Int Cardiovasc Res J.2017;**11**(1):25-29.icrj.37300

International Cardiovascular Research Journal

www.ircrj.com

Evaluation of Celiac Disease in Children with Dilated Cardiomyopathy

Noor Mohammad Noori [1], Iraj Shahramian [2,*], Seyed Mohsen Dehghani [3], Alireza Teimouri [1], Elham Sharafi [1], Maryam Ataollahi [3], Maryam Bahmanyar [3]

[1] Children and Adolescents Health Research Center, Zahedan University of Medical Sciences, Zahedan, IR Iran
[2] Department of Pediatrics, Zabol University of Medical Sciences, Zabol, IR Iran
[3] Department of Pediatric Gastroentrology, Shiraz University of Medical Sciences, Shiraz, IR Iran

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 21 Feb 2016
Revised: 19 Oct 2016
Accepted: 12 Nov 2016

Keywords:
Celiac Disease
Children
Dilated Cardiomyopathy

ABSTRACT

Background: The incidence of Celiac Disease (CD) raises in children with Dilated Cardiomyopathy (DCM).

Objectives: This study aimed to investigate the prevalence of CD in children with DCM compared with controls.

Patients and Methods: This case-control study was conducted on 38 patients with DCM and 76 healthy controls to evaluate tTG and IgA during 2013 - 2014. Echocardiography was performed for all patients to detect cardiomyopathy. The exclusion criteria were IgA deficiency, history of digestive, endocrine, and metabolic disorders, iron deficiency, kidney disease, fever, and chronic diseases. Samples were centrifuged and the separated sera were kept at -70°C until tTG IgA and total IgA were measured by ELISA kit. After all, the data were entered into the SPSS statistical software, version 20 and were analyzed using parametric and non-parametric tests. Significance level was set at $P < 0.05$.

Results: This study was performed on 114 children; 38 in the case and 76 in the control group. The results showed no significant difference between the two groups regarding the means of continuous variables, including sex, tTG status, and diseases. From the 38 patients in the case group, 31 ones (81.58%) had normal tTG (≤ 20) and 7 ones (18.42%) had abnormal tTG (≥ 20). However, 72 participants in the control group (94.74%) showed normal tTG status (≥ 20). The results showed a significant difference between the two groups regarding tTG status (chi-square = 5.031, $P = 0.025$).

Conclusions: The results revealed a positive association between CD and DCM regardless of serology- or pathology-based diagnostic tools. This suggests the need for increasing awareness of patients with DCM regarding CD.

►*Implication for health policy/practice/research/medical education:*
The results of this study could be used for promotion of CD screening in children with DCM. These results could also provide a possible explanation for failure to thrive in patients with DCM.

1. Background

Celiac Disease (CD) is a gluten sensitive immune disorder that occurs in about 10/1000 population in Europe and North America (1). The prevalence of CD ranges from 0.5% to 12% in patients with schizophrenia and Irritable Bowel Syndrome (IBS), respectively. Recently, studies have focused on genetic and environmental factors of CD rather than its prevalence and incidence (2, 3).

Evidence has revealed an sssociation between CD and other autoimmune disorders, such as insulin-dependent diabetes, thyroid disease, and connective tissue disorders. Cardiomyopathy refers to diseases of heart muscles and predominantly affects the left ventricle (3, 4), which includes the leading pumping chamber of the heart. Dilated Cardiomyopathy (DCM) is recognized by left ventricular dilation that is concerned with systolic dysfunction. The incidence of DCM has been reported to be 0.57 per 100

*Corresponding author: Iraj Shahramian, Zabol University of Medical Sciences, Shahid Rajaei St, Zabol, IR Iran, Tel: +71-5422233624,
E-mail: ir_buper@yahoo.com

000 in children, which is higher in males than in females, in black population compared to whites, and in children below one year of age. DCM is one of the main causes of heart failure in childhood (5-7). Several studies have considered immune factors in pathophysiology of DCM and this immunological basis has been supported by positive response to immune active treatments (5, 7, 8). Another condition counted in acquired forms of DCM is nutritional deficiencies (5). Recently, an increase in the risk of CD was noted in patient with DCM associated with immunological processes. Indeed, impaired assembling in CD could be an acquired mechanism for DCM (9, 10). Overall, DCM is a very serious condition and early detection of CD in these patients is very important for early treatment with gluten free diet for improvement of intestinal permeability and prevention of worse conditions (11).

