking daily medications were excluded from the study. None of the participants reported syncope, presyncope, light-headedness, headache, and dizziness. The local ethics committee cleared the protocol.

All the patients in the study had compatible diagnostic features of celiac disease including histologic findings on duodenal biopsy and positive anti-tTG IgA levels. Complete blood count, blood glucose, lipid profile, electrolytes, thyroid stimulating hormone, coagulation parameters, liver function tests and serum vitamin levels were also evaluated in children with celiac disease.

A standard transthoracic echocardiographic imaging including two-dimensional and colour-Doppler examination was performed to all participants. Cardiac functions, cardiac structures and additional cardiac abnormalities were evaluated by the same pediatric cardiologist. 24-hour ambulatory electrocardiogram recordings were used for HRV analysis in all cases. Recordings taken with DMS 400-3A solid-state recorder were evaluated *via* computer by using the Cardioscan II series (DM Software, USA) software. Details of analysis

of HRV are provided in *Web Box* I.

Statistical analyses: The Statistical package for social sciences program version 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses of data. Shapiro - Wilk test was used to assess the normal distribution of variables. According to distribution, Student t test or Mann Whitney U test were used to compare groups. The differences in median values between more than two independent groups were analyzed with the Kruskal–Wallis test. If the result of the Kruskal–Wallis test proved to be significant, the condition causing this difference was determined by Conover non-parametric multiple comparison tests. Correlation between variables was assessed by using Pearson or Spearman correlation based on normality of distribution. Statistical significance level was considered as a *P* value of under 0.05.

RESULTS

Forty-four patients of celiac disease were initially recruited, but only 37 patients and 35 controls completed the study. The mean age of participants was 12.4 years (IQR: 9-16 years). Although all celiac patients were recommended gluten free diet at the time of diagnosis, there were only 20 patients in the study group adhering to gluten free diet. Baseline characteristics of all participants are summarized in *Table* I. The groups were comparable for all parameters except, body mass index was lower in the study group. Mean disease duration in the patients was 2.05 years (IQR: 2.6 years, 2.5 months - 2.8 years), and the mean serum level of anti-tTG was 75.9 mg/dL (IQR:8.8-157 mg/dL). Histological examination of the duodenal biopsy specimens were compatible with Marsh type 3 in all patients. A total of 5 cases were diagnosed as type 3a, 17 cases were diagnosed as type 3b, and 15 cases as type 3c according to modified Marsh classification. All participants were euthyroid and had low C-reactive protein concentration. Anemia and microcytosis was documented in only one case.

Table I Baseline Characteristics of Children With Celiac Disease and Unaffected Controls

Characteristic	Study group (n = 37)	Control group (n = 35)
*Age, y	13 (3,18)	14 (5,18)
Female	22	18
‡Body surface area, kg/m²	17.3 (3.02)	19.8 (3.2)
Systolic BP, mmHg	108.3 (9)	109.5 (8.5)
Diastolic BP, mmHg	63.7 (8.5)	63.6 (7.7)
Disease duration, y	2 (0-10)	-

*All values in mean (SD) except *median (IQR); BP: Blood pressure; ‡P=0.001.*

Echocardiographic evaluation of all participants was normal. Though systolic functions were within normal limits in all participants, both mean (SD) ventricular ejection fraction and shortening fraction were significantly higher in the control group [72.3 (5.1)% *vs* 75.2 (5.3)%; *P*=0.02] and [40.7 (4.4)% *vs* 44.8 (5.0)%; *P*=0.005], respectively.

During 24-hour rhythm Holter monitoring evaluation, one patient had rare extra supraventricular beats in the study group; whereas in the control group, three participants (one with rare extra ventricular beats and the other two with rare extra supraventricular beats) were found. HRV parameters including both time-domain and frequency-domain components are summarized in *Table* II. Statistically significant differences were found in only two parameters *viz* Standard deviation of all the RR intervals (SDNN) and Standard deviation of 5 minute RR interval means (SDANN).

