CASE REPORT

Curious case of missing (A) in coeliac disease with type 1 diabetes mellitus

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SUMMARY

Coeliac screening in type 1 diabetes mellitus (T1DM) is universally recommended, but not all authorities recommend serum IgA estimation before using an IgA-based test. We report a case of T1DM with poor glycaemic control and recurrent episodes of hypoglycaemias and diabetic ketoacidosis (DKA). Recurrent oromucosal and respiratory infections further complicated the course of illness, resulting in the increasing proneness to DKA. The patient was screened for coeliac disease but the IgA-based screening test was negative (IgA tissue transglutaminase) due to the low IgA level, whereas the IgG anti gliadin was positive. The patient benefited from initiation of a gluten-free diet.

BACKGROUND

Coeliac disease (CD) is one of the most frequent autoimmune disorders associated with type 1 diabetes mellitus (T1DM). The prevalence of CD in T1DM varies from 3% to 16%, with a mean prevalence of 8%.¹ Coeliac screening in T1DM is universally recommended but infrequently followed. There is a controversy regarding the test advised for screening, and serum IgA estimation is not universally recommended, though the screening tests recommended are IgA-based tests. IgA deficiency is more common in CD and T1DM, but testing for IgA before using an IgA-based test is not a universal recommendation.^{1–2} Moreover, IgA deficiency in CD is associated with more infections, atopic disorders and more subclinical presentations.³ We present this case to emphasise the need for serum IgA estimation before using an IgA-based test for coeliac screening in patients with T1DM. It will not only result in the diagnosis of missed cases, but will also take care of the additional problems occurring due to IgA deficiency.^{1–3}

CASE PRESENTATION

A 21-year-old male patient, diagnosed as a case of T1DM at the age of 8 years, presented with an episode of diabetic ketoacidosis (DKA). He had been on a basal bolus regimen of insulin since diagnosis. The patient had been on close follow-up regularly, and over the years had repeated episodes of hypoglycaemia and DKA. The episodes of DKA were precipitated by oropharyngeal and respiratory infections and occasionally due to skipping of insulin doses due to the fear of hypoglycaemia. The glycaemic control has been erratic with the average glycated haemoglobin (HbA1c) varying between 9% and 12.5% (the mean HbA1c being 10.2%, 11.6% and 10.5% during the last 3 years).

To complicate the matter, there were also repeated episodes of hypoglycaemia, some of which were severe. The patient's insulin requirement was fluctuating.

The patient has always been short and thin as compared to his peers. He had delayed puberty with the development of secondary sexual characters starting at the age of 16 years.

In February 2013, he presented with another episode of DKA. On admission, he was febrile, mildly dehydrated but haemodynamically stable; he had a dental abscess, trismus and his respiratory examination was suggestive of right middle zone consolidation. The patient had a height of 148 cm and weight of 40 kg (body mass index 18.3 kg/m²). He had normal secondary sexual characters with a testicular volume of 15–20 mm³ and stretched penile length of 12 cm. The rest of the examinations, including the neurological and fundus examinations, were unremarkable.

INVESTIGATIONS

Keeping in mind the history of repeated infections and erratic blood glucose control, short stature and as a part of workup of T1DM, the patient was evaluated for associated CD and other endocrine abnormalities (previous coeliac screening performed by IgA tissue transglutaminase (TTG) was negative twice). He had raised glutamic acid decarboxylase antibodies and was euthyroid and eucortisolaemic, and had normal testosterone and follicle stimulating hormone levels. He was anaemic, (Hb 9.8 g%), being deficient in vitamin B₁₂ (168 pg/mL (range 200–900 pg/mL)) and vitamin D (21 ng/mL (30–100 ng/mL)). The patient had a deficient IgA level (0.2 g/L (0.9–4.5 g/L)) with negative IgA TTG. Hence, an IgG anti gliadin antibody (AGA) level test was performed, which was positive (titre 164; normal <15). The diagnosis was further substantiated by positive IgG TTG (titre 110; normal 0–5). Since the patient had trismus, upper gastrointestinal endoscopy was not performed. Since the antibody titre was more than 10 times the upper limit of normal, the patient was diagnosed with CD and put on a gluten-free diet (GFD), after which he improved symptomatically. A further evaluation of the patient revealed low bone mineral density (BMD) at total body (adjusted z score –4.5 at total body and –3.9 at lumbar spine). At present, he is on 0.2 U/kg of insulin daily of basal insulin glargine and bolus insulin, adjusted according to the pre-meal glucose and diet content (carbohydrate counting), with improved glycaemic

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control, with no episode of DKA or major symptomatic hypoglycaemia since the last few months.

TREATMENT

During current admission, the patient was managed with intravenous fluid replacement, insulin (started as an intravenous drip and then switched to a subcutaneous basal bolus regimen) and intravenous antibiotics. He was initiated on GFD. The basal bolus insulin regimen was continued and the diet and exercise counselling was conducted. The patient was maintained on insulin glargine 0.2 U/kg/day and bolus short-acting insulin (regular), and the dose was adjusted according to the pre-meal glucose and carbohydrate content of the diet. The vitamin D and B₁₂ deficiencies were corrected.

OUTCOME AND FOLLOW-UP

The patient symptomatically improved, gained weight and his glycaemic control improved (HbA1c 7.4% and 7.8%) over the next few months. In the last few months, there was no episode of DKA or severe symptomatic hypoglycaemia. There has been one episode of respiratory tract infection, during which the glycaemic control did worsen (without DKA), but was managed by giving corrective doses of bolus insulin and ensuring adequate hydration, regular diet and insulin dosing.