2. Objectives

Considering what was mentioned above and lack of information on the association between DCM and CD, this study aims to evaluate the relationship between CD and DCM in children.

3. Patients and Methods

This case-control study was conducted on 38 patients with DCM and 76 healthy controls to evaluate tTG and IgA during 2013 - 2014. The patients had referred to Aliasghar Heart Center affiliated to Zahedan University of Medical Sciences, southeast of Iran. The inclusion criteria of the study were aging 1 - 18 years and having quantitative echocardiographic criteria of left ventricular dilation and systolic dysfunction. Healthy children were also selected randomly from those who had referred to this center for annual check-up. Conventional and Doppler echocardiography was performed for all patients who had referred to the heart center for probable cardiomyopathy by My lab 60 with transducer 3, 8 (made in Italy). The exclusion criteria of the study were IgA deficiency, history of digestive, endocrine, and metabolic disorders, iron deficiency, and kidney disease.

First, written informed consents were obtained from all participants. Height was measured using a scaled table in sleeping position for children below 2 years old and by a scale in standing position for others. Besides, weight was measured using a special Mika scale (made in Japan) for infants and by Rasa scale (made in Iran) for other children. Afterwards, three ml blood was drawn from the children at 8:00 A.M. after an overnight fasting. The samples were centrifuged and the separated sera were kept at -70°C until measurement of tTG-IgA and total IgA. Finally, the samples were transferred to the biochemistry laboratory of Zahedan University of Medical Sciences under cold chain. Then, 250 microns of the isolated sera were used for serological tests using recombinant ELISA. It should be noted that the normal limit of tTG-IgA was 20 U/mL.

After all, the data were entered into the SPSS statistical software, version 20 and were analyzed using independent t-test for normal data and non-parametric Mann-Whitney U test for non-normal variables. Significance level was set at $P < 0.05$.

4. Results

This study was conducted on 114 children; 38 in the case and 76 in the control group. The participants included 47 males and 67 females. Among the patients, 27 were female and 11 were male. The control group also included 36 males and 40 females. At first, normality test was run for major variables and the results indicated that all variables were non-normal, except for height and age. The results of non-parametric Mann-Whitney U test for non-normally distributed variables have been presented in Table 1. Accordingly, a significant difference was found between the two groups regarding IgA level ($P = 0.04$).

The echocardiographic data in right and left heart have been depicted in Table 2. Accordingly, the two groups were significantly different concerning all parameters, except for ejection fraction, left acceleration time, left deceleration time, left atrium/aorta ratio, right acceleration time, and right E/A velocity ratio.

Based on the results presented in Table 3, there was no significant difference between the participants with the two tTG statuses (≤20: normal, >20: abnormal) regarding the means of weight, height, Body Mass Index (BMI), and IgA. Similar results were also obtained with respect to sex (Table 4).

Based on Table 5, out of the 38 patients in the case group, 31 (81.58%) had normal tTG (≤ 20) and 7 (18.42%) had abnormal tTG (≥ 20). However, 72 participants in the control group (94.74%) showed normal tTG status. The results showed a significant difference between the two

Table 1. The Results of Non-parametric Mann-Whitney U Test for Non-normally Distributed Variables in the Case and Control Groups

Variables	Group	Mean	SD	Median	IQR	Mann-Whitney U	P value
Weight	Case	19.78	9.37	18.00	17.25	1370.5	0.66
	Control	20.19	9.4	18.50	7.38		
Height	Case	112.87	22.01	114.50	38.00	1442	0.99
	Control	114.05	16.45	114.00	17.00		
BMI	Case	19.78	9.37	18.00	17.25	1374	0.67
	Control	20.17	9.43	18.50	7.38		
TTG	Case	43.31	134.39	4.10	9.00	1216	0.17
	Control	12.2	31.08	87.50	4.20		
IgA	Case	94.95	24.87	87.50	30.00	1097.5	0.04
	Control	125.53	76	108.00	87.75		

