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

Maria Christine Ernst Andersen1 · Stine Dydensborg Sander1 · Gunvor Madsen2 · Søren T. Lillevang3 · Joseph Murray4 · Steffen Husby1

Received: 25 March 2022 / Accepted: 25 May 2022 / Published online: 14 June 2022 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

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 a process that develops gradually and occurs due to specific defects in immunoregulation.

Keywords Celiac disease · IgA deficiency · Children

Introduction

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 HLA-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 in humans is a monomer lacking J chain and not able to bind to pIgR and be secreted as secretory IgA. 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]. Interaction between IgA-producing plasma cells in the systemic circulation and the mucosae has been demonstrated [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; its prevalence ranges from 1:143 in Saudi Arabia [8] to 1:14,800 in Japan [9]. Subjects with IgAD may be asymptomatic or harbor sinopulmonary infectious diseases, bacterial overgrowth of the small intestine, and asthma [10]. 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) [11]. 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 [12].

In a study involving 772 patients with IgAD and 1976 controls, Ferreira et al. [13] 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. However, a definite causation has not yet been discovered.

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 [14]. This problem is only partly alleviated by IgG-based tests for detection of CeD [5, 15].

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 a process that develops gradually and occurs due to specific defects in immunoregulation.

**Case 1**

**Patient Description**

After birth in October 2010, the girl was referred to Hans Christian 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. These criteria allow a diagnosis of CeD without duodenal biopsies provided a repeated blood sample with TG2-IgA above the upper normal limit times 10, a positive IgA endomysial antibody (EMA) as determined by immunofluorescence and positivity for HLA-DQ2 or HLA-DQ8, as well as a positive clinical response to the gluten-free diet [5]. A gluten-free diet was initiated immediately, and the symptoms disappeared shortly after.

**Serology**

CeD was diagnosed based on a high level (> 150 U) of TG2-IgA (Quanta Flash, Inova, San Diego, CA, USA) and a positive EMA-IgA 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**

Seven months after the initial diagnosis of CeD, a gastroscopy was performed including biopsies from the duodenum and the

---

**Fig. 1** Serum IgA levels and biomarkers for celiac disease (tTG 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)
bulb that were analyzed by a pathologist specifically trained in gastroenterology. Crypt hypertrophy and villus atrophy as well as lymphocytosis were observed in the duodenal biopsies, and the diagnosis of celiac disease was substantiated; the changes classified as Marsh 3a. The distribution of T-cell subtypes was as expected, with CD3+, CD8+, and CD4− in the mucosa 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 again made according to the 2012 ESPGHAN criteria. Soon after the patient started on a strict gluten-free diet, and 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 (> 150 U) 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

![Fig. 2 Immunohistopathology for IgA, IgG, and IgM in the duodenal mucosa in case 1 (a) and case 2 (b)](image-url)
stayed at <0.02 g/l thereafter (Fig. 1). Testing for serum anti-IgA antibody was negative.

Endoscopy

Gastroscopy was performed three months after the initial diagnosis of CeD due to continued increase in biomarkers for celiac disease (TG2-IgA and DGP-IgG) and the development of IgAD despite a gluten-free diet and clinical recovery. Gastroscopy showed endoscopically slight inflammation in the stomach and severe adenopathy in the duodenal mucosa. Histologically, no Helicobacter pylori were seen. Seven biopsies from the duodenum [2] showed severe intraepithelial lymphocytosis, no villous atrophy, and no clear crypt hyperplasia, corresponding to Marsh 1 changes [5]. As in case 1, the distribution of T-cell subtypes was CD3+, CD8+, and CD4− in the mucosa and CD4+ in the lamina propria (data not shown). As in case 1, a mixed population of IgA, IgG, and IgM immunoglobulin-producing cells was observed (Fig. 2).

Discussion

We report two young children who developed IgA deficiency after being diagnosed with celiac disease. The IgAD appeared gradually within 1/2–1 year after diagnosis despite the children having a positive clinical response to a gluten-free diet and reduced levels of celiac antibodies including TG2-IgA. The duodenal mucosa showed preserved presence of IgA as well as IgG and IgM. For one of the cases (case 2), the antibody levels decrease at a slower rate than total IgA, suggesting that TG2-IgA at least at this point of time constitutes a significant fraction of the total IgA.

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 10 years of age later reversed their IgAD status, suggesting a functional IgA deficiency in childhood [16].

IgAD has been shown to be only moderately genetically dependent, related to SNPs on chromosome 6 in the HLA region [13]. 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 [17]. However, it should be noted that this discrepancy between IgA in serum and in mucosal tissues has been described 40 years ago in a small series of 8 patients with IgAD [18], so this latter finding may not be directly related to the occurrence of IgAD after the diagnosis of CeD.

