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Delayed presentation of seropositivity in pre-existent coeliac disease in patients with Type 1 diabetes mellitus: a possible co-occurrence?

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Abstract. – OBJECTIVE: The co-occurrence of coeliac disease (CD) and type 1 diabetes mellitus (T1DM) is well described and is mainly explained by sharing of common pathogenic mechanisms, such as common high-risk human lymphocyte antigen (HLA) genotypes (DR-DQ).

PATIENTS AND METHODS: We describe a 12-year-old female patient with T1DM who presented with prolonged and severe glucose dysregulation. Extensive investigations, including coeliac screen, were negative.

RESULTS: 3 years after glucose dysregulation manifested, coeliac screen testing was positive and coeliac disease was confirmed with bowel biopsy. Compliance to a gluten-free diet resulted in improvement of glucose control and seronegativity 9 months post diagnosis.

CONCLUSIONS: This is the first case report describing delayed seropositivity of CD and suggests that CD enteropathy may precede positive serology and could cause severe glucose dysregulation in patients with T1DM.

Key Words:
Type 1 diabetes mellitus, Coeliac disease, Tissue transglutaminase antibodies, Delayed seropositivity.

Introduction

Coeliac disease (CD) is an autoimmune systemic disorder, characterized by villous atrophy and positive IgA or IgG tissue transglutaminase/endomysial antibodies while on a gluten-containing diet. Compliance to a gluten-free diet results in normalization of the histological pathology seen on bowel biopsy and the seropositivity that accompany the disease[1].

CD is associated with autoimmune conditions including type 1 diabetes mellitus (T1DM). The co-occurrence of coeliac disease and T1DM has been estimated as 3-5%, varying between 1.6-11.1% in different populations. This suggests common pathogenetic mechanisms[2-4]. T1DM usually precedes CD[4]. Whereas the risk for developing CD is 5% in patients with T1DM, the risk in the general population is approximately 1%[5]. Of interest, a remarkable interindividual heterogeneity has been described in T1DM in terms of immunopathological features and the age at diagnosis is considered as one of the most important variables involved. Specifically, a lower age at diagnosis has been associated with large numbers of infiltrating immune cells, especially CD20+ B lymphocytes, also referred to as "hyperimmune CD20Hi" pattern[6]. This "hyperimmunity" probably suggests a predisposition to other autoimmune disorders, such as coeliac disease.

Interestingly, a strong association has been identified between CD and haplotypes of human leukocyte antigen (HLA)-DQ2 and -DQ8[7]. Patients with T1DM also express DQ2 or DQ8 at a significant percent (90%), as opposed to the general population where the corresponding percentage is 40%[8]. Therefore, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines recommend that these haplotypes play a key role in the diagnosis of CD and should be used as a screening tool for CD in patients with T1DM. Negativity of HLA-DQ2 or HLA-DQ8 should seize further serological testing, whereas a positive result should be followed by immunoglobulin A (IgA) anti-transglutaminase

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testing (anti-tTG) and total serum IgA determination[9]. If HLA typing is not available, determination of anti-tTG is an alternative option. Screening is recommended soon after diagnosis of T1DM and at 2- and 5-years post-diagnosis if the original screen is negative[10], since the majority of pediatric patients with T1DM will develop CD within the first 5 years after initial diagnosis[4]. In order to exclude a false negative screening test in the incidence of IgA deficiency and knowing that the prevalence of IgA deficiency is higher in patients with T1DM (10-fold higher risk)[11], anti-tTG is the recommended initial screening test accompanied by total serum IgA[10].

The aim of the present report is to provide an overview of theoretical and clinical aspects of these two autoimmune conditions, T1DM and CD, which not rarely co-exist. Also, the aim of the study was to describe a case of an adolescent girl with T1DM and CD, in which the serological confirmation of CD occurred after a long period of severe glucose dysregulation. Informed consent was obtained from the patient's parents for participation in the study.

