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Case Report

Behaviour of Anti-transglutaminase Antibodies in Pediatric Population with Type 1 Diabetes: Is It Possible to Save the Biopsy?

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Abstract

Objectives: The prevalence of Celiac Disease (CD) is higher in Type 1 Diabetes Mellitus (T1DM) patients. Our aim is to describe the prevalence of positive Anti-Transglutaminase (anti-tTGA) serology in a cohort of T1DM patients and their tendency in order to stablish a CD diagnosis.

Materials and Methods: Retrospective, descriptive, multicenter study of patients with onset of T1DM between 2010-2020, recording demographic, disease-specific and other relevant autoimmune data. Patients were classified in two groups according to whether they had CD and TDM1 (T1DM-CD group) or TMD1 alone (non-CD T1DM group). Anti-tTGA were considered positive in ranges >10NV and indeterminate if <10NV.

Results: Information from 262 patients was analyzed. The CD prevalence was 6.4%. 258 patients were tested for anti-tTGA titers at T1DM onset: 18 positive, eight had titers >10NV and were diagnosed with CD. The other 10 had indeterminate titers, from these 2 had persistent elevated antibodies therefore a biopsy was done, being confirmatory of CD. The 8 remaining patients had a serologic negativization and not diagnosed with CD. A lower presence of other antibodies was found in the T1DM-CD group compared to the non-CD T1DM group ($p<0.05$). An increased incidence of CD was observed in patients under 5 years ($p=0,551$), female gender ($p<0.05$) and abdominal pain ($p<0.05$).

Conclusion: In T1DM patients it could not be necessary to take a biopsy if the anti-tTGA titers are positive since there is no evidence of a generalized autoimmune status during T1DM onset. If the titers remain indeterminate a biopsy should be done in order to make the CD diagnosis.

Keywords: Celiac Disease; Type 1 Diabetes Mellitus; Anti-Transglutaminase Antibodies

Introduction

Celiac Disease (CD) and type 1 diabetes mellitus (T1DM) are immune-mediated diseases which are commonly associated, possibly due to the sharing of common susceptibility factors such as human lymphocyte antigen (HLA) genotypes. Both diseases have increasing incidences and recent evidence suggests common non-genetic and/or environmental factors may play an important role to increase risk of both CD and T1DM [1].

CD may present with classic symptoms such as diarrhea, abdominal pain and weight loss, but it may also express itself through non-gastrointestinal manifestations, which include failure to thrive, anemia, osteopenia or delayed puberty. Though these are the symptoms for classical CD it has been already published that children with T1DM may have silent or symptomless CD, thus the importance for active screening of the disease [2].

Patients with T1DM have a higher risk of developing autoimmune diseases, including celiac disease, vitiligo, autoimmune thyroid disorders among others. CD has a prevalence of 1% in the general population and this prevalence is even higher in individuals with T1DM, varying between 3 and 16% [3-5], being this the reason why screening for CD in T1DM is advised at diagnosis and every year after T1DM diagnosis [6], specially in the first 5 years after diagnosis, when the risk is higher [1,5].

The duration of total screening is not clear, and it is an issue that has been addressed by several studies [5,7]. According to the recent European Guidelines (ESPGHAN) [8] the diagnosis of CD in the general population is made when anti-tissue transglutaminase IgA (anti-tTGA) titers are >10 times the normal value (>10NV) in two different samples, with normal IgA titers, and anti-endomysial antibodies (EMA) are positive in the second blood sample. However these guidelines still contemplate the need of a biopsy to establish the diagnosis of CD in T1DM patients since it is thought that in the context of the debut there is a generalized immune response that could raise different antibodies, including the anti-tTGA, in an unespecific way. Nonetheless, it is known that in a high proportion of children with positive celiac serology but with low anti-tTGA titers (<10NV) these normalize spontaneously within the first 12 months after the diagnosis of T1DM, despite continuing gluten intake [4].

With regard to the control of diabetic disease in the celiac population, it is known that the burden of coexisting both diseases may be expected to negatively impact glycemic control, although existing data are conflicting [9]. Several studies have shown no difference in glycemic control among people with type 1 diabetes, with or without CD [10].

The aim of this study is to describe the prevalence of positive anti-tTGA serology and the incidence of CD in a cohort of T1DM patients, whether they can be diagnosed of CD or not depending on the anti-tTG titers and their tendency without the need of a biopsy, in order to describe a profile risk to develop CD and to state a celiac screening strategy in these specific population. We also want to see if these patients behave different amb if there is worse metabolic control in this specific group of patients and to see if this cohort has more autoimmunity compared to the T1DM cohort.

