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The Prevalence of Celiac Disease in Down syndrome Children with and without Congenital Heart Defects

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Abstract

Background

The prevalence of celiac disease (CD) is remarkably varied in Down syndrome (DS) patients compared with other diseases. This study aimed to assess celiac disease prevalence in Down syndrome children with and without congenital heart defects (CHD) and its comparison with controls.

Materials and Methods

This case-control study was performed at a single center on 132 participants in three groups. Clinical and genetic tests were performed on all patients suspected with Down syndrome to confirm their diseases. After that in patients with confirmed Down syndrome echocardiography was carried out to diagnosis of CHD. Healthy children selected randomly among those who referred to the center for annual check-up. Statistical evaluation was done using SPSS-16.

Results

For the factors of age, weight, height and Body Mass Index (BMI) not observed significant differences between three groups of participants, but it would be observed statistically differences for the variable of tTG- IgA. For variables of weight, tTG- IgA and BMI was observed statistically different in the case and controls. The status of tTG- IgA (normal or <= 20 and abnormal or >20) had significant correlation with three groups of controls, Down syndrome with and without CHD. The status of tTG- IgA also had significant correlation with groups of case and controls. In comparison of tTG- IgA in DS patients with and without CHD, no significant differences were observed.

Conclusion

The prevalence of CD in DS patients was higher compared the controls population; and in DS patients with CHD was higher compared the DS patients without CHD.

Key Words: Celiac disease, Children, Congenital Heart Defect, Down syndrome, Prevalence.

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1- INTRODUCTION

Celiac disease (CD) is a systemic disorder of immune-mediated which is caused by dietary gluten habits in genetically susceptible persons. Gluten is a protein complex found in wheat, and barley. Celiac disease is characterized by a broad range of clinical presentations. It is a long term disease with a prevalence of 1-2% in European population and affects 0.6 to 1.0%, around the world with a wide difference in western countries with unclear reason. The prevalence of CD has been reported of 0.3% in Germany and 2.4% in Finland with a wide range in each (1). Celiac disease is related with increasing of risk of both lymphoma and mortality (2) and recently is increasing in many developing regions such as North Africa (3) and the Middle East (4), because of strong changes in diet due to changes in wheat production and preparation and increased awareness of the disease. Accordance with many studies could be said that the prevalence of CD of women is higher about 1.5 to 2 folds than men (1). In the last decades, CD was presumed to be rare because of low awareness and a low index of suspicion in Iran.

In Iranian population the major staple diet is wheat and barley production about 95% of the rural and 85% of the urban especially in the Southeastern area and according to information from the Iran Ministry of Agriculture, the per capita consumption of wheat by Iranian people is 160 kg per year, which seems much more than the world average and this will rank Iranian as one of the top wheat consuming populations in the world (5).
Nonetheless, CD was considered uncommon in Iran until a decade ago, but following the application of simple serological tests for diagnosis of CD in the Europe countries, several studies have been conducted on the prevalence of CD because of its importance(6).

The prevalence of CD are varied in different subgroups population and patients with various diseases so that this prevalence ranged from 0.5% among schizophrenia patients to 12% in patients with irritable bowel syndrome (IBS) (5).

Recent screening studies performed in the general population and at-risk groups in different geographical areas in Iran with a large consumption of wheat have shown that the prevalence of gluten sensitivity is similar to that of Western countries. However, there might be a different prevalence of CD between the Northern versus the Southern areas in Iran, because of higher level of wheat consumption in south (6). In India, celiac disease was mainly observed in the Northwestern part, where wheat was a staple food of the inhabitants (7), and in china, has been observed in children with chronic diarrhea (8). There is a high different in CD prevalence in patients with other diseases. Celiac disease increases among individuals who have affected in first-degree relative (10 to 15%), type I diabetes (3 to 16%), Hashimoto's thyroiditis (5%) or other autoimmune diseases (including autoimmune liver diseases, Sjogren's syndrome, and immunoglobulin A [IgA] nephropathy), Down's syndrome (0 to 19%) , Turner's syndrome (3%), and IgA deficiency (9%)(1).

