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Research Article

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Pediatric Celiac disease and Selective IgA Deficiency: Unexpected Sequence of Events

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Abstract

Purpose: Selective IgA deficiency (IgAD) is the most common primary immunodeficiency, frequently leading to only minor clinical complaints. IgAD may be associated with autoimmune diseases such as celiac disease (CeD). Although IgAD is thought to precede CeD and autoimmunity, the association between the two conditions has not been clarified.

Methods: Routine techniques were used to measure serum IgA and celiac diagnostic markers as transglutaminase 2 IgA (TG2-IgA) and deamidated gliadin IgG, and for immunohistochemistry for IgG, IgM and IgA.

Results: We report two childhood cases of complete IgA deficiency that evolved after the diagnosis of CeD and the start of a gluten-free diet. Histology showed persistence of IgA in the intestinal mucosa.

Conclusion: Both children with CeD showed IgA deficiency that unexpectedly developed after the initiation of a gluten-free diet. This supports IgA deficiency as being an autoimmune process that develops gradually and occurs due to specific defects in immunoregulation.

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Introduction

Celiac disease

Celiac disease (CeD) is a chronic inflammatory disease of the gastrointestinal tract that has autoimmune components and is elicited by gluten from grains such as wheat, rye, and barley (1). CeD is closely related to the haplotypes HLA-DQ2 and –DQ8 (2) but is also associated with a number of genes, particularly those coding for inflammatory markers (3). The most prominent diagnostic biomarker for CeD is IgA tissue transglutaminase antibody (TG2-IgA), which has a diagnostic accuracy close to 95% (4,5).

IgA is the second most prevalent antibody in serum after IgG. IgA in its dimeric form is the dominant immunoglobulin in luminal secretions (such as saliva, tears, bronchial and nasal mucosal secretions) and mucous secretions of the small intestine, and it comprises at least 70% of all immunoglobulins produced in the human body (6,7). Serum IgA is produced by B-lymphocytes in the bone marrow and germinal centers as a result of class switching, and secretory IgA is synthesized locally at the mucosal surfaces (6). There is a strong correlation between serum IgA concentrations and mucosal IgA concentrations (7).

IgA deficiency (IgAD) is defined as a serum IgA level below 0.07 g/L alongside normal IgM and IgG levels in an individual aged over 4 years old. IgAD is the most common primary immunodeficiency, afflicting approximately 1:600 individuals, but its prevalence ranges from 1:143 in Saudi Arabia to 1:18500 in Japan (7). Subjects with IgAD may be asymptomatic or harbor sinopulmonary infectious diseases, bacterial overgrowth of the small intestine, and asthma (8). IgAD is frequently associated with IgG subclass deficiencies, with a variable clinical significance. Additionally, IgAD may be part of the rarer common variable immunodeficiency (CVID) (9). As 30% of IgAD cases have autoimmune diseases such as CeD or Type 1 diabetes, a genetic overlap is suggested between IgAD and autoimmune disorders (10).

In a study involving 772 patients with IgAD and 1,976 controls, Ferreira et al. (12) surveyed 118 non-HLA autoimmunity loci and found significant enrichment of association with autoimmunity loci as compared to non-autoimmunity loci ($p = 9.0 \times 10(-4)$) or random SNPs across the genome ($p < 0.0001$), supporting the hypothesis that autoimmune mechanisms may contribute to the pathogenesis of IgAD. A definite causation has not yet been discovered, however.

In clinical practice, the diagnosis of CeD may be complicated by IgAD, which occurs in an increased frequency in CeD patients (5-10%) and gives rise to false-negative TG2-IgA in serum (13). This problem is only partly alleviated by IgG-based tests for detection of CeD (5; 14).

In this case report, we describe two cases of IgA deficiency evolving after the diagnosis of celiac disease and the start of a gluten-free diet, which we believe is a novel finding. The cases contribute to the hypothesis that

the development of IgA deficiency in celiac disease is an autoimmune process that develops gradually and occurs due to specific defects in immunoregulation.

Case 1

Patient description

After its birth in October 2010, Case 1 was referred to H. C. Andersen Children's Hospital at Odense University Hospital, Denmark, due to kidney hypoplasia with normal kidney function and normotension. Birth weight 3400 g, length 54 cm, and head circumference 37 cm were all within normal range. The patient has two siblings who are well. No family member has celiac disease or other autoimmune disease.

CeD was diagnosed at the age of 16 months due to symptoms of fatigue and stomach pain. The diagnosis was established based on the ESPGHAN 2012 diagnostic criteria (5). A gluten-free diet was initiated immediately, and the symptoms disappeared shortly after.

