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Milk Protein-Induced Villous Atrophy and Elevated Serologies in Four Children with Celiac Disease on a Gluten-Free Diet

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Abbreviations: CD: Celiac Disease; CM: Cow's Milk; CMPA: Cow's Milk Protein Allergy; DGP: Deamidated Gliadin Peptide Igg; EGD: Esophagogastroduodenoscopy; EMA: Endomysial Iga; GFD: Gluten-Free Diet; IEL: Intraepithelial Lymphocytes; TTG: Tissue Transglutaminase Iga; VA: Villous Atrophy.

Abstract

Background & Aims: Most children with Celiac Disease (CD) respond to a Gluten-Free Diet (GFD). Rarely elevation of celiac autoantibodies or Villous Atrophy (VA) persist almost always related to ongoing incidental gluten ingestion; yet some patients remain refractory despite the strictest GFD. Cow's Milk Protein Allergy (CMPA) can cause enteropathy and recently was associated with elevated Tissue Transglutaminase IgA (TTG). We report here, for the first time, the occurrence of CMPA causing both persistently elevated celiac serologies and VA in four patients with CD on a GFD that only responded to further elimination of milk protein.

Methods: Data on symptoms, growth, laboratory results, and histology were retrospectively collected on 4 patients from two institutions with nonresponsive celiac disease to create a case series.

Results: Four female pediatric patients were diagnosed with CD based on abnormal celiac autoantibodies and duodenal histology. All patients improved symptomatically with the GFD; however, all had persistent autoantibody elevation and VA on repeated duodenal biopsies despite a strictly reviewed GFD. After additionally eliminating Cow's Milk Protein (CM), all four had prompt serologic normalization for the first time. In two patients who had repeat endoscopies, a complete normalization of the duodenal mucosa was also documented.

Conclusions: We present four cases of pediatric CD with persistently elevated TTG, EMA, and VA despite a strict GFD that responded promptly to milk protein elimination with serologic normalization and documented histologic recovery in two cases so far. This demonstrates a concomitant CMPA may be responsible for some nonresponsive CD, and a CM-GFD should be tried before labeling a patient refractory.

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Introduction

Celiac Disease (CD) is an autoimmune disease triggered by gluten ingestion which can develop in genetically predisposed individuals. The vast majority of children with CD respond to a Gluten-Free Diet (GFD) with remission of symptoms and normalization of celiac-specific serology and small intestinal changes. In some cases, however, elevation of Tissue Transglutaminase IgA (TTG) or Endomysial Antibodies (EMA) as well as Villous Atrophy (VA) of the duodenal mucosa may persist.

Non-responsive CD is defined as the recurrence or persistence of symptoms or persistent VA despite a strict GFD for 6-12 months [1]. Ongoing incidental gluten ingestion is most frequently the underlying cause of non-responsive CD. Refractory CD on the other hand can be defined as persistent symptoms or VA despite a gluten contamination elimination diet and is thought to be caused by a gluten-independent activation of the immune system [1].

Refractory CD can be further categorized into type 1 which demonstrates normal Intra-Epithelial Lymphocyte (IEL) phenotypes with polyclonality of the T-cell gene receptor and type 2 which demonstrates abnormal monoclonality of the T-cell gene receptor. The latter, considered extremely rare in the pediatric age range, is associated with high morbidity and mortality with increased risk of enteropathy-associated T-cell lymphoma [1,2]. Refractory CD often requires treatment with immunosuppressant medications, although treatment is often unsuccessful in refractory type 2 CD [1].

Cow's Milk Protein Allergy (CMPA) is a known cause of enteropathy especially in children. In a recent case report, Merikas et al described a pediatric patient with CD with persistent TTG elevation on a GFD who later eliminated milk protein from her diet due to symptoms with milk ingestion and atopy patch testing which was positive for milk. Her TTG normalized for the first time following cow's milk elimination [3]. This possible association inspired a trial of a Cow's Milk and Gluten-Free Diet (CM-GFD) in our group of patients with non-responsive CD.

We report here the occurrence of CMPA causing both persistent elevations of celiac serologies and abnormal duodenal histology in four patients with nonresponsive CD on a GFD that promptly responded to milk protein elimination from their diet.

Methods

This case series included 3 patients treated at the University of Chicago Celiac Disease Center and 1 patient treated by the Division of Pediatric Gastroenterology at the University of New Mexico who all had a diagnosis of CD based on abnormal celiac serologies including TTG and EMA and histologic confirmation with increased IELs and VA on duodenal histology. A chart review was performed to collect data on clinical symptoms, dietary history, laboratory results, growth, endoscopic appearance, and histopathology from duodenal biopsies.