There was a statistically significant negative correlation between age and minimum HR, maximum HR, average HR (r=-0.474; -0.358; and -0.553, respectively; all *P*=0.003, *P*=0.03, *P*<0.001). In addition, a positive

Table II Time-domain and Frequency-domain Variables in Children With Celiac Disease and Unaffected Controls

	Celiac disease (n = 37)	Control group (n = 35)
Heart rate, bpm		
Minimum	52.7 (7.92)	49.5 (7.28)
Maximum	163.8 (16.59)	163.7 (23.52)
Average	88.5 (13.12)	86.3 (16.41)
*SDNN, ms	133.9 (41.2)	163.0 (46.43)
SDNNi, ms	69.4 (26.99)	72.5 (19.83)
*SDANN, ms	115.9 (36.84)	144.0 (45.45)
RMSSD, ms	44.8 (17.13)	45.9 (14.51)
pNN50, %	19.2 (11.48)	20.9 (10.490
Power, ms		
Total	4507.5 (2781.06)	5330.0 (2634.35)
VLF	2777.9 (2027.12)	3318.4 (2022.19)
HF	636.1 (382.03)	657.9 (315.19)
LF	1026.7 (536.86)	1186.5 (493.53)
LF/HF	1.93 (0.85)	1.96 (0.75)

*All values in mean (SD); SDNN; standard deviation of all the RR intervals, SDANN; standard deviation of 5 minute RR interval means, SDNNi; the mean of the 5 minute RR interval standard deviations, RMSSD; the square root of the mean of the squared differences of two consecutive RR intervals, pNN50; the percentage of the beats with consecutive RR interval difference of more than 50 ms, VLF; very low-frequency power, LF; low-frequency power, HF; high-frequency power; *P<0.01.*

correlation was duration of diagnosis found between age and SDNN (r=0.339; *P*=0.04). Ratio of LF/HF was positively correlated with duration of diagnosis (r =0.516; *P*=0.001). No correlation was found between serum anti-tTG IgA levels and HRV parameters. When participants were divided into three groups as patients with celiac disease adhering to gluten-free diet, not adhering to gluten-free diet, and healthy controls, statistically significant difference between controls and celiac patients adhering to gluten-free diet were present in only time domain parameters of SDNN and SDANN (*P*=0.01).

DISCUSSION

We studied HRV parameters among 37 children with celiac disease and 36 unaffected controls, and found two parameters (SDNN and SDANN) to be abnormal in the children with celiac disease.

In adult studies, the frequency of neurologic involvement in celiac disease is reported to be 22-45% [2,8]. On the other hand, despite limited information, neurologic and psychiatric symptoms are lower and observed in 13-33% of the pediatric patients with celiac disease [9,10].

Autonomic neuropathy is considered to be a complication of celiac disease, developing without any neurological symptoms [2]. HRV parameters calculated on the basis of the mean of the RR change, such as, RMSSD, p NN50 are less influenced by the cardiac circadian rhythm and these parameters are considered to be the most sensitive to parasympathetic drive. However, SDNN and SDANN are the best known of time-dependent variables and have been widely used to provide information in the evaluation of HRV [3,4]. We carried out HRV analysis as it is the most feasible, reliable and easiest method for studying autonomic involvement in the pediatric population [4,6]. HRV parameters have been reported to be significantly lower in CD patients than in healthy people [11,12]. The results of our research are compatible with previous reports.

Although, it is difficult to define which component of autonomic nervous system is affected mainly in children with celiac disease, we estimate that they have asymptomatic dysautonomia and sympathetic-parasympathetic imbalance. The increase in high frequency power (HF) reflects parasympathetic activity and the increase in low frequency power (LF) reflects mainly sympathetic activity. LF/ HF ratio is an index of sympathovagal balance and total power (TP) is used to evaluate the entire action of ANS [3-6]. All parameters of these two methods have a strong correlation. Our results are consistent with the data published by Felus, *et al.*

[11], reported about 20% of the patients had parasympathetic dominance whereas 36% had sympathetic over-activity. We found a positive correlation between disease duration and ratio of LF/HF. LF/HF ratio is known as a measure sympathovagal balance [3,4]. This positive correlation can possibly be attributed to the duration of the gluten-free diet; through the numbers were small to confirm this premise.

The possible mechanisms leading to neurologic complications include immune interaction and changes secondary to malabsorption of vitamins and micro-elements [13,14]. In adult studies, some markers of celiac disease like anti ganglioside antibody titers or IL-10 have been reported to have a predictor role for autonomic nervous system impairment [15]. Our findings showed that there was no relationship between anti-tTG IgA levels and HRV parameters. We think this may be due to the fact that pathogenic antibodies (anti-gliadin, anti-tTG or others) need time to penetrate the nervous system and produce permanent damage [7].

The limitations of this study are that the sample size is small, and the study was performed in a heterogeneous patient population in terms of the period of gluten-free diet and disease follow-up. In addition, studies comparing children with celiac disease and children with other gastrointestinal disorders in terms of HRV will provide more information about the mechanism of impaired autonomic nervous system activity. Other limitations originate from the method of 24-hour rhythm Holter monitoring itself, which can be affected from daily physical activity and posture of individuals. However, this study is important in that it focuses attention on autonomic involvement in children with celiac disease, which is usually not appreciated by clinicians.

