Postural Orthostatic Tachycardia Syndrome in Pediatric Patients with Celiac Disease and Relationship with Tissue Transglutaminase Antibody Levels and HLA Tissue Group

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Abstract

Introduction: Celiac disease is an autoimmune disease triggered by gluten in cereals. Many other system involvements may occur in Celiac disease. One of them is the autonomic nervous system. The role of autoimmunity in the etiology of postural orthostatic tachycardia syndrome (POTS) is also discussed recently. In this study, we aimed to investigate the presence of POTS and its relationship with serum antibody levels and HLA tissue group in patients with newly diagnosed Celiac disease and gluten-free diet not yet started.

Methods: Active standing test was applied to patients with the Celiac disease with orthostatic symptoms. POTS diagnosis was made for those who had orthostatic complaints for six months and who were found to be positive for the active standing test and who have not systemic disease and anemia.

Results: POTS positivity was found in 16 patients (34%) out of 47 patients who met the inclusion criteria. In POTS positive patients, female gender (62.5%) was higher than male gender (37.5) (p=0.023). POTS was positive in 13 (41%) of 31 patients with anti-Tg IgA levels above 200 U/ml and POTS positive in three (18%) of 16 patients with anti-Tg IgA levels below 200 U/ml (p=0.04). Twenty-one patients had HLADQ2, four patients had HLADQ8, 15 patients had HLADQ2 and HLADQ8 positivity. Out of the 15 patients who were found to be HLADQ2 and HLADQ8 positive, nine patients (65%) were POTS positive, out of the 21 patients who were found to be HLADQ2 positive, seven patients had POTS positivity (33%) (p=0.04).

Discussion and Conclusion: In our study, we showed that POTS frequency increased with an increase in the Anti-Tg IgA level and HLADQ2 and DQ8 association. This supports that POTS is an autoimmune disease. The presence of POTS should be kept in mind in the presence of orthostatic symptoms in pediatric celiac disease.

Keywords: Anti-Tg IgA; celiac disease; HLA; postural orthostatic tachycardia syndrome.

Celiac disease (CD) is an autoimmune enteropathy that occurs in the presence of genetic predisposition against gluten and gluten-related prolamines found in grains, such as wheat, rye, barley. Although its true prevalence is not known exactly, in a screening study all over Turkey performed by Dalgiç et al., serological positivity rates were reported as 1/94, and biopsy-proven celiac disease was reported as 1/212 in the 6-17 age range. Malabsorption, which is characteristic of CD, and related gastrointestinal symptoms are well-defined. Due to the underlying autoimmunity in CD, intestinal system involvement and related symptoms can also be seen. The mode of the
emergence of CD has changed over the years, besides the typical symptoms associated with malabsorption, findings not related to the gastrointestinal system have also become more common in the course of the disease[4]. Articles about autonomic nervous system involvement in pediatric Celiac patients[5]. Postural orthostatic tachycardia (POTS) is an indicator of autonomic dysfunction. In our study, the relationship between postural orthostatic tachycardia (POTS) and tissue group, tissue transglutaminase IgA levels were evaluated in pediatric newly diagnosed CD patients who had not yet started a gluten-free diet (GFD).

Materials and Methods

Fifty-eight patients (24 boys, 34 girls) who were diagnosed with CD based on esophagogastroduodenoscopic and histopathological evaluation and had not yet started a gluten-free diet (GFD) were included in this study. All patients were evaluated by 12-lead electrocardiography and echocardiography. The criteria for exclusion from this study were the use of medication, the presence of anemia, thyroid dysfunction, rhythm disturbance, additional systemic or cardiac disease, presence of orthostatic hypotension (low blood pressure in the standing systolic BP/diastolic BP more than 20/10 mmHg), failure to meet diagnostic criteria of POTS. Patients with hypothyroidism (n=3), diabetes mellitus (n=2), Down syndrome and VSD (n=2), and those with serum Hb levels below 10 g/dl (n=4) were excluded from this study.

Forty-seven patients included in this study were grouped according to their tissue groups (HLA-DQ2, HLA-DQ8), histopathological staging and tissue transglutaminase IgA (Anti-Tg IgA) levels. Among these patients, 28 patients with orthostatic symptoms, such as palpitations, chest pain or discomfort, dizziness, blurred vision, shortness of breath, headache, nausea, and fatigue, were applied for the last six months underwent the active standing test.

Blood pressure was measured in a horizontal position and standing position with an automatic sphygmomanometer. After resting for five minutes in the supine position, patients were evaluated at 0, 1, 3, 5, 10 minutes while standing, synchronized with electrocardiographic monitoring of heart rate.

When changing from horizontal position to vertical position, the test was considered positive if the heart rate increased 40/minute or the heart rate exceeded 120/minute within the first 10 minutes without any drop in systolic/diastolic blood pressure more than 20/10 mmHg[6]. In the last six months, patients with orthostatic symptoms, without orthostatic hypotension (blood pressure dropping more than 20/10 mmHg in standing position) and meeting the criteria for POTS with the active standing test were diagnosed as POTS[7]. Informed consent was obtained from all patients. This study was approved by the ethics committee of Umamiye Training and Research Hospital.

Statistical Analysis

SPSS 22 software package (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to determine the normality of distribution. Data were expressed as numbers and percentages (%). A Chi-square test was used to compare the groups. P<0.05 was accepted as the level for statistical significance.

