

## Serological Evaluation of Celiac Disease in Children with Congenital Heart Defect; A Case Control Study

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### ABSTRACT

#### BACKGROUND

Due to the increased prevalence of celiac disease in chromosomal anomalies and other congenital anomalies, this study was conducted to evaluate the seroprevalence of celiac disease (CD) in patients with congenital heart defects (CHD).

#### METHODS

This case-control study was done on 1002 children in two groups of CHD patients (n=402) and controls (n=600). The serum tissue transglutaminase (TTG) levels were investigated. The two groups were compared in terms of TTG IgA levels and  $p < 0.05$  was considered as the significant level.

#### RESULTS

The means of serum TTG IgA levels in children with CHD and the control groups were  $19.17 \pm 46.67$  and  $7.77 \pm 10.02$  u/mL respectively ( $p = 0.001$ ). After ANOVA analysis a significant difference between two cyanotic and acyanotic subgroups of cases and control groups was observed ( $p = 0.000$ ). The follow up tukey test showed only non-significant difference between the cyanotic and acyanotic cases. The frequency of TTG IgA with the consideration of 20 u/mL as cut-off point showed a significant association with groups ( $X^2 = 28.31$  and  $p = 0.000$ ).

#### CONCLUSION

According to the results the serum TTG IgA levels were significantly higher in patients with CHD than normal children and screening for CD in children with CHD is recommended.

#### KEYWORDS

Celiac disease; Congenital; Heart Defect; Children

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### INTRODUCTION

Congenital heart diseases (CHD) are principal causes of death dur-

ing the first year of life. They occur in about 8 of 1000 live births.<sup>1</sup> CHD are caused by defects or malformations in one or more structures of the heart or blood vessels that occur during the 3-8 weeks of the first trimester of pregnancy when the heart is being formed.<sup>2</sup> Also, there is an association between CHD, malnutrition, and growth retardation among children. Such patients are prone to malnutrition for several reasons such as decreased energy intake, increased energy requirements, or both.<sup>2</sup> Clinically, cachexia is a process of losing weight, which is different from malnutrition and anorexia. End-stage of congestive heart failure (CHF) is cardiac cachexia. If cardiac cachexia is diagnosed late or inaccurately, it can ultimately lead to decreased blood flow to the skeletal muscle and finally to deteriorating endothelial vascular function.<sup>2,3</sup>

There is an increased risk for celiac disease (CD) in various conditions and these associations are on the basis of similar autoimmune mechanism or genetic defects in similar accountable genes.<sup>4</sup> It is open to debate that CHD have an association with an increased risk of CD. Celiac disease is recognized as a common genetic disorder in Europe and Asia pacific region with a prevalence of 2.67%. Similar to Western countries a high prevalence of CD has been reported in Iranian general population (about 1%).<sup>5</sup> Celiac disease as an elevated risk in a clinical varied spectrum has a relationship with multiple congenital anomalies such as face, neck, ear, heart or digestive tract.<sup>6</sup> MCNeish and Anderson have reported this probable association by presenting two children with celiac disease and coarctation of aorta.<sup>7</sup> Some issues support the possible association between CHD and CD.<sup>6,8,9</sup> The abnormal immunological profiles of both cellular and humoral immune system in CD similar to CHD has a genetic basis.<sup>10</sup> Additionally, CD is similar to CHD in showing a higher prevalence of some chromosomal disorders such as Down syndrome.<sup>4</sup> Celiac disease might be common in patients with CHD because of mother and infant' separation in which caused an impractical issue in breastfeeding. Moreover, patients with CHD commonly fail to thrive, which impacted in early cereal feeding that can be considered as a logical reason for devel-

oping CD.<sup>9</sup> Endothelial damages due to CHD can be a way for gluten to be exposed to immune system for initiating CD process in susceptible patients.<sup>10</sup> Measurement of TTG IgA is a test of choice for screening CD with specificity higher than 95%.<sup>11,12</sup> Having considered this fact that a comprehensive study on this issue has not been yet done in this area of Iran, the present study was done with the objective of serological screening of CD in patients with CHD by anti-TTG IgA measurement.

## MATERIALS AND METHODS

In this case-control study, which was done during 2008-2013, 402 children with final diagnosis of CHD (149 patients with cyanotic and 253 with acyanotic types) aged from 1 to 16 years and 600 children for control group who were selected randomly from apparently healthy children referring for annual medical investigations were included. The control group did not have history and physical examination compatible with CHD and were matched with CHD patients in terms of age and sex. All the patients underwent physical examination and their medical history was taken. Besides, chest radiography, electrocardiography, and echocardiography were performed for diagnosis of CHD. Total TTG IgA levels were measured for all participants and those with TTG IgA deficiency were excluded. Every patient was diagnosed through echocardiography and classified in two cyanotic and acyanotic groups by arterial blood gas and the control group had no cardiac involvement.