Methods

We conducted a retrospective, descriptive, multicenter observational study of patients with onset of T1DM between 2010 and 2020, based on medical files in two hospitals. According to clinical practice guidelines CD was screened at onset and at follow-up determining anti-tTGA titers.

Anti-tTGA were considered positive in ranges >10 NV and indeterminate if they were positive but < 10NV. Patients were diagnosed according to the current guidelines at time of presenting with positive celiac serology: by biopsy before the year 2012 or by ESPGHAN 2012 criteria regarding simptomatology, serology and HLA-typing. Other parameters, such as gender, age at T1DM onset, anti-glutamic acid decarboxylase antibodies (anti-GAD), anti-tyrosine phosphatase-related Islet Antigen 2 (anti-IA2), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (Anti-Tg) antibodies, EMA, IgA levels, HLA-typing, symptoms and glycated hemoglobin (Hb1Ac) were also collected.

Patients were classified in two groups according to whether they had CD and TDM1 (T1DM-CD group) or TMD1 alone (non-CD T1DM group). Demographic, clinical, immunological and metabolic control differences were identified between both groups at debut and at follow up.

Statistics

Data were expressed as means (SD) for continuous variables or as numbers/percentages for categorical variables. The normality of distribution and equality of variances were evaluated through the Kolmogorov-Smirnov test and Levene's test respectively. A Pearson chi-square test was used to compare categorical variables between groups. The U Mann-Whitney was used to compare independent and related continuous variables. The Statistical Package for Social Science SPSS version 23.0 was used to perform all the statistical analyses, establishing the significance at $p < 0.05$.

Ethics

This study was conducted following the declaration of Helsinki and has received written approval from the ethics committee of the Germans Trias i Pujol Hospital.

Results

269 patients under <18 years were diagnosed with T1DM between 2010 and 2020. Six patients were excluded since we could not collect all data from their medical files and another 1 was excluded because he followed a gluten-free diet without having a correct diagnosis of CD, leaving 262 for the final analysis. Of these, 131 (50%) were female. The mean age of DM1 diagnosis was 8,46.

The prevalence of CD in our cohort was 6.4% (a total of 17 patients), four of them had been diagnosed with CD previously to the onset of T1DM and a follow-up of their anti-tTGA titers was not made, therefore they were excluded from further analysis. 8 (47%) were diagnosed at the time of onset of the T1DM and the remaining 5 (29.4%) were diagnosed with CD in the first 24 months of follow-up. All the celiac patients had normal levels of IgA, positive EMA antibodies in a second blood sample and positive HLA D2 and/or DQ8.

258 patients were tested for anti-tTGA titers at the T1DM onset, being 18 (6,97%) positive. Of these, eight had anti-tTGA titers > 10NV and postive EMA serology or confirmatory biopsy and therefore were diagnosed with CD. Among the other 10, who had indeterminate anti-tTGA titers, 2 had persistent elevated antibodies therefore a biopsy was done, being the 2 of them confirmatory of CD. The 8 remaining patients had a negativization of the anti-tTGA antibodies at a median time of 16 months despite gluten intake, so they were not diagnosed with CD.

3 of the 17 celiac patients had negative antibodies at the T1DM onset and they became positive at the first year of follow-up (Figure 1 and 2).

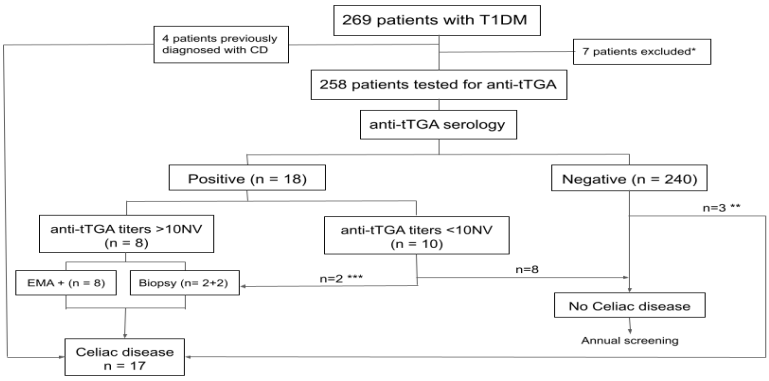

Figure 1: Study participants flow chart: * 6 with no test for anti-tTGA available in medical records, 1 with incorrect diagnosis of CD and following a gluten-free diet. ** anti-tTGA >10NV during follow-up screening controls with EMA positive serology. *** persistent anti-tTGA titers <10NV