DISCUSSION

CD is an autoimmune enteropathy characterised by immune-mediated damage to the small intestinal mucosa triggered by the ingestion of gluten, a protein complex found in wheat, rye, oat and barley. There are many diseases which are associated with the increased prevalence of CD, for example, Down's syndrome, Turner's syndrome, IgA deficiency, William's syndrome, T1DM and autoimmune thyroiditis.¹

CD and T1DM have common autoimmune origins. Both are associated with the major histocompatibility complex class II antigen DQ2 encoded by the alleles, DQA1*501 and DQB1*201, thus providing a common genetic basis for disease expression.¹ The concomitant presence of CD results in poor glycaemic control, short stature, poor BMD and nutritional deficiencies.¹⁻⁴

IgA deficiency is commonly associated with both conditions. Studies looking at IgA deficiency in the general population have reported rates from 1 in 400 to 18 500 people. A deficiency is 10–15 times more common in patients with coeliac disease than in healthy patient, and it is also highly prevalent in T1DM (5.3%).²⁻⁵ Cataldo *et al*³ reported the prevalence of IgA deficiency in CD to be 2.6%. IgA deficiency in CD was associated with silent forms, atopic diseases and respiratory infections. IgA deficiency in CD was associated with a different cytokine profile (higher interferon- γ and interleukin-10 levels).⁶

Serological tests have become the preferred methods of diagnosing CD in symptomatic and asymptomatic patients. However serum IgA estimation prior to using IgA based tests (which is universally recommended) is not routinely practiced and not universally recommended. Therefore, IgA-based tests are fallacious in the presence of IgA deficiency, the prevalence of which in T1DM is 5.3%.⁵

We presented a case of a male patient of short stature with T1DM, repeated episodes of hypoglycaemia, DKA, poor BMD and anaemia.¹ This led to a high pre-test probability of CD. However, the patient had a deficient IgA level with negative IgA TTG. Hence, an IgG AGA level test was performed which was positive and confirmed the diagnosis of CD, which was further substantiated by IgG TTG antibody. Endoscopy is recommended

for the diagnosis of CD, but there are more and more data to suggest that it is not universally required to confirm the diagnosis, and a strongly positive antibody titre (10>times elevated above the normal range) and response to GFD is enough to substantiate the same (as seen in our case); also, the presence of trismus in our case made endoscopy difficult.⁷⁻⁹ There is a discrepancy in the recommendations by various societies regarding coeliac screening. Many diabetic associations (such as the International Society for Pediatric and Adolescent Diabetes, American Diabetes Association and Canadian Diabetes Association) recommend IgA estimation before IgA TTG while the gastroenterology association (the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) merely recommends the measurement of IgA TTG.¹

In conclusion, patients with CD with IgA deficiency have the IgG isotype of antibodies to the same antigens (endomysial antibody, AGA and TTG antibody) as do the patients with CD with normal IgA. The measurement of the IgA level and use of the IgG-based assays in patients with IgA deficiency will enhance the reliability of the serological methods of detecting symptomatic and asymptomatic forms of CD.

The concomitant presence of IgA deficiency increases the risk of acute and chronic respiratory infection which may lead to bronchiectasis and also increase the susceptibility to drug allergies, atopic disorder and other autoimmune diseases.

This article emphasises the need for serum IgA estimation before the screening of CD with an IgA-based assay, which is not universally recommended.

Learning points

- ▶ Coeliac autoimmunity should be routinely screened for in a case of type 1 diabetes mellitus.
- ▶ Sufficiency of IgA should be ensured before using an IgA-based screening test.
- ▶ Recurrent oromucosal infections in IgA deficiency may increase diabetic ketoacidosis.

Contributors All the authors have contributed equally to the management and writing of the case, as well as in the drafting the article and revising it critically. They also approved the draft submitted.

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REFERENCES

- 1 Sud S, Marcon M, Assor E, *et al*. Celiac disease and pediatric type 1 diabetes: diagnostic and treatment dilemmas. *Int J Ped Endocrinol* 2010;2010:161285.
- 2 Kumar V, Jarzabek-Chorzelska M, Sulej J, *et al*. Celiac disease and immunoglobulin A deficiency: how effective are the serological methods of diagnosis? *Clin Diagn Lab Immunol* 2002;9:1295.
- 3 Cataldo F, Marino V, Ventura A, *et al*. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working Groups on Coeliac Disease. *Gut* 1998;42:362–5.
- 4 Joshi A, Varthakavi P, Chadha M, *et al*. Study of bone mineral density and its determinants in type 1 diabetes mellitus. *J Osteoporos* 2013;2013:397814.
- 5 Landgraf LF, Rosario N, Moura JF, *et al*. High prevalence of immunoglobulin A deficiency in patients with type 1 diabetes mellitus detected by ELISA. *Einstein* 2008;6:26–30.
- 6 Cataldo F, Lio D, Marino V, *et al*. Cytokine genotyping (TNF and IL-10) in patients with celiac disease and selective IgA deficiency. *Am J Gastroenterol* 2003;98:850–6.

- 7 Mubarak A, Walters VM, Gerritsen SA, *et al*. A biopsy is not always necessary to diagnose celiac disease. *J Pediatr Gastroenterol Nutr* 2011;52:554–7.
- 8 Hills PG, Holmes GK. Coeliac disease: a biopsy is not always needed for diagnosis. *Aliment Pharmacol Ther* 2008;27:572–7.
- 9 Husby S, Koletzko K, Korponay Szabo IR, *et al*. European society of pediatric gastroenterology hepatology and nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–60.

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