Shahramian has reported that the prevalence of CD in diseases of thalassemia (11.5%) were versus controls (3.5%), and CHD 18.41% versus controls (7.35%) (9, 10). Down syndrome (DS) is the most common chromosomal disorder and occurs in approximately 1 out of every 800 livebirths (or 12.8 per 10,000 livebirths) in the United States (1, 11). Children with DS have typical dysmorphic features and cognitive impairment. They are known to be shorter than their normal counterparts and may suffer a multitude of debilitating problems, including congenital heart disease, gastrointestinal anomalies,

leukemia, Alzheimer's disease, immune dysfunction, hypothyroidism, diabetes mellitus, and vision and hearing problems (1, 11). Celiac disease is characterized by delayed psychomotor development and accounts for 8% of all registered cases of congenital anomalies (11, 12). Recent decades have seen a substantial increase in the life expectancy of children with DS. This has been due in majority to the successful early surgical treatment of congenital heart disease (13) and the improvement of treatment of congenital anomalies of the gastrointestinal tract (14). Preventive health care programs for these children also have contributed to improved overall outcome and quality of life (15). In approximate, many countries do not have national guidelines for CD screening in DS or DS patients with CHD.

Patients with DS are advised to have high awareness and refer to do a serology test for CD in regards to the presence of clinical features (16). Multiple comorbidities can compromise quality of life for individuals with DS. Prevalent conditions in children with DS include dysmorphic features of the head and neck, congenital heart defects, gastrointestinal defects, celiac disease, seizures, hematologic disorders, thyroid disease, intellectual disability, emotional and behavioral disorders and autism (17). This study was originally designed to identify the prevalence of CD in DS patients with and without CHD and comparison with controls in the city of Zahedan, the province of Sistan and Baluchestan, Iran.

2- MATERIALS AND METHODS

2-1. Study Design and Population

This case-control study was performed in Zahedan University of Medical Sciences' (ZaUMS) hospitals located in the city of Zahedan, South East of Iran, with collaboration of gastroenterology and cardiology clinics. The study conducted on 132 participants with the distribution of 88, 24 and 20 for control, Down syndrome with CHD and Down syndrome without CHD patients respectively.

All Down syndrome patients who have had referred to Ali Asghar and Ali-ebne-Abitalib hospitals of ZaUMS, from Jan 2014 to Dec 2015 entered to the study. Among these 44 DS patients, 24 had CHD. Healthy children selected randomly among those who referred to the centers for annual check-up. The participant's age was ranged from 1 to 18 years.

2-2. Methods

Clinical and genetic tests were performed on all patients suspected with Down syndrome to confirm their diseases. After that in patients with confirmed Down syndrome echocardiography was carried out to diagnose CHD.

2-3. Measuring tests

Children over 2 years old were weighted using RASA Mark made in Islamic Republic of Iran by an error level of 100 gr, while those under 2 years old were weighted by MIKA Mark recumbent weighting scale made in Japan by an error level of 10 gr. In addition, the heights of under 2-year-old children were measured in the recumbent position by using a flat wooden calibration table, while that of the children above 2 years old were measured in the standing position with a scale ruler (10). Body mass index (BMI) was calculated in dividing a person's weight in kilograms by the square of height in meters and categorized in three main groups of underweight (<18.5), healthy (18.5-25) and Overweight (>25) (18).

Venipuncture conditions were similar for all samples using sterile catheters in blue color made of Supa factory. Venipuncture site sterilized by cotton soaked with 70% alcohol. Three ml blood was taken from the children that were in fast at 8:00 am in the position of supine by fixed and skillful nurse in each center from hand's vein.

Samples were centrifuged and separated serum was kept in a -70°C. Then the samples were transported to the biochemistry laboratory, University of Medical Sciences, Zahedan under the cold chain compliance. Finally, 250 microns of the isolated serum of these samples were used for serologic tests with recombinant ELISA to measure tissue transglutaminase (tTG)- IgA. Normal limit of tTG- IgA was 20 U/ml (19).