Chance of celiac antibodies detection and celiac disease diagnosis as function of time from DM1 diagnosis											
Diagnosis of celiac disease	Transglutaminase antibodies evolution wishes the diagnosis of Diabetes							Anti-Endomesial		Biopsy results	Genetic markers
	0 m	6 m	1 ys	2 ys	3 ys	4 ys	5 ys	0 m	Tracing		
Pre-diabetes diagnosis	●●		○	◊	◊	◊	◊	●●		positive	DQ2
Pre-diabetes diagnosis	●●	●●	◊	◊	◊	◊	◊	●●		positive	DQ2
Pre-diabetes diagnosis	◊	◊	◊	◊	◊				●●	positive	DQ2
Pre-diabetes diagnosis			●●							minimal changes	DQ 8
Diagnosis on diabetic debut	●●	◊	◊	◊	◊	◊	◊	●●	◊	positive	DQ2; DQ8
Diagnosis on diabetic debut	●●	○	◊	◊	◊			●●		N/A	DQ2
Diagnosis on diabetic debut	●●	○	○	○	○	○	○	●●		N/A	DQ2
Diagnosis on diabetic debut	●●		○	◊	◊			●●		N/A	DQ2; DQ8

Diagnosis on diabetic debut	●●	○	○	◊	◊				●●	N/A	DQ2
Diagnosis on diabetic debut	●●	◊						●●		N/A	N/A
Diagnosis on diabetic debut	●●	●●	○	○				●●		N/A	DQ2
Diagnosis on diabetic debut	●●							●●		minimal changes	DQ2; DQ8
Post-diabetes diagnosis	○	◊	○					●●		positive	DQ2
Post-diabetes diagnosis	○		●●	●●						positive	DQ2
Post-diabetes diagnosis	◊		●●	●●					●●	N/A	DQ2
Post-diabetes diagnosis	◊		●●	◊					●●	N/A	DQ2; DQ8
Post-diabetes diagnosis	◊	◊	◊	●●	◊				●●	positive	DQ2; DQ8

Figure 2: Evolution of anti-tTGA titers during follow-up.

Analyzing differences between groups, clinically, our patients presented constipation, failure to thrive, anemia, diarrhea and abdominal pain. Differences were found between the T1DM-CD group and the non-CD T1DM group, more positive symptomatology was found in the T1DM-CD group, being statistically significant the presence of abdominal pain (58.8%, p <0.05) and failure to thrive (23.5%, p<0.05).

Regarding the presence of positive autoantibodies, in the T1DM-CD group, 58,82% and 23,53% had positive antiGAD and antiIA2 autoantibodies, respectively, less presence of positive T1DM-related antibodies compared to the non CD group (67,75% and 59,59%, respectively). As for the thyroid autoantibodies, in the non celiac group we found a positive serology for anti-TPO and anti-Tg of 9,79% and 6,53% respectively, and in the T1DM-CD group none of our patients had positive anti-Tg and only one had a positive test for anti-TPO autoantibodies (5.9%). The only statistically significant is the antiIA2 antibodies (low in CD-T1DM group) comparing both groups (p<0.05) (table 1).

	Total (n= 262)	**CD-T1DM (n= 17)**	**T1DM-non CD (n=245)**	**p**
Girls, n (%)	127 (48,5)	14 (82,4)	113 (46,1)	**<0.005**
Age <5 years at T1DM onset, n (%)	60 (22,9)	5 (29,41)	55 (22,4)	0.551
Age at T1DM onset (years), mean (SD)	8,46	7,92 (4,30)	8,57 (4,22)	0.482
Coeliac symptomatology, n (%)	35 (13,4)	10 (58,82)	25 (10,20)	**<0.005**
anti-TPO, n (%)	25 (9,7)	1 (5,9)	24 (10)	0.491
anti-Tg, n (%)	16 (6,2)	0	16 (6,7)	0.323
anti-GAD, n (%)	175 (73.5)	10 (66.7)	165 (74)	0.551
anti-IA2, n (%)	148 (61.7)	4 (26.7)	144 (64)	**<0.05**
HbA1C at T1DM onset (%)	11,09	10,98	11,13	0.675
median HbA1C at follow-up	7.88	8.1	7.86	0.193

Table 1: Demographic, clinical and biological characteristics of our cohort.

To evaluate the glycemic control we collected the median Hb1Ac during the study period. In the T1DM-CD group the median HbA1c was 8.1% compared to 7.86% in the non celiac group, being a non-significant difference.