Results

POTS positivity was detected in 16 (34%) out of 47 patients included in this study. The mean age of the patients was 14.3±2.8. Among POTS- positive cases, female patients (10/16; 62.5%) were greater in number than male patients (6/16; 37.5) (p=0.023). POTS positivity was detected in 13 (41%) of 31 patients with anti-Tg IgA levels above 200 U/ml and in three (18%) of 16 patients with anti-Tg IgA levels below 200 U/ml. The frequency of POTS was found to be increased in patients with anti-Tg IgA levels above 200 U/ml (p=0.04).

A positive correlation was found between the anti-Tg IgA levels and the heart rate at the 2nd and 5th minutes of the tests in POTS- positive patients (r=0.62, p=0.001; r=0.60, p=0.001). Twenty-one patients had HLADQ2, four patients had HLADQ8, 15 patients had HLADQ2 and HLADQ8- positivity. HLA tissue results of seven patients could not be obtained. Out of the15 patients who were found to be HLADQ2 and HLADQ8 positive, nine patients (65%) were POTS positive, out of the 21 patients who were found to be HLADQ2 positive, seven patients had POTS positivity (33%) (p=0.04) (Table 1).

| Table 1. Number of POTS positive and POTS negative patients and distribution of the patient numbers according to HLA tissue groups and levels of Anti-Tg IgA |
|-----------------|-----------------|-----------------|-----------------|
| POTS (+)        | POTS (-)        |
| Anti-Tg IgA <200 U/ml, % | 3/16 (18)       | 13/16 (81)      |
| Anti-TgA >200 U/ml, % | 13/31 (41)   | 18/31 (19)      |
| HLADQ2, %       | 7/21 (33)       | 14/21 (67)      |
| HLADQ8, %       | 1/4 (25)        | 3/4 (75)        |
| HLADQ2+8, %     | 9/15 (65)       | 6/15 (35)       |
Discussion

POTS represents a common form of orthostatic intolerance. POTS is an autonomic nervous system disease with orthostatic intolerance symptoms, such as orthostatic tachycardia, dizziness, palpitation and non-orthostatic symptoms such as fatigue, myofascial pain, nausea, migraine and headache\[8\]. The frequency of POTS is 0.2% and its incidence is higher in women\[9\].

While normally, in a standing position, venous collection in the lower extremity and gravity effect decreases venous return to the heart due to fluid transfer to the interstitial space. Cardiac filling and stroke volume decrease, and blood pressure decrease. The autonomic nervous system tries to compensate by increasing sympathetic activity on the heart and blood vessels and decreasing parasympathetic activity. Heart rate and systemic vascular resistance are increased; the initial drop in blood pressure is normalized.

With these compensatory mechanisms, an increase of 10-20 bpm in peak heart rate and a negligible increase in systolic and diastolic blood pressures occur. The necessary hemodynamic compensation does not occur in the presence of autonomic dysfunction. In the presence of orthostatic symptoms, a detailed history should be taken from the patient and the use of medication should be questioned. Since congenital heart disease, thyroid dysfunction, arrhythmia, and anemia may also cause orthostatic symptoms, they should be excluded before the diagnosis of POTS was made.

It has been reported that celiac patients often have extraintestinal symptoms, such as palpitations, dizziness and presyncope, which may be associated with the autonomic nervous system\[10,11\]. In contrast, in patients diagnosed with POTS, symptoms related to the gastrointestinal tract, such as nausea, bloating, abdominal pain, constipation and diarrhea outside the cardiovascular system, have been identified at a rate of 15-40%\[8,12\]. Autonomic system dysfunction most likely underlies these complaints concerning the gastrointestinal tract.

Patients with the diagnosis of POTS reported having complaints with gluten intake. In addition, the frequency of biopsy-proven celiac disease was found to be increased in patients with POTS compared to the normal population\[13\]. POTS, which has many pathophysiological mechanisms, is thought to have an autoimmune etiology in recent years\[14,15\]. It has been found that many autoimmune diseases, such as rheumatoid arthritis, Sjögren’s syndrome, Hashimoto’s thyroiditis, and antiphospholipid syndrome, may develop before or after the diagnosis of POTS\[16\]. Antibodies, such as ANA, atypical ANCA, antiphospholipid antibody, Sjögren antibody, which are autoimmunity markers, were found to be increased in POTS patients compared to the general population\[16\]. In our study, the frequency of POTS was significantly higher in patients with Anti-Tg IgA levels above 200 U/ml. This finding shows that autoimmunity may play a role in the mechanism of POTS.

The incidence of autoimmune diseases in HLADQ2-positivity has increased compared to the normal population\[14,17\]. The coexistence of the HLADQB1 has been shown in POTS patients\[18\]. In our study, we found that the frequency of POTS increased significantly in the coexistence of HLADQ2 and HLADQ8 when compared to the presence of the only HLADQ2. This finding supports the idea that POTS has an autoimmune origin.

Conclusion

In our study, increased incidence of POTS with high Anti-Tg IgA levels and with the coexistence of HLADQ2 and DQ8 supports the idea of autoimmune origin of the POTS. In the presence of orthostatic symptoms in children with celiac disease, POTS should be considered and cardiologic evaluation of the patients should be performed.

Ethics Committee Approval: This study was approved by the ethics committee of Ümraniye Training and Research Hospital.

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