In both groups, there were no history of digestive, endocrine, metabolic disorders, anemia, iron deficiency, kidney disease, fever, and chronic diseases. They were enrolled after obtaining informed consent forms from their parents.

Five mL blood was drawn from each child before breakfast at 8:00 am. The samples were centrifuged at 3000 g for 10 minutes at 5° C. The separated sera were held in a -70° C fridge until Anti-TTG IgA measurements. Finally, they were transferred to the Laboratory of Biochemistry under the cold chain compliance, in Zahedan University of Medical Sci-

ences. Then, using 250 microns of the isolated sera, the Anti-TTG IgA serum levels were measured by ELISA (ORGENTEC Diagnostika GmbH, Mainz, Deutschland and humanity type) and the levels higher than 20 ng/mL was considered as positive for CD.

In this study, children over 2 years old were weighted using RASA Mark made in Islamic Republic of Iran by an error factor of 100 gr, while those under 2 years old were weighted by MIKA Mark recumbent weighting scale made in Japan by an error factor 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. Finally for head circumferences a tape in cm scale was used. Required data were collected and analyzed using SPSS 20. Analytical and descriptive statistics, ANOVA for three groups in comparison, and independent t tests were used as appropriated.  $p < 0.05$  was considered as statistically significant.

## RESULTS

A total of 1002 children were enrolled, 402 children (case group) had CHD and 600 were healthy children (control group). The sex distribution of patients with CHD was 235 (62.2%) male and 167 (37.7%) female children. There were also 324 (54%) male and 276 (46%) female children in the control group. There was no significant difference between the two groups ( $p = 0.085$ ) in terms of sex distribution. Our findings based on ANOVA and independent t tests showed no significant difference in age among three groups of participants ( $F = 0.098$ ,  $p = 0.906$ ) as well for two case and control groups ( $t = -0.24$ ,  $p = 0.81$ ).

Our findings reported in tables 1 and 2 show that all factors of weight (kg), height, and head circumference (cm) along with TTG IgA levels have statistical significance when our consideration are focused on three groups (table 1). After changing our concentration only on groups of case and control, same results with a little difference are observed.

Mean TTG IgA levels in patients and controls show a significant difference ( $t = -5.79$ ,  $p = 0.001$ , table 2). According to the type of CHD (cyanotic and acyanotic) needed to be reported that what type of patients have significant difference with the control group. The follow-up tukey test shows that for all the factors except age, both types of patients in the case group, cyanotic and acyanotic ones have significant difference with the controls. Forty four patients (11%) and 20 (3.50%) healthy children had positive serological levels for CD, which showed a statistically significant difference ( $p = 0.001$ , table 3). Figure 1 shows the frequency distribution of congenital heart disease for our case group. According to the figure most of our patients suffered from ventricular septal defect (VSD) (117), followed by tetralogy of fallot (TF) (72), patent ductus arteriosus (PDA) (42), and atrial septal defect (ASD) (34). The other CHDs are atrioventricular septal defect (AVSD) (32), double outlet right ventricle (DORV) (25), pulmonary stenosis (PS) (18), transposition of great arteries (TGA) (14), total anomalous pulmonary venous connection (TAPVC) (14), single ventricle (SV) (8), coarctation of C (CoA) (6), tricuspid atresia (TA) (5), aortic stenosis (AS) (5) and others (10).

## DISCUSSION

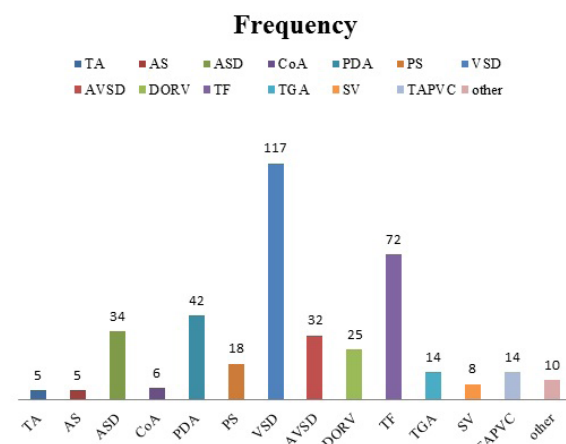
This study showed a significant increase in serum TTG IgA level in patients with CHD in comparison with the healthy children. Seropositivity for CD in CHD groups was 11% that was significantly different from the control group with prevalence of 3.5% ( $p = 0.001$ ). There was a male dominance in all groups, resembling Wingren's study, which showed that male sex was an intense risk factor for CD and congenital anomalies.<sup>6</sup> Also, there were considerable differences between the case and control groups in terms of height and head circumference, denoting that failure to thrive (FTT) in patients with CHD might be due to various causes such as the effects of cardiac defect, severity of cardiac involvement, respiratory infections, chromosomal abnormalities, and perhaps CD.<sup>9</sup> Celiac disease is frequently ob-