Regarding risk factors that predispose to CD, in our cohort, an increased incidence of CD was observed in cases of patients under 5 years (29.4%, p = 0,551), female gender (n=14, p<0.05) and those with abdominal pain (58.8%, p <0.05) and failure to thrive (23.5%, p<0.05).

Discussion

We found a prevalence of 6.4% of CD in our cohort. The prevalence of positive celiac serology at the onset of T1DM was 6.97%, both data similar to other series [11-13].

Among patients with T1DM diagnosed with CD, 60% to 70% are asymptomatic or have minimal symptoms and it is suggested that these patients have a milder phenotype than CD alone [2,7.13]. In our cohort, the majority of CD and T1DM patients were asymptomatic, being the only statistically significant symptom abdominal pain and failure to thrive compared to the non CD group. Other symptoms such as iron deficiency, diarrhea and constipation were recollected but no significance was found. The number of symptomatic patients and the most relevant symptoms differ widely among the different reports published in literature [13-16], and though we found these differences between groups we have to acknowledge that some of these symptoms may not be actively explored in the control visits at the outpatient clinic of the T1DM patients if their anti-tTGA antibodies are negative. Since patients with T1DM who develop CD can be symptomless the recommendation for close follow-up and screening is even more advised specially the first 24 months after the T1DM onset [11,17].

Although routine screening for CD has been recommended in T1DM, there is no consensus on the appropriate frequency or periodicity of control. It is quite clear that it should be performed at the time of diabetes diagnosis [6,18], but the follow-up intervals remain controversial. In our study, almost all the patients with CD were diagnosed in the debut of T1DM or within the first 2 years of follow-up, this is in sintony with other series [4,19] hence we think this should be the minimum time of screening with anti-tTGA antibodies and exploring symptomatology related to CD.

We wanted to explore the possibility of using anti-tTGA titers for diagnosis of CD in T1DM patients without the need of a duodenal biopsy. Results from a prospective study [20] of 128 children with CD (including T1DM and non-T1DM patients), diagnosed with a positive duodenal biopsy showed that anti-tTGA >10NV had a 100% positive predictive value for patients with CD and a positive duodenal biopsy, including asymptomatic patients.

As for the need to describe a higher risk group that could predispose to CD the only demographic feature that was statistically significant in our cohort was the female gender ($p<0.05$). This has already been stated in different cohorts from different countries [5,21] and regardless to what we expected, age <5 years was not proven to be statistically significant, which is in discordance to many of the cohorts that have been published [11,22], which could be explained by the number of patients studied in our cohort.

There is controversial data regarding metabolic control and its association with T1DM and CD. Some studies have reported better metabolic control (lower HbA1c values) in patients with both diseases [23,24], while others have observed no difference between the children with only T1DM and children with T1DM and CD [10,25]. In our cohort, the glycemic control was similar in both groups. Therefore, in our cohort having CD added to T1DM does not lead to a worse metabolic control. Though we could not find statistically significant differences, some studies have shown the effects of following a gluten-free diet on the glycemic metabolism, since the intake of carbohydrates in children with CD is lower compared to the general population, this difference could be explained by the higher cost of the gluten-free products and its poor palability [26], although, on the other hand, the glycemic index of gluten-free foods can be higher than the normal diet.

The main limitation of our study was the limited size sample and the retrospective character of design.

Conclusion

CD has a high prevalence in patients with T1DM, with the highest risk on the onset or along the first 2 years of follow-up, thus it is recommended a scheduled screening should be undertaken periodically, being specially alert with girls under 5 years of age with or without gastrointestinal symptomatology. We could cautiously state that In this specific population it could not be necessary to take a biopsy if the anti-tTGA titers are positive (>10NV) in a second blood sample, since there is no evidence that there is a generalized autoimmune status during the T1DM onset. It should also be taken into account the impact a biopsy may have in the child and their families lives, as well as the risks it carries. If the titers remain elevated but not more than 10NV (indeterminate) a biopsy should be done in order to make the diagnosis of CD. Our results should be ascertained with more prospective and with higher size studies in order to give specific recommendations for T1DM patients.

Conflict of interest:

The authors declare that they have no conflict of interest.

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Participating investigators:

- Montserrat Montraveta: served as scientific advisor and critically reviewed the study proposal
- Paula Sol Ventura: participated in technical editing of the manuscript and served as statistic advisor
- Maria Clemente: provided and cared for study patients
- Oscar Segarra: provided and cared for study patients
- Marta Murillo-Vallés: served as scientific advisors and provided and cared for study patients

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