2-4. Exclusion criteria

Exclusion criteria were IgA deficiency, history of digestive diseases, endocrine, metabolic disorders, iron deficiency, kidney disease and fever**.**

2-5. Ethical considerations

Informed consent was obtained from the parents of all participants before inclusion in the study. The investigation approved by the Research Deputy'(RD) ethics committee of the ZaUMS.

2-6. Data analyses

Statistical evaluation was done using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used for variables normality. Permanent variables were described as mean ± standard deviation (SD) or median (interquartile range), and nominal variables were expressed as number of patients and percentages. To compare the groups, data analysis was performed using non parametric Mann-Whitney U, Kruskal-Wallis test and crosstabs contingency coefficient. Significance level of $P<0.05$ was considered.

3- RESULTS

The present study conducted on 132 participants with distribution of 88, 24 and 20 of control, down with CHD and down without CHD respectively. In the other view could be divided in control and case groups with 88 and 44 participants respectively. The sex ratio of participants was 54(40.9%) and 78(59.1%). Out of 88 participants in the control group, 48.9% were males when the trends of male distribution for down patients with CHD and down patients without CHD were 33.3% and 15% respectively. Accordance with one-sample Kolmogorov–Smirnov test (K–S test or KS test), all study variables had not normal distribution ($P<0.05$). Means age of participants were 7.19 ± 3.04, 7.854 ± 4.432 and 7.30 ±3.891 for control, down with CHD and down without CHD respectively.

Table.1 showed the results of Kruskal-Wallis test for main variables of the study. For the variables of age (P=0.817), weight (P=0.086), height (P=0.177) and BMI (P=0.086), not observed significant differences between groups of participants, but it was observed statistically differences for the variable of tTG- IgA (P= 0.000).

Table.2 showed the results of Mann-Whitney U test for the main variables of the study. The table revealed that the values of the variables of weight (Mann-Whitney U= 1530.5, P= 0.050), tTG- IgA (Mann-Whitney U= 1090, P= 0.000), and BMI (Mann-Whitney U= 1530.5, $P<0.05$) were statistically different in the case and controls.

Table.3 showed the results of correlation between tTG- IgA status (normal or <= 20 and abnormal or >20) and groups of participants, case-control, gender and BMI. The frequency distribution of participants in different status of tTG- IgA were different significantly and showed an association between 3-groups- participants namely control, down with CHD and down without CHD (Contingency Coefficient= 0.332, P=0.000) two groups participant (Contingency Coefficient= 0.331, P= 0.000) and gender (Contingency Coefficient = 0.264 , P= 0.004).

Table.4 showed the results of no significant correlation between tTG- IgA

status and some categorical variables in the study for the patients. The frequency distribution of patients (with and without CHD) in different status of tTG- IgA showed no significant association of status of tTG- IgA with groups of patients, gender and the level of BMI (P > 0.05).

Table-1: Differences of anthropometric indices, age and tTG- IgA in participants who belonged to the different groups

Variables	Groups	N	Mean	SD	Mean Rank	Chi-square	P-value
Age (year)	Control	88	7.119	3.0400	65.43	0.405	0.817
	Down with CHD	24	7.854	4.4318	70.96		
	Down without CHD	20	7.300	3.8913	65.88		
	Total	132	7.280	3.4438			
Weight (kg)	Control	88	22.495	8.9277	71.11	4.906	0.086
	Down with CHD	24	17.583	8.1075	51.85		
	Down without CHD	20	20.150	7.5221	63.80		
	Total	132	21.247	8.7390			
Height (cm)	Control	88	115.03	15.379	70.79	3.463	0.177
	Down with CHD	24	106.08	20.100	55.98		
	Down without CHD	20	108.50	17.969	60.25		
	Total	132	112.42	17.004			
tTG- IgA (U/ml)	Control	88	12.622	32.3772	19.729	19.729	0.000
	Down with CHD	24	56.587	85.1993	94.88		
	Down without CHD	20	14.505	21.7058	74.75		
	Total	132	20.901	48.2140			
BMI	Control	88	22.495	8.9276	71.11	4.906	0.086
	Down with CHD	24	17.583	8.1075	51.85		
	Down without CHD	20	20.150	7.5220	63.80		
	Total	132	21.247	8.7389			

