

Relation between Anti-Transglutaminase IgA e Anti-Thyroperoxidase in a Pediatric Patient Cohort

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ABSTRACT

Several studies have been reported an association between celiac disease and other auto-immune disorders. However, very few reports in the literature showed the correlation between these disorders in pediatric age. In this observational study we selected a large case series of pediatric patients on which the serological analysis of anti-tissue transglutaminase (anti-tTGA) and concomitantly serological analysis of the antithyroid (anti-TPO) autoantibodies has been performed. We showed that the subjects positive to both tests have a significant female gender prevalence and a temporal difference between anti-tTGA positivity and anti-TPO positivity with a median of anti-tTGA positivity lower than that of anti-TPO positivity. Our data could suggest the importance of the dosage for both autoantibodies, in order to evaluate the possible appearance of autoimmune thyroid disease, for a careful monitoring of pediatric patients.

Abbreviations: Anti-tTGA: Anti-Tissue Transglutaminase; Anti-TPO: Antithyroid; CD: Celiac Disease; ATD: Auto-Immune Thyroid Disease; TAI: Thyroid Autoimmunity; ELISA: Enzyme-Linked Immunosorbent Assay; ECLIA: Electro-Chemiluminescence Immunoassay

Introduction

Celiac Disease (CD) is an autoimmune disorder characterized by inflammation, villous atrophy, and crypt hyperplasia of small bowel mucosa after ingestion of dietary gluten and recovery when gluten-containing cereals are withdrawn from diet [1]. Patients with celiac disease are at high risk of having other autoimmune disorder. In fact, CD has frequently linked to type 1 diabetes, Addison's disease, IgA nephropathy, pernicious anemia and autoimmune thyroid disease (ATD) [2]. In 2008, Elfstrom, et al. reported a two-to fourfold in-creased risk of ATD in patients with CD and similarly that CD was more common in patients with ATD. A number of studies also report that thyroid-related antibodies are more frequent in CD [3]. Anyhow, the prevalence of other autoimmune disease appeared to be closely related to age at diagnosis, or to the duration of gluten exposure. Very few observations in the literature report the correlation between Celiac disease and other autoimmune disorders in pediatric age.

A large Italian multicenter study enrolled 343 consecutive pediatric patients, 230 girls and 113 boys (median age, 8.5 years), highlighted that ATD was found in 90 of 343 (26.2%) patients with CD, even those on a gluten-free diet. In particular, 37 celiac patient reported positivity to the antithyroid autoantibodies (anti-TPO) [4]. Among the clinical investigations necessary for the diagnosis of both diseases there is the measurement of serological levels by luminescence methods: the immunometric evaluation of anti-tissue transglutaminase IgA (anti-tTGA) and IgG (anti-tTGG) antibodies indicative of a possible celiac disease, anti-thyroperoxidase (anti-TPO) antibodies evaluation, indicative of thyroid autoimmunity (TAI).

In this observational study we selected a large case series of pediatric patients on which the serological analysis of anti-tTGA and concomitantly serological analysis of the anti-TPO has been performed.

Case Series

This is a retrospective observational study of pediatric patients from Campania Region in southern Italy admitted at the Santobono-Pausilipon Hospital of Naples. From June 2011 to December 2019 a cohort of 3771 children subjected to the anti-tTGA and anti-TPO tests have been selected. This study was approved by the Research Ethics Committee of the institution, and informed consent was obtained from the patients' parents. Clinical analyses

were performed using commercial kits. Immunoglobulin A anti-tTG antibodies were screened through time-resolved enzyme-linked immunosorbent assay (ELISA) technique and values lower than 16 U/ml were considered negative and positive those >16 U/ml. Anti-TPO antibodies were detected by electro-chemiluminescence immunoassay (ECLIA) and values lower than 10 U/ml were considered negative and positive those >10 U/ml. Selected patients were aged between 0 to 16 years with an median age of 84 months (Table 1).

Table 1: Median age in months and gender distribution of pediatric patients.

Age	<85 months old	2043 (54,2)
	> 85 months old	1728 (45,8)
Gender	Female	2037 (54)
	Male	1734 (46)

In our series 99 (2.5%) patients were positive for the anti-tTGA test (> 16 U/ml) and negative for anti TPO-test, 216 (5.8%) patients were positive for the anti-TPO test (> 10 U/ml) and negative for anti-tTGA test. Instead, both tests were negative in 3449 (91.3%) and positive in 13 (0.34%) patients (Table 2). Considering the 13 positive patients to both autoantibodies 10 (76.9%) children were female highlighting a gender prevalence (Table 2). Furthermore,

a temporal difference between anti-tTGA positivity and anti-TPO positivity has been detected, confirmed by the calculation of the median age in months, with a median of anti-tTGA positivity lower than that of anti-TPO positivity (Table 3). In addition, the median in months of anti-tTGA positivity of patients positive to both autoantibodies (96 months) is higher than the patients positive only for anti-tTGA (36 months) (Table 3).

Table 2: Age and gender patients distribution for anti-TPO and tTGA tests.