Abbreviations: BMI, body mass index; TTG, tissue transglutaminase; IgA, immunoglobulin A

Table 2. Echocardiographic Data of Left and Right Heart

Parameters	Group	Mean	SD	Mann-Whitney U	P value
Left Ventricular end-diastolic dimension	Case	46.584	7.713	238	< 0.001
	Control	39.993	4.098		
Left ventricular end-systolic dimension	Case	30.181	7.451	380.5	0.028
	Control	26.517	3.23		
Left myocardial performance index	Case	0.549	0.181	115	< 0.001
	Control	0.325	0.051		
Left Isovolumic contraction time	Case	0.03	0.01	190	< 0.0010
	Control	0.017	0.007		
Left Isovolumic relaxation time	Case	0.107	0.026	213.5	< 0.001
	Control	0.094	0.012		
Left E/A velocity ratio	Case	1.657	0.757	361	0.014
	Control	1.842	0.461		
Left Pre-ejection period	Case	0.128	0.156	159	< 0.001
	Control	0.094	0.101		
Left Pre-ejection period/ejection time	Case	0.357	0.058	157.5	< 0.001
	Control	0.294	0.039		
Left Ejection time	Case	0.25	0.026	328	0.004
	Control	0.263	0.02		
Left Interventricular septal dimension in diastole	Case	6.319	1.294	324	0.003
	Control	5.43	0.887		
Left Ventricular posterior wall dimension in diastole	Case	4.211	1.222	290.5	0.001
	Control	3.343	0.507		
Left Interventricular septal dimension in systole	Case	9.276	1.761	356.5	0.012
	Control	8.283	1.08		
Left Interventricular septal dimension in systole	Case	4.251	1.246	271.5	< 0.001
	Control	3.363	0.524		
Left Ventricular Mass Index	Case	27.0069	10.6484	188	< 0.001
	Control	16.4649	5.47652		
Right myocardial performance index	Case	0.582	0.147	60	< 0.001
	Control	0.316	0.05		
Right Isovolumic relaxation time	Case	0.11	0.022	326.5	0.004
	Control	0.096	0.012		
Right deceleration time	Case	0.128	0.012	381.5	0.027
	Control	0.12	0.018		
Right Peak E velocity	Case	68.413	17.158	325.5	0.004
	Control	57.706	14.139		
Right Peak A velocity	Case	50.366	13.852	325.5	0.004
	Control	42.119	9.916		
Right Pre-ejection period	Case	0.085	0.015	220	< 0.001
	Control	0.076	0.008		
Right Pre-ejection period/ejection time	Case	0.34	0.06	112	< 0.001
	Control	0.289	0.03		
Right Ejection time	Case	0.246	0.021	309.5	0.002
	Control	0.264	0.024		

groups regarding tTG status (Chi-square = 5.031, P = 0.025). It should be mentioned that all participants in the control group with high tTG were under endoscopy to confirm CD. Out of these 7 patients, only 3 underwent endoscopy that confirmed their CD.

Based on Ross's classification, 2 out of the 10 patients in class one died due to disease progression. Besides, all the 9 participants in the second group survived until the end of follow-up. Among the 10 patients in group 3 also, one died and one had heart transplantation. Finally, out of the eight patients in group 4, two received heart transplantation, one had a three-chamber pacemaker (died), and two withdrew from the study.

5. Discussion

This study was performed on 114 children; 38 in the case and 76 in the control group. Out of the 114 participants, 47 were male. Additionally, 27 patients were female. In the control group, 36 and 40 subjects were male and female, respectively. Among the 38 patients in the case group, 31 (81.58%) had normal tTG (≤ 20) and 7 (18.42%) had abnormal tTG (≥ 20). However, 72 participants in the control group (94.74%) had normal tTG status (≥ 20). The results revealed a significant difference between the two groups with regard to tTG status.