Case Presentation

A nearly 13-year old girl, diagnosed with T1DM at the age of 4 years, presented with deterioration of her glycemic control at the age of 9 years. Glucose measurements were unexpectedly elevated, whereas prolonged, severe, unexplained hypoglycemia was present for long periods throughout the day, particularly during the morning hours and noon. The patient experienced severe hypoglycemic episodes with loss of consciousness on two occasions at school. She often required huge amounts of fast-acting carbohydrates in order to normalize her glucose concentrations after a hypoglycemic episode, which resulted in weight gain. Increased stress levels due to fear of severe hypoglycemia were reported by both the patient and her parents, that also resulted in poor school attendance and academic performance. In order to reduce prolonged hypoglycemic episodes, the parents either reduced insulin administration or omitted insulin for breakfast and lunch. Nonetheless, low glucose measurements persisted occasionally, whereas post-prandial hyperglycemia was also often documented. For the rest of the day and night, glucose concentrations were mostly significantly increased. Interestingly, there was no repetitiveness in the glucose pattern on different days and none of the undertaken interventions, including changes in carbohydrate ratios and insulin doses and re-education regarding carbohydrate counting, seemed to improve glycemic control. The patient's glucose levels were monitored using continuous Flash Glucose Monitoring system. However, soon after glucose instability began, capillary blood glucose measurements were also undertaken to confirm the scanned values due to the patient's and her parents' anxiety.

The patient was on multiple daily injection (MDI) therapy, with the basal-bolus regimen consisting of insulin glargine once daily and pre-meal short-acting insulin. At the age of 9 years the patient's weight was 32 kg and total daily insulin requirements were 33 units. The insulin-to-carbohydrate ratios varied between 1 unit of short-acting insulin for every 10 grams of carbohydrates (1:10) and 1 unit of short-acting insulin for every 12 grams of carbohydrates (1:12). Insulin sensitivity factor was 1:55 (1 unit of short-acting insulin lowered glucose levels by 55 mg/dl). At the age of 12 years the total daily insulin requirements were relatively lower, 35 units, and the patient's weight was 53 kg. The insulin-to-carbohydrate ratios were 1:15-1:20 and the insulin sensitivity ratio was 1:50. Switching to insulin pump therapy was proposed by the therapeutic team particularly when glucose dysregulation began, however the parents were reluctant.

In order to explain unexpected hypoglycemia, the possibility of insulin manipulation and intentional overdosing by the patient when not witnessed, was considered. The mother was advised to change her working hours so that the patient was never on her own when administering insulin and insulin pens were kept in a safe position by the parents. The scenario of the patient eating secretly occasionally without self-injecting, was also considered, in order to explain unexpected hyperglycemias. The schoolteacher was asked to check on her snack at school and confirmed that insulin was administered appropriately. After school, either the mother or the father was always with the patient. Despite the above, no improvement was noticed in glucose regulation.

The patient was otherwise asymptomatic, and the family history was negative for coeliac disease, T1DM or other autoimmune diseases. She never experienced any gastrointestinal symptoms or extra-intestinal symptoms associated with coeliac disease. She had a normal and steady height gain but became overweight overtime. At the age of 9 years her BMI% was between the 50th and 75th percentiles, whereas at the age of 12 years it was between the 85th and 90th percentiles. Coeliac screen using tissue transglutaminase antibodies was repeated on a yearly basis and was always negative. Total IgA was also within the reference

range. Other systematic diseases, including adrenal insufficiency, were excluded. Endogenous insulin secretion was also excluded by measuring c-peptide, which was always undetectable. The patient was also hospitalized for 5 days on three occasions within two years in order to have her glucose monitored under controlled conditions. Severe, prolonged hypoglycemia was not identified in any of the three hospitalizations, however, the glucose measurements were unexplained and difficult to control. Specifically, both unexpected hyperglycemias and hypoglycemia were observed, and glucose changes were unpredictable and highly variable despite the standardized conditions regarding the meals offered and the patient's activity levels during hospitalization.