Conclusion

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

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-022-01297-3.

Acknowledgements The patients’ families are thanked for their acceptance and positive attitude towards the publication of this case report.

Author Contribution 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; and all authors accepted the last version of the manuscript.

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

Declarations

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.

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.

References

1. Jabri B, Chen X, Sollind LM. How T cells taste gluten in celiac disease. Nat Struct Mol Biol. 2014;21:429.
2. Sollind LM, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E. Evidence for a primary association of celiac disease to a particular HLA-DQ/heterodimer. J Exp Med. 1989;169:345–50.
3. Trynka G, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nat Genet. 2011;43:1193.

4. Giersiepen K, Lelgemann M, Stuhldreher D, Ronfani Z, Husby S, Koletzko S, Korponay-Szabo IR. Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report. J Pediatr Gastroenterol Nutr. 2012;54:229.

5. Husby S, Koletzko S, Korponay-Szabo I, Kurppa K, Mearin ML, Ribes-Koninckx C, Shamir R, Tromcone R, Auricchio R, Castillejo G, Christensen R, Dolinsk J, Gillett P, Hrůbjartsson A, Koltai T, Maki M, Nielsen SM, Popp A, Stordal K, Werkstetter K, Wessels M. European Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141–56.

6. Mestecky J, Strober W, Russell M, Cheroutre H, Lambrecht BN, Kelsall B. Mucosal immunology. Academic Press; 2015.

7. Isho B, Florescu A, Wang AA, Gommerman JL. Fantast IgA plasma cells and where to find them. Immunol Rev. 2021;303(1):119–37.

8. Al-Attas RA, Rahi AHS. Primary antibody deficiency in Arabs: first report from eastern Saudi Arabia. J Clin Immunol. 1998;18:368–71.

9. Kanoha T, Mizumotoa T, Yasudaa N, Koyaa M, Ohnoa Y, Uchi noa H, Yoshimurab Y, Ohkubob Y, Yamaguchib H. Selective IgA deficiency in Japanese blood donors: frequency and statistical analysis. Vox Sang. 1986;50:81–6.

10. Smith CIE, Islam KB, Vofechovský I, Olerup O, Wallin E, Rabbani H, Baskin B, Hammarström L, X-linked agammaglobulinemia and other immunodeficiencies. Immun Rev. 1994;138:159–83.

11. Ludvigsson JF, Neovius M, Hammarström L. Association between IgA deficiency & other autoimmune conditions: a population-based matched cohort study. J Clin Immunol. 2014;34(4):444–51.

12. Hammarstrom L, Smith CIE. Genetic approach to common variable immunodeficiency and IgA deficiency. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases: a molecular and genetic approach. New York: Oxford University Press; 1999. p. 250–62.

13. Ferreira RC, Pan-Hammarström Q, Graham RR, Gateva V, Fontán G, Lee AT, Ortmann W, Urcelay E, Fernández-Arquero M, Núñez C, Jorgensen G, Ludviksson BR, Koskinen S, Haimila K, Clark HF, Klareskog L, Gregersen PK, Behrens TW, Hammarström L. Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. Nat Genet. 2010;42(9):777–80.

14. Chow MA, Lebwohl B, Reilly NR, Green PH. Immunoglobulin A deficiency in celiac disease. J Clin Gastroenterol. 2012;46(10):850–4.

15. Shahnavaz A, Maguire G, Parker R, Heuschkel RB, Zilbauer M. Tissue transglutaminase antibody levels predict IgA deficiency. Arch Dis Child. 2013;98(11):873–6.

16. Tim CK, Dahle C, Elvin K, Andersson BA, Rönnelid J, Melén E, Bergström A, Truedsson L, Hammarström L. Reversal of immunoglobulin A deficiency in children. J Clin Immunol. 2015;35:87–91.

17. Grosserichter-Wagener C, Franco-Gallego A, Ahmadi F, Mondaca-Vélez M, Dalm VA, Rojas JL, Orrego JC, Correa Vargas N, Hammarström L, Schreurs MW, Dik WA, van Hagen PM, Boon L, van Dongen JJ, van der Burg M, Pan-Hammarström Q, Franco JL, van Zelm MC. Defective formation of IgA memory B cells, TH1 and TH17 cells in symptomatic patients with selective IgA deficiency. Clin Transl Immunol. 2020;9(5):e1130.

18. Scotta MS, Migliore G, de Giacomo C, Martini A, Burgio VL, Ugazio AG. IgA-containing plasma cells in the intestinal mucosa of children with selective IgA deficiency. J Clin Lab Immunol. 1982;9(3):173–5.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.