Case presentations

Patient 1 is a female who initially presented to an outside gastroenterologist at 20 months of age with vomiting, diarrhea, weight loss, and irritability. Her workup included an elevated TTG of >100U (nml < 20U), positive EMA, but normal deamidated gliadin peptide IgG (DGP). She underwent an esophagogastroduodenoscopy (EGD) 3 months later. Duodenal histology from that endoscopy demonstrated VA and increased IELs, therefore confirming a diagnosis of CD. She began a GFD with complete resolution of her presenting symptoms and continued with normal growth velocity; however, her TTG rechecked at 6, 12, and 17 months on the GFD remained >100U despite careful dietary review by a dietician on numerous occasions. She underwent a repeat EGD 18 months on the GFD due to her persistently elevated TTG which showed again VA and increased IELs. She was then referred to the University of Chicago Celiac Disease Center for a second opinion. Her diet was again reviewed to ensure strict adherence to the GFD. Two years after her initial diagnosis, she started a gluten contamination elimination diet comprised of only unprocessed foods. Four months later her TTG at our lab was 790U and EMA was positive with a titer of 1:80. She had a third EGD at that time and her duodenal histology remained consistent with CD. Immunophenotyping ruled out type 2 refractory CD. She also had a work-up for other etiologies of elevated TTG and VA including thyroid, autoimmune, and inflammatory conditions which was all negative. She was followed conservatively for the next 18 months as she was clinically asymptomatic with normal growth. Four years into a GFD, we started a strict cow's milk protein-free diet (CM-GFD) hypothesizing that CMPA could cause the persistent VA and elevated serology. Six months into that diet her TTG had drastically improved to 22U (nml <20U) **(Figure 1).** Twelve months later her serology was normal for the first time since diagnosis with a TTG of 14U and a now negative EMA. Her DGP remained normal throughout her entire course. She underwent a repeat EGD at that time which showed, for the first time, completely normal duodenal histology.

Patient 2 is a female who first presented to an outside gastroenterologist at 13 months of age with diarrhea, abdominal distention, and poor mood. Her TTG was found to be elevated at >100U (nml <4U) with a positive EMA and normal DGP. An EGD was done 3 months later which had duodenal histology consistent with CD. She started on a GFD with resolution of her symptoms and continued with normal growth. Her TTG 13 months into the GFD remained >100U. At that time oats were also eliminated from her diet to exclude possible cross-contamination. She was referred to the University of Chicago Celiac Disease Center for a second opinion 2 months later when her TTG was quantified at 6072U (nml < 20). Our dietician reviewed and judged her diet as strictly GF. Five months later despite strict adherence her TTG had increased to 9278U and EMA was positive at a titer of 1:320. She underwent a repeat EGD 2 months later which demonstrated persistent VA and increased IELs. Extensive workup for other causes of TTG elevation and VA was also negative in her case. After our experience with patient 1, we also started patient 2 on a CM-GFD. Two and half months later her TTG had dramatically dropped to 289U and EMA down to a borderline positive titer of 1:10. After an additional 5 months on the CM-GFD her TTG improved to 65U and her EMA became negative for the first time. Now thirteen months on the CM-GFD her TTG is 35U (nml <20) **(Figure 1).** She has not yet undergone a repeat EGD on the CM-GFD.

Patient 3 is a female who presented to an outside gastroenterologist at 17 months of age with intermittent non-bloody, non-bilious emesis, weight loss, and loss of her developmental milestones which all began following what appeared to be a viral respiratory infection. She had labs drawn which revealed an elevated TTG of 182U (nml <3U). She underwent an EGD which demonstrated gross atrophy in the duodenal bulb and the second portion of the duodenum. Histology revealed increased IELs and VA in the second portion of the duodenum consistent with