Serology

CeD was diagnosed based on a high level of TG2-IgA (Quanta Flash, Inova, San Diego, California, USA) and a positive EMA-IgA (fluorescence) in a second blood sample, as well as demonstration of positivity for HLA-DQ2. Four months later, decreased levels of IgA were noticed, progressing to frank IgA deficiency with total serum IgA < 0,02 g/l (Fig. 1).

Endoscopy

A gastroscopy was performed including biopsies from the duodenum and the bulb that were analyzed by a pathologist specifically trained in gastroenterology. Crypt hypertrophy and villus atrophy were observed in the duodenal biopsies, and the diagnosis of celiac disease was substantiated. The distribution of T-cell subtypes was as expected, with +CD8, -CD4, and CD4+ in lamina propria (data not shown). A mixed population of IgA, IgG, and IgM immunoglobulin-producing cells was observed (Fig. 2).

Case 2

Patient description

A girl born in October 2016 with birth weight 3370 g and length 51 cm. Ten days after birth, she was diagnosed with supraventricular tachycardia and treated with adenosine and prophylactic beta blocker that was administered for almost a year.

CeD was diagnosed at 13 months of age. Symptoms were chronic constipation, failure to thrive, and fatigue. The diagnosis was made according to the 2012 ESPGHAN criteria.. Soon after the patient started on a strict

gluten-free diet, the family reported alleviation of fatigue and constipation. The patient was followed closely as an outpatient and had a distinctly meteoristic abdomen for 2-3 months after initiation of the gluten-free diet.

Serology

The diagnosis of celiac disease was based on a high-positive TG2-IgA and a positive EMA-IgA in a second blood sample, as well as demonstration of HLA-DQ2. Serum IgA levels decreased after 6-12 months and stayed at < 0.02 g/l thereafter (Fig. 1). Testing for serum anti-IgA antibody was negative.

Endoscopy

Gastroscopy was performed due to continued increase in biomarkers for celiac disease (TTG-IgA and DGP-IgG) and the development of IgAD despite a gluten-free diet and clinical recovery. Gastroscopy showed slight inflammation in the stomach and severe adenopathy in the duodenal mucosa. Seven biopsies from the duodenum (2) showed no villous atrophy and no clear crypt hyperplasia. However, the immunohistochemical staining showed severe intraepithelial lymphocytosis. As in Case 1, the distribution of T-cell subtypes was +CD3, +CD8, and -CD4 in the submucosa and +CD4 in the lamina propria (data not shown).

Discussion

We report two young children who developed IgA deficiency after being diagnosed with celiac disease. The IgAD appeared gradually within ½-1 year after diagnosis despite the children having a positive clinical response to a gluten-free diet and reduced levels of celiac antibodies including IgA anti-transglutaminase 2 antibody. The duodenal mucosa showed preserved presence of IgA as well as IgG and IgM.

IgAD has traditionally been considered permanent as sub-normal IgA levels remain static and persist after 20 years of observation. Up to 40% of IgAD patients develop anti-IgA antibodies. However, more than 20% of Swedish children who were diagnosed before ten years of age later reversed their IgAD status, suggesting a functional IgA deficiency in childhood (15).

IgAD has been shown to be only moderately genetically dependent, related to SNPs on chromosome 6 in the HLA region (12). Our finding that serum IgAD coincided with IgA observed in the duodenal mucosa suggests that antibody production in the bone marrow during clinically active CeD occurred under maximal stress. When the stress disappeared, IgA production ceased in the bone marrow whereas the more long-lived IgA-producing cells in the tissues were still present (16). To our knowledge, this discrepancy between IgA in serum and in mucosal tissues has not been described previously.

Conclusion

These two cases illustrate the development of IgA deficiency in celiac disease as a defect in immune regulation. It is not known how often this late development of IgA deficiency occurs. Regular cohort studies may help to investigate this sequence of events and lead to a better understanding of IgA deficiency.

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Competing Interests: Joseph Murray has received consultancy fees from Bionix, Lilly Research Laboratory, Johnson & Johnson, Dr. Schar USA, UCB Biopharma, Celimmune, Intrexon Corporation, Chugai Pharma, Kanyos, and Boehringer Ingelheim; holds patents licensed to Evelo Biosciences; and receives royalties from Thorax Medical. Steffen Husby has received research funding from Takeda and Thermo-Fisher. The other authors have nothing to declare.

Availability of data and material: Further data are kept in SharePoint at Hans Christian Andersen Children's Hospital, Odense University Hospital, and will be available upon reasonable request.

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Authors' Contributions: SH made the clinical observation; SH, SDS, and JM developed the idea further; MEA and SH wrote the manuscript with input from the other authors; all authors accepted the last version of the manuscript.

Ethics approval: No extra blood samples or other biological material was used for this publication, so the Regional Scientific Ethical Committees for Southern Denmark did not regard an accept as necessary.