Zahmatkeshan reported that 2.5% of DCM cases had positive tTG antibody level and negative intestinal biopsy,

Table 3. The Results of Non-parametric Mann-Whitney U Test for Non-normally Distributed Variables Based on tTG Status

Variables	tTG	Mean	SD	Median	IQR	Mann-Whitney U	P value
Weight	≤ 20	19.94	9.52	18.00	9.50	517	0.63
	> 20	21.09	7.92	18.00	15.00		
Height	≤ 20	112.87	22.01	114.00	23.00	461	0.311
	> 20	114.05	16.45	118.00	31.00		
BMI	≤ 20	19.92	9.54	18.00	9.50	517	0.63
	> 20	21.09	7.92	18.00	15.00		
IgA	≤ 20	115.78	67.32	90.00	60.00	534	0.75
	> 20	111.18	41.56	110.00	50.00		

Abbreviations: BMI, body mass index; TTG, tissue transglutaminase; IgA, immunoglobulin A

Table 4. The Results of Non-parametric Mann-Whitney U Test for Non-normally Distributed Variables Based on Gender

Variables	Sex	Mean	SD	Median	IQR	Mann-Whitney U	P value
Weight	Male	20	10.3	18.00	8.00	1499.5	0.67
	Female	20.08	8.71	18.00	11.00		
BMI	Male	20	10.3	18.00	8.00	1499.5	0.67
	Female	20.06	8.74	18.00	11.00		
TTG	Male	8.88	23.19	4.00	4.40	1399.5	0.31
	Female	32.17	104.85	4.89	7.20		
IgA	Male	110.91	55.54	90.00	60.00	1528	0.79
	Female	118.43	71.38	90.00	61.00		

Abbreviations: BMI, body mass index; TTG, tissue transglutaminase; IgA, immunoglobulin A

Table 5. Comparison of the Case and Control Groups Regarding the Prevalence of tTG

Variable	Category	Statistics	tTG			Pearson Chi-Square	P value
			≤ 20	> 20	Total		
Group	Case	%	31	7	38	5.031	0.025
		n	81.58	18.42	100		
	Control	%	72	4	76		
		n	94.74	5.26	100		
	Total	%	103	11	114		
		n	90.35	9.65	100		

which was classified as potential CD in the children with DCM. They also found that 17% of patients had borderline antibody levels. In the present study, 18.42% of the patients had positive tTG three of whom were under endoscopy and had positive intestinal biopsy for CD. This dissimilarity seems to be due to immunological factors, high level of gluten diet, and lifestyle (12).

Prati performed a study and reported that 1.9% of the patients who were candidate for heart transplantation had positive tTG compared to 0.37% in the controls. Similar results were also obtained by Curione and Fonager, which is in agreement with the findings of the current investigation (18.42% in the patients and 5.26% in the controls) (13-15).

Frustaci carried out a study on 187 consecutive patients with myocarditis to assess cardiac autoantibodies, tTG-IgA, and anti-endomysial antibodies. Presence of common autoimmune processes against myocardial antigens and small bowel were found in 4% of the patients with myocarditis. Hence, they concluded that immune suppression and a gluten-free diet could be effective in treatment of these patients (16). In the same line, the results of our study performed on the patients with DCM indicated tTG positive values in approximately 18% of the patients. Emilsson also studied 29000 CD patients and 144429 healthy controls who were matched regarding age, sex, and place of residence to evaluate the risk of idiopathic DCM. The results demonstrated a non-significant increase in the risk of DCM in patients with CD compared to their counterparts in the control group (17).

Not et al. also investigated CD and the related comorbidities in patients with DCM (familial and sporadic) and their relatives. The study subjects consisted of 238 patients with DCM, 418 relatives, and 2000 healthy blood donors by anti tTG-IgA), IgG, and Anti-Endomysia Antibodies (AEAs). They came to the conclusion that the prevalence of CD was higher in the patients with DCM compared to their relatives and blood donors (18).