Table-2: Differences of anthropometric indices, age and tTG- IgA in case and controls

Variables	Groups	N	Mean	SD	Mean Rank	Sum of Ranks	Mann-Whitney U	P- value
Age (year)	Control	88	7.119	3.0400	65.43	5757.50	1841.5	0.646
	Case	44	7.602	4.1562	68.65	3020.50		
Weight (kg)	Control	88	22.495	8.9277	71.11	6257.50	1530.5	0.050
	Case	44	18.750	7.8633	57.28	2520.50		
Height (cm)	Control	88	115.03	15.379	70.79	6229.50	1558.5	0.068
	Case	44	107.18	18.980	57.92	2548.50		
tTG –IgA (U/ml)	Control	88	12.6227	32.37729	56.89	5006.00	1090	0.000
	Case	44	37.4591	67.38066	85.73	3772.00		
BMI	Control	88	22.4955	8.92768	71.11	6257.50	1530.5	0.050
	Case	44	18.7500	7.86329	57.28	2520.50		

Table-3: The correlation of tTG- IgA status with groups of participants, case-control, gender and BMI

Variables	Categorize	Statistics	tTG- IgA			Contingency Coefficient	P-value
			<=20 (Normal)	>20 (Abnormal)	Total		
Groups of participants	Control	n	83	5	88	0.332	0.000
		%	94.3	5.7	100.0		
	Down with CHD	n	16	8	24		
		%	66.7	33.3	100.0		
	Down without CHD	n	14	6	20		
		%	70.0	30.0	100.0		
	Total	n	113	19	132		
		%	85.6	14.4	100.0		
Case-control	Control	n	83	5	88	0.331	0.000
		%	94.3	5.7	100.0		
	Case	n	30	14	44		
		%	68.2	31.8	100.0		
	Total	n	113	19	132		
		%	85.6	14.4	100.0		
Gender	Male	n	52	2	54	0.264	0.004
		%	96.3	3.7	100.0		
	Female	n	61	17	78		
		%	78.2	21.8	100.0		
	Total	n	113	19	132		
		%	85.6	14.4	100.0		
BMI	underweight(<18.5)	n	46	7	53	0.035	0.923
		%	86.8	13.2	100.0		
	healthy(18.5-25)	n	31	6	37		
		%	83.8	16.2	100.0		
	Overweight(>25)	n	36	6	42		
		%	85.7	14.3	100.0		
	Total	n	113	19	132		
		%	85.6	14.4	100.0		

Table-4: The correlation between tTG IgA status and groups of patients (DS with and without CHD), gender and BMI

Variables	Categorize statistics	Statistics	tTG- IgA			Contingency Coefficient	P-value
			<=20 (Normal)	>20 (Abnormal)	total		
Groups of patients	Down with CHD	n	16	8	24	0.036	0.813
		%	66.7	33.3	100.		
	Down without CHD	n	14	6	20		
		%	70	30	100		
	Total	n	30	14	44		
		%	68.2	31.8	100		

Gender	Male	n	10	1	11	0.271	0.062
		%	90.9	9.1	100		
	Female	n	20	13	33		
		%	60.6	39.4	100		
	Total	n	30	14	44		
		%	68.2	31.8	100		
BMI	Underweight (<18.5)	n	17	5	22	0.208	0.370
		%	77.3	22.7	100		
	Healthy (18.5-25)	n	3	3	6		
		%	50.0	50.0	100.0		
	Overweight (>25)	n	10	6	16		
		%	62.5	37.5	100.0		
	Total	n	30	14	44		
		%	68.2	31.8	100		

4- DISCUSSION

The results of the study showed that variables of age, weight, height and BMI had not significant differences in participants, but tTG- IgA had significant differences. Mean weight, mean tTG- IgA and mean BMI were different between case and controls. Serum tTG- IgA level for all participants in the case of control, DS with CHD and DS without CHD, in the case of patients and controls and gender had significant correlation.