Consent to participate and for publication: the caregivers of the two children in words and in writing consented to the use of file material for publication.

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Figure caption list:

Fig. 1. Serum IgA levels and biomarkers for celiac disease (tTTG IgA and DGP IgG) in two patients with celiac disease after start of a gluten-free diet (Case 1 in blue, Case 2 in red)

Fig. 2 Immunohistopathology for IgA, IgG and IgM in the duodenal mucosa in case 1 (a) and case 2 (b)

Figures

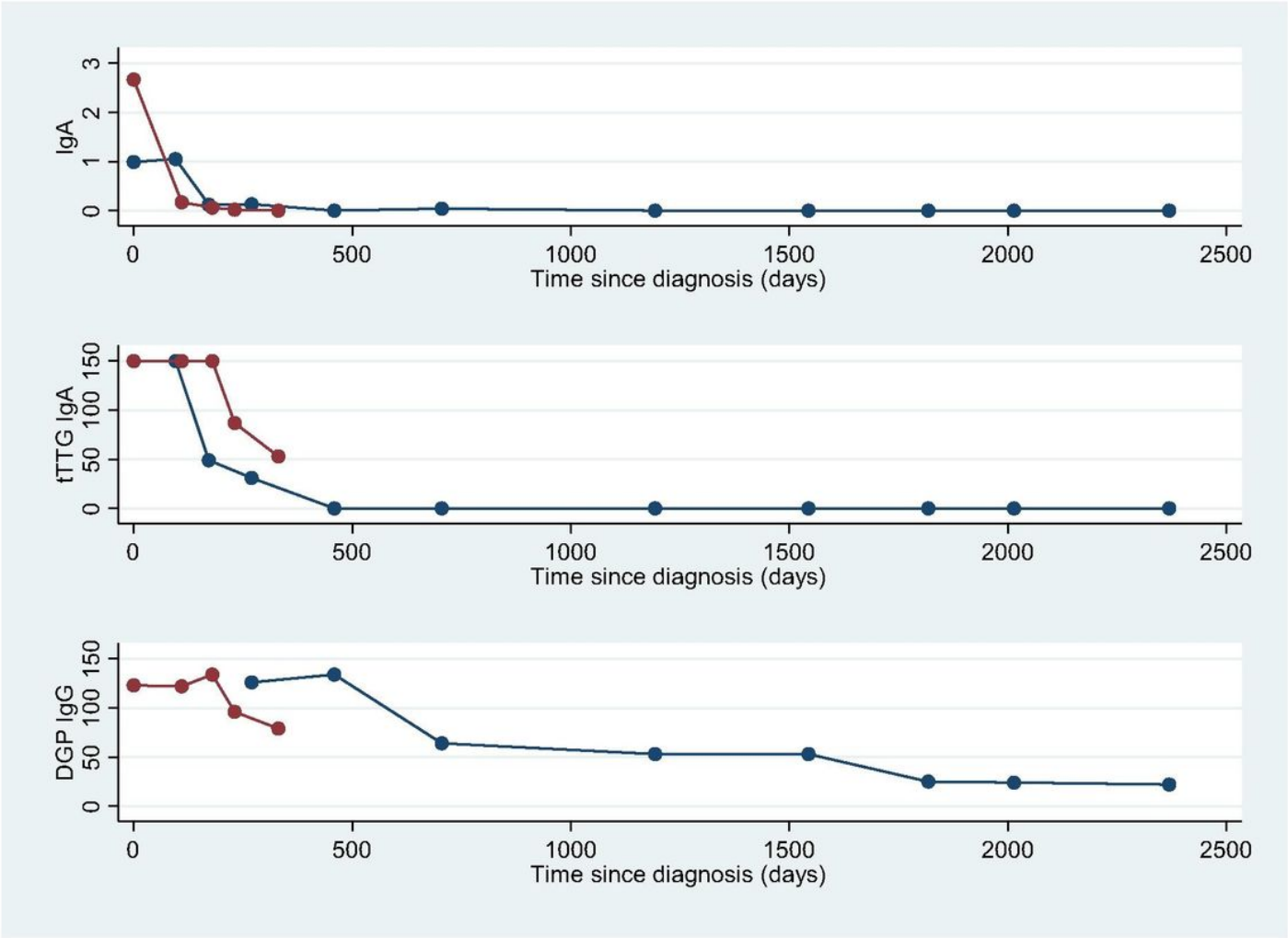
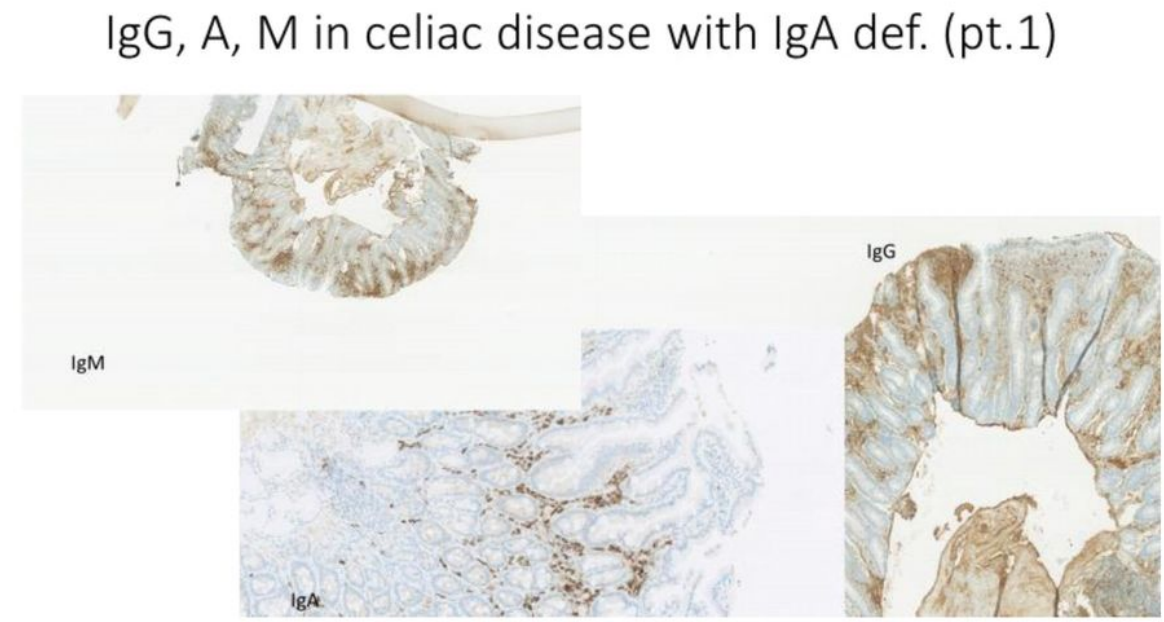