Anti-TPO and tTGA Tests		tot	Median Age (months)	Female	Male
	Negative	3449 (91,3)	84	1741 (52,4)	1583 (47,6)
	Positive only for anti-TPO	216 (5,8%)	108	224 (66,7)	112 (33,3)
	Positive only for anti-tTGA	99 (2,5 %)	36	64 (65,3)	34 (34,7)
	Positive for anti-TPO and anti-tTGA	13 (0,34%)	117	10 (76,9)	3 (23,10)

Table 3: Median in months of anti-tTGA positivity of patients positive to both autoantibodies and for patients positive only for anti-tTGA.

Median Age	
Patients anti-tTGA>16 UI/ml + anti-TPO >10 UI/ml	
anti-tTGA	anti-TPO
96	119

Since our case series has been selected analyzing data contained in the archive of a pediatric hospital, as results of routine diagnostics, the patients are not subjected to the two measurements in the same chronological order.

Discussion

In order to analyze the potential relation between celiac disease and autoimmune thyroid disease in pediatric age, we selected a total of 3771 pediatric patients subjected to the measurement of the anti-tTGA and anti-TPO auto-antibodies, over a period of approximately

8 years. Once we extrapolated the data from our hospital archive, we identified the total patients positive for anti-tTGA and those positive for anti-TPO auto-antibodies, and following a cross-check, 13 subjects positive for both tests were selected. Many studies have been reported an association between celiac disease and other auto-immune disorders, including type 1 diabetes [5] Addison's disease [2], IgA nephropathy [2], and pernicious anemia [2]. A large study reported a two- to fourfold increased risk of ATD in patients with CD [2], and similarly that CD was more common in patients with ATD. A number of studies also report that thyroid-

related antibodies are more frequent in CD [2]. Regarding pediatric population, a large multicenter study was performed on a large Italian patient population from Torino, Bologna, Foggia, Rome, Naples, and Bari to establish the prevalence of autoimmune thyroid involvement in a large group of untreated and treated pediatric patients with CD [4].

This study showed an increased prevalence of serologic and/or echographic evidence of thyroid autoimmunity among pediatric patients with CD. Other studies reported the presence of serum organ-specific autoantibodies in patients with CD seems related to the presence of a second autoimmune disease and does not appear to be gluten-dependent [5]. In addition, in a very large Italian study, the prevalence of other autoimmune diseases appeared to be closely related to age at diagnosis and to the duration of gluten exposure [6]. In our study, the percentage of patients with pathological values for both autoantibodies is about 0.34%. By focusing on anti-tTGA positive patients, 11.6% are also positive for anti-TPO. This data are in line with the scientific literature [3,4,7,8]. Similarly, if we consider anti-TPO positive subjects, the percentage of patients also positive for anti-tTGA is 6.05%. This result is also in line with the data from the literature [9]. The new and interesting data of our study is the prevalence of the female gender among the tTGA positive subjects, also found in the 13 patients with positivity to both auto-antibodies. Furthermore, we have observed, as hypothesized in previous studies [7], that the appearance of autoantibodies directed against thyroperoxidase is closely associated with the age of diagnosis of CD patients.

In fact, in the 13 subjects with both auto-antibodies, we have shown that the median age in months of positivity for anti-tTGA is higher than positivity only for anti-tTGA. This finding therefore seems to confirm the hypothesis that the delayed diagnosis of CD and therefore the prolonged exposure to gluten is probably co-responsible for the subsequent production of anti-TPO. The coexistence of CD and the diseases of autoimmune thyroid has been highlighted twenty years ago in a study in which it was performed the evaluation of antithyroid anti-bodies in children with CD. Data showed that elevated titles of anti-TPO antibodies TPO have been detected in children with coeliac disease (11.7%) in comparison to control group, suggesting the need for performing the screening tests for antithyroid antibodies in children with CD [8]. Moreover, several studies in the literature reported a correlation between CD and ATD also supported by a genetic pattern screening [9,10]. Hadithi, et al. analyzed 104 patients with Hashimoto's thyroiditis and five patients positive for celiac serology, with documented villous atrophy, were diagnosed. Genetic pattern HLA-DQ2 (and/or -DQ8) was present in all the five patients [9]. Furthermore, the clinical significance of the presence of these autoantibodies is still unclear, and long-term follow-up of a larger series in controlled studies would be needed to better describe the phenomenon.

Conclusion

In the future it would be interesting to conduct further studies on screening of genetic pattern of pediatric patients that report pathological values of both auto-antibodies, focusing on the HLA complex characterization.

It would also be appropriate to suggest careful monitoring of pediatric patients by suggesting the antibody dosage for both anti-tissue transglutaminase and antithyroid autoantibodies in order to avoid future immune decompensation, avoiding a delayed diagnosis of celiac disease and over time the possible appearance of autoimmune thyroid disease.

Consent

Our patients signed informed consent form for the material presented to appear in the publication above and in related publications, prior to submission.

Funding

None

Conflicts of Interest

None.

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