At the age of 12 years, nearly 3 years after unexplained hypoglycemia and poor glucose control were first observed, anti-tTG autoantibodies were found positive for the first time on annual screening. Anti-tTG titers exhibited a 6-fold increase above the upper normal limit (anti-tTG IgA: 50,52 IU/ml and anti-tTG IgG: 10,85 IU/ml, reference range: <8 IU/ml for both antibodies). A small bowel biopsy was performed by a Paediatric Gastroenterologist and confirmed the diagnosis of coeliac disease. The biopsy report was suggestive of moderate lymphohyperplastic infiltrations and increased number of intraepithelial lymphocytes, with normal mucosal architecture and without villous atrophy or crypt hyperplasia. Intraepithelial lymphocytes were counted using immunochemistry for CD3. No significant inflammation was noted, and *Helicobacter pylori* was not detected by Giemsa stain. The findings were described as consistent with type 1 (infiltrative) coeliac disease according to the modified Marsh classification. The patient was started on a strict gluten free diet and at present, 9 months later, her glucose regulation is improved to a significant degree, whereas no prolonged hypoglycemias are experienced. The patient's time in range has increased from 57% before gluten-free diet was started to 76% currently. Her current HbA1c is 7.2%, whereas during the previous 3 years, before gluten-free diet was applied, HbA1c varied between 8.3% and 9.5%. The anti-tTG titres have also normalized.

Discussion

This case report demonstrates a case of a girl with T1DM and significant, unexplained deterioration in her glucose regulation at the age of 9 years. Extensive investigations were performed, including coeliac screening serology tests, and the patient's compliance to diabetes management instructions was questioned. After nearly 3 years of unexplained poor diabetes control, serology testing was indicative of CD, which was confirmed with a small bowel biopsy. We conclude that histopathological changes in the gastrointestinal system caused by CD may be present and may affect serum glucose concentrations before serology testing confirms the disease.

Anti-tTG test has a very high sensitivity and specificity with a positive predictive value of 72%[12]. In the case of IgA deficiency, IgG-tTG and/or IgG deaminated gliadin testing is recommended[13]. Although significantly elevated anti-tTG levels have a good prognostic capacity, a small bowel biopsy is needed for a definite diagnosis to be made before lifelong compliance to a gluten-free diet is recommended. The biopsy may not be necessary if the anti-tTG titer exceeds 10x the assay upper normal limit or in the presence of CD-related symptoms or high-risk HLA genes[9].

Symptoms that should prompt investigations for CD regardless of prior history of screening include gastrointestinal symptoms, such as weight loss, abdominal pain, abdominal distention, nausea, vomiting, constipation, loose stools. Also, non-gastrointestinal symptoms include poor growth, delayed puberty, anemia, osteopenia and depression[12]. A common presentation of CD in patients with T1DM includes unexplained and prolonged hypoglycemia[10]. Nonetheless, absence of symptoms related to CD is common in patients with T1DM.

Interestingly, it has already been described that not all cases of CD can be diagnosed through serology testing. Specifically, a rare form of seronegative CD has been described. In this form, despite negative serology (both for IgA/IgG tTG antibodies and IgA/IgG endomysial antibodies), villous atrophy is present on duodenal biopsy and a gluten free diet results in histological response[1]. The diagnosis is supported by the presence of HLA-DQ2 or DQ8 for CD or a positive family history[14]. Of note, seronegative CD represents the most common cause of serology-negative villous atrophy, accounting for 30% of the cases, whereas the remaining proportion is attributed to other rare forms of gluten-independent enteropathy[15]. Similarly, our case demonstrates that negative coeliac screening does not necessarily confirm absence of the disease. However, as opposed to seronegative CD, the present case suggests that seropositivity can occur, but at a later stage.

Conclusions

This is a literature review on the current knowledge of the co-occurrence of T1DM and CD. A relatively common co-occurrence of the two conditions is demonstrated in the literature and common pathogenic mechanisms, including sharing of common high-risk human lymphocyte antigen (HLA) genotypes (DR-DQ), are proposed. One of the most important points highlighted by the present report is the possibility of delayed presentation of seropositive CD in patients with T1DM and pre-existing CD-related histological lesions. There are several literature reports about seronegative CD, an uncommon and not well-defined condition. However, to the best of our knowledge, this report is the first to suggest that CD-related enteropathy may be present long before anti-tTG serology is positive, thus confirmatory of the disease. Therefore, in the presence of symptoms associated with CD or other clinical indications of CD, the diagnosis cannot be safely excluded by using serological criteria only. A bowel biopsy should be considered and decided on an individualized basis by the diabetologist and the family when the appropriate investigations are not supportive of alternative diagnoses or in order to avoid unnecessary investigations and delays in optimal glucose control.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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