Figure 1

Serum IgA levels and biomarkers for celiac disease (tTTG IgA and DGP IgG) in two patients with celiac disease after start of a gluten-free diet (Case 1 in blue, Case 2 in red)

a)



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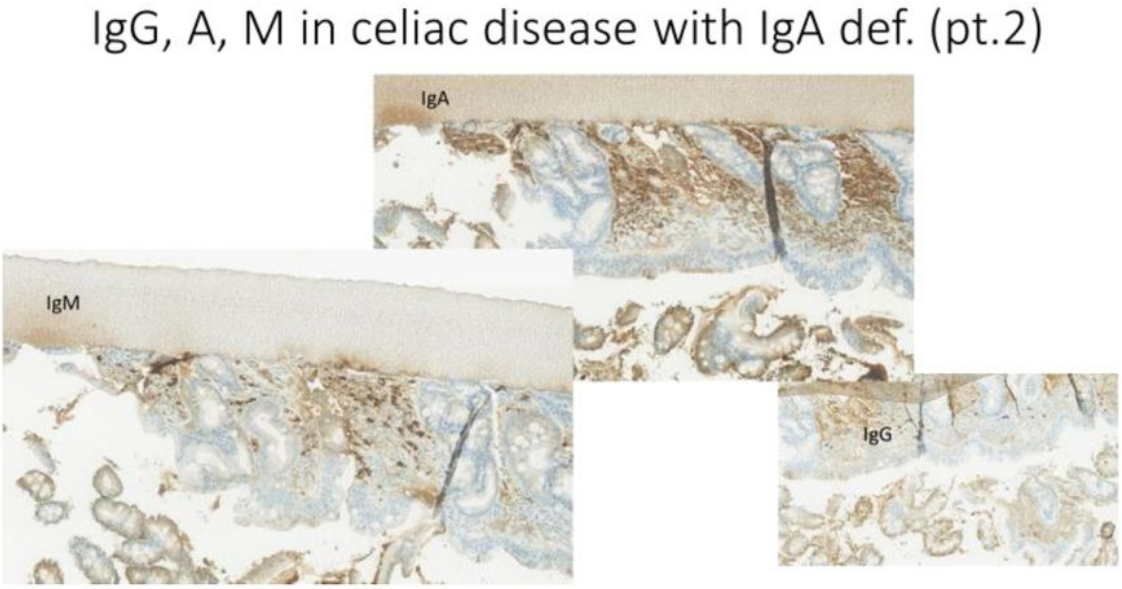

Figure 2

Immunohistopathology for IgA, IgG and IgM in the duodenal mucosa in case 1 (a) and case 2 (b)

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