In conclusion, celiac disease causes disturbances of the autonomic activity in pediatric population, which is lower than adults, but may have implications for management and outcome.

REFERENCES

1. Rubio-Tapia A, Murray JA. Celiac disease. Curr Opin Gastroenterol. 2010;26:116-22.
2. Usai P, Usaý Satta P, Laý M, Corda MG, Pýras E, Calcara C, *et al*. Autonomic dysfunction and upper digestive

functional disorders in untreated adult coeliac disease. Eur J Clin Invest. 1997;27:1009-15.

3. Acharya, UR, Joseph KP, Kannathal N, Min LC, Suri JS. Heart rate variability.*In*:Advances in Cardiac Signal Processing; 2007: Springer.p.121-65.

4. Heart rate variability. Standards of Measurement, Physiological Interpretation, and Clinical Use Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93:1043-65.

5. Malliani A, Pagani M, Lombardi F,Cerutti S. Cardiovascular neural regulation exploredin the frequency domain. Circulation. 1991;84:1482-92.

6. Sztajzel J. Heart rate variability: A noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Medil Wkly. 2004;134:514-22.

7. Lerner A, Makhoul BF, Eliakim R. Neurological manifestations of celiac disease in children and adults. Eur Neurol J. 2012;4:15-20.

8. Briani C, Zara G, Aleadini A, Grassivaro F, Ruggero S, Toffain E, *et al*. Neurological complications of celiac disease and autoimmune mechanisms: A prospective study. J Nuroimmunol. 2008;195:171-5.

9. Isikay S, Kocamaz H. The Neurological face of celiac disease. Arq Gastroenterol. 2015;52:167-70.

10. Diaconu G, Rigore I, Anton DT, Trandofir LM. Celiac disease with neurologic manifestations in children. Rev Med Chir. 2013;17:88-94.

11. Przybylska-Felus M, Furgala A, Zwolinska-Wcislo M, MazurM, Widera A, Thor P, *et al*. Disturbances of autonomic nervous system activity and diminished response to stress in patients with celiac disease. J Physiol Pharmacol. 2014; 65:833-41.

12. Barbato M, Curione M, Amato S, Carbone J, Briani C, Pannove V. Autonomic imbalance in celiac children. Minerva Pediatr. 2010;62:333-8.

13. Setty M, Hormaza L, Guandalini S. Celiac disease: Risk assessment, diagnosis, and monitoring. Mol Diagn Ther. 2008;12:289-98.

14. Tursi A, Giorgetti GM, Lani C, Arciprete F, Brandimarte G, Capria A,*et al*., Peripheral neurological disturbances, autonomic dysfunction, and antineuronal antibodies in adult celiac disease before and after a gluten-free diet. Dig Dis Sci. 2006;51:1869-74.

15. Przybylska-Felus M, Zwolinska-Wcislo M, Piatek-Guziewicz A, Furgala A, Salapa K, Mach T, *et al.* Concentrations of antiganglioside M1 antibodies, neuron-specific enolase, and interleukin 10 as potential markers of autonomic nervous system impairment in celiac disease. Pol Arch Med Wewn. 2016;126: 763-71.

Web Box I Details of Heart Rate Variability Analysis

Heart rate variability analysis was done using time domain and frequency domain methods based on the measurement of changes in consecutive RR intervals on 24 hour rhythm Holter recordings.

Analysis of time domain: Done from the variation of heart rate during a standard time interval based on RR distances between two consecutive sinus beats. By this analysis, parameters including; the standard deviation of all RR intervals (SDNN), the standard deviation of 5 minute RR interval means (SDANN), the mean of the 5 minute RR interval standard deviations (SDNNi), the square root of the mean of the squared differences of two consecutive RR intervals (RMSSD), the percentage of the beats with consecutive RR interval difference of more than 50 ms (pNN50) were calculated.

Frequency domain analysis: This was done from periodic signals, an average of 500 sequential R-R intervals divided into various bands of frequency response. Total power (the area under the spectral curve from 0.01 to 1.0 Hz,TP), very low-frequency power (the area under the spectral curve from 0.0033 to 0.04 Hz, VLF), low-frequency (the area under the spectral curve from 0.04 to 0.15 Hz, LF), and high frequency band power (the area under the spectral curve from 0.15 to 0.40 Hz, HF) were examined by this analysis and LF / HF ratio was calculated.