CD. She initiated a strict GFD with dramatic improvement in her gastrointestinal symptoms. After 5 months of the GFD there was a notable drop in her TTG to 57U (nml <3). Of interest, she also had an elevation of her absolute eosinophil count at that time to 450/mmc (9%). At follow-up 7 months later, she had a rise in her TTG to 125U. With the assumption of accidental gluten ingestion, the diet was again reviewed with a trained dietician and recommendations were made to remove potential gluten contaminants. The family eliminated these items in addition to limiting meals out of the house. Despite these alterations, the TTG remained elevated at 177U when repeated 5 months later. She was monitored clinically over the next two years as she was asymptomatic with normal growth. Despite strict adherence to the GFD, however, her TTG remained elevated when repeated at 6 month intervals over those 2 years which prompted a trial of oral Budesonide. She was also noted to be EMA Positive and HLA DQ2 positive during this time. A repeat EGD with biopsies was performed 3 months later, now 5 years from her original diagnosis, which again demonstrated VA increased IELs consistent with ongoing active CD. She then began a gluten contamination elimination diet consisting only of unprocessed foods, but a repeat EGD 6 months later demonstrated no improvement and her TTG remained elevated at 76U (nml <3U). At that time, she only had complaints of intermittent mild generalized abdominal pain and had slow, but steady height and weight growth. She was seen at the University of Chicago Celiac Disease Center for a second opinion where additional testing revealed a positive EMA and elevated DGP of >250U (nml <15U). She was also placed on a CM-GFD. Her TTG repeated 3 months later was noted, for the first time since diagnosis, to be normal at <2U (nml <20U) with negative EMA and dramatically improved DGP at 21U (nml <20U) **(Figure 1).** She underwent a repeat EGD with biopsies 2 months later with a normal gross duodenal appearance and complete recovery of the intestine histologically. The patient was also noted to have a further rise in both her weight and height growth and complete resolution of her mild intermittent abdominal pain.

Patient 4 is a female who presented to the University of New Mexico Pediatric Gastroenterology clinic at 17 months of age with a 2-month history of vomiting, diarrhea, weight loss, irritability, and lethargy as well as refusal to walk for 3 weeks. Laboratory testing revealed an elevated TTG >225U (nml <15U) as well as DGP >225 (nml <15U), hypoalbuminemia of 1.9, normal thyroid studies, and HLA-DQ2 positivity. An EGD was performed at 20 months of age which demonstrated increased IELs, subtotal to complete villous blunting, and crypt hyperplasia. Her symptoms resolved after initiating a GFD which was strict and excluded any processed foods or foods containing more than 4 ingredients. Despite this strict GFD, her TTG remained elevated to 132U at 3 months, >225U at 10 months, and >250U at 12 months with a positive EMA at a titer of 1:80 at that time. Interestingly, her DGP normalized within a year of starting the GFD. Two years after her diagnosis, she underwent a repeat EGD which again demonstrated increased IELs and VA. Immunophenotyping was performed and the majority of the IELs were CD3+/CD8+, a normal celiac immunophenotype not supportive of type 2 refractory CD. Since her TTG remained elevated >250U, a 3rd EGD was done 20 months into the GFD which again demonstrated increased IELs and mild villous blunting. After a 3-month trial of oral steroids, her TTG decreased to 161U but increased again to >250U within 6 months of discontinuing the steroids. Four years after her diagnosis, she underwent a 4th EGD which again was consistent with CD. Based on hearing the experience at the University of Chicago Celiac Disease Center, she was also placed on a CM-GFD. Her TTG significantly improved to 49U at 5 months and then 24.8U at 8 months with a now negative EMA after starting the CM-GFD **(Figure 1).** She has not had a repeat EGD at this time.