Barrio in a case-report presented that rapid progression of heart failure and DCM that required heart transplantation was associated with CD (19). Generally, it has been accepted that nutritional manifestations of CD will improve after strict elimination of wheat, barley, rye, and oat. Yet, many challenges exist concerning the association between gluten avoidance and reversibility of CD, indicating complete or partial recovery and prevention of progression of cardiomyopathy linked to CD (16, 20-22).

The considerable correlation between CD and DCM could be explained by several reasons. Nutritional deficiencies

and iron deficiency anemia are often seen in both DCM and CD (18). Carnitine deficiency is another common deficiency in patients with CD (23). Indeed, it is more severe in patients with CD and DCM compared to those with isolated DCM (24). The most possible reason for the association between CD and DCM is that both conditions might have inflammatory and autoimmune bases. Chronic inflammation in CD is common whether before or after diagnosis and might manipulate the myocardial function (25). According to the results of our study and those mentioned above, screening for CD may be beneficial in DCM children even without gastrointestinal symptoms. Additionally, gluten-free diet may be effective in treatment of CD and heart failure. Cardiac indices also restore intestinal permeability, allowing adequate assimilation of drugs and micronutrients used in treatment. Therefore, gluten-free diet may minimize the progression of DCM and delay heart failure as well as comorbidities, especially CD (16, 20-22).

5.1. Conclusion

The results of the present study demonstrated a positive association between DCM and CD. Therefore, screening for CD is strongly recommended in children with DCM and other probable comorbidities. Yet, further studies on larger sample sizes are required to confirm the relationship between CD and DCM.

Acknowledgements

There is no acknowledgment.

Authors' Contribution

Noori, Shahramian, and Dehghani designed the study and wrote the manuscript. Bahmanyar, Ataollahi, and Sharafi collected the data. Teimouri analyzed the data.

Funding/Support

There is no funding/support.

Financial Disclosure

There is no financial disclosure.