**Table 1:** ANOVA test for demographic factors in the control and two cases groups

Factor	Groups	Mean	S.D	95% CI		F	p
				LB	UB		
Age(month)	Control	43.33	41.76	39.98	46.67	0.098	0.906
	Cyanotic	43.81	40.86	37.19	50.42		
	Acyanotic	42.11	44.06	36.65	47.58		
	Total	43.09	42.18	40.48	45.71		
Weight(kg)	Control	14.42	8.96	13.72	15.11	18.64	<0.001
	Cyanotic	11.15	5.97	10.18	12.12		
	Acyanotic	11.42	6.74	10.58	12.56		
	Total	13.17	8.02	12.67	13.67		
Height(cm)	Control	91.90	24.91	89.90	93.90	7.601	0.001
	Cyanotic	84.55	22.83	80.85	88.25		
	Acyanotic	86.72	24.02	83.75	89.69		
	Total	89.49	24.55	87.96	91.01		
Head circumference(cm)	Control	47.78	4.92	47.38	48.17	4.497	0.009
	Cyanotic	46.69	5.03	45.88	47.50		
	Acyanotic	46.86	5.12	46.22	47.49		
	Total	47.38	5.01	47.07	47.69		
Serum TTG IgA(Iu/ml)	Control	7.77	10.02	6.97	8.58	18.73	<0.001
	Cyanotic	15.27	21.42	11.80	18.74		
	Acyanotic	21.46	56.41	14.48	28.45		
	Total	12.34	31.04	10.42	14.27		

**Table 2:** Independent t test for demographic factors in the control and case groups

Factor	Diag2	Mean	SD	t	p
Weight	Case	11.32	6.46	-6.11	<0.001
	Control	14.42	8.70		
TTG (IgA)	Case	19.17	46.67	5.78	<0.001
	Control	7.78	10.02		
Height	Case	85.92	23.58	-3.81	<0.001
	Control	91.92	24.92		
Head	Case	46.80	5.09	-3.04	0.002
	Control	47.78	4.93		
Age	Case	42.74	42.85	-0.24	0.81
	Control	43.40	41.76		



**Fig. 1:** Distribution frequency of congenital heart disease

served with genetic disorder with the prevalence of 2.67% in general population and the characteristic immunologic response to gluten that might be silent.<sup>5</sup> Seroprevalence of CD in control group of this study was 3.5% that is higher than other studies reported in Iran like a study conducted in healthy blood donors showing a prevalence of 0.6%.<sup>13</sup> In

another study, prevalence of 0.55 for occult CD in schoolchildren in Tehran was reported.<sup>14</sup> This difference between our and other studies might be due to early cereal introduction to infant diets in this area. Patients with thyroid and Addison diseases, pernicious anemia, autoimmune thrombocytopenia, sarcoidosis, insulin dependent diabetes mellitus,

**Table 3: Distribution of serum TTG IgA according to the cut-off point of 20**

Groups	Statistics	TTG		Total	x <sup>2</sup>	p
		< 20 (Negative)	≥20 (Positive)			
Control	f	580	20	600	28.42	0.001
	%	92.65	7.35			
Case	f	391	44	402		
	%	81.59	18.41			
Total	f	883.00	118.00	1001		
	%	88.21	11.79			

alopecia, and cardiomyopathies have higher risk of celiac disease than normal population. Down, Turners, and Williams syndromes have shown increased prevalence of CD as well.<sup>4</sup> In the study conducted by Wingren in Sweden during 1987-1993, CHD was one of the most common congenital anomalies accompanied by celiac disease.<sup>6</sup> In two cases with coarctation of aorta reported by McNeish and Anderson, association between CHD and CD was stated.<sup>7</sup> Similarly, Maniram Kumhar reported this relationship.<sup>15</sup> Frustaci showed a higher risk of CD in patients with idiopathic congestive heart failure and concluded a potential association between inflammatory myocardial injury and autoimmunity.<sup>16</sup> Additionally, several reports have suggested that both CD and idiopathic dilated cardiomyopathy have an immune process with respect to the heart and intestine.<sup>17,18</sup> Polat showed subclinical systolic dysfunction of the left ventricle by Doppler echocardiography in patients suffering from CD.<sup>9</sup> Likewise, Lionetti showed lower contractility indexes in cases with CD.<sup>19</sup> An up-regulation of mRNA for TTg and probable association between TTG and cardiac damage has been stated.<sup>20,21</sup> Celiac disease bears a close resemblance to CHD in reversal CD4+/CD8+ ratios. Also there is an abnormality in humoral and cellular immune system. And both of them are similar in complicating the protein losing enteropathy. An intestinal inflammatory process might be attributed to the pathophysiology of CD in children with CHD.<sup>10</sup>

This study revealed the greater prevalence of CD in patients with CHD. Screening for CD in children with congenital cardiac defects is suggested. And

also complementary investigations such as taking biopsy samples seem logical.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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