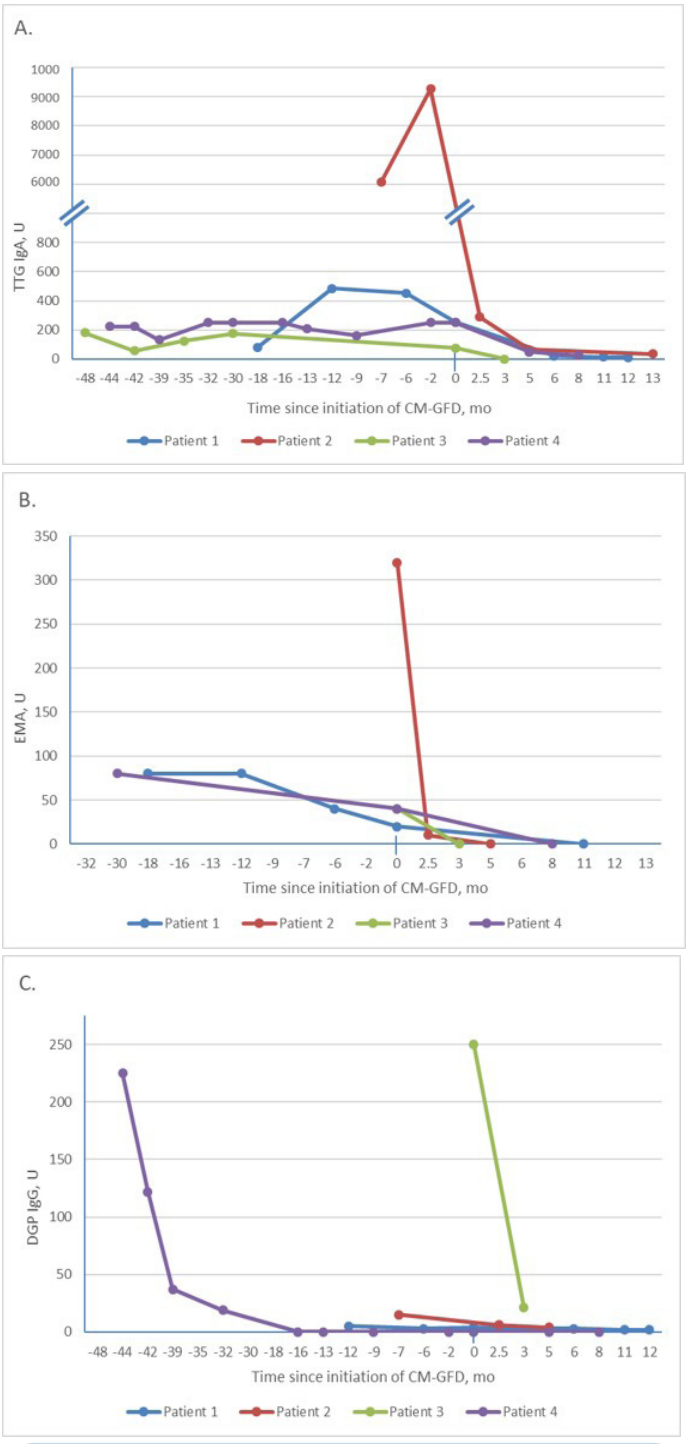

Figure 1: Celiac Autoantibodies in Relation to Initiation of Cow's Milk Gluten Free Diet (CM-GFD).

TTG IGA: Tissue transglutaminase IgA
EMA: Anti-endomysial IgA
DGP IGG: Deamidated gliadin peptide IgG

Discussion

We present four cases of pediatric CD responding with symptomatic resolution to the GFD but with persistently elevated celiac autoantibodies and VA despite a very strict GFD, and eventually responding only to milk protein elimination. In all four cases there was rapid and complete normalization of the autoantibodies; and a complete histologic recovery could also be

documented in the two patients who have undergone repeat EGD so far. Therefore, we conclude that a simultaneous CMPA may cause patients with CD to have ongoing elevations of their celiac serologies and villous atrophy. Moreover, we suggest that a CM-GFD should be attempted in any CD patients who do not respond to a controlled, strict GFD before labeling them as refractory.

For most patients with CD, symptoms begin to improve within weeks of starting a GFD, and especially gastrointestinal symptoms appear to resolve promptly [4]. A reported 5-19% of children with CD however will have persistent enteropathy on duodenal histology despite adhering to a GFD for 1 year [1,5]. Adults with CD have an even worse response with up to 40% of patient with persistent enteropathy after being on the GFD for 2yrs [1].

Since the persistence of enteropathy is thought to be related in the majority of cases to ongoing incidental gluten ingestion, the gluten contamination elimination diet can be used to further limit the possibility of gluten contamination through the allowance of only whole, fresh, unprocessed foods [1]. We now propose that in pediatric cases of apparent unresponsiveness in spite of such a highly controlled diet, the possibility of a CMPA should be considered and evaluated.

As for the mechanisms of the association, and the unexpected finding that CD-specific autoantibodies are persistently elevated due to CMPA in these patients, we can only speculate. It is conceivable that the enteropathy associated with CD led to an increase in mucosal permeability resulting in increased likelihood of an immune response to various dietary antigens, including milk proteins. Interestingly, there is also a homologous amino acid sequence between β-casein found in milk and gliadin which could result in antigenic mimicry. Additionally, TTG binds to glutamine (Q) and proline (P) rich proteins such as gluten, and casein is also rich in these amino acids thus explaining the etiology of the elevated celiac autoantibodies with the CMPA [6].

This hypothesis of antigenic mimicry is supported by other studies which have linked milk protein and gluten. A study demonstrated significantly increased mucosal inflammation in rectal patch testing with both milk powder and gluten in patients with CD compared to controls despite RAST testing being negative in all of them [7]. In another study, IgA for both gliadins and caseins were immunodetected from the sera of patients with CD [8].

Conclusion

In summary, we describe for the first time four cases of pediatric CD asymptomatic while on a GFD but with persistent celiac autoimmunity and villous atrophy with complete response to elimination of CM protein. All four patients had a prompt response to a milk and gluten-free diet with full normalization of celiac serologies. More impressive, two have undergone repeat EGD with biopsies on the CM-GFD so far and both had complete histologic recovery. This suggests that a child with CD whose CD-specific serology and duodenal mucosa changes do not respond to a highly controlled, strict GFD should undergo a trial of a CM-GFD prior to being labeled refractory CD.

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