References

1. Dube C, Rostom A, Sy R, Cranney A, Saloojee N, Garritty C*, et al.* The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. *Gastroenterology*. 2005;**128**(4 Suppl 1):S57-67.
2. Khoshbaten M, Rostami Nejad M, Sharifi N, Fakhari A, Golamnejad M, Hashemi SH*, et al.* Celiac disease in patients with chronic psychiatric disorders. *Gastroenterology and hepatology from bed to bench*. 2012;**5**(2):90-3.
3. Shahramian I, Dehghani SM, Haghighat M, Noori NM, Teimouri A, Sharafi E*, et al.* Serological Evaluation of Celiac Disease in Children with Congenital Heart Defect; A Case Control Study. *Middle East journal of digestive diseases*. 2015;**7**(2):98-103.
4. Shahramian I, Dehghani SM, Haghighat M, Noori NM, Teimouri AR, Sharafi E*, et al.* Serologic evaluation of celiac disease in patients with beta thalassemia major and control. *Gastroenterology and hepatology from bed to bench*. 2015;**8**(2):153-9.
5. Noori N, Shahramian I, Mahjoobifar M, Teymoori A, Shahraki Z. Comparison of calcitonin gene related peptide level between children with dilated cardiomyopathy and control group. *International Cardivascular Research Journal*. 2015;**9**(2):100-5.
6. Noori NM, Mahjoubifard M, Shahramian I, Teimouri A, Jahangirifard A. Comparison between procalcitonin, brain natriuretic peptide, and uric acid in children with cardiomyopathy and controls. *BioMed research international*. 2015;**2015**:510450.
7. Noori NM, Rajaei S. Serum uric acid correlation with echocardiographic indices in children with dilated cardiomyopathy. *The Journal of Tehran University Heart Center*. 2009;**4**(4):230-3.
8. Marriott JB, Goldman JH, Keeling PJ, Baig MK, Dalgleish AG, McKenna WJ. Abnormal cytokine profiles in patients with idiopathic dilated cardiomyopathy and their asymptomatic relatives. *Heart*. 1996;**75**(3):287-90.
9. Felix SB, Staudt A, Landsberger M, Grosse Y, Stangl V, Spielhagen T*, et al.* Removal of cardiodepressant antibodies in dilated cardiomyopathy by immunoadsorption. *Journal of the American College of Cardiology*. 2002;**39**(4):646-52.
10. Mahon NG, Madden BP, Caforio AL, Elliott PM, Haven AJ, Keogh BE*, et al.* Immunohistologic evidence of myocardial disease in apparently healthy relatives of patients with dilated cardiomyopathy. *Journal of the American College of Cardiology*. 2002;**39**(3):455-62.
11. Boskovic A, Kitic I, Prokic D, Stankovic I. Cardiomyopathy associated with celiac disease in childhood. *Case reports in gastrointestinal medicine*. 2012;**2012**:170760.
12. Zahmatkeshan M, Fallahpoor M, Amoozgar H. Prevalence of celiac disease in children with idiopathic dilated cardiomyopathy. *Iranian journal of pediatrics*. 2014;**24**(5):587-92.
13. Curione M, Barbato M, De Biase L, Viola F, Lo Russo L, Cardi E. Prevalence of coeliac disease in idiopathic dilated cardiomyopathy. *Lancet*. 1999;**354**(9174):222-3.
14. Fonager K, Sorensen HT, Norgard B, Thulstrup AM. Cardiomyopathy in Danish patients with coeliac disease. *Lancet*. 1999;**354**(9189):1561.
15. Prati D, Bardella MT, Peracchi M, Porretti L, Cardillo M, Pagliari C*, et al.* High frequency of anti-endomysial reactivity in candidates to heart transplant. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2002;**34**(1):39-43.
16. Frustaci A, Cuoco L, Chimenti C, Pieroni M, Fioravanti G, Gentiloni N*, et al.* Celiac disease associated with autoimmune myocarditis. *Circulation*. 2002;**105**(22):2611-8.
17. Emilsson L, Andersson B, Elfstrom P, Green PH, Ludvigsson JF. Risk of idiopathic dilated cardiomyopathy in 29 000 patients with celiac disease. *Journal of the American Heart Association*. 2012;**1**(3):e001594.
18. Not T, Faleschini E, Tommasini A, Repetto A, Pasotti M, Baldas V*, et al.* Celiac disease in patients with sporadic and inherited cardiomyopathies and in their relatives. *European heart journal*. 2003;**24**(15):1455-61.
19. Barrio JP, Cura G, Ramallo G, Diez M, Vigliano CA, Katus HA*, et al.* Heart transplantation in rapidly progressive end-stage heart failure associated with celiac disease. *BMJ case reports*. 2011;**2011**.
20. Curione M, Barbato M, Viola F, Francia P, De Biase L, Cucchiara S. Idiopathic dilated cardiomyopathy associated with coeliac disease: the effect of a gluten-free diet on cardiac performance. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2002;**34**(12):866-9.
21. Lerner A, Matthias T. Celiac Disease: Intestinal, Heart and Skin Interconnections. *International Journal of Celiac Disease*. 2015;**3**(1):28-30.
22. Winter Del RJ, Gabrielli NL, Greig D, Inchauste G, Quezada F, Torres MJ*, et al.* [Dilated cardiomyopathy in celiac disease: report of one case]. *Revista medica de Chile*. 2009;**137**(11):1469-73.
23. Ciacci C, Peluso G, Iannoni E, Siniscalchi M, Iovino P, Rispo A*, et al.* L-Carnitine in the treatment of fatigue in adult celiac disease patients: a pilot study. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2007;**39**(10):922-8.
24. Curione M, Danese C, Viola F, Di Bona S, Anastasia A, Cugini P*, et al.* Carnitine deficiency in patients with coeliac disease and idiopathic dilated cardiomyopathy. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2005;**15**(4):279-83.
25. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointestinal endoscopy*. 2003;**57**(2):187-91.