More than half of our patients with Down syndrome had heart disease with the proportion of 54.55%. Several studies reported the prevalence of CD in general population who were under blood donor in various areas of Iran such as Shiraz (0.5%), Kerman (1.18%) and Sari (0.9%) (20); and abroad area such as North of India (0.32%), Africa (5%) (7), Germany (0.3%) and Finland (2.4%).

We resulted the celiac prevalence of 5.7% in general population that was higher from all the regions. Also, the differences may are be due to higher age structure for blood donors for other studies and wheat dietary for our area. In a review study by Rostami Nejad reported that some of population groups with various diseases are most at risk in CD such as Chronic diarrhea (6.5-20%), Inflammatory bowel disease (7.8%), Autoimmune hepatitis (3.6-10%), Type-1 diabetes mellitus (2.4%) and Iron deficiency anemia of unknown origin (14.6%) in children. This survey did not report any prevalence for Down syndrome and CHD (6).

Children with DS are at increasing risks for complications beyond usual childhood and are at high risk for many growth disorders such as celiac disease and hypothyroidism (21).

More recently, efforts have been made to evaluate the prevalence of CD in DS patients. Therefore, similarly with our findings related study has led to the conclusion that CD is significantly more frequent in DS patients than in the general population (22).

Korkmaz, Stordal, Roizen and Ciccocioppo operated different studies in different areas with the prevalence of 3-18% of children with DS had CD (12, 23-25). We resulted that the prevalence of CD in our DS patients was 31.8% compared with controls (5.7%). This showed that the prevalence of CD in our DS patients was much higher than mentioned results. It would be seemed that the increase was due to CHD for many DS patients and wheat-dietary in our study.

In the present study the prevalence of heart diseases in DS patients resulted as 55% in which was similar with Roizen report that concluded 55% (26). In the Boskovic study various reports have been observed in cardiomyopathy association with celiac disease in childhood and a range of 1.9% to 5.8% were reported for prevalence of CD in patients with idiopathic dilated cardiomyopathy (27). Frustaci reported a greater prevalence than 4% of celiac in patients with myocarditis (28). Shahramian received to the conclusion of CD prevalence in CHD patients that was 2.5 times more than controls that is lower than our study (10). Our results of data analysis in three groups of participants (control, DS with CHD and DS without CHD) found a higher prevalence of CD for DS patients with CHD compared with patients without CHD; and both types patients (DS with CHD and DS without CHD) had higher prevalence than controls significantly. Accordance with our results, the prevalence of CD in DS patients with CHD (33.3%) was a little higher but not significant than patients without CHD (30.0%).

In many studies have been suggested that CD associated with cardiomyopathy (left ventricular systolic and diastolic dysfunction). One of the possible suggestions is chronic malabsorption, which is frequent in CD that is a reason for nutritional deficits and leading to cardiomyopathy. The next suggestion could be intestinal absorption abnormalities that may be caused by infectious agents and antigens, which causes immune mechanisms that was could be a reason of myocardial damage. Sari reported that the cardiac involvement may be is the direct immune response that occurs both in the myocardium and small intestine and may be is a cause of myocardial damage and chronic malabsorption (29).

Body mass index is the best growth marker for all population even for its subgroup such as patients with DS, CD and CHD. In the present study we achieved that height and weight of healthy ones were similar in patients with Down syndrome and patients with DS and CHD. Slight difference was observed for weight in comparison of healthy group and DS patients regardless of CHD comorbidity. Aburawi, Afifi and Su reported that patients with DS had lower weight and height compared with controls (30-32). In compared with our findings, mean weight had similar results with three late studies.

4-1. Limitations of the study

The study was conducted in two years and within this duration 44 patients with DS diagnosed and the low number of patients was the limitation of the study.

5. CONCLUSION

We tried to find the prevalence of celiac disease in Down syndrome patients along with congenital heart defect, and we found that the prevalence of celiac disease in Down syndrome patients was higher compared the controls population. Also, resulted that among Down syndrome patients those who had congenital heart defect were more in celiac disease at risk. Recommended that with regarding to high prevalence of celiac disease in Down syndrome patients, these patients screened for celiac disease with tTG- IgA specially-in patients with congenital heart defect.

6- CONFLICT OF INTEREST: None.

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